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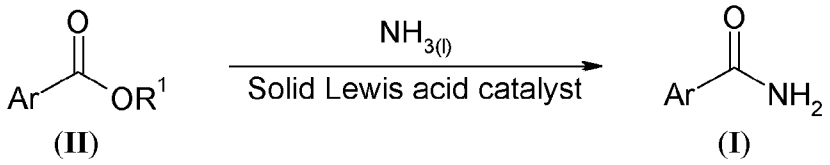
(54) Title: PROCESS FOR THE PREPARATION OF AROMATIC PRIMARY AMIDES



(II) (I)

(57) Abstract: The invention relates to a novel process for preparing aromatic primary amides. The process involves reacting a compound of formula (II) with liquid ammonia in the presence of a solid Lewis acid catalyst to form a compound of formula (I) wherein Ar and R^1 are as defined in the claims.

PROCESS FOR THE PREPARATION OF AROMATIC PRIMARY AMIDES

The present invention relates to a novel process for preparing aromatic primary amides.

These can be valuable compounds themselves, or can be useful for preparing a wide range of compounds containing amide bonds, including both pharmaceutical and agrochemical compounds.

Various syntheses of primary amides are well known, but often the production of an activated carboxylic acid derivative, such as an acid chloride, followed by more reaction steps will be required.

Direct amination of carboxylic acids to give amides is discussed in WO 2010/072631 and WO 2010/072632.

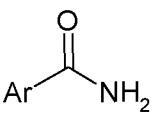
J. Am. Chem. Soc. (**1938**, *60* (3), pp 579–581) describes the preparation of benzamide from ethyl benzoate and liquid ammonia using Brønsted acid catalysts based on ammonium. However, there is an ongoing need for improvement in the production of aromatic primary amides in order to reduce production costs.

Direct amination of carboxylic acids using gaseous ammonia in the presence of alkyltin catalysts is described in US 4,277,410.

J. Catal. (**1998**, *173*, pp 84-94) illustrates that amides are a by-product in the reaction of various esters with gaseous ammonia in the presence of several Brønsted and Lewis acid catalysts.

Surprisingly it has been found that aromatic primary amides may be prepared from aromatic esters and liquid ammonia in the presence of a solid Lewis acid catalyst.

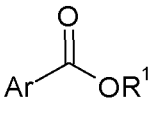
Thus, according to the present invention there is provided a process for the preparation of a compound of formula (**I**)



(**I**)

wherein Ar is an aromatic moiety,

wherein a compound of formula (**II**)



(**II**)

wherein Ar is an aromatic moiety and R^1 is an organic radical, is reacted with liquid ammonia in the presence of a solid Lewis acid catalyst.

The solid Lewis acid catalyst should at least partially not dissolve in the reaction mixture at room temperature and pressure, or under the reaction conditions.

Preferred solid Lewis acid catalysts comprise a metal salt, a metal oxide or a metalloid oxide. Elements generally considered to be metalloids are boron, silicon, germanium, arsenic, antimony, tellurium and polonium. Preferably, the metalloid is silicon.

More preferably, the solid Lewis acid catalyst comprises a transition metal salt, or an oxide of a transition metal, an oxide of aluminium or an oxide of silicon. Preferably, the transition metal should belong to group 4, group 5, group 11 or group 12 of the periodic table. The catalyst may comprise one or more of the above salts and oxides.

Examples of solid Lewis acid catalysts include:

copper (I) chloride; copper (I) acetate; copper (II) acetate; copper (II) oxide; zinc oxide; niobium oxides; titanium oxides; aluminium oxide; Silica.

Niobium oxides include niobium monoxide, niobium dioxide, niobium pentoxide, $Nb_{3n+1}O_{8n-2}$ (where n ranges from 5 - 8 inclusive, e.g. Nb_8O_{19}), $Nb_{12}O_{29}$ and $Nb_{47}O_{116}$.

Titanium oxides include titanium dioxide, titanium(II) oxide, titanium(III) oxide, Ti_3O, Ti_2O, δ-TiO_x (x= 0.68 - 0.75), Ti_nO_{2n-1} where n ranges from 3 - 9 inclusive, e.g. Ti_3O_5, Ti_4O_7, etc. Titanium dioxide is preferred, and anatase is the preferred modiciation of titanium dioxide.

Preferred examples of solid Lewis acid catalysts include:

copper (I) chloride; copper (I) acetate; copper (II) acetate; copper (II) oxide; zinc oxide; niobium pentoxide; titanium dioxide; silica; alumina (aluminium oxide).

Preferred solid Lewis acid catalysts are metal oxides.

Most preferably, the solid Lewis acid catalyst comprises titanium dioxide and/or alumina (aluminium oxide), and preferably the solid Lewis acid catalyst is titanium dioxide or alumina (aluminium oxide).

In one group of reactions, particularly where Ar is optionally substituted phenyl or napthyl, preferred solid Lewis acid catalysts comprise one or more of the following:

titanium dioxide; alumina (aluminium oxide); copper (II) oxide; zinc oxide; niobium pentoxide; titanium dioxide; silica.

In this group of reactions preferred solid Lewis acid catalysts are metal oxides and most preferably, the solid Lewis acid catalyst comprises titanium dioxide and/or alumina (aluminium oxide), preferably the solid Lewis acid catalyst is titanium dioxide or alumina (aluminium oxide).

Preferably, reference herein to titanium dioxide means anatase.

The solid Lewis acid catalyst may be used in stoichiometric amounts relative to the compound of formula (II), or in super- or sub-stoichiometric amounts.

The process is conveniently carried out using liquid ammonia as solvent. Other inert solvents may or may not be present. It may be advantageous to include an additional solvent to aid solubility of the starting material or products and to help processing e.g. it may be easier to remove the ammonia leaving a liquid rather than a solid.

Typically, up to 80% v/v of other solvents may be present compared to the volume of ammonia. Preferably, up to 40% v/v of the other solvents may be present. More preferably, no more than 20% v/v of the other solvents may be present. Even more preferably, substantially no other solvent is present. Suitable inert solvents include aromatic or halogenated aromatic solvents such as toluene, xylene and chlorobenzene; and alkanes such as hexanes or ethers such as THF.

During the process, water may or may not be present. Typically, no more than 50% v/v of water may be present compared to the volume of ammonia. Preferably, no more than 40% v/v of water may be present. More preferably, no more than 20% v/v or less of water may be present. Even more preferably, the reaction should be conducted substantially in the absence of water. Reducing the amount of water can reduce the competing and detrimental hydrolysis of the compounds of formula (II) to the corresponding carboxylic acids.

The liquid ammonia is usually employed in an excess, for example from 10 to in excess of 1000 equivalents relative to the compounds of formula (II). The liquid ammonia may be employed with an excess of 1000 equivalents relative to the compounds of formula (II), for example, up to 1000 equivalents relative to the compounds of formula (II). Typically the ammonia is employed with at least 10 equivalents of ammonia relative to the compounds of formula (II).

The process is conveniently carried out at a temperature in the range of 25°C to 175°C, for example, from 50°C to 150°C, and typically from 75°C to 140°C. The process may be carried out at a temperature of at least 25°C, for example at least 50°C, and typically at least

75°C. The process is conveniently carried out at a temperature up to 175°C, for example, up to 150°C, and typically up to 140°C.

As the ammonia must be maintained in the liquid phase, the person skilled in the art will appreciate that this will require special equipment to contain the high pressure created.

The time the process takes will depend upon, *inter alia*, the catalyst:substrate ratio and the temperature at which the reaction is carried out. For example, the process may be performed for 1 minute to 24 hours, usually 10 minutes to 6 hours, typically 10 minutes to 1 hour. The process may be performed for at least 1 minute, usually at least 10 minutes. The process may be performed for up to 24 hours, usually up to 6 hours, typically no more than 1 hour. The skilled person will be able to optimise the time needed for the reaction to provide a desired conversion to product.

Conveniently, the reaction can be performed either as a batch reaction or a flow reaction, wherein a mobile phase mixture comprising the liquid ammonia and the aromatic ester is contacted with a stationary phase comprising the solid Lewis acid catalyst, e.g. by passing the mobile phase over the stationary phase. The flow reaction may be continuous or intermittent. Preferably, continuous flow conditions are used.

In flow reactions, preferably 0.1-10 molar equivalents of the solid Lewis acid catalyst compared to the compounds of formula (II) are used, typically between 1-5 molar equivalents. The flow process may be carried out in the presence of at least 0.1 molar equivalents of the solid Lewis acid catalyst compared to the compounds of formula (II), typically in the presence of at least 1 molar equivalent. The process may be carried out in the presence of up to 10 molar equivalents of the solid Lewis acid catalyst compared to the compounds of formula (II), typically in the presence of up to 5 molar equivalents. The person skilled in the art will understand that it is important to ensure a suitable contact time between the reagents and the catalyst in these cases.

In a flow system, the liquid ammonia is employed in a large excess in a flow system where an excess of 1000 molar equivalents of the compound of formula (II) is not uncommon.

In batch reactions, preferably 0.01-1 molar equivalents of the solid Lewis acid catalyst compared to the compounds of formula (II) are used, typically between 1-5 molar equivalents. In batch reactions, preferably at least 0.01 molar equivalents of the solid Lewis acid catalyst relative to the compound of formula (II) are used, typically at least 0.1 molar equivalents. In

batch reactions, preferably no more than 1 molar equivalents of the solid Lewis acid catalyst relative to the compound of formula (II) are used, typically no more than 0.5 molar equivalents.

A schematic illustration of a typical continuous flow reactor is provided in Fig. 1. In this case, a peristaltic pump (2) may be used to pump the reaction mixture through the packed bed reactor (3), through to a collecting vessel (6). It may be preferential to use the first chamber of one pump head (2b) as a pre-cooling chamber. For greater control of the reaction conditions, an oven (4) and back-pressure regulator (5) may also be used. Higher conversions can be readily achieved with multiple passes. Typically this would involve connecting the outlet back to the feed vessel or feedline although the product maybe optionally removed first.

Preferred values of R^1, Ar, and their optional substituents are set out below, which may be combined in any combination.

Preferably, R^1 is a branched or unbranched alkyl group containing from 1 to 6 carbon atoms and is, for example, methyl, ethyl, *n*-propyl, *n*-butyl, *iso*-propyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl or *n*-hexyl. Conveniently it is methyl or ethyl.

Preferably, Ar is an optionally substituted phenyl, naphthyl or 5-6 membered heterocyclic ring containing 1-3 atoms selected from nitrogen, sulphur and oxygen. Any such ring should not contain sulphur or oxygen atoms adjacent to another sulphur or oxygen atom.

More preferably, Ar is an optionally substituted phenyl ring or an optionally substituted pyrazole group.

Where a moeity may be optionally substituted, typical substituents include halogen, CN, NO_2, OH, NH_2, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, CO(C_1-C_8 alkyl), COH, SH, C_1-C_8 alkylthio, C_1-C_8 alkylsulphinyl, C_1-C_8 alkylsulphonyl, alkylamine, dialkylamine, CO_2H, CO_2(C_1-C_8 alkyl), O(CO)C_1-C_8 alkyl, O(CO)H, CON(C_1-C_8 alkyl)$_2$, CONH(C_1-C_8 alkyl), NHCO(C_1-C_8 alkyl), NHCOH, N(C_1-C_8 alkyl)CO(C_1-C_8 alkyl) or NHCO(C_1-C_8 alkyl), wherein the alkyl, alkoxy, cycloalkyl, alkenyl and alkynyl are optionally substituted by one or more groups independently selected from halogen, CN, NH_2, NO_2, OH, C_1-C_4 alkyl, C_1 C_4-haloalkyl, C_1-C_4 alkoxy and C_1-C_4 haloalkoxy.

Preferred optional substituents include halogen, CN, NO_2, OH, NH_2, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, wherein the alkyl, alkoxy, cycloalkyl, alkenyl and alkynyl are optionally substituted by one or more groups independently selected

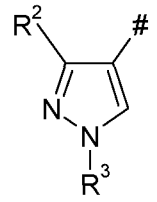
from halogen, CN, NH_2, NO_2, OH, C_1-C_4 alkyl, C_1 C_4-haloalkyl, C_1-C_4 alkoxy and C_1-C_4 haloalkoxy.

Even more preferred optional substituents include hydrogen, halogen, CN, NO_2, OH, NH_2, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, wherein the alkyl, alkoxy, cycloalkyl, alkenyl and alkynyl are optionally substituted by one or more groups independently selected from halogen, methyl, CN, methoxy, halomethyl and halomethoxy.

Optional substituents which are again more preferred include halogen, C_1-C_4 alkyl, CN, C_1-C_4 alkoxy, C_1-C_4 haloalkyl and C_1-C_4 haloalkoxy.

Yet more preferred optional substituents include halogen, methyl, CN, methoxy, halomethyl and halomethoxy.

Even more preferably, Ar represents cycle A-1



(A-1)

wherein R^2 represents C_1-C_4 haloalkyl, preferably difluoromethyl or trifluoromethyl, most preferably difluoromethyl; R^3 represents C_1-C_4 alkyl, preferably methyl or ethyl, most preferably methyl.

The following non-limiting examples illustrate the invention in more detail.

Figures

Figure 1 shows a schematic diagram illustrating a typical set up for a continuous flow reactor:

1) Feed vessel
2) Peristaltic pump
2a) Pump head
2b) Pump head
3) Packed bed
4) Oven
5) Back pressure regulator
6) Collection vessel

Examples

Batch reactions

Example 1: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (10 mg), copper (I) chloride (6.0 mg), copper (I) acetate (2.8 mg) and copper (II) acetate (7.3 mg) were charged to a 5mL Swagelok 316ss tube (4.6 mm ID), followed by liquid ammonia (4 mL). The sealed column was placed in an oven and heated to 100°C for 1 hour. Then the tube was cooled by liquid nitrogen and washed out by methanol. The conversion was checked by HPLC (6.4% conversion).

Comparative Example 1: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (12.4 mg) and ammonium chloride (13.7 mg) were charged to a 5mL Swagelok 316ss tube (4.6 mm ID), followed by liquid ammonia (4 mL). The sealed column was placed in an oven and heated to 100°C for 1 hour. Then the tube was cooled by liquid nitrogen and washed out by methanol. The conversion was checked by HPLC (2.3% conversion).

Continuous reactions

For each of the following reactions, the continuous reaction apparatus schematically represented in fig. 1 was used. A peristaltic pump (2; Agilent peristaltic water cooled pump 1200 binary) was used throughout. The feed went from the feed vessel (1) through to the first chamber of pump head 2b. This was used as a pre-cooling chamber. The feed then passed to pump head 2a and through a packed bed reactor (3) located in an oven (4), followed by a back pressure regulator (5), leading to a collecting vessel (6).

For the packed bed, stainless steel columns of dimension 250mm x 4.6mm i.d. were used unless otherwise specified.

Where not specifically mentioned, the flow rate through the apparatus was 0.3mL min^{-1}.

Comparative Example 2: Preparation of benzamide

Methyl benzoate (1.5mL) was dissolved in liquid ammonia (10mL). A column was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia start pumping. The column was first flushed by pure liquid ammonia for 10 min. Then the reaction mixture was fed through for 30 min at 0.3mL min^{-1}. Finally, the column was rinsed with pure liquid ammonia (80 min) at the same flow rate. No sample was been taken during the reaction, after the run was finished, sample was heated at 80°C to free ammonia and methanol. After that, the mass balance was recorded by weighing and purity was checked by HPLC. No conversion to amide was observed.

Example 2: Preparation of benzamide

Methyl benzoate (1.193 mL) was dissolved in liquid ammonia (10 mL). A column packed with aluminium oxide (2.16 g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through at 0.3mL min^{-1}. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. The column was first flushed by pure liquid ammonia for 10 min. Then the reaction mixture was fed through for 30 min at 0.3mL min^{-1}. Finally, the column was rinsed with pure liquid ammonia (80 min) at the same flow rate. No sample was taken during the reaction. After the run was finished, a sample was heated at 80°C to free ammonia and methanol. After that, the mass balance was recorded by weighing and purity was checked by HPLC (36% yield, no visible impurities**).**

Example 3: Preparation of benzamide

Methyl benzoate (1.193 mL) was dissolved in liquid ammonia (10 mL). A column packed with TiO_2 (anatase modification; 2.45 g) was placed in the oven and the temperature raised to 100°C before pure liquid ammonia was pumped through at 0.3mL min^{-1}. The pressure was adjusted to 100 bar via adjustable back pressure regulator after the pure liquid ammonia started pumping. The column was first flushed by pure liquid ammonia (10 min). Then the reaction mixture was fed for 30 min at 0.3mL min^{-1}. Finally, the column was rinsed with pure liquid ammonia (80 min) at the same flow rate. No sample was taken during the reaction. After the run was finished, a sample was heated at 80°C to free ammonia and

methanol. After that, the mass balance was recorded by weighting and purity was checked by HPLC (15% yield, no visible impurities).

Example 4: Preparation of benzamide

Methyl benzoate (46 µL) was dissolved in liquid ammonia (10 mL). A column packed with aluminium oxide (4.4 g) was placed the oven and the temperature was raised to 120°C before pure liquid ammonia was pumped through. Then pure liquid ammonia was pumped through the system at 0.3 mL min^{-1} and the pressure adjusted to 120 bar using an adjustable back pressure regulator.

The system was left pumping pure liquid ammonia for 10 minutes then switched to the reaction solution. After the reaction mixture, pure liquid ammonia was pumped through the system for another 1 hour at 0.3mL min^{-1}. All the reaction solution was collected as it exited the reaction column. At the end of reaction, the ammonia was allowed to evaporate, resulting in colourless crystals. The residue was dissolved in methanol and analysed by HPLC (>99% yield).

Example 5: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (496.8 mg) was dissolved in liquid ammonia (10 mL). A column packed with aluminium oxide (2.16 g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through at 0.3mL min^{-1}. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. The column was first flushed by pure liquid ammonia (10 min), then the reaction solution (30 min) at 0.3mL min^{-1} and finally liquid ammonia was used to flush the column (80 min) at 0.3mL min^{-1}. No sample was taken during the run. After the run finished, the reaction content was dissolved in methanol and then heated to 35°C overnight to free ammonia and ethanol. After that, the mass balance was recorded by weighting and purity was checked by HPLC (25% conversion, 90% selectivity).

Example 6: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (511.3 mg) was dissolved in liquid ammonia (10 mL). A column packed with TiO_2 (anatase modification; 2.16 g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through at 0.3mL min^{-1}. The pressure was adjusted to 100 bar via adjustable back pressure regulator after the pure liquid ammonia started pumping. The column was first flushed by pure liquid ammonia (10 min), followed by the reaction solution (30 min) at 0.3mL min^{-1}. Finally, the column was flushed with liquid ammonia (80 min) at 0.3mL min^{-1}. No sample was taken during the run. After the run finished, the reaction content was dissolved in methanol and then heated to 35°C overnight to free ammonia and methanol. After that, the mass balance was recorded by weighting and purity was checked by HPLC (21% conversion, 60% selectivity).

Example 7: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (498 mg) was dissolved in liquid ammonia (10 mL). A column packed with acid clay and silica gel (675 mg of each) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through at 0.3mL min^{-1}. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. The column was first flushed by pure liquid ammonia (10 min), followed by the reaction solution (30 min) at 0.3mL min^{-1}. Finally, liquid ammonia was used to flush the column (80 min) at 0.3mL min^{-1}. No sample was taken during the run. After the run was finished, the reaction content was dissolved in methanol and then heated to 35°C overnight to free ammonia and methanol. After that, the mass balance was recorded by weighting and purity was checked by HPLC (2.1% conversion, 60% selectivity).

Example 8: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (515 mg) was dissolved in liquid ammonia (10 mL). A column packed with ZnO, CuO and Nb_2O_5 (853 mg of each) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through at 0.3mL min^{-1}. The pressure was adjusted to 100 bar via

adjustable back pressure regulator after the pure liquid ammonia started pumping. The column was first flushed by pure liquid ammonia (10 min), followed by the reaction mixture (30 min) at 0.3mL min^{-1}. Finally liquid ammonia was used to flush the column (80min) at 0.3mL min^{-1}. No sample was taken during the run. After the run was finished, the reaction content was dissolved in methanol and then heated to 35°C overnight to free ammonia and methanol. After that, the mass balance was recorded by weighting and purity was checked by HPLC (3.7% conversion, 88% selectivity).

Example 9: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (51.4 mg) was dissolved in liquid ammonia (10mL). A column packed with TiO_2 (anatase modification; 2.262 g) was placed in the oven and the temperature was raised to 80°C before pure liquid ammonia was pumped through the system at 0.2 mL min^{-1} and the pressure adjusted to 100 bar using an adjustable back pressure regulator.

The system was left pumping pure liquid ammonia for 10 minutes then switched to the reaction solution (0.3 mL min^{-1}) for 50 min. Pure liquid ammonia was then pumped through the system for another 1 hour

The ammonia was allowed to evaporate, the residue was dissolved in methanol and analysed by HPLC (25% conversion, 93% selectivity).

Example 10: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (53.3 mg) was dissolved in liquid ammonia (10 mL). A column (500mm x 4.6mm i.d.) packed with aluminium oxide (4.501 g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. Then pure liquid ammonia was pumped through the system at 0.3 mLmin^{-1} and the pressure adjusted to 100 bar using an adjustable back pressure regulator.

The system was left pumping pure liquid ammonia for 10 minutes then switched to the reaction solution at 0.3mL min^{-1}for30 min. At this time, pure liquid ammonia was pumped through the system for another 1 hour at 0.3mL min^{-1}. All the reaction solution was collected

as it exited the reaction column, at the end of the reaction, the ammonia was allowed to evaporate, the residue was dissolved in methanol and analysed by HPLC (87-91% conversion, 98.4% selectivity).

Example 11: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (52.3 mg) was dissolved in liquid ammonia (10 mL). A column packed with TiO_2 (anatase modification; 2.558 g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through the system at 0.3 mL min^{-1} and the pressure adjusted to 100 bar using an adjustable back pressure regulator.

The system was left pumping pure liquid ammonia for 10 minutes then switched to the reaction solution at 0.3mL min^{-1} for 30 min. At this time, pure liquid ammonia was pumped through the system for another 1 hour same as previous. All the reaction solution was collected as it exited the reaction column, at the end of the reaction the ammonia was allowed to evaporate, the residue was dissolved in methanol and analysed by HPLC (39-59% yield).

Example 12: Preparation of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (54.0 mg) was dissolved in liquid ammonia (10 mL). A column (500mm x 4.6mm i.d.) packed with aluminium oxide (4.336 g) was placed in the oven and the temperature was raised to 120°C before pure liquid ammonia was pumped through the system at 0.3 mL min^{-1} and the pressure adjusted to 120 bar using an adjustable back pressure regulator.

The system was left pumping pure liquid ammonia for 10 minutes then switched to the reaction solution at 0.3mL min^{-1} for 30 min. At this time, pure liquid ammonia was pumped through the system for another 1 hour. All the reaction solution was collected as it exited the reaction column, at the end of reaction, the ammonia was allowed to evaporate, the residue was dissolved in methanol and analysed by HPLC (88-90% conversion, 99.4% selectivity).

Example 13: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with TiO_2 (anatase modification; 2.45g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 28%

Example 14: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with TiO_2 (rutile modification; 3.07g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 1.5%

Example 15: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with aluminium oxide (2.16g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once

the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 40%

Example 16: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with copper (II) oxide (3.78g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 0.7%

Example 17: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with zinc oxide (1.79g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 1%

Example 18: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with niobium pentoxide (1.13g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid

ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 1%

Example 19: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with silica gel (1.24g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 5%

Example 20: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with acid clay (1.24g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 3%

Example 21: Preparation of benzamide

Methyl benzoate (1.5mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). Two columns in series, both packed with aluminium oxide (1.30g and 1.23g) were placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 35%. Reaction is not equilibrium.

Example 22: Preparation of benzamide

Methyl benzoate (1.2mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with aluminium oxide (1.13g) was placed in the oven and the temperature was raised to 125°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 40%

Example 23: Preparation of benzamide

Methyl benzoate (1.2mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with aluminium oxide (1.13g) was placed in the oven and the temperature was raised to 125°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again

after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 28%

Example 24: Preparation of benzamide

Methyl benzoate (1.2mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with aluminium oxide (1.13g) was placed in the oven and the temperature was raised to 125°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 24%

Example 25: Preparation of benzamide

Methyl benzoate (1.2mL) and biphenyl (trace) were dissolved in liquid ammonia (10mL). A column packed with fresh aluminium oxide (1.32g) was placed in the oven and the temperature was raised to 100°C before pure liquid ammonia was pumped through. The pressure was adjusted to 100 bar via adjustable back pressure regulator after pure liquid ammonia started pumping. Timing was started once the system was filled with the ammonia. After 10 minutes the first sample (column pre-flush) was collected and sampled by HPLC. Then the reaction mixture was fed to the pump. Pure liquid ammonia was fed through again after the reaction mixture was finished and samples were collected every 10 minutes. Once the samples were ammonia free, they were dissolved in methanol and analysed by HPLC. Mean conversion between 10-40 minutes: 48%.

This indicates that the aluminium oxide catalyst is slowly deactivated by this reaction.

Example 26: Preparation of benzamide

Methyl benzoate (596µL) and methanol (1931µL) were dissolved in liquid ammonia (10mL). A column packed with aluminium oxide (2.14g) was placed the oven and the

temperature was raised to 100°C before pure liquid ammonia was pumped through. Then pure liquid ammonia was pumped through the system at 0.3 mL min^{-1} and the pressure adjusted to 100bar using an adjustable back pressure regulator.

The system was left pumping pure liquid ammonia for 10 minutes then switched to the pre-mixed reaction solution. The ammonia from the reactor was collected in 3mL aliquots (10 minutes duration). At the end of the reaction pure liquid ammonia was pumped through the system for another 1 hour. For each sample the ammonia was allowed to evaporate, the residue was dissolved in methanol and analysed by HPLC. Steady conversion percentage: 13.7%.

This reaction indicated that methanol appears to deactivate the aluminium oxide catalyst.

Please note that due to the benzamide has a longer retention time on the reaction column than methyl benzoate. Due to this, the conversions stated in Examples 13-25 may actually be lower than the true conversion.

HPLC methods

Benzamide

Column: Hewlett Packard, Hypersil AA-ODS, 5 um, 2.1 x 200mm, DE39G05949

Stop time: 20 minutes

Solvent gradient:

Time (min)	Solvent A (%)	Solvent B (%)
1	95	5
11	5	95
13	5	95
16	95	5

Solvent A: water 50mM Na_2HPO_3 PH adjusted to 2.6 by H_3PO_4

Solvent B: methanol

Injection volume: 5µl

UV: 258nm, slit 4nm

Column temperature: 30°C

Compound Retention times:

Methyl benzoate: 9.92 min

Benzamide: 5.78 min

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

Column: HICHROM HIRPB-5923, 2.1 x 150mm, 5um

Stop time: 20 minutes

Solvent gradient

Time (min)	Solvent A (%)	Solvent B (%)
1	95	5
11	5	95
13	5	95
16	95	5

Solvent A: water 50mM Na_2HPO_3 PH adjusted to 2.6 by H_3PO_4

Solvent B: methanol

Injection volume: 5µl

UV: 218nm, slit 4nm

Column temperature: 30°C

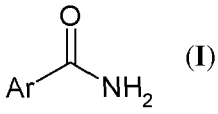
Compound Retention times:

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester: 10.72 min

3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide: 12.46 min

Claims

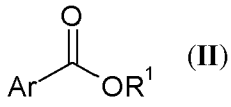
1. A process for the preparation of a compound of formula (**I**)



(**I**)

wherein Ar is an aromatic moiety,

wherein a compound of formula (**II**)



(**II**)

wherein Ar is an aromatic moiety and R^1 is an organic radical, is reacted with liquid ammonia in the presence of a solid Lewis acid catalyst.

2. A process according to claim 1 wherein the solid Lewis acid catalyst comprises a metal salt, a metal oxide and/or a metalloid oxide.

3. A process according to claim 2 wherein the solid Lewis acid catalyst comprises a transition metal salt, an oxide of a transition metal, an oxide of aluminium and/or an oxide of silicon.

4. A process according to claim 3 wherein the transition metal belongs to group 4, group 5, group 11 or group 12.

5. A process according to any preceding claim wherein the solid Lewis acid catalyst comprises one or more of the following group: copper (I) chloride; copper (I) acetate; copper (II) acetate; copper (II) oxide; zinc oxide; niobium oxides; titanium oxides; aluminium oxides; acid clay; and silica.

6. A process according to any preceding claim wherein the solid Lewis acid catalyst is a metal oxide.

7. A process according to any any preceding claim, wherein the solid Lewis acid catalyst comprises titanium dioxide and/or aluminium oxide.

8. A process according to any any preceding claim, wherein the solid Lewis acid catalyst comprises anatase and/or aluminium oxide.

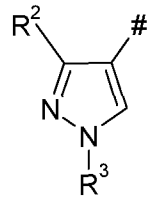
9. A process according to any preceding claim, wherein the process is carried out substantially in the absence of water.

10. A process according to any preceding claim, wherein the reaction is carried out in the absence of solvents other than liquid ammonia.

11. A process according to any preceding claim, wherein Ar represents an optionally substituted phenyl, naphthyl or 5-6 membered heterocyclic group.

12. A process according to any preceding claim, wherein Ar represents an optionally substituted phenyl group or an optionally substituted pyrazole group.

13. A process according to any preceding claim, wherein Ar represents cycle A-1



(A-1)

wherein R^2 represents C_1-C_4 haloalkyl and R^3 represents C_1-C_4 alkyl.

14. A process according to any preceding claim, wherein R^1 represents methyl or ethyl, R^2 represents difluoromethyl or trifluoromethyl, and R^3 represents methyl or ethyl.

15. A process according to any one of claims 1 to 14, wherein the process is a flow reaction.

16. A process according to any one of claims 1 to 15, wherein up to 80% v/v of other solvents may be present compared to the volume of ammonia.

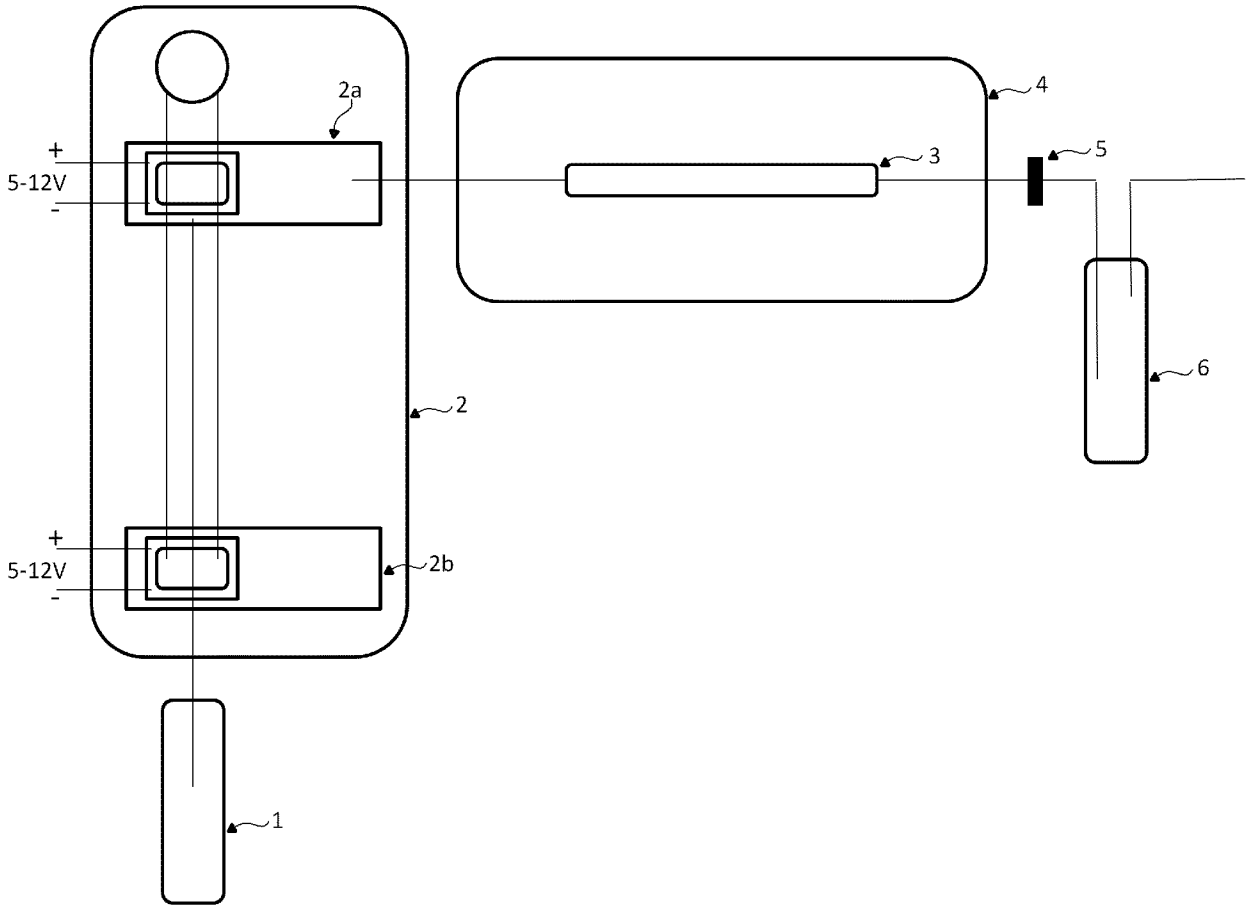


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/054005

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C231/02 C07C233/58 C07C233/65
ADD.

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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"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)

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Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2012	20/08/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 3 253 006 A (EDISON DAVIS JERRY) 24 May 1966 (1966-05-24) Figure 1; column 2, lines 22-54; column 3, line 38 - column 4, line 42; claims	1-16
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Y	KUMAR, PRADEEP ET AL: "Acylation of alcohols, thiols and amines with carboxylic acids catalyzed by yttria-zirconia-based Lewis acid", JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL, vol. 181, 2002, pages 207-213, XP002681260, page 209, Table 1, entries 1 and 2; Table 3, entries 1 and 2; page 213, point 4. Conclusion	1-16

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Information on patent family members

International application No
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