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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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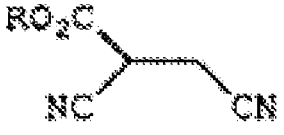
(54) **Title**: PROCESS FOR PREPARATION OF CYANOALKYLPROPIONATE DERIVATIVES



[I]

(57) **Abstract**: A process for preparation of the compound (I) and salts thereof is provided. The process comprises reacting an alkali cyanide and paraformaldehyde to form a slurry of glycolonitrile followed by neutralizing, mixing the neutralized slurry containing glycolonitrile with an alkali ethoxide and an cyanoacetate to obtain the alkali salt of compound (I), and neutralizing the alkali salt of compound (I) to obtain the compound (I), wherein R represents a straight or branched chain alkyl having C_1-C_{18} carbon atoms.

PROCESS FOR PREPARATION OF CYANOALKYLPROPIONATE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of cyanoalkylpropionate derivatives which are used as intermediates in the synthesis of pesticides.

BACKGROUND OF THE INVENTION

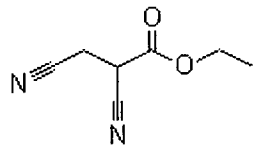
Ethyl 2, 3-Dicyano propionate

CAS Number: 40497-11-8

Molecular Formula:$C_7H_8N_2O_2$

Molecular Weight:152.15

Structure:



Use: It is used as intermediates in the synthesis of pesticides.

Ethyl 2,3-dicyanopropionate was first prepared and characterized by Higson and Thorpe (J.Chem.Soc. 89, 1460 (1906)) who obtained the material in good yield (70-81%) by reaction of formaldehyde cyanohydrin with the sodium salt of ethyl cyanoacetate.

Dickinson (J. Am. Chem. Soc 82, 6132 (I960)) repeated this work. This method of preparing the dicyanopropionate suffers from a significant drawback in that it is first

necessary to isolate the intermediate formaldehyde cyanohydrin. This highly water soluble cyanohydrin is obtained by lengthy continuous extraction and has a limited stability, often gets decomposed violently upon attempted distillation. Furthermore, this reaction requires care given the risk of formation of dimeric side-products.

The preparation of dicyanopropionates has also been described by Whiteley and Marianelli (Synthesis (1978), 392) with the process leading to 2,3- disubstituted succinodinitriles from the cyanoacetate, an aldehyde (a 1 to 3 carbon alkylaldehyde or benzaldehyde) and potassium cyanide via 3-substituted-2,3- dicyanopropionates. However, the yield decreases dramatically from isobutyraldehyde to acetaldehyde.

In the same manner Smith and Horwitz (J. Am. Chem. Soc. 1949, 21, 3418) described the same reaction with a ketone with a yield of 70%. This prior art therefore teaches that yields improve with increasing size of group adjacent to the carbonyl group.

Australian patent AU725472 (B2) discloses the synthesis of 2,3-dicyano ethylpropionate by reacting potassium cyanide with ethyl cyanoacetate and paraformaldehyde in ethanol solvent. The potassium salt on dissolution in water, acidification to pH 4 and extraction with dichloromethane gave 77 % yield of 2,3-dicyano ethylpropionate. The process disclosed in Australian patent AU725472 avoids use of formaldehyde cyanohydrin.

Chinese Patent CN1785966 discloses a process for synthesizing ethyl-2,3-dicyano-propionate. Said process includes the following steps: reacting ethyl cyanoacetate, paraformaldehyde and sodium cyanide to synthesize ethyl-2,3-dicyano-propionate in dimethyl sulfoxide medium; extracting the ethyl-2,3-dicyano-propionate using solvent dichloromethane from medium dimethyl sulfoxide, desolventizing the extracted product under reduced pressure to obtain crude product and rectifying said crude product so as to obtain the refined product (ethyl-2,3-cyano-propionate). The purity of the obtained product is greater than 98%.

The methods for the synthesis of cyanoalkylpropane derivatives as disclosed in the prior art suffer significant drawback in that it is first necessary to extract or isolate the intermediate formaldehyde cyanohydrin (glycolonitrile), which is highly water soluble. The isolation of cyanohydrin involves a tedious and lengthy continuous extraction process (counter current extraction with polar solvent such as ether). Further, cyanohydrin has a limited stability and often gets decomposed violently upon attempted distillation. Furthermore, the reaction requires care given the risk of formation of dimeric side-products.

Thus there is a need for a process for the synthesis of cyanoalkylpropane derivatives which avoids isolation of glycolonitrile.

OBJECTS OF THE INVENTION

It is an object of the invention to provide a process for the preparation of cyanoalkylpropane derivatives.

It is another object of the invention to provide a process for the preparation of cyanoalkylpropane derivatives which employs in-situ generated glycolonitrile.

It is still another object of the present invention to provide a process for the preparation of cyanoalkylpropane derivatives which avoids isolation of glycolonitrile.

It is yet another object of the present invention to provide an energy saving and eco friendly process which avoids addition of excess raw material such as ethyl cyanoacetate.

It is a further object of the present invention to provide a process for the preparation of cyanoalkylpropane derivatives which is simple, safe, convenient, easy to operate on commercial scale and cost-effective.

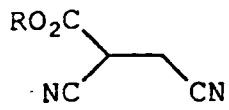
It is still further object of the present invention to provide a process which involves use/addition of raw material in optimum molar quantities.

It is another object of the present invention to provide a process which involves quantification of glycolonitrile formation by GC analysis at crude stage.

It is another object of the present invention to provide a process for the preparation of cyanoalkylpropane derivatives which provides highly pure product with high yield.

SUMMARY OF THE INVENTION

In accordance with the present invention there is provided a process for preparing a compound of formula [I] and salt thereof:



[I]

Wherein R represent a straight or branched chain alkyl having C_1-C_{18} carbon atoms;

said process comprising the following steps:

a. reacting an alkali metal cyanide and paraformaldehyde in the presence of a solvent to obtain a slurry containing glycolonitrile followed by neutralization of the slurry using dry HCl gas;

b. mixing the neutralized slurry containing glycolonitrile with an alkali ethoxide and cyanoacetate of formula [II]:

$ROOC\text{-}CH_2CN$

[II]

Wherein R represents straight or branched chain alkyl having C_1-C_{18} carbon atoms;

to obtain an alkali salt of compound of formula [I];

c. neutralizing the alkali salt of compound of formula [I] by using dry HCl gas followed by removal of sodium chloride by filtration to obtain a clear filtrate; and

d. concentrating the filtrate at a temperature of about 55°C to about 60°C to remove alcohol followed by distillation under reduced pressure to obtain a compound of formula [I].

Typically, the alkali metal cyanide is sodium cyanide.

Typically, the solvent is at least one selected from the group consisting of polar protic solvents and polar aprotic solvents.

Typically, the polar protic solvent is a C_1-C_4 alcohol.

Preferably, the polar protic solvent is anhydrous ethanol.

Typically, the polar aprotic solvent is at least one selected from the group consisting of dimethyl sulfoxide, N-methylpyrrolidone, dimethylacetamide and dimethylformamide.

Typically, the molar ratio of cyanide and paraformaldehyde is 1:1.01.

Typically, the alkali ethoxide is sodium ethoxide.

Typically, the cyanoacetate is alkyl cyanoacetate.

Typically, the cyanoacetate is ethyl cyanoacetate.

Typically, the process is carried out at a temperature in the range of about -10 to about 10°C.

Preferably the process is carried out at a temperature in the range of about 0 to 10°C.

In accordance with one aspect of the present invention the compound of formula [I] is 2,3 dicyano ethyl propionate.

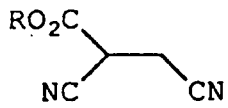
DETAILED DESCRIPATION OF THE INVENTION

Glycolonitrile, also called as hydroxyacetonitrile or formaldehyde cyanohydrin (CAS#107-16-4), is an organic compound with the formula $HOCH_2CN$. It is the simplest cyanohydrin derived from formaldehyde. It is used in the synthesis of cyanoalkylpropane derivatives.

The methods for the synthesis of cyanoalkylpropane derivatives as disclosed in the prior art suffer significant drawback in that it is first necessary to extract or isolate the intermediate formaldehyde cyanohydrin (glycolonitrile), which is highly water soluble. The isolation of cyanohydrin involves a tedious and lengthy continuous extraction process (counter current extraction with polar solvent such as ether). Further, cyanohydrin has limited stability and often gets decomposed violently upon attempted distillation. Furthermore, the reaction requires care given the risk of formation of dimeric side-products.

In accordance with the present invention there is provided a process for the synthesis of cyanoalkylpropane derivatives which employs in-situ generated glycolonitrile instead of employing distilled glycolonitrile which is obtained by tedious and lengthy continuous extraction process.

In accordance with the present invention there is provided a process for preparing a compound of formula [I] and salt thereof:



[I]

Wherein R represent a straight or branched chain alkyl having C_1-C_{18} carbon atoms.

The process comprising the following steps:

First step involves reacting an alkali metal cyanide and paraformaldehyde in the presence of a solvent to obtain a slurry containing glycolonitrile. This slurry is then neutralized using dry HCl gas.

In accordance with the present invention the alkali metal cyanide employed in above step is sodium cyanide.

In accordance with the present invention the solvent used in the reaction is at least one selected from the group consisting of polar protic solvents and polar aprotic solvents.

In accordance with one of the embodiments of the present invention the solvent used in the reaction is polar protic solvent which include C_1-C_4 alcohol.

In accordance with the preferred embodiment of the present invention the polar protic solvent employed is anhydrous ethanol.

In accordance with another embodiment of the present invention the solvent used in the reaction is polar aprotic solvent which is at least one selected from the group consisting of dimethyl sulfoxide, N-methylpyrrolidone, dimethylacetamide and dimethylformamide.

The second step involves mixing the neutralized slurry containing glycolonitrile with an alkali ethoxide and cyanoacetate of formula [II]:

$$ROOC\text{-}CH_2CN$$

[II]

Wherein R represent a straight or branched chain alkyl having C_1-C_{18} carbon atoms;

to obtain an alkali salt of compound of formula [I].

In accordance with preferred embodiment of the present invention the alkali ethoxide employed in second step is sodium ethoxide.

In accordance with the present invention the cyanoacetate employed in second step is alkyl cyanoacetate.

In accordance with preferred embodiment of the present invention the cyanoacetate employed in second step is ethyl cyanoacetate.

In accordance with another embodiment of the present invention the molar ratio of cyanide and paraformaldehyde is 1:1.01.

In accordance with the present invention the process is carried out at a temperature in the range of about -10 to 10°C.

In accordance with preferred embodiment of the present invention the process is carried out at a temperature in the range of about 0 to 10°C.

The obtained alkali salt of compound of formula [I] is then neutralized by using dry HCl gas followed by removal of sodium chloride by filtration to obtain a clear filtrate.

The filtrate is further concentrated at a temperature of about 55°C to about 60°C to remove alcohol followed by distillation under reduced pressure at high temperature to obtain a compound of formula [I].

In accordance with preferred embodiment of the present invention the compound of formula [I] is 2,3 dicyano ethyl propionate.

The invention will now be described with respect to the following examples which do not limit the invention in any way and only exemplify the invention.

Examples

Example 1

Sodium cyanide (98 g) was added to 500 cc of anhydrous ethanol to obtain a mixture which was then cooled to 0 to 10 °C. To this cooled mixture, 61.2 g of paraformaldehyde was added slowly for a period about 1 hour while maintaining the reaction temperature. The obtained mixture was stirred for 2 hours to obtain a slurry. Dry HCl gas was then passed to acidify the slurry. After equilibration a slurry containing glycolonitrile was filtered to remove NaCl.

The above slurry containing glycolonitrile was further mixed with 196 g of ethyl cyanoacetate at -5 to 0 °C. To this, 116 g of sodium ethoxide in 310 g ethanol was added slowly at 0 to 10°C for a period of about 4 hours. After equilibrating at 0 to 10°C for 1 hour, the temperature was raised to 30°C for a period of about 2 hours to obtain an organic mixture containing sodium salt of 2,3-dicyano ethylpropionate which was then acidified by passing dry HCl gas.

The obtained organic mixture was filtered to remove NaCl. The clear filtrate and wash was then concentrated under reduced pressure to remove ethanol at 55 to 60°C. The residual mass was dissolved in dichloromethane and the organic layer was washed with cold water and dried over magnesium sulphate. On distillation under reduced pressure, 2,3-dicyano ethylpropionate was obtained. Yield: 67 %.

Example 2

Sodium cyanide (98 g) was added to 500 cc of anhydrous ethanol to obtain a mixture which was then cooled to 5 to 10°C. To this cooled mixture, 60.6 g paraformaldehyde was added slowly at 5 to 10 °C over a period of about 1 hour. The reaction mixture was maintained at this temperature for further 3 hours. The reaction mixture was then acidified by passing dry HCl gas. After equilibration, the pH was shifted to 3 by adding NaOEt to obtain a glycolonitrile slurry was filtered to separate sodium chloride. The obtained cake was washed with ethanol. The filtrate and wash containing glycolonitrile was used for next step.

The solution containing glycolonitrile was then charged in the reactor and cooled to 0 to 10 °C. To this, slurry of sodium salt of ethyl cyanoaceate (prepared by adding 198 g of ethyl cyanoacetate to 1.70 moles of NaOEt in 310 g ethanol at 30 to 40 °C) was added over 3 hours. After equilibration, dry HCl was bubbled, reaction mass was filtered and concentrated. On distillation under reduced pressure 2,3-dicyaco ethyl propionate (174 g) was obtained. Yield: 65 %.

Example 3: Glycolonitrile preparation and distillation:

Sodium cyanide (99 g) was added to 500 ml of anhydrous ethanol in a mechanically agitated reactor at 30 °C and cooled the content to 5 to10°C. To this mixture, 62.3 g of paraformaldehyde was added uniformly over 1 hour and the resultant mixture was stirred at 5 to 10 °C for 3 hours. After 3 hours, 80 g of dry HCl gas was added at 5 to 10°C to acidify the mixture. The mixture was equilibrated at the same temperature for further 1

hour. The obtained slurry was filtered at the same temperature and the cake was washed with 75 ml of ethanol. Ethanol was vacuum distilled from the filtrate and wash at 50 to 55°C. Then glycolonitrile was vacuum distilled at 68 to 70°C vapor temperature to collect 109.8 g distillate with 94.3 % purity. Yield is 90.8 %.

Example 4: Synthesis of 2,3-dicyano ethyl propionate with distilled Glycolonitrile

In another reactor, 38.6 g of sodium was dissolved in 500 ml of ethanol. The obtained sodium ethoxide solution was added to 201 g of ethyl cyanoacetate over 0.5 hour to get a slurry of sodium salt of ethyl cyanoacetate. The above slurry was added to 107 g of distilled glycolonitrile (94.3 %) in 330 ml ethanol at 5-10 °C over 3 hours. The addition of slurry of sodium salt of ethyl cyanoacetate to glycolonitrile results in clear solution with the liberation of heat. The solution was stirred at 5 to 10 °C for additional 1 hour and then raised the liquid temperature to 30°C and equilibrated for 4 hours.

The mixture was then cooled to 5 to 10 °C and acidified.

The slurry was further equilibrated for 1 hour. The mixture was filtered at 10 °C and washed the cake with ethanol. Then ethanol was distilled from the filtrate and wash under reduced pressure at 50 to 55 °C. The crude 2,3-dicyano-ethyl propionate was dissolved in dichloromethane and the solution was washed with cold water followed by 10 % soda ash solution. The organic layer containing 2,3-dicyano ethyl propionate was further dried

over $MgSO_4$ and concentrated to recover dichloromethane. The oily layer was distilled under reduced pressure over a column at 125-128 °C (1-2 mm). Yield : 79.6 %.

Example 5: Reaction of Glycolonitrile solution in ethanol with sodium salt of ethyl cyanoacetate.

Sodium cyanide (74.2 g) was added to 400 ml of anhydrous ethanol in a mechanically agitated reactor at 30 °C and the content was then cooled to 5-10 °C. To this mixture, 46.9 g of paraformaldehyde was added uniformly over 1 hour and the resultant mixture was stirred at 5-10 °C for 3 hours. After 3 hours, dry HCl was passed slowly to shift the pH of the slurry to strongly acidic at 5-10 °C over 3 – 4 hours. The slurry was filtered and the cake was washed with ethanol. A small aliquot was concentrated under reduced pressure to constant weight and quality established by GC. Remaining organic layer is taken for next step.

In another reactor, 29.5 g of sodium was dissolved in 450 ml of ethanol. The obtained sodium ethoxide solution was added to 154 g of ethyl cyanoacetate to get a slurry of sodium salt of ethyl cyanoacetate. The slurry of sodium salt of ethyl cyanoacetate was added to the glycolonitrile solution in ethanol as obtained above over a period of 4 hours at 5 to 10 °C. The resultant clear solution was further equilibrated at the same temperature for further 2 hours. Then the temperature was gradually increased to 30 °C and the mixture was further stirred for 4 hours.

The mixture was then cooled to 5 to 10°C and acidified. The resultant slurry was equilibrated for 1 hour. The mixture was filtered at 10 °C and the cake was washed with ethanol. Ethanol was distilled under reduced pressure from the filtrate and wash at 50 to 55°C. The crude 2,3-dicyano ethyl propionate was dissolved by adding dichloromethane and the solution was washed with water followed by 10 % soda ash solution. The organic layer containing 2,3-dicyano ethyl propionate was dried over $MgSO_4$ and concentrated to recover dichloromethane. The oily layer was distilled under reduced pressure over a column at 125 to 128 °C (1-2 mm). Yield: 75.2 %.

Technical advance:

- The process disclosed in the present invention employs in-situ generated glycolonitrile for the preparation of 2,3-dicyaco ethyl propionate.
- Quantification of glycolonitrile which is formed during the reaction is done at crude stage by using GC analysis.
- The process disclosed in the present invention is energy saving and eco friendly which avoids addition of excess raw material such as ethyl cyanoacetate i.e. process disclosed in the present invention involves use/addition of raw material in optimum molar quantities depending on the quantification of glycolonitrile in the reaction.

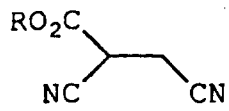
- Further, the process disclosed in the present invention avoids employing distilled glycolonitrile which is obtained by tedious and lengthy continuous extraction process. The isolation of glycolonitrile suffers with practical difficulties such as extraction of glycolonitrile from aqueous stream involves counter current

extraction with polar solvents like ether over a long period. Secondly, isolation of glycolonitrile by vacuum distillation has potential hazards of explosion.

While considerable emphasis has been placed herein on the specific steps of the preferred process, it will be appreciated that many steps can be made and that many changes can be made in the preferred steps without departing from the principles of the invention. These and other changes in the preferred steps of the invention will be apparent to those skilled in the art from the disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to be interpreted merely as illustrative of the invention and not as a limitation.

Claims:

1. A process for preparing a compound of formula [I] and salts thereof:



[I]

Wherein R represent a straight or branched chain alkyl having C_1-C_{18} carbon atoms;

said process comprising the following steps:

a. reacting an alkali cyanide and paraformaldehyde in the presence of a solvent to obtain a slurry containing glycolonitrile followed by neutralization of the slurry using dry HCl gas;

b. mixing the neutralized slurry containing glycolonitrile with an alkali ethoxide and cyanoacetate of formula [II]:

ROOC-CH_2CN

[II]

Wherein R represents straight or branched chain alkyl having C_1-C_{18} carbon atoms;

to obtain an alkali salt of compound of formula [I];

c. neutralizing the alkali salt of compound of formula [I] by using dry HCl gas followed by removal of sodium chloride by filtration to obtain a clear filtrate; and

d. concentrating the filtrate at a temperature of about 55°C to about 60°C to remove alcohol followed by distillation under reduced pressure to obtain a compound of formula [I].

2. The process as claimed in claim 1, wherein the alkali cyanide is sodium cyanide.

3. The process as claimed in claim 1, wherein the solvent is at least one selected from the group consisting of polar protic solvents and polar aprotic solvents.

4. The process as claimed in claim 3, wherein the polar protic solvent is a C_1-C_4 alcohol.

5. The process as claimed in claim 3, wherein the polar protic solvent is anhydrous ethanol.

6. The process as claimed in claim 3, wherein the polar aprotic solvent is at least one selected from the group consisting of dimethyl sulfoxide, N-methylpyrrolidone, dimethylacetamide and dimethylformamide.

7. The process as claimed in claim 1, wherein the molar ratio of cyanide and paraformaldehyde is 1:1.01.

8. The process as claimed in claim 1, wherein the alkali ethoxide is sodium ethoxide.

9. The process as claimed in claim 1, wherein the cyanoacetate is alkyl cyanoacetate.

10. The process as claimed in claim 1, wherein the cyanoacetate is ethyl cyanoacetate.

11. The process as claimed in claim 1 is carried out at a temperature in the range of about -10 to about 10°C.

12. The process as claimed in claim 1 is carried out at a temperature in the range of about 0 to about 10°C.

13. The process as claimed in claim 1, wherein the compound of formula [I] is 2,3 dicyano-ethyl propionate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2010/000382

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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)

IPC: C07C253/-; C07C255/-

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)

WPI; EPODOC; CNPAT; CNKI; STN: alkali cyanide, paraformaldehyde, formaldehyde, glycolonitrile, cyanohydrin, alkali ethoxide, cyanoacetate, 105-56-5, 50-00-0, 8005-38-7, 8006-07-3, 8013-13-6, 30525-89-4, 40497-11-8

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO97/32843A1(RHONEPOULENC AGROCHIMIE), 12 Sep. 1997(12.09.1997), pages 1-6 and example 1 in description	1-13
A	WO2006/003501A1(PFIZER LIMITED), 12 Jan. 2006(12.01.2006), pages 4-5 in description	1-13
A	CN1785966A(LUAN, Zhongyue), 14 Jun. 2006(14.06.2006), pages 1-8 in description	1-13
A	WANG, Yaoliang Synthesis of ethyl dicyanopropionate. MODERN AGROCHEMICALS, 2004, Vol. 3, No. 6, pages 12-13	1-13

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"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

"T" 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

"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

"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

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 Oct. 2010(12.10.2010)	**02 Dec. 2010 (02.12.2010)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer DAI, Nianzhen Telephone No. (86-10)82245732

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2010/000382

Continuation of:

A. CLASSIFICATION OF SUBJECT MATTER:

C07C253/16(2006.01)i

C07C253/00(2006.01)i

C07C255/19(2006.01)i

C07C255/04(2006.01)i

C07C255/00(2006.01)i

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2010/000382

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO9732843A1	12.09.1997	WO9732843A1	12.09.1997
		AU1924897A	22.09.1997
		ZA9701855A	26.08.1998
		CZ9802809A3	16.12.1998
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		EP0888291B1	23.01.2002
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