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(54) **Title:** HIGHLY CHEMOSELECTIVE REACTIONS IN PRESENCE OF AROMATIC AMINO GROUPS

(57) **Abstract:** : The invention discloses a novel process for highly chemoselective reactions of substituted anilines without any de-
tectable reaction at aromatic amino group. The invention also relates to a novel process for preparation of neostigmine methyl-
sulphate via chemoselective reaction of 3-amionphenol and aryl dimethylcarbamates.



HIGHLY CHEMOSELECTIVE REACTIONS IN PRESENCE OF AROMATIC AMINO GROUPS

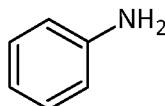
Technical Field

The present invention relates to a novel process for highly chemoselective reactions in presence of aromatic amino groups without any detectable reaction at aromatic amino groups.

The invention also relates to a novel process for preparation of aromatic amino derivatives which can be used or being used as an intermediate for the synthesis of a large number of compounds of biological and physiological importance.

Background and Prior art:

Aromatic amines are a rich class of compounds finding applications in many fields of biological and physiological importance. The simplest form of aromatic amine is called Aniline or phenylamine or aminobenzene and is given by structural formula as:



Aniline itself and many simple aniline derivatives are used in the manufacture of dyes, medicines, resins, varnishes, perfumes, shoe blacks, etc. Many other simple and substituted aromatic amines are either used for myriad of applications or are used for the manufacture of such substances, some of which are exemplified below.

4-aminophenol is used in the manufacture of acetaminophen also called paracetamol which is analgesic and antipyretic drug. One more analgesic prepared from same compound is Bufen.

Aflatoxin is an aromatic amino drug used as skeletal muscle relaxant.

Amfenac and Bromfenac are amino benzophenone derivatives used as anti-inflammatory drugs.

Aminacrine also called 9-aminoacridine is used as antiseptic drug.

Benzocaine, Butacaine, Butamben, Butethamine, chlorprocaine, procaine, Proparacaine, Propoxycaine, tricaine and Betoxycaïne are esters of aminobenzoic acid and are used as anesthetic.

Benzonate is an ester of 4-aminobenzoic acid and is used as Antitussive drug.

2,4-biphenyldiamine, 2,2--dichlorobenzidine and 3,3--dichlorobenzidine are used in the manufacture of azo dyes.

Bromopride and Metoclopramide are an amide of aminobenzoic acid used as antiemetic drugs.

2,4-di aminoanisole is used in the preparation of hair and fur dyes.

Glyceryl p-aminobenzoate is an aminobenzoic acid ester used as cosmetic in sunscreen preparation.

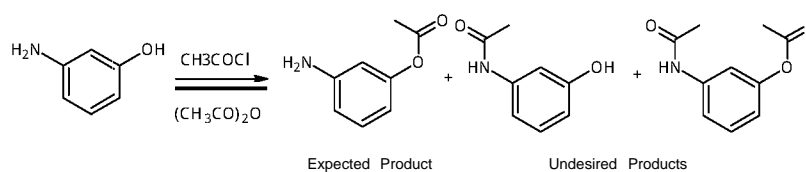
Menthyl Anthranilate is an aminobenzoic acid ester used as ultraviolet screen.

Sulfadiazine is a class of compounds containing 4-aminophenylsulfamide unit attached to various aromatic and heterocyclic systems.

Selectivity in organic synthesis is one of the most essential tools to efficiently synthesize a large variety of compounds. The term selectivity comes in to picture when there are two or more groups on a substrate with almost similar reactivity resulting in to formation of more than one desired products. In such a case, controlling the reaction conditions to preferentially produce one compound is

rather a difficult task and even more difficult when the reaction has to be optimized for industrial scale.

Aromatic amines consist of groups such as NH_2 , NHalkyl or NHcycloalkyl attached to aryl or heteroaryl rings. These groups are often reactive especially with carboxylic acid (either in the absence or presence of coupling reagents) and highly reactive with their active counterparts such as acid chloride, anhydride, etc., resulting in to formation of amides. To carry out the reaction of carboxylic acids or their active counterparts such as acid chlorides, anhydrides, etc. with alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), alkylamines, etc. selectively in presence of aromatic amines is trivially more difficult. So as depicted in the scheme shown below, acetylation of 3-aminophenol with acetylchloride or acetic anhydride would most probably results in the formation of undesired N-acetyl and N,O-diacetyl products in substantial quantities where as the desired O-acetyl product would be formed in traces or either not formed.



The same would have been true if phenolic group in above reaction would have been replaced by either alcohol (Alkyl OH), thiol (Alkyl SH) or thiophenol (Aryl SH) groups the result would have been almost similar except for the alkyl amine group where the formation of N,O-T-diacyl compound is more desirable. This can be explained on the basis that the groups such as alcohols, phenols, thiol, thiophenols, etc are acidic in nature and hence behave as a very weak nucleophile compared to aromatic or aliphatic amines which are mild bases.

Developing a process whereby the groups such as alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), alkylamines, etc. are selectively reacted in presence of aromatic amino group would result in to easy access to a large number of active aromatic amino derivatives of biological and

physiological importance or can be used as intermediates in the development of active compounds.

The above study is also proved on the basis of literature given below. As the nucleophilicity of an amino group is much greater than that of alcohol (Alkyl OH), thiol (Alkyl SH) or thiophenol (Aryl SH) groups, amines can selectively be acylated to give the corresponding amide, even in the presence of excess amount of alcohols and/or water. This chemoselectivity has been well utilized for several highly efficient amidation reactions e.g. in the synthesis of acetaminophen. US 2998450 A describes synthesis of acetaminophen (N-acetyl-p-aminophenol) prepared by acetylation of para-aminophenol with acetic anhydride.

The article published in Tetrahedron, 1995, 51(45), 12263-12276; describes a general procedure for chemoselective acylation of substituted aminophenols. The N-acylated derivatives of corresponding aminophenols were prepared by treating aminophenols with 3-(trimethylacetyl)-1,3-thiazolidine-2-thione in 70 - 100% yield.

Arkivoc 2004, (i), 55 - 63 discloses acylation of amines with anhydrides in an aqueous medium. The article also highlights excellent selectivity for aryl amines over phenols and thiols.

The article titled "Chemoselective Acylation of Amines in Aqueous Media" mentioned in European Journal of Organic Chemistry, 2004, 1254 - 1260; reports reactions of 4-aminophenol with acetic anhydride, propionic anhydride, benzoic anhydride, succinic anhydride and phthalic anhydride resulting in 99%, 97%, 98%, 87% and 91% of N-acylated products respectively.

Synthetic Communications 2010, 40, 295 - 302 discloses additive-free chemoselective acylation of amines with anhydrides in ethyl acetate at room temperature. The article reports chemoselective acetylation of 2-aminophenol and 2-aminothiol resulting in N-acetylated derivatives in 98% and 65% yield

respectively. In case of 2-aminothiol 20% of N, S-diacylated product is also obtained after column chromatography separation.

Yakugaku Zasshi, 1962, V82, 875 - 883 reports selective benzoylation reactions using sodium benzoylthiosulphate. Comparative examinations were made on the application of benzoyl chloride and sodium benzoylthiosulfate on aminophenol and o-aminothiophenol. In the alkaline reaction, application of benzoyl chloride gave N, O or N, S-di benzoyl compounds alone or a mixture of that and N-benzoyl compounds, whereas that of sodium benzoylthiosulphate gave only the O or S-benzoylated compounds. It is necessary that a large excess of sodium benzoylthiosulphates is required (1.75 - 2.2 equivalent) to react with aminophenols or aminothiols to get the desired results resulting in to substantial loss of active acid. This is because sodium benzoylthiosulphates hydrolyses slowly in aqueous alkaline solutions. The reaction cannot be carried out in organic solvents because of its poor solubility. So it is difficult to optimize the reaction in large scale. The US patent US3090785 describes the synthesis of sodium benzoylthiosulphate using various acid chlorides. The yield of various derivatives of sodium benzoylthiosulphates, one of which is used in the above reaction as a reagent is very low (50 -60%). There is an overall substantial loss of active acid in the process of making O or S-benzoylated compounds using sodium benzoylthiosulphates so the method is not economical. The method has one more drawback as it is dependent on the conversion of the acid in to its active acid chloride which is later converted in to sodium benzoylthiosulphates involving multiple steps.

J. Am. Chem. Soc. 2008, 130, 2944 - 2945 discloses tetranuclear zinc cluster $Zr_4(OCOCF_3)_6$ -catalyzed transesterfication of aliphatic amino alcohols with PhCCbMe. The reaction provides benzoylated aliphatic amino alcohols at the alcoholic group with remarkable chemo-selectivity without any detectable mono-benzoylation at the amino group and with the formation of 7 - 23% of N,O-dibenzoylated products. However, the article is silent about the chemoselective O-benzoylation in presence of aromatic amines. Moreover, the tetranuclear zinc

clusters are not easily available and very difficult to synthesize. Hence such processes cannot be utilized industrially.

Bulletin of the Korean Chemical Society, 2009, 30(5), 1071-1076 discloses TME DA catalyzed acylation of alcohols, phenols and thiols under solvent-free condition. The article exemplifies TME DA catalyzed acetylation of m-aminobenzyl alcohol with acetic anhydride resulting in poor yield (68%) of O-acetylated product. It is a known fact that acetic anhydride or any other anhydride when comes in contact with anilines in presence of a base leads to the formation of amide. This article mentions the reactions which are carried out in microgram scale where such kind of O-acylation or aroylation in presence of anilines is possible. However, such reactions are difficult in large amounts. The reaction is carried out in solvent free conditions where acetic anhydride itself acts as a solvent as well as acylating agent thus required in excess amount making the process uneconomical. Such method will only be feasible with anhydrides which are liquids at normal atmospheric pressure and temperatures i.e. lower aliphatic and aromatic anhydrides. Also the anhydrides of higher acids are difficult to manufacture. Acylation or aroylation using anhydride results in formation of one equivalent of acid thus leading in to loss of one equivalent of acid which can otherwise be utilized for the synthesis of ester. Thus the process is not economical and industrially not feasible.

Comptes Rendus Chimie, 2011, 4(12), 1109-1116 discloses transesterification of diethyl malonate with various alcohols using metal aluminophosphates as catalyst. The article mentions the reaction of diethyl malonate and 4-aminobenzyl alcohol using Fe-aluminophosphate. The results shows 67% conversion of diethyl malonate with 42.2% selectivity for 4-aminobenzyl ethyl malonate and 35.8% selectivity for bis(4-aminobenzyl) malonate.

Journal of Chemical Research, 2011, 35(9), 536-539 discloses a green method for selective acetylation of primary alcohols using ethyl acetate and solid potassium carbonate. Accordingly, 3-aminobenzyl alcohol was acylated to yield 3-

aminobenzyl acetate in 90% yield. The article describes the reaction in solvent free condition where ethyl acetate itself acts as solvent as well as acylating agent thus it is required in excess amount. Such method is economical only with aliphatic esters which are used as solvents in industry. The process is uneconomical when higher molecular weight esters are used. The method will only be feasible with low molecular weight esters which are liquids at normal atmospheric pressure and temperatures i.e. lower aliphatic and aromatic esters. The use of solvents for acylation or arylation results in dilution of the reagent leading to incomplete or no reaction thus making the process industrially inappropriate. Thus the process is not economical and industrially notfeasible.

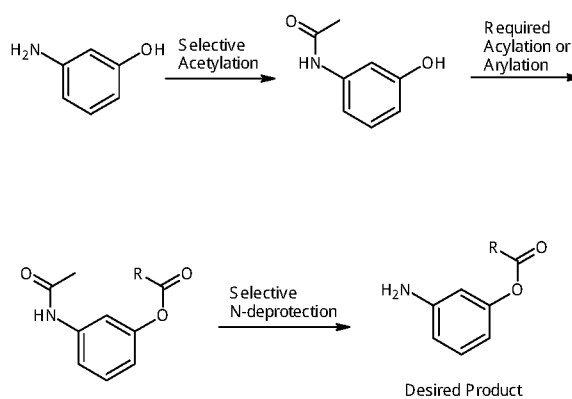
Bioorganic & Medicinal Chemistry Letters, 2012, 22(17), 5748-5751 mentions carbamoylation of 1-amino-2-naphthol with dimethyl carbamoyl chloride (MezNCOCl) in CS_2CO_3 and acetone. The reaction was carried out overnight at room temperature to provide (1-amino-2-naphthyl)N,N-dimethylcarbamate. However, the article fails to highlight the yield and selectivity of the product.

Tetrahedron 2012, 68, 9068 - 9075 discloses N,N,N-,N-,N_-pentamethyldi ethylenetriamine (PMDETA)-catalyzed selective benzylation of alcohols with trichloromethyl phenyl ketone. The reaction is carried out in acetonitrile at 20 - 25°C for 2 hours. The article exemplifies the reaction of m- and p-aminobenzyl alcohol with trichloromethyl phenyl ketone. However, in both the reactions the product contains 13 to 14 % of N-benzoylated derivatives.

Organic Letters 2014, 16(7), 2018 - 2021 discloses lanthanum(III) triflate catalyzed direct amidation of esters. The article exemplifies only one example of selective amidation of aliphatic amino group in 4-aminobenzylamine using ethyl acetate and lanthanum(III) triflate as a catalyst. The article describes the reaction in solvent free conditions where ethyl acetate itself acts as a solvent as well as an acylating agent thus required in excess amount. Such method will only be feasible with low molecular weight esters which are liquids at normal atmospheric

pressure and temperatures i.e. lower aliphatic and aromatic esters. The reaction is carried out in milligram scale. Absolute dry conditions are maintained by flame drying the apparatus as well as the catalyst under reduced pressure. However, the reaction requires 24 hours to yield the desired product. Moreover the use of costly lanthanum(III)triflate catalyst with such stringent conditions is not possible on industrial scale. The use of solvents for acylation or arylation results in dilution of the reagent leading to incomplete or no reaction thus making the process industrially inappropriate.

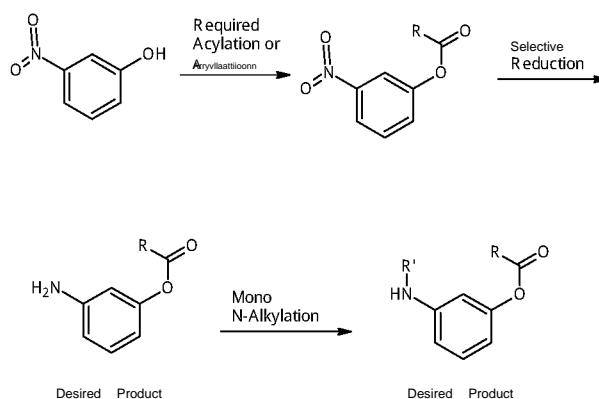
In contrast the chemoselective acylation of groups such as alcohols, phenols, thiol, thiophenols, alkyl amines, etc. in the presence of aromatic amino groups is not a trivial task. Accordingly, the common strategy to synthesize selective acylated or arylated compounds of alcohols, phenols, thiol, thiophenols, alkyl amines, etc. in the presence of an aromatic amino group would involve the protection of an amino group by its conversion into the corresponding amide or carbamate, followed by the acylation of the hydroxyl functionality, and final selective N-deprotection. One of the strategies is exemplified in the scheme.



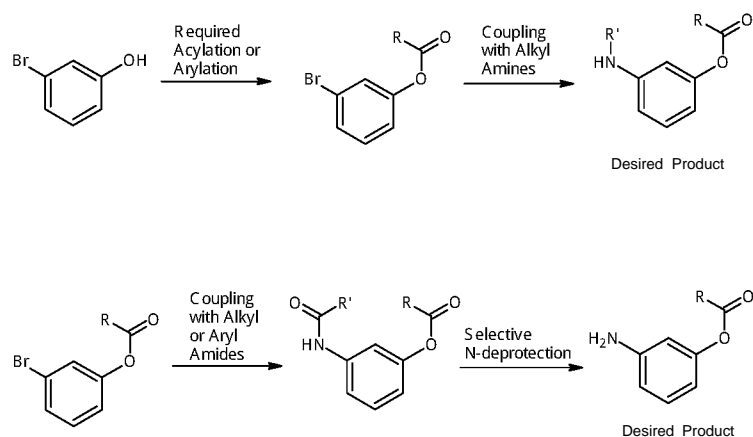
Such process for the manufacture of aryl amines would be multistep with lower overall yields, uneconomical and produce chemical waste.

Yet another strategy for the synthesis of desired aromatic amino derivatives would be reacting nitrophenyl derivatives substituted with alcohols, phenols, thiol,

thiophenols, alkyl amines, etc. with acylating or aroylating agent and selectively reducing the nitrogroup to amino group using a reducing agent. Such process for the manufacture of aryl amines would be multistep requiring a hydrogenation step in presence of catalysts which are pyrophoric. Such reactions are only carried out in autoclaves. Such method would be uneconomical and produces chemical waste. The preparation of monoalkylated aromatic amines would require an additional step of alkylation. One of the strategies is exemplified in the scheme.



Yet another strategy for the synthesis of desired aromatic amino derivatives would be reacting halophenyl derivatives substituted with alcohols, phenols, thiol, thiophenols, alkyl amines, etc. with acylating or aroylating agent and introducing the amino functionality by coupling the halophenyl derivatives with alkyl amines and amides. Such process for the manufacture of aryl amines would be multistep with lower overall yields, uneconomical and produces chemical waste. If an aryl amide is used as one of the substrate in coupling reaction then an additional step is required to convert it in to amine functionality. One of the strategies is exemplified in the scheme.



Moreover such sequences of preparing aromatic amine derivatives may require an additional stoichiometric amount of reagents resulting in the formation of more than a stoichiometric amount of chemical waste. In terms of atom-economy and environmental concerns, the direct O-selective acylation in the presence of unprotected amines is highly desirable.

The prior art literature does not disclose nor propose a suitable process which can be used in large scale for obtaining the highly chemoselective reactions of alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), alkyl amine groups, etc. with active carboxylic acid group to form esters, thioesters and amides, etc. of aliphatic amines without any detectable reaction at aromatic amino group.

Therefore, there is still a long-felt demand to develop a process for highly chemoselective or site specific reactions which can easily be utilized in the synthesis of large number of active aromatic amino derivatives or salts of biological and physiological importance or can be used as intermediates in the development of active compounds.

It is also advantageous to develop a highly chemoselective process by making use of raw materials which are easily available or which can be easily synthesized in high yields and are easy to store or handle.

To achieve this difficult task it was desirable to optimize some parameters taking into consideration such as-

1. The affinity of aromatic amino group towards active carboxylic acid groups resulting in to formation of amide and
2. Considerably low reactivity of groups such as alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), etc. except alkyl amine group, towards active carboxylic acid group to form esters, thioesters and amides of aliphatic amines.

This was achieved as follows:

1. The carboxylic acid group was converted in to active aryl ester (such as phenyl ester) consisting of electron withdrawing group (such as nitro). This considerably reduced the electropositivity of the carbonyl carbon thereby making them practically non-reactive with aromatic amino groups even at high temperature.
2. Use of strong base to abstract protons of acidic groups such as alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), etc. groups except alkyl amine group making them reactive towards carboxylic acid aryl ester (such as phenyl ester) consisting of electron withdrawing group (such as nitro) at moderate to high temperatures.
3. The reaction of alkyl amine with carboxylic acid aryl ester (such as phenyl ester) consisting of electron withdrawing group (such as nitro) would probably not require the presence of additional amount of base.

Object of the invention:

It is therefore an object of the invention to overcome or ameliorate at least one disadvantage of the prior art or to provide a useful alternative.

Another object of the invention is to provide a novel and highly chemoselective reactions of alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), alkyl amine groups, etc. in the presence of aromatic amino group without any detectable reaction at aromatic amino group, by making use of cheap

and easily available raw materials thus avoiding use of hazardous and expensive reagents or catalysts.

Yet another object of the invention is to overcome long-felt demand to develop a process for highly chemoselective or site specific reactions which can easily be utilized in the synthesis of large number of active aromatic amino derivatives or salts of biological and physiological importance or can be used as intermediates in the development of active compounds.

Yet another object of the invention is to provide highly chemoselective process by making use of raw materials which are easily available or which can be easily synthesized in high yields and are easy to store or handle.

A further object of the invention is to utilize the process for the industrial scale and economical synthesis of muscle relaxant drug such as Neostigmine methyl sulfate.

Yet another object of the invention is to utilize simple aryl carboxylic acid esters which can be synthesized in different ways such as but not limited to 1. Converting carboxylic acids into active carboxylic acid chlorides and then reacting them with phenols having electron withdrawing group, 2. Reacting aryl carboxylic acids with aryl carbonates and phosphates such as but not limited to bis-(4-nitrophenyl)carbonate and tris-(4-nitrophenyl)phosphate and c. reacting aryl carbonates such as but not limited to bis-(4-nitrophenyl) carbonate with primary or secondary amines.

Summary of the invention:

In accordance with the above objectives, the present invention provides a simple and mild process for chemoselective reactions with alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), alkyl amine groups, etc. in the

presence of aromatic amino group by using aryl carbamates and aryl esters without using catalyst, thus making the process feasible, economical and environmentally friendly.

The present invention also describes novel, highly chemoselective or site specific reactions which can easily be utilized in the synthesis of large number of active aromatic amino derivatives or salts of biological and physiological importance or can be used as intermediates in the development of active compounds.

Detailed description of the invention:

Unless specified otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any methods and material or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described. To describe the invention, certain terms are defined herein specified as follows:

Unless stated to the contrary, any of the words :having~, :including ~, :includes~, :comprising " and :comprises~ mean including without limitations " and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention are given for the purpose illustration rather than limitation of the invention as set forth the appended claims.

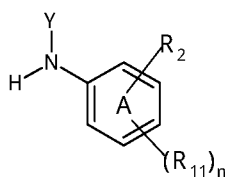
In an embodiment, the present invention provides a novel and highly chemoselective reactions of alcohols (alkyl OH), phenols (aryl OH), thiol (alkyl SH), thiophenols (aryl SH), alkyl amine groups, etc. with active carboxylic acid group to form esters, thioesters and amides, etc. of aliphatic amines without any detectable reaction at aromatic amino group.

The process of the present invention is carried out by reacting substituted aromatic amino compounds e.g. aminophenols, aminothiophenols, aminobenzylalcohols and aminobenzyl amines with aryl carbamates and carboxylic acid esters. High chemoselectivity is achieved under simple and mild reaction conditions without using a catalyst. In other words the reactions are highly site specific where the aryl carbamates and carboxylic acid esters do not react with the aromatic amino group.


In another embodiment the invention discloses a process for highly chemoselective or site specific reactions which can easily be utilized in the synthesis of large number of active aromatic amino derivatives or salts of biological and physiological importance or can be used as intermediates in the development of active compounds.

In yet another embodiment the invention discloses a process for preparation of neostigmine methylsulphate via novel chemoselective reaction of 3-amionphenol with aryl dimethyl carbamates and further methylating the intermediate with a methylating agent.

Accordingly, the present invention provides a novel process for chemoselective reaction of aromatic amino derivatives of formula (II)



Formula (II)

Wherein, Ring system  represents aryl, heteroaryl or fused rings, such as Benzene, Naphthalene, Anthracene, Phenanthrene, Azulene, pyrene, Fluorene, Pyrrole, Pyrazole, Imidazole, Pyridine, Pyrazine, Pyrimidine, Triazine, Indole, Benzimidazole, Quinoline, Isoquinoline, Phthalazine, Furan, Benzofuran, Thiophene, Benzothiophene, Oxazole, Thiazole, Tetrazole, Oxadiazole,

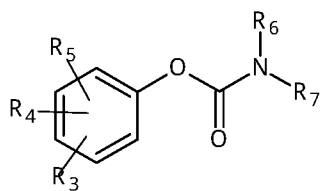
Thiadiazole, Triazole or such 2 or 3 similar or different ring systems are fused or are connected either by a single bond or heteroatoms selected from O, N and S;

R_2 is independently, $-OH$, $-SH$, $-X_pB_qZ_rOH$, $-X_pB_qZ_rSH$, or $-X_pB_qZ_rNH(Y)$ where in X and Z are independently, heteroatom selected from O, N and S, optionally substituted $-C_MO$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; B is optionally substituted ring systems mentioned above or such 2 or 3 similar or different rings are fused or are connected either by a single bond or heteroatoms selected from O, N and S; Y is Hydrogen, optionally substituted $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; p is 0 or 1, q is 0 or 1, r is 0 or 1, provided that at least one of p, q and r is 1, also provided that $X_pB_qX_rNH(Y)$ forms an aliphatic amino group;

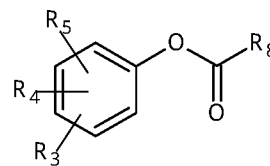
R_{ii} is independently, hydrogen, $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; $-C_{1-7}$ alkylphenyl, $-phenyl$, $-phenyl(Ci-7\text{ alkyl})$, $-C_{1-7}$ alkoxy, $-C_{1-7}$ alkoxyphenyl, $-phenoxy$, $-phenoxy(Ci-7\text{ alkyl})$, $-C_{1-7}$ Salkyl, $-C_{1-7}$ Salkylphenyl, $-Sphenyl$, $-Sphenyl(Ci-7\text{ alkyl})$, $-NO_2$, $-CN$, halogen, $-NH_2$, $-NH(Ci-7\text{ alkyl})$, $-NH(Ci-7\text{ alkylphenyl})$, $-NH(phenyl)$, $-NH(phenyl\ C_{1-7}\text{ alkyl})$, $-N(Ci-7\text{ alkyl})(Ci-7\text{ alkyl})$ or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(Ci-7\text{ alkyl})(Ci-7\text{ alkylphenyl})$ or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(Ci-7\text{ alkylphenyl})(Ci-7\text{ alkylphenyl})$, $-N(phenyl)(phenyl)$, $-N(phenyl)(Ci-7\text{ alkyl})$ or the alkyl and phenyl groups attached to N form an optionally substituted 4 to 7 member cyclic ring

which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, CHO , $\text{C(0)Ci}_{-7}\text{alkyl}$, $\text{C(0)Ci}_{-7}\text{alkylphenyl}$, C(0)phenyl , $\text{C(0)phenyl(C}_{1-7}\text{alkyl)}$, CO_2H , $\text{C(0)O C}_{1-7}\text{alkyl}$, $\text{C(0)O C}_{1-7}\text{alkylphenyl}$, C(0)O phenyl , $\text{C(0)O phenyl(C}_{1-7}\text{alkyl)}$, $\text{OC(0) C}_{1-7}\text{alkyl}$, $\text{OC(0) C}_{1-7}\text{alkylphenyl}$, OC(0) phenyl , $\text{OC(0) phenyl(C}_{1-7}\text{alkyl)}$, CONH_2 , $\text{C(0)NH C}_{1-7}\text{alkyl}$, $\text{C(0)NH C}_{1-7}\text{alkylphenyl}$, C(0)NH phenyl , $\text{C(0)NH phenyl(C}_{1-7}\text{alkyl)}$, $\text{C(0)N (Ci}_{-7}\text{alkyl)(Ci}_{-7}\text{alkyl)}$ or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $\text{C(0)N (Ci}_{-7}\text{alkyl) (Ci}_{-7}\text{alkylphenyl)}$ or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $\text{C(0)N(Ci}_{-7}\text{alkyl phenyl)(Ci}_{-7}\text{alkylphenyl)}$, $\text{C(0)N (phenyl)(phenyl)}$, $\text{NHC(O) C}_{1-7}\text{alkyl}$, $\text{NHC(O) C}_{1-7}\text{alkylphenyl}$, NHC(O) phenyl , $\text{NHC(O) phenyl(Ci}_{-7}\text{alkyl)}$, $\text{N(Ci}_{-7}\text{alkyl)C(O) C}_{1-7}\text{alkyl}$, $\text{N(Ci}_{-7}\text{alkyl)C(O) C}_{1-7}\text{alkylphenyl}$, $\text{N(Ci}_{-7}\text{alkyl)C(O)phenyl}$, $\text{N(Ci}_{-7}\text{alkyl)C(O) phenyl(Ci}_{-7}\text{alkyl)}$, $\text{SO}_2\text{C}_{1-7}\text{alkyl}$, $\text{SO}_2\text{C}_{1-7}\text{alkylphenyl}$, SO_2phenyl , $\text{SO}_2\text{phenyl(Ci}_{-7}\text{alkyl)}$, SO_2NH_2 , $\text{SO}_2\text{NHCi}_{-7}\text{alkyl}$, $\text{SO}_2\text{NHCi}_{-7}\text{alkylphenyl}$, $\text{SO}_2\text{NHphenyl}$, $\text{SO}_2\text{NHphenyl(Ci}_{-7}\text{alkyl)}$, $\text{NHSO}_2\text{C}_{1-7}\text{alkyl}$, $\text{NHSO}_2\text{C}_{1-7}\text{alkylphenyl}$, $\text{NHSO}_2\text{phenyl}$, $\text{NHSO}_2\text{phenyl(Ci}_{-7}\text{alkyl)}$, or R_{11}, R_{11} placed ortho to each other form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring or R_{11} placed ortho to either of $\text{-X}_p\text{BqX}_r\text{OH}$, $\text{-X}_p\text{BqX}_r\text{SH}$ and $\text{-X}_p\text{BqX}_r\text{NH(Y)}$ form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring; n is 0 to 4;

with a compound of formula (IIia) or (IIIb)



Formula (IIa)



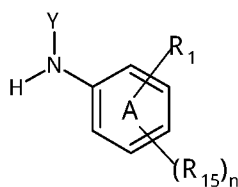
Formula (IIIb)

wherein R_3 is an electron withdrawing group selected from but not limited to nitro, cyano, halogen, dicyanovinyl, tricyanovinyl;

R_4 and R_5 are independently hydrogen, electron withdrawing groups selected from but not limited to nitro, cyano, halogen, dicyanovinyl, tricyanovinyl, $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; $-C_{1-7}$ alkylphenyl, $-phenyl$, $-phenyl(Ci-7 \text{ alkyl})$, $-C_{1-7}$ alkoxy, $-C_{1-7}$ alkoxy phenyl, $-phenoxy$, $-phenoxy(Ci-7 \text{ alkyl})$, $-C_{1-7}$ Salkyl, $-C_{1-7}$ Salkylphenyl, $-Sphenyl$, $-Sphenyl(Ci-7 \text{ alkyl})$, $-NO_2$, $-CN$, halogen, $-N(Ci-7 \text{ alkyl})(Ci-7 \text{ alkyl})$, $-C(O)Ci-7 \text{ alkyl}$, $-C(O)phenyl$, $-C(O)O-C_{1-7} \text{ alkyl}$, $-C(O)Ophenyl$, $-CONH_2$, $-C(O)NH-C_{1-7} \text{ alkyl}$, $-C(O)NHphenyl$, $-C(O)N(Ci-7 \text{ alkyl})(Ci-7 \text{ alkyl})$, $-C(O)N(phenyl)(phenyl)$, $-NHC(O)-C_{1-7} \text{ alkyl}$, $-NHC(O)phenyl$, $-SO_2C_{1-7} \text{ alkyl}$, $-SO_2phenyl$, $-SO_2NH-C_{1-7} \text{ alkyl}$, $-SO_2NHphenyl$, $-NH-SO_2C_{1-7} \text{ alkyl}$, $-NH-SO_2phenyl$, or R_4 and R_5 placed ortho to each other form benzene, naphthalene or an optionally substituted 3 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring;


R_6 and R_7 are independently H, optionally substituted $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring or R_6, R_7 along with nitrogen form an optionally substituted 3 to 7 member heterocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring; R_8 is hydrogen, optionally substituted $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which includes at least one heteroatom selected from O, N

and S in the cyclic ring or optionally substituted aryl, heteroaryl or fused rings, such as Benzene, Naphthalene, Anthracene, Phenanthrene, Azulene, pyrene, Fluorene, Pyrrole, Pyrazole, Imidazole, Pyridine, Pyrazine, Pyrimidine, Triazine, Indole, Benzimidazole, Quinoline, Isoquinoline, Phthalazine, Furan, Benzofuran, Thiophene, Benzothiophene, Oxazole, Thiazole, Tetrazole, Oxadiazole, Thiadiazole, Triazole or such 2 or 3 similar or different ring systems are fused or are connected either by a single bond or heteroatoms selected from O, N and S; in presence of base or solvent or both; to provide a compound of formula (I)



Formula (I)



Wherein, Ring system  represents aryl, heteroaryl or fused rings, such as Benzene, Naphthalene, Anthracene, Phenanthrene, Azulene, pyrene, Fluorene, Pyrrole, Pyrazole, Imidazole, Pyridine, Pyrazine, Pyrimidine, Triazine, Indole, Benzimidazole, Quinoline, Isoquinoline, Phthalazine, Furan, Benzofuran, Thiophene, Benzothiophene, Oxazole, Thiazole, Tetrazole, Oxadiazole, Thiadiazole, Triazole or such 2 or 3 similar or different ring systems are fused or are connected either by a single bond or heteroatoms selected from O, N and S;

R_1 is $OC(O)N(R_6)R_7$, $SC(O)N(R_6)R_7$, $-X_pB_qZ_r$, $OC(O)N(R_6)R_7$, $-X_pB_qZ_r$, $SC(O)N(R_6)R_7$, $-X_pB_qZ_rN(Y)(C(O)N(R_6)R_7)$, $OC(O)R_8$, $SC(O)R_8$, $-X_pB_qZ_r$, $OC(O)R_8$, $-X_pB_qZ_r$, $SC(O)R_8$, $-X_pB_qZ_rN(Y)(C(O)R_8)$; X, B, Z, Y, R_6 , R_7 , R_8 p, q, r are as described above.

R_{15} is hydrogen, -C1-10 alkyl, -C2-10 alkenyl, -C2-10 alkynyl, -C3-10 cycloalkyl, -C3-10 cycloalkenyl, -C5-10 cycloalkynyl, -Ci-7 alkylphenyl, -phenyl, -phenyl C1-7 alkyl, -Ci-7 alkoxy, -Ci-7 alkoxyphenyl, -phenoxy, -phenoxy (Ci-7 alkyl), C1-7-Salkyl, Ci-

$-Salkylphenyl$, $-Sphenyl$, $-Sphenyl(C_{1-7} alkyl)$, $-NO_2$, $-CN$, halogen, $-NH_2$, $-NH(C_{1-7} alkyl)$, $-NH(C_{1-7} alkylphenyl)$, $-NH(phenyl)$, $-NH(phenyl C_{1-7} alkyl)$, $-N(C_{1-7} alkyl)(C_{1-7} alkyl)$ or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(C_{1-7} alkyl)(C_{1-7} alkylphenyl)$ or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(C_{1-7} alkylphenyl)(C_{1-7} alkylphenyl)$, $-N(phenyl)(phenyl)$, $-N(phenyl)(C_{1-7} alkyl)$ or the alkyl and phenyl groups attached to N form an optionally substituted 4 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-CHO$, $-C(=O)C_{1-7} alkyl$, $-C(=O)C_{1-7} alkylphenyl$, $-C(=O)phenyl$, $-C(=O)phenyl(C_{1-7} alkyl)$, $-CO_2H$, $-C(=O)OC_{1-7} alkyl$, $-C(=O)OC_{1-7} alkylphenyl$, $-C(=O)Ophenyl$, $-C(=O)Ophenyl(C_{1-7} alkyl)$, $-OC(=O)C_{1-7} alkyl$, $-OC(=O)C_{1-7} alkylphenyl$, $-OC(=O)phenyl$, $-OC(=O)phenyl(C_{1-7} alkyl)$, $-CONH_2$, $-C(=O)NH(C_{1-7} alkyl)$, $-C(=O)NH(C_{1-7} alkylphenyl)$, $-C(=O)NHphenyl$, $-C(=O)NHphenyl(C_{1-7} alkyl)$, $-C(=O)N(C_{1-7} alkyl)(C_{1-7} alkyl)$ or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-C(=O)N(C_{1-7} alkyl)(C_{1-7} alkylphenyl)$ or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-C(=O)N(C_{1-7} alkylphenyl)(C_{1-7} alkylphenyl)$, $-C(=O)N(phenyl)(phenyl)$, $-NHC(=O)C_{1-7} alkyl$, $-NHC(=O)C_{1-7} alkylphenyl$, $-NHC(=O)phenyl$, $-NHC(=O)phenyl(C_{1-7} alkyl)$, $-N(C_{1-7} alkyl)C(=O)C_{1-7} alkyl$, $-N(C_{1-7} alkyl)C(=O)phenyl$, $-N(C_{1-7} alkyl)C(=O)phenyl(C_{1-7} alkyl)$, $-SO_2C_{1-7} alkyl$, $-SO_2C_{1-7} alkylphenyl$, $-SO_2phenyl$, $-SO_2phenyl(C_{1-7} alkyl)$, $-SO_2NH_2$, $-SO_2NH(C_{1-7} alkyl)$, $-SO_2NH(C_{1-7} alkylphenyl)$, $-SO_2NHphenyl$, $-SO_2NHphenyl(C_{1-7} alkyl)$, $-NHSO_2C_{1-7} alkyl$, $-NHSO_2C_{1-7} alkylphenyl$, $-NHSO_2phenyl$, $-NHSO_2phenyl(C_{1-7} alkyl)$, or R_{11}, R_{11} placed ortho

to each other form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring or R₁₁ placed ortho to R₁ form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring; X, B, Y, R₆, R₇, R_s, n, p, q, r are as described above.

Other aspects and embodiments will be apparent to those skilled in the art from the following detailed description.

As used in the present specification, the following words and phrases are generally intended to have the meaning as set forth below, except to the extent that the context in which they are used indicates otherwise.

A dash ('-') that is not between two letters or symbols is used to indicate point of attachment of a substituent. For example, -C(0)OH is attached through carbon atom.

By 'optional _' or 'optionally _' is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occur and instances in which it does not. For example, 'Optionally substituted alkyl _' encompasses both 'alkyl _' and 'substituted alkyl _' such as but not limited to methyl, ethyl, isopropyl, 2-methylpropyl, neopentyl, 2-chloroethyl, 2-methoxyethyl, 2-nitropropyl, 3-acetyloxypropyl, 2-cyclobutyl methyl, etc. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

'Aryl _' encompasses: carbocyclic aromatic ring for example benzene; bicyclic ring systems such as carbocyclic and aromatic ring systems, for example, naphthalene, and azulene; tricyclic ring systems such as carbocyclic and aromatic ring systems, for example, anthracene, phenanthrene, etc. For example, aryl includes

carbocyclic aromatic ring fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms selected from N, O and S. For such fused ring systems where in only one of the ring is carbocyclic aromatic ring the point of attachment is at the carbocyclic aromatic ring. `Aryl _ however does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic ring is fused with a heterocycloalkyl aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

`Heteroaryl _ encompasses: 5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon;

bicyclic heteroaryl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring; and

tricyclic heteroaryl rings containing one or more, for example, from 1 to 5, or in certain embodiments, from 1 to 4, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring.

For example, heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the aromatic rings contains one or more heteroatoms, the point of attachment is at aryl or heteroaryl ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another.

`Fused rings _ encompasses: bicyclic, tricyclic or polycyclic, aryl or heteroaryl rings where in two rings share a common C-C or C-N connecting bonds, for example, Naphthalene, Anthracene, Phenanthrene, benzofuran, benzothiophene, dibenzofuran, dibenzothiophene, and the like.

`Alkyl _ encompasses straight chain and branched chain having the indicated number of carbon atoms, usually from 1 to 20 carbon atoms, for example 1 to 8 carbon atoms, such as 1 to 6 carbon atoms. For example C₁-C₆ alkyl encompasses both straight and branched chain alkyl or from 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, and the like. Alkylene is another subset of alkyl, referring to the same residues as alkyl, but having two points of attachment. Alkylene groups will usually have from 2 to 20 carbon atoms, for example 2 to 8 carbon atoms, such as from 2 to 6 carbon atoms. For example, Coalkylene indicates a covalent bond and C₁ alkylene is a methylene group. When an alkyl residue having a specific number of carbons is named, all branched and straight chain versions having that number of carbons are intended to be encompassed; thus, for example, `butyl _ is meant to include n-butyl, sec-butyl, isobutyl and t-butyl; `propyl _ includes n-propyl and isopropyl. 'Lower alkyl _ refers to alkyl groups having one to four carbons. Alkenyl is yet another subset of alkyl, referring to the same residues as alkyl, but having at least one carbon-carbon double bond. For example, ethenyl, 2-propenyl, 1-methylethenyl, etc. Alkynyl is yet another subset of alkyl, referring to the same residues as alkyl, but having at least one carbon-carbon triple bond. For example, 2-pentynyl, 3-pentynyl, etc.

'Cycloalkyl _ encompasses a non-aromatic carbocyclic ring, usually having from 3 to 7 ring carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, as well as bridged and caged saturated ring groups such as norbornane.

'Cycloalkenyl _ encompasses a non-aromatic carbocyclic ring, usually having from 4 to 7 ring carbon atoms and one or more carbon-carbon double bonds. Examples of cycloalkenyl groups include cyclopentenyl, cyclohexenyl, etc.

'Cycloalkynyl _ encompasses a non-aromatic carbocyclic ring, usually having from 5 to 7 ring carbon atoms and one or more carbon-carbon triple bonds. Examples of cycloalkynyl groups include cyclohexynyl, cycloheptynyl, etc.

`Cyclic ring_ encompasses: a non-aromatic carbocyclic ring, usually having from 3 to 7 ring carbon atoms which optionally includes at least one carbon-carbon double bonds or carbon-carbon triple bonds in the ring. For example, cyclopropyl, cyclobutyl, cyclopentenyl, cyclohexenyl, cyclohexynyl, cycloheptynyl, etc. For example, Cyclic ring includes non-aromatic carbocyclic ring fused to a aryl ring, heteroaryl ring or 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms selected from N, O and S. For such fused ring systems where in only one of the ring is cyclic ring the point of attachment is at the cyclic ring. `Cyclic ring_ however does not encompass or overlap in any way with heterocyclic ring, separately defined below. Hence, if one or more heteroatom is included in the cyclic ring, the resulting ring system is heterocyclic ring, not cyclic, as defined herein.

'Heterocyclic ring_ encompasses: a non-aromatic carbocyclic ring, usually having from 3 to 7 ring atoms which includes one or more heteroatom included in the cyclic ring selected from N, O and S.

By 'alkyl phenyl_ is meant an group of formula (alkyl)(phenyl) attached through the alkyl carbon wherein the alkyl group has the indicated number of carbon atoms. Thus a C₁₋₇ alkylphenyl is straight or branched alkyl group with 1 to 7 carbon atoms with a phenyl group substituted over it. For example, benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, and the like.

By 'phenylalkyl _ is meant an group of formula (phenyl)(alkyl) attached through the phenyl ring carbon wherein the alkyl group has the indicated number of carbon atoms. Thus a phenylC₁₋₇ alkyl is phenyl group with straight or branched alkyl group with 1 to 7 carbon atoms substituted over it. For example, 2-methylphenyl, 3-ethyl phenyl, 4-ethyl phenyl, 2-propyl phenyl, 3-(2-propyl)phenyl, and the like.

By 'alkoxy _ is meant an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentyloxy, 2-pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, 2-hexyloxy, 3-hexyloxy, 3-methyl pentyloxy, and the like. C₁₋₇ alkoxy groups will usually have from 1 to 7 carbon atoms attached through the oxygen bridge. 'Lower alkoxy _ refers to alkoxy groups having one to four carbons.

By 'cycloalkoxy _ is meant a cycloalkyl group attached through an oxygen bridge such as, for example, cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, and the like. The cycloalkyl group of a cycloalkoxy group generally is of C₂₀ or below, such as C₁₃ or below, for example, C₆ or below.

By 'alkoxyphenyl _ is meant an alkylphenyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, benzyl oxy, 2-phenylethoxy, 2-phenyl propoxy, and the like. C₁₋₇ alkoxyphenyl groups are alkoxy groups which will usually have from 1 to 7 carbon atoms attached through the oxygen bridge and a phenyl ring substituted over it.

By 'phenoxyalkyl _ is meant a phenylalkyl group of the indicated number of carbon atoms in the alkyl group attached through an oxygen bridge such as, for example, 2-methyl phenoxy, 2-ethylphenoxy, 4-ethylphenoxy, and the like. PhenoxyC₁₋₇ alkyl groups are phenoxy groups attached through the oxygen bridge and which will usually have alkyl group from 1 to 7 carbon atoms.

By '-Salkyl _ is meant an alkyl group of the indicated number of carbon atoms attached through a sulfur bridge such as, for example, methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio, tert-butylthio, n-pentylthio, 2-pentylthio, isopentylthio, neopentylthio, hexylthio, 2-hexylthio, 3-hexylthio, 3-methylpentylthio, and the like. C₁₋₇ -Salkyl groups will usually have from 1 to 7 carbon atoms attached through the sulfur bridge. 'Lower -Salkyl _ refers to alkylthio groups having one to four carbons.

By '-Salkyl phenyl _ is meant an alkylphenyl group of the indicated number of carbon atoms attached through a sulfur bridge such as, for example, benzylthio, 2-phenylethylthio, 2-phenyl propylthio, and the like. C₁₋₇ -Salkylphenyl groups are

alkylthio groups which will usually have from 1 to 7 carbon atoms attached through the oxygen bridge and a phenyl ring substituted over it. For example, phenyl methylthio, 2-phenylethylthio, 1-phenylethylthio, and the like.

By -SPhenyl is meant a phenyl group is attached through a sulfur bridge, example, phenylthio.

By -Sphenylalkyl is meant a phenylalkyl group of the indicated number of carbon atoms in the alkyl group attached through a sulfur bridge such as, for example, 2-methylphenylthio, 2-ethylphenylthio, 4-ethylphenylthio, and the like.

The $\text{-Sphenyl(Ci-7 alkyl)}$ groups are phenylthio groups attached through the sulfur bridge and which will usually have alkyl group from 1 to 7 carbon atoms substituted over phenyl. For example, 2-methylphenylthio, 2-ethylphenylthio, 4-ethylphenylthio, and the like.

The electron withdrawing group is selected from nitro, halogen, cyano, COR, COOR^{\sim} , $\text{CONR}^{\sim}\text{R}^{\sim\sim}$, CF_3 , $\text{SO}_2\text{R}^{\sim}$ or $\text{SO}_3\text{R}^{\sim}$; wherein R^{\sim} and $\text{R}^{\sim\sim}$ are alkyl containing 1 to 7 carbon atoms.

In a preferred aspect R_3 is nitro or cyano; R_4 is hydrogen or nitro; and R_5 is hydrogen.

Preferably the process of the present invention is carried out in the presence of a base and in a suitable solvent.

The base which may be used in the present invention is an organic or inorganic base. Examples of organic base include tertiary amines such as trialkyl amine. Examples of inorganic base include alkali metal carbonate, alkaline earth metal carbonate, alkali metal bicarbonate, alkaline earth metal bicarbonate and mixture thereof. Examples of alkali metal carbonate include sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonate include sodium bicarbonate and potassium bicarbonate. Examples of alkaline earth metal carbonate include calcium carbonate and magnesium carbonate. Examples of

alkaline earth metal bicarbonate include calcium bicarbonate and magnesium bicarbonate. The preferred base is triethyl amine, sodium hydroxide or sodium methoxide.

The base is conveniently used in an amount, relative to the compound of formula (II), preferably in a range between 0.8 to 2.5 equivalents, more preferably 1.0 to 2.0 equivalents. The most preferred quantity of the base is 1.3 to 1.5 equivalents.

The solvent may be selected from polar or nonpolar solvents. The preferred solvent is polar aprotic solvents. The solvent may be selected from acetone, N,N-dimethylformamide, acetonitrile, dimethyl sulfoxide, dioxane, tetrahydrofuran, hexamethylphosphoramide, ethyl acetate, toluene, methyl ethyl ketone, formic acid, n-butanol, isopropanol, ethanol, n-propanol, methanol, acetic acid or water. The most preferred solvent is dimethyl sulfoxide.

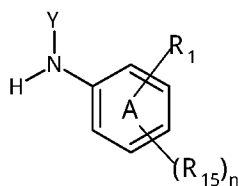
The process of the present invention may be carried out at suitable temperature. To minimize the decomposition of products and impurity formation the reaction is carried out at 40 to 120°C, more preferably at 60 to 100 °C.

The reaction normally completes in a span of 1 to 8 hours, more preferably 2 to 6 hours, most preferably 3 to 5 hours.


The process of the present invention provides site specific reaction without any reaction at aromatic amino group. Therefore tedious procedure of purification or separation of byproducts is not required during isolation of the required products. Further the process is carried out using simple and mild reaction conditions avoiding the use of any organic as well as organometallic catalyst mentioned in the prior art. Hence the process is feasible, economical, environmentally friendly and industrially applicable.

In the second embodiment, the present invention discloses a novel process for preparation of quaternary ammonium compounds comprising the following step:

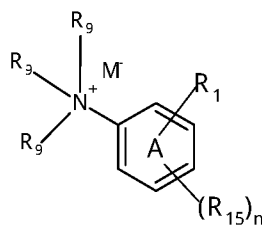
a. reaction of compound of Formula (I)




Formula (I)

Wherein, Ring system , R_1 , and R_{15} are as described above, Y is hydrogen, Methyl, Ethyl;

with methylating or ethylating agents in presence of base or suitable solvent to provide a compound of formula (IV)



Formula (IV)

Wherein, Ring system , R_1 , R_{15} and n are as described above, R_9 is independently methyl or ethyl and M^- is an anion selected from ethyl sulfate, methyl sulfate, methane sulfonate, benzene sulfonate, toluene sulfonate or halogen;

Preferably the steps (a) is carried out in the presence of a base and a suitable solvent. The base which may be used in the present invention is an inorganic base. Examples of inorganic base include alkali metal carbonate, alkaline earth metal carbonate, alkali metal bicarbonate and mixture thereof. Examples of alkali metal carbonate include sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonate include sodium bicarbonate and potassium bicarbonate. Examples of alkaline earth metal carbonate include calcium carbonate and magnesium carbonate. The preferred base is sodium bicarbonate or calcium carbonate.

The base for the step (a) is conveniently used in an amount, preferably in a range between 0.8 to 8 equivalents, more preferably 1.0 to 4.0 equivalents. The most preferred quantity of the base is 1.5 to 3 equivalents.

The solvent for the step (a) may be selected from polar or nonpolar solvents. The preferred solvent for the step (a) is polar solvents. The solvent may be selected from acetone, acetonitrile, dimethyl sulfoxide, dioxane, tetrahydrofuran, ethyl acetate, toluene, methyl ethyl ketone, n-butanol, isopropanol, ethanol, n-propanol or methanol. The most preferred solvent for the step (a) is acetone.

The step (a) may be carried out at suitable temperature. To minimize the decomposition of products and impurity formation the reaction is carried out at 0 to 120°C, more preferably at 20 to 100 °C and most preferably at 25 to 50 °C.

The process is exemplified for the synthesis of neostigmine methylsulphate in highly economic and industrially feasible way with enhanced purity.

Further details of the process of the present invention will be apparent from the examples presented below highlighting the chemoselectivity and yield of the products. Examples presented are purely illustrative and are not limited to the particular embodiments illustrated herein but include the permutations, which are obvious as set forth in the description.

Examples:

Example: 1

Preparation of 4-nitrophenyl dimethyl carbamate

A 250 ml round bottom flask was charged with bis(4-nitrophenyl)carbonate (100 g) and acetonitrile (300 ml) and the flask was cooled to 0 ° - 5 ° -C. Dimethylamine (45 ml, 40% aq. solution) was diluted with 45 ml water and added drop wise to the flask at 0 ° - 5 ° -C. After completion of addition the flask was kept at room temperature for stirring for 3 hours. The reaction mixture was diluted with water

and the solid obtained was collected by filtration. The crude product was dried and recrystallized from toluene to afford 4-nitrophenyl dimethyl carbamate.

Yield : 62 gm (89.7%)

MP : 103 - 105 °C (Lit. MP = 104 - 106 °C, BE532057)

Example: 2

Preparation of 2-nitrophenyl dimethyl carbamate

2-nitrophenyl dimethyl carbamate was prepared according to the example 1 using bis(2-nitrophenyl)carbonate (100 gm), Dimethylamine (45 ml, 40% aq. solution) and acetonitrile (300 ml). The reaction mixture after usual workup affords pure 2-nitrophenyl dimethyl carbamate as oil which was used directly in next step.

Yield : 60 gm (87%), Lit. Oil, US2933383

Example: 3

Preparation of 4-nitrophenyl diethyl carbamate

4-nitrophenyl diethyl carbamate was prepared according to the example 1 using bis(4-nitrophenyl) carbonate (100 gm), Diethylamine (30 ml) and acetonitrile (300 ml). The reaction mixture after usual workup affords pure 4-nitrophenyl diethyl carbamate as oil which was used directly in next step.

Yield : 73 gm (93.23%), Lit. Oil, BP = 280 °C, CN104829493A

Example: 4

Preparation of 2-nitrophenyl diethyl carbamate

2-nitrophenyl diethyl carbamate was prepared according to the example 1 using bis(2-nitrophenyl)carbonate (100 gm), Diethylamine (30 ml) and acetonitrile (300 ml). The reaction mixture after usual workup affords pure 2-nitrophenyl diethyl carbamate as oil which was used directly in next step.

Yield : 70 gm (89.4%)

Example: 5

Preparation of (4-nitrophenyl) pyrrolidine-1-carboxylate

(4-nitrophenyl) pyrrolidine-1-carboxylate was prepared according to the example 1 using bis(4-nitrophenyl)carbonate (100 gm), pyrrolidine (30 ml) and acetonitrile (300 ml). The resulting solid was recrystallized from toluene to afford pure (4-nitrophenyl) pyrrolidine-1-carboxylate.

Yield : 71.5 gm (91.3%)

MP : 95 - 97 °C, (Synlett 2, 243-246, 2006)

Example: 6

Preparation of (2-nitrophenyl) pyrrolidine-1-carboxylate

(2-nitrophenyl) pyrrolidine-1-carboxylate was prepared according to the example 1 using bis(2-nitrophenyl)carbonate (100 gm), pyrrolidine (30 ml) and acetonitrile (300 ml). The resulting solid was recrystallized from toluene to afford pure (2-nitrophenyl) pyrrolidine-1-carboxylate.

Yield : 72.8 gm (92.9%)

MP : 68 - 69 °C

Example: 7

Preparation of 4-nitrophenyl dibenzyl carbamate

4-nitrophenyl dibenzyl carbamate was prepared according to the example 1 using bis(4-nitrophenyl) carbonate (100 gm), Dibenzylamine (72 ml) and acetonitrile (300 ml). The resulting solid was recrystallized from toluene to afford pure 4-nitrophenyl dibenzyl carbamate.

Yield : 115 gm (96.7%)

MP : 104 - 105 °C (Lit. MP = 105 - 106 °C, Organic Preparations and Procedures 1(4) 263-6, 1969)

Example: 8

Preparation of 2-nitrophenyl dibenzyl carbamate

2-nitrophenyl dibenzyl carbamate was prepared according to the example 1 using

bis(2-nitrophenyl)carbonate (100 gm), Dibenzylamine (72 ml) and acetonitrile (300 ml). The resulting solid was recrystallized from toluene to afford pure 2-nitrophenyl dibenzyl carbamate.

Yield : 112 gm (94.1%)

MP : 63 - 65 °C, Lit. Oil, Synth. Commun. 35, 11, 1471-1479

Example: 9

Preparation of 3-aminophenyl dimethyl carbamate

A clean and dry 500 ml 4 neck round bottom flask was charged with DMSO (100 ml), 3-aminophenol (67.5 gm) and NaOH (24.7 gm). The reaction mixture was heated at 75 - 80°C for 4 hours. 4-Nitrophenyl-N,N-dimethyl carbamate (100 g) was added portion wise at 75 - 80°C along with 100 ml DMSO. The reaction temperature was raised to 110 - 120 °C and maintained the reaction mixture at this temperature for 2 hours. The reaction completion was confirmed by TLC analysis.

The reaction mixture was quenched with 1% NaOH solution (1500 ml) and extracted with MDC. The MDC layer was washed with water, dried over sodium sulfate and concentrated to provide crude solid. The solid was recrystallized from toluene to afford pure 3-aminophenyl dimethyl carbamate.

Yield : 62 gm (72.2%)

MP : 83 - 85 °C (Lit. MP: 80 - 86 °C, FR 1498834)

Example: 10

Preparation of 3-aminophenyl dimethyl carbamate

3-Aminophenyl dimethyl carbamate was prepared according to the example 9 using 2-nitrophenyl-N,N-dimethyl carbamate (20 gm), 3-aminophenol (13.5 gm), sodium hydroxide (4.94 g) and dimethyl sulfoxide (60 ml). The resulting solid was recrystallized from toluene to afford pure 3-aminophenyl dimethyl carbamate.

Yield : 13.6 gm (79.2%)

MP : 83 - 85 °C (Lit. MP: 80 - 86 °C, FR 1498834)

Example: 11

Preparation of neostigmine methyl sulfate

A clean and dry 1000 ml 4 neck round bottom flask was charged with 3-aminophenyl dimethyl carbamate (50 gm), Sodium bicarbonate (116 gm) and acetone (300 ml). The reaction mixture was stirred for 5 min. Dimethyl sulphate (128.3 gm) was added to the reaction mixture and stirred at 25 ° - 30 °C for 16 - 18 hours. The reaction completion was confirmed by TLC analysis.

The reaction mixture was filtered to remove sodium bicarbonate. Later cooled to 0 ° - 5 °C and solid thus formed was collected to afford crude compound which was crystallized from isopropanol to provide pure neostigmine methyl sulfate.

Yield : 70 gm (73%)

MP : 142 - 145 °C

Example: 12

Preparation of neostigmine methyl sulfate

A clean and dry 1000 ml 4 neck round bottom flask was charged with 3-aminophenyl dimethyl carbamate (50 gm), Calcium carbonate (50 gm) and acetone (300 ml). The reaction mixture was stirred for 5 min. Dimethyl sulphate (128.3 gm) was added to the reaction mixture and stirred at 25 ° - 30°C for 16 - 18 hours. The reaction completion was confirmed by TLC analysis.

The reaction mixture was filtered to remove calcium carbonate. Later cooled to 0 ° - 5 °C and solid thus formed was collected to afford crude compound which was crystallized from isopropanol to provide pure neostigmine methyl sulfate.

Yield : 81 gm (84.6 %)

MP : 142 - 145 °C

Example: 13

Preparation of 4-aminophenyl dimethyl carbamate

4-Aminophenyl dimethyl carbamate was prepared according to the example 9 using 4-nitrophenyl-N,N-dimethyl carbamate (20 gm), 4-aminophenol (13.5 gm), sodium hydroxide (4.94 g) and dimethyl sulfoxide (60 ml). The resulting solid was

recrystallized from toluene to afford pure 4-aminophenyl dimethyl carbamate.

Yield : 12 gm (70.0 %)

MP : 79 - 80 -C

Example: 14

Preparation of 4-aminophenyl dimethyl carbamate

4-Aminophenyl dimethyl carbamate was prepared according to the example 9 using 2-nitrophenyl-N,N-dimethyl carbamate (20 gm), 4-aminophenol (13.5 gm), sodium hydroxide (4.94 g) and dimethyl sulfoxide (60 ml). The resulting solid was recrystallized from toluene to afford pure 4-aminophenyl dimethyl carbamate.

Yield : 14gm (81.6 %)

MP : 79 - 80 -C

Example: 15

Preparation of 3-aminophenyl diethyl carbamate

3-Aminophenyl diethyl carbamate was prepared according to the example 9 using 4-nitrophenyl-N,N-diethyl carbamate (20 gm), 3-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethyl sulfoxide (60 ml). The resulting crude oil obtained after usual workup was passed through small silica bed to afford pure 3-aminophenyl diethyl carbamate as oil.

Yield : 14.3 gm (81.7%), Lit. Oil, WO2006123145A1

Example: 16

Preparation of 3-aminophenyl diethyl carbamate

3-Aminophenyl diethyl carbamate was prepared according to the example 9 using 2-nitrophenyl-N,N-diethyl carbamate (20 gm), 3-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethyl sulfoxide (60 ml). The resulting crude oil obtained after usual workup was passed through small silica bed to afford pure 3-aminophenyl diethyl carbamate as oil.

Yield : 14.8 gm (84.6%), Lit. Oil, WO2006123145A1

Example: 17

Preparation of 4-aminophenyl diethyl carbamate

4-Aminophenyl diethyl carbamate was prepared according to the example 9 using 4-nitrophenyl- N,N-diethyl carbamate (20 gm), 4-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from diisopropylether to afford pure 4-aminophenyl diethyl carbamate.

Yield : 13.2 gm (75.4%)

MP : 132 - 135 °C

Example: 18

Preparation of 4-aminophenyl diethyl carbamate

4-Aminophenyl diethyl carbamate was prepared according to the example 9 using 2-nitrophenyl- N,N-diethyl carbamate (20 gm), 4-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from diisopropylether to afford pure 4-aminophenyl diethyl carbamate.

Yield : 14.2 gm (81.1%)

MP : 132 - 135 °C

Example: 19

Preparation of (3-aminophenyl) pyrrolidine-1-carboxylate

(3-aminophenyl) pyrrolidine-1-carboxylate was prepared according to the example 9 using (4-nitrophenyl) pyrrolidine-1-carboxylate (20 gm), 3-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from isopropyl alcohol to afford pure (3-aminophenyl) pyrrolidine-1-carboxylate.

Yield : 13.7 gm (78.3%)

MP : 122 - 124 °C

Example: 20

Preparation of (3-aminophenyl) pyrrolidine-1-carboxylate

(3-aminophenyl) pyrrolidine-1-carboxylate was prepared according to the example 9 using (2-nitrophenyl) pyrrolidine-1-carboxylate (20 gm), 3-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethyl sulfoxide (60 ml). The resulting solid was recrystallized from isopropyl alcohol to afford pure (3-aminophenyl) pyrrolidine-1-carboxylate.

Yield : 12.5 gm (71.4%)

MP : 122 - 124 -C

Example: 21

Preparation of (4-aminophenyl) pyrrolidine-1-carboxylate

(4-aminophenyl) pyrrolidine-1-carboxylate was prepared according to the example 9 using (4-nitrophenyl) pyrrolidine-1-carboxylate (20 gm), 4-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethyl sulfoxide (60 ml). The resulting solid was recrystallized from isopropyl alcohol to afford pure (4-aminophenyl) pyrrolidine-1-carboxylate.

Yield : 15.2 gm (86.8%)

MP : 92 - 94 -C

Example: 22

Preparation of (4-aminophenyl) pyrrolidine-1-carboxylate

(4-aminophenyl) pyrrolidine-1-carboxylate was prepared according to the example 9 using (2-nitrophenyl) pyrrolidine-1-carboxylate (20 gm), 4-aminophenol (12.0 gm), sodium hydroxide (4.36 g) and dimethyl sulfoxide (60 ml). The resulting solid was recrystallized from isopropyl alcohol to afford pure (4-aminophenyl) pyrrolidine-1-carboxylate.

Yield : 14.4 gm (82.3%)

MP : 92 - 94 -C

Example: 23

Preparation of 3-aminophenyl dibenzyl carbamate

3-aminophenyl dibenzyl carbamate was prepared according to the example 9 using 4-nitrophenyl-N,N-di benzyl carbamate (20 gm), 3-aminophenol (7.8 gm), sodium hydroxide (2.9 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from diisopropylether to afford pure 3-aminophenyl dibenzyl carbamate.

Yield : 15.1 gm (82.7%)

MP : 95 - 97 -C

Example: 24

Preparation of 3-aminophenyl dibenzyl carbamate

3-aminophenyl dibenzyl carbamate was prepared according to the example 9 using 2-nitrophenyl-N,N- dibenzyl carbamate (20 gm), 3-aminophenol (7.8 gm), sodium hydroxide (2.9 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from diisopropylether to afford pure 3-aminophenyl dibenzyl carbamate.

Yield : 16 gm (87.6%)

MP : 95 - 97 -C

Example: 25

Preparation of 4-aminophenyl dibenzyl carbamate

4-aminophenyl dibenzyl carbamate was prepared according to the example 9 using 4-nitrophenyl-N,N- dibenzyl carbamate (20 gm), 4-aminophenol (7.8 gm), sodium hydroxide (2.9 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from diisopropylether to afford pure 4-aminophenyl dibenzyl carbamate.

Yield : 15.3 gm (83.8%)

MP : 122-124 -C

Example: 26

Preparation of 4-aminophenyl dibenzyl carbamate

4-aminophenyl dibenzyl carbamate was prepared according to the example 9 using 4-nitrophenyl-N,N-di benzyl carbamate (20 gm), 4-aminophenol (7.8 gm), sodium hydroxide (2.9 g) and dimethylsulfoxide (60 ml). The resulting solid was recrystallized from diisopropylether to afford pure 4-aminophenyl dibenzyl carbamate.

Yield : 14.7 gm (80.5%)

MP : 122-124 -C

Example: 27

Preparation of 3-aminophenyl benzoate

3-Aminophenyl benzoate was prepared according to the example 9 using 4-nitrophenyl benzoate (16 g), 3-aminophenol (9.3 g), sodium hydroxide (3.52 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 3-aminophenyl benzoate.

Yield : 11 gm (78.6 %)

MP : 72-73 -C (Lit. MP : 70-71 °C, Yakugaku Zasshi, 1962, 82, 875)

Example: 28

Preparation of 3-aminophenyl benzoate

3-Aminophenyl benzoate was prepared according to the example 9 using 2-nitrophenyl benzoate (16 g), 3-aminophenol (9.3 g), sodium hydroxide (3.52 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 3-aminophenyl benzoate.

Yield : 12.2 gm (87.1 %)

MP : 72-73 -C (Lit. MP : 70-71 °C, Yakugaku Zasshi, 1962, 82, 875)

Example: 29

Preparation of 4-Aminophenyl benzoate

4-Aminophenyl benzoate was prepared according to the example 9 using 4-

nitrophenyl benzoate (16 g), 4-aminophenol (9.3 g), sodium hydroxide (3.52 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 4-aminophenyl benzoate.

Yield : 13 gm (92.8 %)

MP : 153 - 155 °C (Lit. MP = 153 - 154 °C, Yakugaku Zasshi, 1962, 82, 875)

Example: 30

Preparation of 4-Aminophenyl benzoate

4-Aminophenyl benzoate was prepared according to the example 9 using 2-nitrophenyl benzoate (16 g), 4-aminophenol (9.3 g), sodium hydroxide (3.52 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 4-aminophenyl benzoate.

Yield : 12.5 gm (89.3 %)

MP : 153 - 155 °C (Lit. MP = 153 - 154 °C, Yakugaku Zasshi, 1962, 82, 875)

Example: 31

Preparation of 3-aminophenyl 4-methyl benzoate

3-Aminophenyl 4-methyl benzoate was prepared according to the example 9 using 4-nitrophenyl 4-methyl benzoate (16 g), 3-aminophenol (8.8 g), sodium hydroxide (3.2 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 3-aminophenyl 4-methyl benzoate.

Yield : 11.2 gm (79.6%)

MP : 85 - 87 °C

Example: 32

Preparation of 3-aminophenyl 4-methyl benzoate

3-Aminophenyl 4-methyl benzoate was prepared according to the example 9 using 2-nitrophenyl 4-methyl benzoate (16 g), 3-aminophenol (8.8 g), sodium hydroxide (3.2 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene

to afford pure 3-aminophenyl 4-methylbenzoate.

Yield : 10.5 gm (74.6%)

MP : 85 - 87 °C

Example: 33

Preparation of 4-aminophenyl 4-methylbenzoate

4-Aminophenyl 4-methylbenzoate was prepared according to the example 9 using 4-nitrophenyl 4-methylbenzoate (16 g), 4-aminophenol (8.8 g), sodium hydroxide (3.2 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 4-aminophenyl 4-methylbenzoate.

Yield : 10.9 gm (77.5%)

MP : 103 -105 °C

Example: 34

Preparation of 4-aminophenyl 4-methylbenzoate

4-Aminophenyl 4-methylbenzoate was prepared according to the example 9 using 2-nitrophenyl 4-methylbenzoate (16 g), 4-aminophenol (8.8 g), sodium hydroxide (3.2 g) and dimethylsulfoxide (50 ml). The solid was recrystallized from toluene to afford pure 4-aminophenyl 4-methylbenzoate.

Yield : 12.2 gm (87.0%)

MP : 103 -105 °C

Example: 35

Preparation of 4-aminobenzyl benzamide

A clean and dry 50 ml 4 neck round bottom flask was charged with 4-aminobenzyl amine (0.308 gm), 4-nitrophenyl benzoate (0.486 gm) and DMF (5 ml). The reaction mixture was heated at 50°C for 3 hours. The reaction mixture was quenched with water and worked-up to provide a crude product which was purified by column chromatography to afford pure 4-aminobenzyl benzamide.

Yield : 0.355 gm (78%)

MP : 142 - 144 °C (Lit. MP: 142 - 143 °C, Helvetica Chimica Acta

2007, 90(6), 1043)

Example: 36

Preparation of 4-aminobenzyl benzamide

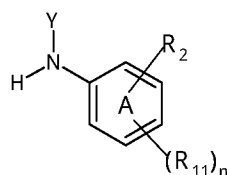
Similarly was prepared 4-aminobenzyl benzamide according to example 13 from 4-aminobenzyl amine (0.308 gm), 2-nitrophenyl benzoate (0.486 gm) and DMF (5 ml). The reaction mixture was quenched with water and worked-up to provide a crude product which was purified by column chromatography to afford pure 4-aminobenzyl benzamide.

Yield : 320 mg (70.3%)

MP : 142 ° - 144 °C (Lit. MP: 142 ° - 143 °C, Helvetica Chimica Acta 2007, 90(6), 1043)


We claim,

1. A chemoselective acylation process comprising reaction of aromatic amino derivatives of formula (II)



Formula (II)



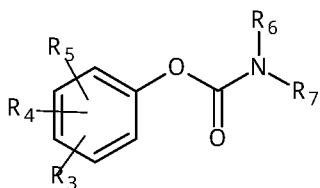
Wherein, Ring system  represents aryl, heteroaryl or fused rings, such as Benzene, Naphthalene, Anthracene, Phenanthrene, Azulene, pyrene, Fluorene, Pyrrole, Pyrazole, Imidazole, Pyridine, Pyrazine, Pyrimidine, Triazine, Indole, Benzimidazole, Quinoline, Isoquinoline, Phthalazine, Furan, Benzofuran, Thiophene, Benzothiophene, Oxazole, Thiazole, Tetrazole, Oxadiazole, Thiadiazole, Triazole or such 2 or 3 similar or different ring systems are fused or are connected either by a single bond or heteroatoms selected from O, N and S;

R_2 is independently, $-OH$, $-SH$, $-X_p B_q Z_r OH$, $-X_p B_q Z_r SH$, or $-X_p B_q Z_r NH(Y)$ where in X and Z are independently, heteroatom selected from O, N and S, optionally substituted $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; B is optionally substituted ring systems mentioned above or such 2 or 3 similar or different rings are fused or are connected either by a single bond or heteroatoms selected from O, N and S; Y is Hydrogen, optionally substituted $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; p is 0 or 1, q is 0 or 1, r is 0 or 1, provided that at least one of p, q and r is 1, also provided that $X_p B_q Z_r NH(Y)$ forms an aliphatic amino group;

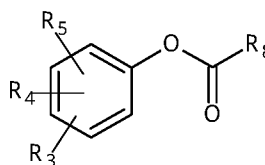
R_{11} is independently, hydrogen, $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; $-C_{1-7}$ alkylphenyl, $-phenyl$, $-phenylC_{1-7}$ alkyl, $-C_{1-7}$ alkoxy, $-C_{1-7}$ alkoxyphenyl, $-phenoxy$, $-phenoxy(C_{1-7}$ alkyl), $-C_{1-7}$ Salkyl, $-C_{1-7}$ Salkylphenyl, $-Sphenyl$, $-Sphenyl(C_{1-7}$ alkyl), $-NO_2$, $-CN$, halogen, $-NH_2$, $-NH(C_{1-7}$ alkyl), $-NH(C_{1-7}$ alkylphenyl), $-NH(phenyl)$, $-NH(phenyl C_{1-7}$ alkyl), $-N(C_{1-7} \text{ alkyl})(C_{1-7}$ alkyl) or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(C_{1-7} \text{ alkyl})(C_{1-7}$ alkylphenyl) or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(C_{1-7} \text{ alkylphenyl})(C_{1-7}$ alkylphenyl), $-N(phenyl)(phenyl)$, $-N(phenyl)(C_{1-7}$ alkyl) or the alkyl and phenyl groups attached to N form an optionally substituted 4 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-CHO$, $-C(O)C_{1-7}$ alkyl, $-C(O)C_{1-7}$ alkylphenyl, $-C(O)phenyl$, $-C(O)phenyl(C_{1-7}$ alkyl), $-C(O)phenyl(C_{1-7}$ alkylphenyl), $-C(O)O$ C_{1-7} alkyl, $-C(O)O$ C_{1-7} alkylphenyl, $-C(O)O$ phenyl, $-C(O)O$ phenyl(C_{1-7} alkyl), $-OC(O)C_{1-7}$ alkyl, $-OC(O)C_{1-7}$ alkylphenyl, $-OC(O)phenyl$, $-OC(O)phenyl(C_{1-7}$ alkyl), $-CONH_2$, $-C(O)NH$ C_{1-7} alkyl, $-C(O)NH$ C_{1-7} alkylphenyl, $-C(O)NH$ phenyl, $-C(O)NH$ phenyl(C_{1-7} alkyl), $-C(O)N(C_{1-7} \text{ alkyl})(C_{1-7}$ alkyl) or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-C(O)N(C_{1-7} \text{ alkyl})(C_{1-7}$ alkylphenyl) or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-C(O)N(C_{1-7} \text{ alkylphenyl})(C_{1-7}$ alkylphenyl), $-C(O)N(phenyl)(phenyl)$, $-NHC(O)C_{1-7}$ alkyl, $-NHC(O)C_{1-7}$ alkylphenyl, $-NHC(O)phenyl$, $-NHC(O)phenyl(C_{1-7}$ alkyl), $-N(C_{1-7} \text{ alkyl})C(O)C_{1-7}$ alkyl, $-N(C_{1-7} \text{ alkyl})C(O)C_{1-7}$ alkylphenyl, $-N(C_{1-7} \text{ alkyl})C(O)phenyl$, $-N(C_{1-7}$

alkyl)C(O) phenyl(Ci-₇ alkyl), $\text{SO}_2\text{C}_{1-7}$ alkyl, $\text{SO}_2\text{Ci-}_7\text{alkylphenyl}$, SO_2phenyl , $\text{SO}_2\text{phenyl(Ci-}_7\text{ alkyl)}$, SO_2NH_2 , $\text{SO}_2\text{NHCi-}_7\text{ alkyl}$, $\text{SO}_2\text{NHCi-}_7\text{alkylphenyl}$, $\text{SO}_2\text{NHphenyl}$, $\text{SO}_2\text{NHphenyl(Ci-}_7\text{ alkyl)}$, $\text{NHSO}_2\text{C}_{1-7}$ alkyl, $\text{NHSO}_2\text{C}_{1-7}$ alkylphenyl, $\text{NHSO}_2\text{phenyl}$, $\text{NHSO}_2\text{phenyl(Ci-}_7\text{ alkyl)}$, or $\text{R}_{11}, \text{R}_{11}$ placed ortho to each other form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring or R_{11} placed ortho to either of $-\text{X}_p\text{BqX}_r\text{OH}$, $-\text{X}_p\text{BqX}_r\text{SH}$ and $-\text{X}_p\text{BqX}_r\text{NH(Y)}$ form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring; n is 0 to 4;

with a compound of formula (IIIa) or (IIIb)



Formula (IIIa)



Formula (IIIb)

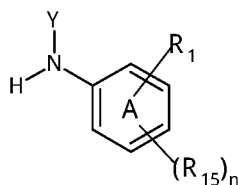
wherein R_3 is an electron withdrawing group selected from but not limited to nitro, cyano, halogen, dicyanovinyl, tricyanovinyl;

R_4 and R_5 are independently hydrogen, electron withdrawing groups selected from but not limited to nitro, cyano, halogen, dicyanovinyl, tricyanovinyl, $-\text{C}_{1-10}$ alkyl, $-\text{C}_{2-10}$ alkenyl, $-\text{C}_{2-10}$ alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring; $-\text{Ci-}_7$ alkylphenyl, $-\text{phenyl}$, $-\text{phenylCi-}_7$ alkyl, $-\text{Ci-}_7$ alkoxy, $-\text{Ci-}_7$ alkoxy phenyl, $-\text{phenoxy}$, $-\text{phenoxy(Ci-}_7\text{ alkyl)}$, $-\text{Ci-}_7$ Salkyl, $-\text{Ci-}_7$ Salkylphenyl, $-\text{Sphenyl}$, $-\text{Sphenyl(Ci-}_7\text{ alkyl)}$, $-\text{NO}_2$, $-\text{CN}$, halogen, $-\text{N(Ci-}_7\text{ alkyl)(Ci-}_7\text{ alkyl)}$, $-\text{C(O)Ci-}_7\text{ alkyl}$, $-\text{C(O) phenyl}$, $-\text{C(O)O C}_{1-7}$ alkyl, $-\text{C(O)O phenyl}$, $-\text{CONH}_2$, $-\text{C(O)NH C}_{1-7}$ alkyl, $-\text{C(O)NH phenyl}$, $-\text{C(O)N (C}_{1-7}\text{ alkyl)(Ci-}_7\text{ alkyl)}$, $-\text{C(O)N (phenyl)(phenyl)}$, $-\text{NHC(O) C}_{1-7}$ alkyl, $-\text{NHC(O) phenyl}$, $-\text{SO}_2\text{C}_{1-7}$ alkyl, $-\text{SO}_2\text{phenyl}$, $-\text{SO}_2\text{NHCi-}_7$ alkyl, $-\text{SO}_2\text{NHphenyl}$, $-\text{NHSO}_2\text{C}_{1-7}$


alkyl, NHSCbphenyl , or R_4 and R_5 placed ortho to each other form benzene, naphthalene or an optionally substituted 3 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring;

R_6 and R_7 are independently H, optionally substituted -C_{1-10} alkyl, -C_{2-10} alkenyl, -C_{2-10} alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which optionally includes at least one heteroatom selected from O, N and S in the cyclic ring or R_6, R_7 along with nitrogen form an optionally substituted 3 to 7 member heterocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring; R_8 is hydrogen, optionally substituted -C_{1-10} alkyl, -C_{2-10} alkenyl, -C_{2-10} alkynyl, or form an optionally substituted 3 to 7 member cyclic ring which includes at least one heteroatom selected from O, N and S in the cyclic ring or optionally substituted aryl, heteroaryl or fused rings, such as Benzene, Naphthalene, Anthracene, Phenanthrene, Azulene, pyrene, Fluorene, Pyrrole, Pyrazole, Imidazole, Pyridine, Pyrazine, Pyrimidine, Triazine, Indole, Benzimidazole, Quinoline, Isoquinoline, Phthalazine, Furan, Benzofuran, Thiophene, Benzothiophene, Oxazole, Thiazole, Tetrazole, Oxadiazole, Thiadiazole, Triazole or such 2 or 3 similar or different ring systems are fused or are connected either by a single bond or heteroatoms selected from O, N and S; in presence of base or solvent or both base and solvent;

to provide a compound of formula (I)



Formula (I)


Ring system  represents aryl, heteroaryl or fused rings, such as Benzene, Naphthalene, Anthracene, Phenanthrene, Azulene, pyrene, Fluorene, Pyrrole, Pyrazole, Imidazole, Pyridine, Pyrazine, Pyrimidine, Triazine, Indole,

Benzimidazole, Quinoline, Isoquinoline, Phthalazine, Furan, Benzofuran, Thiophene, Benzothiophene, Oxazole, Thiazole, Tetrazole, Oxadiazole, Thiadiazole, Triazole or such 2 or 3 similar or different ring systems are fused or are connected either by a single bond or heteroatoms selected from O, N and S;

R_1 is $O C(0) N(R_6)R_7$, $SC(0) N(R_6)R_7$, $-X_p B_q Z_r$, $O C(0) N(R_6)R_7$, $-X_p B_q Z_r$, $SC(0) N(R_6)R_7$, $-X_p B_q Z_r N(Y)(C(0) N(R_6)R_7)$, $O C(0)R_8$, $SC(0)R_8$, $-X_p B_q Z_r$, $O C(0)R_8$, $-X_p B_q Z_r SC(0)R_8$, $-X_p B_q Z_r N(Y)(C(0)R_8)$; X, B, Z, Y, R_6 , R_7 , R & p, q, r are as described above.

R_{15} is hydrogen, $-C_{1-10}$ alkyl, $-C_{2-10}$ alkenyl, $-C_{2-10}$ alkynyl, $-C_{3-10}$ cycloalkyl, $-C_{3-10}$ cycloalkenyl, $-C_{5-10}$ cycloalkynyl, $-C_{1-7}$ alkylphenyl, -phenyl, -phenyl C_{1-7} alkyl, $-C_{1-7}$ alkoxy, $-C_{1-7}$ alkoxyphenyl, -phenoxy, -phenoxy(C_{1-7} alkyl), $-C_{1-7}$ Salkyl, $-C_{1-7}$ Salkylphenyl, -Sphenyl, -Sphenyl(C_{1-7} alkyl), $-NO_2$, $-CN$, halogen, $-NH_2$, $-NH(C_{1-7}$ alkyl), $-NH(C_{1-7}$ alkylphenyl), $-NH(phenyl)$, $-NH(phenyl C_{1-7} alkyl)$, $-N(C_{1-7} alkyl)(C_{1-7} alkyl)$ or two alkyl groups attached to N form an optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(C_{1-7} alkyl)(C_{1-7} alkylphenyl)$ or the alkyl groups attached to N along with alkylphenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-N(C_{1-7} alkylphenyl)(C_{1-7} alkylphenyl)$, $-N(phenyl)(phenyl)$, $-N(phenyl)(C_{1-7} alkyl)$ or the alkyl and phenyl groups attached to N form an optionally substituted 4 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $-CHO$, $-C(0)C_{1-7} alkyl$, $-C(0)C_{1-7} alkylphenyl$, $-C(0) phenyl$, $-C(0) phenyl(C_{1-7} alkyl)$, $-CO_2H$, $-C(0)O C_{1-7} alkyl$, $-C(0)O C_{1-7} alkylphenyl$, $-C(0)O phenyl$, $-C(0)O phenyl(C_{1-7} alkyl)$, $-OC(0) C_{1-7} alkyl$, $-OC(0) C_{1-7} alkylphenyl$, $-OC(0) phenyl$, $-OC(0) phenyl(C_{1-7} alkyl)$, $-CONH_2$, $-C(0)NH C_{1-7} alkyl$, $-C(0)NH C_{1-7} alkylphenyl$, $-C(0)NH phenyl$, $-C(0)NH phenyl(C_{1-7} alkyl)$, $-C(0)N(C_{1-7} alkyl)(C_{1-7} alkyl)$ or two alkyl groups attached to N form an

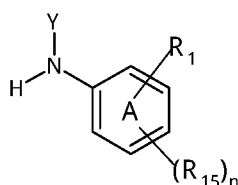
optionally substituted 3 to 7 member cyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $^-\text{C}(\text{O})\text{N}(\text{C}_{1-7}\text{ alkyl})(\text{C}_{1-7}\text{ alkylphenyl})$ or the alkyl groups attached to N along with alkyl phenyl group form an optionally substituted 3 to 7 member cyclic or benzocyclic ring which optionally includes additional 1 or 2 heteroatoms selected from O, N and S in the cyclic ring, $^-\text{C}(\text{O})\text{N}(\text{C}_{1-7}\text{ alkyl phenyl})(\text{C}_{1-7}\text{ alkylphenyl})$, $^-\text{C}(\text{O})\text{N}(\text{phenyl})(\text{phenyl})$, $^-\text{NHC}(\text{O})\text{C}_{1-7}\text{ alkyl}$, $^-\text{NHC}(\text{O})\text{C}_{1-7}\text{ alkylphenyl}$, $^-\text{NHC}(\text{O})\text{phenyl}$, $^-\text{NHC}(\text{O})\text{phenyl}(\text{C}_{1-7}\text{ alkyl})$, $^-\text{N}(\text{C}_{1-7}\text{ alkyl})\text{C}(\text{O})\text{C}_{1-7}\text{ alkyl}$, $^-\text{N}(\text{C}_{1-7}\text{ alkyl})\text{C}(\text{O})\text{C}_{1-7}\text{ alkylphenyl}$, $^-\text{N}(\text{C}_{1-7}\text{ alkyl})\text{C}(\text{O})\text{phenyl}$, $^-\text{N}(\text{C}_{1-7}\text{ alkyl})\text{C}(\text{O})\text{phenyl}(\text{C}_{1-7}\text{ alkyl})$, $^-\text{SO}_2\text{C}_{1-7}\text{ alkyl}$, $^-\text{SO}_2\text{C}_{1-7}\text{ alkylphenyl}$, $^-\text{SO}_2\text{phenyl}$, $^-\text{SO}_2\text{phenyl}(\text{C}_{1-7}\text{ alkyl})$, $^-\text{SO}_2\text{NH}_2$, $^-\text{SO}_2\text{NHC}_{1-7}\text{ alkyl}$, $^-\text{SO}_2\text{NHC}_{1-7}\text{ alkylphenyl}$, $^-\text{SO}_2\text{NHphenyl}$, $^-\text{SO}_2\text{NHphenyl}(\text{C}_{1-7}\text{ alkyl})$, $^-\text{NHSO}_2\text{C}_{1-7}\text{ alkyl}$, $^-\text{NHSO}_2\text{C}_{1-7}\text{ alkylphenyl}$, $^-\text{NHSO}_2\text{phenyl}$, $^-\text{NHSO}_2\text{phenyl}(\text{C}_{1-7}\text{ alkyl})$, or R_{11} , R_{11} placed ortho to each other form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring or R_{11} placed ortho to R_1 form an optionally substituted 4 to 7 member cyclic ring which optionally includes 1 to 3 heteroatoms selected from O, N and S in the cyclic ring; X, B, Y, R_6 , R_7 , R_8 , n, p, q, r are as described above.

2. The process as claimed in claim 1, wherein ring system  represents benzene, naphthalene or anthracene.

3. The process as claimed in claim 1 and 2, wherein R_2 is $^-\text{O}^-\text{H}$, $^-\text{S}^-\text{H}$, ^-X pBqX rOH , or ^-X pBqX $\text{rNH}(\text{Y})$, X is $^-\text{C}_{1-10}\text{ alkyl}$, Y is H or $^-\text{C}_{1-10}\text{ alkyl}$, B is benzene or naphthalene, p is 0 or 1, q is 0 or 1, r is 0 or 1, provided that at least one of p, q and r is 1, also provided that X pBqX $\text{rNH}(\text{Y})$ forms an aliphatic amino group;


4. The process as claimed in claims 1, wherein R_3 is nitro or cyano; R_4 is hydrogen, $^-\text{C}_{1-10}\text{ alkyl}$ or nitro; and R_5 is hydrogen.

5. The process as claimed in claim 1, wherein the base is selected from organic base or inorganic base.
6. The process as claimed in claim 5, wherein the base is selected from alkali metal hydroxides, alkali metal alkoxides or tertiary amines.
7. The process as claimed in claim 6, wherein the base is sodium hydroxides, sodium methoxide or triethyl amine.
8. The process as claimed in claim 1, wherein the solvent is selected from polar solvent or non-polar solvent.
9. The process as claimed in claim 8, wherein the solvent is selected from dimethyl sulfoxide, dimethyl formamide, acetonitrile, acetone, methanol, ethanol or dimethylacetamide.
10. A process for preparation of quarternary ammonium compounds comprising: reaction of compound of Formula (I)

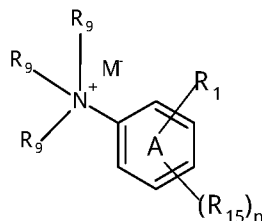


Formula (I)




Wherein, Ring system , R_1 , R_{15} and n are as described above, Y is hydrogen, methyl or ethyl group; with methylating or ethylating agents in presence of base or suitable solvent;

to provide a compound of formula (IV)



Formula (IV)



Wherein, Ring system , R₁, R₁₅ and n are as described above, R₉ is independently methyl or ethyl and M⁻ is an anion selected from methyl sulfate, ethyl sulfate, methane sulfonate, benzene sulfonate, toluene sulfonate or halogen.

11. The process as claimed in claim 10, wherein, R₁ is OC(0)N(R₆)R₇, SC(0)N(R₆)R₇, OC(0)R₈, SC(0)R₈, X is -C₁₋₁₀ alkyl, Y is H or -C₁₋₁₀ alkyl, B is benzene or naphthalene, p is 0 or 1, q is 0 or 1, r is 0 or 1, provided that at least one of p, q and r is 1, also provided that X_pBqX_rNH(Y) forms an aliphatic amino group.

12. The process as claimed in claim 10, wherein the base is selected from inorganic base.

13. The process as claimed in claim 12, wherein the base is selected from alkali metal carbonate, alkaline earth metal carbonate, alkali metal bicarbonate or mixture thereof.

14. The process as claimed in claim 13, wherein the base is selected from calcium carbonate, sodium bicarbonate or mixture thereof.

15. The process as claimed in claims 10, wherein the solvent is selected from polar solvent or non-polar solvent.

16. The process as claimed in claim 15, wherein the solvent is selected from acetonitrile, acetone, methanol, ethanol or ethyl methyl ketone.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2017/050074

A. CLASSIFICATION OF SUBJECT MATTER
C07C269/00, C07C271/00 Version=2 017.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012131699 A1; Oct 04, 2012; NEON LABORATORIES LTD. see claims, example 1-9	1 - 16
A	US 2010/113819 A1; May 06, 2010; SABIC INNOVATIVE PLASTICS IP BV. see fig. 1, para [0041].	1 - 16
A	US 3801625 A; Apr 02, 1974; FMC CORP. see examples .	1 - 16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12-05-2017

Date of mailing of the international search report

12-05-2017

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/050074

Citation	Pub.Date	Family	Pub.Date
US 2010/113819 A1	06-05-2010	WO 2010062490 A2	03-06-2010
		EP 2362867 A2	07-09-2011
		CN 102203050 A	28-09-2011