

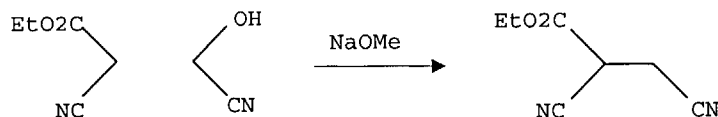
Process For Preparing Synthetic Intermediates Useful In Preparing Pyrazole Compounds

This invention relates to a process for preparing certain cyanomethylpropane derivatives (such as 2,3-dicyanopropionates) and the use of these compounds in the synthesis of pesticides and pesticide intermediates. In particular, the present invention relates to the formation of ethyl-2,3-dicyanopropionate.

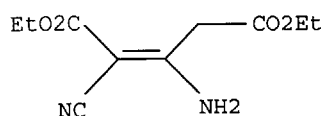
Ethyl-2,3-dicyanopropionate is an intermediate used in the formation of aryl pyrazole rings, many of which are lethal to a wide spectrum of ectoparasites. In particular, 2,3-dicyanopropionate derivatives are particularly useful in the preparation of 1-phenyl pyrazoles and 1-pyridyl pyrazole compounds.

Initially alkylation of ethylcyanoacetate was attempted with chloroacetonitrile using DMF/K₂CO₃ (D.A.White, Synth. Commun., 7(8), 559, 1977) and DBU/Toluene (N.Cho et al, Bull. Chem. Soc. Jpn., 156, 1716-19, 1979). Both methods are said to give exclusively monoalkylation, however in practice only dialkylation is observed in both cases.

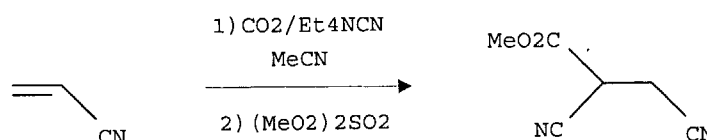
The method of Thorpe and Higson (J.F.Thorpe, A. Higson, JCS, 89, 1455, 1906) involves alkylating ethylcyanoacetate using NaOMe and an ethanolic solution of formaldehyde cyanohydrin (also known as glycolonitrile) at or above room temperature as follows:



Unfortunately glycolonitrile is only available as an aqueous solution which has to be soxhlet extracted with ether before solvent replacement with ethanol. This method has the disadvantage of giving low and gave variable yields, typically between 20-50% and mostly in the lower end of the range. One problem with this particular reaction is that most of the ethylcyanoacetate self-condenses as identified by H.Junek, W.Wilfinger, Monatsch. Chem., 1970(101), 1208, giving the unsaturated product:



Another literature method (D.A.White, JCS Perkin I 1926, 1976) illustrated below using acrylonitrile with CO₂ and tetraethyl ammonium cyanide gave some of the desired 2,3-dicyanopropionate product. However this process also had the disadvantage of producing in addition a number of by-products.



The preparation of ethyl 2,3-dicyanopropionate by reaction of formaldehyde cyanohydrin with the sodium salt of ethyl cyanoacetate as reported by Thorpe and Higson suffers from a significant drawback in that it is first necessary to isolate the intermediate formaldehyde cyanohydrin as discussed above. EP 888291 attempts to overcome the disadvantages associated with using formaldehyde cyanohydrin by providing a process for preparing cyanomethyl propane derivatives which avoids completely the use of formaldehyde cyanohydrin and consequently which avoids the dimerisation side reaction associated with formaldehyde cyanohydrin. Unfortunately, this process has the problem that a cyanide salt must be used and thus careful handling is needed at all times and the reaction conditions must always be kept at a basic pH to ensure hydrogen cyanide is not liberated. The reaction also requires a supply of formaldehyde or paraformaldehyde which presents further handling difficulties.

It is an aim of the present invention to provide a process for preparing 2,3-dicyanopropionate derivatives which overcomes the problems occurring in the prior art methods. It is also an aim to provide a process which satisfies one or more of the following objects: avoiding the use of formaldehyde and a cyanide salt, avoiding the

dimerisation side reaction reported in the literature, and providing the desired product directly in high yield and with high purity.

It is also an aim to provide a route to 2,3-dicyanopropionate derivatives which offers an improved yield relative to the existing routes. It is a further aim of the process of the present invention to avoid the use of unnecessary synthetic steps or reagents and /or purification steps. An important aim therefore is to provide a process which minimizes the number of synthetic steps required and which avoids the problem of competing reactions and/or the disposal of hazardous materials. It is also an aim to provide a quick and thus economical route to 2,3-dicyanopropionate derivatives.

It is an also aim of the present invention to provide a convenient route to aryl pyrazole derivatives, preferably in a reaction which can be completed in a relatively short time. It is thus an aim of the present invention to provide a synthetically efficient process for the production of aryl pyrazole derivatives which allows access to novel compounds.

Despite all the literature reports and the problems observed in EP 888291, we have found a novel process in which an 2,3-dicyanopropionate derivative can be prepared in excellent yield using formaldehyde cyanohydrin.

We have found that careful control of the temperature in the reaction between a cyanoacetate and formaldehyde cyanohydrin gave a very clean complete reaction. Furthermore, we have found that it is possible to conduct the reaction using glycolonitrile without the need for purification of the glycolonitrile before use.

In particular, we have found that the reaction between ethylcyanoacetate and aqueous glycolonitrile can be performed in a polar solvent, such as DMF, and in the presence of an inorganic base, such as K_2CO_3 , provided that there is careful control of the temperature. In practice this means ensuring the temperature does not rise above 20°C. The reaction of the present invention works well and produces the desired product in very good yields, with yields of up to 95% being obtained.

There is the further advantage that the process of the present invention uses aqueous glycolonitrile and yet avoids the need for the soxhlet extraction of aqueous glycolonitrile. This fact allows a major saving in time and expense since to date it

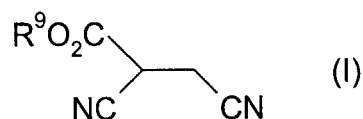
has always been necessary to purify the glycolonitrile before use. This is normally achieved by extracting aqueous glycolonitrile continuously with diethyl ether in a Soxhlet extractor. However, there is the problem that glycolonitrile is heated in this process and consequently it may disproportionate to hydrogen cyanide and formaldehyde. This is a significant problem. In addition, aqueous glycolonitrile normally also contains stabilising agents which are lost when the material is refluxed in a Soxhlet extractor. This too leads to decomposition of the glycolonitrile.

A further disadvantage of the prior art processes is that the process of purification is also time consuming. Thus this adds complexity to the process making the process less economical to run. The process of the present invention surprisingly can be effected without the need for this purification step provided that the conditions are carefully controlled. This represents a significant time and cost saving.

The process of the present invention also has the advantage over the prior art processes that the reagents are in liquid form whereas in the prior art processes solid reagents are required. The handling of solid or gaseous reagents is far more problematical than handling liquids, particularly when the materials involved are toxic or hazardous. There is also the advantage that additions of liquid reagents are much more controllable than is the case for solid or gaseous additions.

Allowing the temperature to rise above 20°C results in significantly reduced yield and gives rise to a major impurity; it is speculated that this impurity may be the one reported by Thorpe and Higson.

According to one aspect of the present invention, there is provided a process for preparing a compound of formula (I):

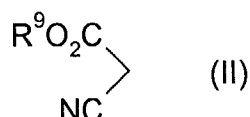


wherein

R⁹ is selected from: C₁₋₈ alkyl, C₃₋₈ cycloalkyl, (CH₂)_nPh and (CH₂)_n heteroaryl wherein n = 0, 1 or 2, each of which groups may be optionally substituted on any carbon atom

by one or more groups selected independently from: halogen, hydroxy, cyano, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkanoyl, C₁₋₄ haloalkanoyl, C₁₋₄ alkylsulphinyl, C₁₋₄ haloalkylsulphinyl, C₁₋₄ alkylsulphonyl, C₁₋₄ haloalkylsulphonyl, C₃₋₈ cycloalkyl and C₃₋₈ halocycloalkyl; and R⁹ can be hydrogen;

which process comprises the reaction of a cyanoacetate of formula (II):



wherein R⁹ is as defined above, with formaldehyde cyanohydrin and an inorganic base in a polar solvent at a temperature not exceeding 20°C.

Preferably, R⁹ is H; C₁₋₈ alkyl, CH₂Ph or Ph, each being optionally substituted by one or more groups independently selected from: halogen, hydroxy, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy halogen atoms which may be the same or different.

Most preferably R⁹ is methyl or ethyl.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Alkyl and alkoxy groups containing the requisite number of carbon atoms, except where indicated, can be unbranched-or branched-chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable inorganic bases include alkali metal carbonates and hydroxides.

The product may conveniently be isolated once the reaction mixture is acidified, for example with a mineral acid such as sulphuric acid or hydrochloric acid, to give the compound of formula (I) in high yield. In one embodiment, high yields can be obtained when the reaction mixture is acidified without the addition of water.

The reaction is generally performed using about 1 molar equivalent of a compound of formula (II); about 0.95 to 1.0 molar equivalents of the inorganic base, and about 1

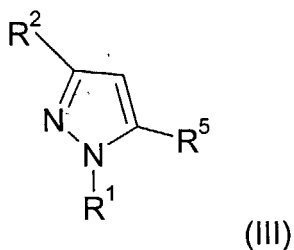
molar equivalent of formaldehyde cyanohydrin.

The reaction may be carried out in the presence of a solvent. Preferably, the reaction is performed in a polar solvent. The solvent should, in a preferred embodiment, be water miscible. The solvent is usually an alcohol such as methanol, ethanol, or propanol; or may be selected from dimethyl formamide (DMF); DMSO (dimethyl sulphoxide); DMAC (dimethyl acetamide); MeCN; N-methyl pyrrolidone (NMP); dioxan; tetrahydrofuran (THF); or dimethoxyethane. Especially preferred solvents are C₁–C₈ alcohols such as methanol or ethanol.

The temperature of the reaction is critical and the reaction must be performed at a temperature not exceeding 20°C. Generally best results are obtained by introducing the inorganic base after the other reactants have been combined.

The compound of formula (I) is useful in the preparation of pesticidally active compounds, for example as described in European Patent Publication Nos. 0295117 and 0234119, and W093/06089.

In particular, the process of the invention may form part of an in situ preparation of another pesticidal intermediate. Thus, in a further aspect the present invention provides a process for the preparation of a compound of formula (III):



wherein

R¹ is aryl or heteroaryl optionally substituted by one or more groups independently selected from: hydrogen; halo; C₁₋₆ alkyl and C₁₋₆ alkoxy each of which may be optionally substituted with one or more independently selected halo atoms; -S(O)_nC₁₋₆ alkyl; and pentafluorothio; cyano; C₁₋₆ alkanoyl which may be optionally substituted with one or more independently selected halo atoms;

R^2 is selected from: hydrogen; halo; C_{1-6} alkyl; $-S(O)_n C_{1-6}$ alkyl; $-(CH_2)_m C_{3-8}$ cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; cyano; nitro; $-(CH_2)_m NR^a R^b$; C_{1-6} alkanoyl which may be optionally substituted by one or more groups independently selected from halo and C_{1-4} alkoxy; phenyl; oxadiazole; $-C(O)NR^a R^b$; $-NR^a C(O)R^b$; C_{2-6} alkenyl; and C_{2-6} alkynyl;

R^5 is selected from: hydrogen; hydroxy; C_{1-6} alkyl; $NR^a R^b$; halo and C_{1-6} alkoxy;

each n is independently 0, 1 or 2;

each m is independently 0, 1, 2 or 3;

and wherein

het represents a four- to seven-membered heterocyclic group, which is aromatic or non-aromatic and which contains one or more heteroatoms selected from nitrogen, oxygen, sulfur and mixtures thereof, and wherein said heterocyclic ring is optionally substituted and/or terminated where the valence allows with one or more substituents selected from: halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $OC(O)C_{1-6}$ alkyl, $C(O)C_{1-6}$ alkyl, $C(O)OC_{1-6}$ alkyl, and $NR^a R^b$;

each C_{1-6} alkyl group can independently be branched or unbranched and optionally substituted by one or more groups selected independently from: cyano; halo; hydroxy; nitro; C_{1-6} alkoxy; $NR^a R^b$; $S(O)_n C_{1-6}$ alkyl; $S(O)_n C_{3-8}$ cycloalkyl; $S(O)_n C_{1-6}$ alkylhet; C_{3-8} cycloalkyl; and phenyl;

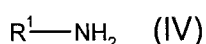
each phenyl may be optionally substituted by one or more substituents independently selected from: cyano; halo; hydroxy; nitro; C_{1-6} alkyl; C_{1-6} haloalkyl; and C_{1-6} alkoxy; and

each R^a and R^b are independently selected from hydrogen; C_{1-6} alkyl; and C_{3-8} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; or R^a and R^b may be taken together with the nitrogen atom to which they are attached to form a 4 to 7-membered ring;

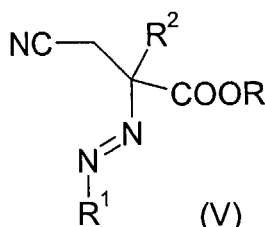
which process comprises:

(a) reacting a cyanoacetate of formula (II) as defined above, with a cyanide salt and formaldehyde or a source thereof, to give a compound of formula (I) as defined above; and

(b) reacting the compound of formula (I) thus obtained with the diazonium salt of a compound of formula (IV):



wherein R¹ is as defined above, to give a compound of formula (V):



wherein R, R¹, and R² are as defined above, followed by the cyclisation of said compound of formula (V).

In an embodiment, it is preferred that R¹ is phenyl or pyridyl, and it is more preferred that R¹ is phenyl.

Preferably, the R¹ group when it is phenyl is tri-substituted, and more preferably it is substituted at the 2-, 4-, and 6- positions with an optional substituent selected from the group comprising: halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, SF₅ and -COOC₁₋₈ alkyl, wherein each of these optional substituent groups may itself be substituted where chemically possible by one or more halogen atoms selected independently.

More preferably, R¹ is 2,4,6-trisubstituted phenyl wherein the 2- and 6-substituents are each independently selected from: hydrogen and halo; and the 4-substituent is selected from: C₁₋₄ alkyl which may be optionally substituted with one or more independently selected halo atoms, C₁₋₄ alkoxy which may be optionally substituted

with one or more independently selected halo atoms; $S(O)_n C_{1-4}$ alkyl which may be optionally substituted with one or more independently selected halo atoms; halo and pentafluorothio;

More preferably, R^1 is a phenyl group which bears substituents at the 2-, 4-, and 6-positions, the substituents at those positions being independently selected from chloro, trifluoromethyl, trifluoromethoxy, and pentafluorothio.

Still more preferably, R^1 is a phenyl group in which the 2- and 6- substituents are chloro and the 4- substituent is selected from: trifluoromethyl, trifluoromethoxy, and pentafluorothio.

It is also preferred that R^1 is 3,5-disubstituted pyridin-2-yl wherein the 3-substituent is selected from: hydrogen and halo; and the 5-substituent is selected from: C_{1-6} alkyl optionally substituted as defined above; C_{1-6} alkoxy which may be optionally substituted with one or more independently selected halo atoms; $S(O)_n C_{1-6}$ alkyl; halo and pentafluorothio.

Preferably het represents a 5- or 6-membered heterocyclic group containing 1, 2 or 3 heteroatoms, which are independently selected from 1 N atom, 1 or 2 O atoms and 1 or 2 S atoms.

More preferably, het is preferably selected from pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, pyrrolyl, and pyridyl wherein the aforementioned groups may be optionally substituted by one or more groups independently selected from C_{1-6} alkyl and halogen.

More preferably, het is selected from: pyridyl, pyrazolyl, oxazolyl and isoxazolyl.

Most preferably, het is selected from: pyridyl and oxazolyl.

Preferably, R^2 is selected from cyano; C_{1-6} alkyl; and C_{3-8} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; C_{1-6} alkanoyl which may be optionally substituted by one or more groups independently selected from halo and C_{1-4} alkoxy; and halo.

More preferably R^2 is selected from C_{1-6} alkyl; and cyano.

Still more preferably R^2 is selected from trifluoromethyl and cyano.

Most preferably R^2 is cyano.

Preferably, R^5 is $-(CH_2)_m NR^aR^b$ where R^a and R^b are as defined above, more preferably where $m=0$, and most preferably R^5 is amino.

Compounds of formula (V) above possess a chiral centre giving rise to different enantiomers, and also may exist as different geometric isomers or mixtures thereof. All such forms are embraced by the present invention.

In this process, the product of reaction step (a) is generally acidified with an alcoholic solution of a mineral acid, preferably an ethanolic solution of hydrogen chloride. This also ensures that any acid by-product of the reaction step (a) (leading to the corresponding compound of formula (I) in which R is replaced by hydrogen) is re-esterified.

Reaction step (b) is generally performed in the presence of an inert solvent, for example water, acetonitrile, dichloromethane or DMF, or more preferably an alcoholic solvent (e.g. methanol or ethanol) and is optionally buffered (e.g. with sodium acetate).

The diazonium salt of a compound of formula (IV) may be prepared using diazotising agents known in the literature and is conveniently prepared with a molar equivalent of sodium nitrite and a mineral acid (e.g. hydrochloric or sulphuric acid), at a temperature of from about -10°C to about 50°C , more preferably from about 0°C to about 5°C . The diazonium salt of the compound of formula (IV) is generally prepared in situ as solvents such as alcohols tend to reduce diazonium salts quickly. In the present reaction, the reaction of the diazonium salt of the compound of formula (IV) to give a compound of formula (V) above generally occurs faster than the reduction of the diazonium salt.

Subsequent hydrolysis, preferably using mild conditions with a base such as aqueous sodium hydroxide, sodium carbonate or ammonia, may be necessary to

effect the cyclisation of the compound of formula (V) to a compound of formula (III).

The molar ratio of the compounds of formula (II):(IV) is generally from about 1.5:1 to about 1:4, preferably from about 1.3:1 to about 1:1, more preferably about 1.1:1.

The following non-limiting examples illustrate the invention.

Example 1

Process for the preparation of ethyl- $\alpha\beta$ -dicyanopropionate

Ethylcyanoacetate was stirred in 5ml/g of DMF and 1equivalent of the glycolonitrile added dropwise maintaining the temperature below 20°C. This was followed by addition of the K₂CO₃ in portions again controlling the temperature as a slight exotherm is observed on addition of the base. The reaction was left to stir overnight at room temperature. Excess K₂CO₃ was filtered off and the filtrate acidified to pH4 with 4N HCl. Solvents were stripped under medium vacuum and the residue dissolved in CH₂Cl₂, dried with MgSO₄ and stripped to an orange/red oil in a 95% yield. The superiority of the process of the present invention is thus clearly evident relative to the prior art.

Example 2

Ethyl cyanoacetate (511.7g; 4.52mol) was dissolved in DMF (1.81L) and the solution stirred at ambient temperature. The glycolonitrile was then added to the above solution over a 5 minute period maintaining a reaction temperature of not more than 20°C with ice/water cooling. Potassium carbonate (625.3g, 4.52mol) was then added portionwise to the reaction mixture over 30 minutes, maintaining the reaction temperature between 15 and 25°C with ice/water cooling and once addition was complete the reaction was left to stir for 16 hours. The reaction mixture was then filtered to remove the inorganic components and the pH of the reaction mixture was adjusted to pH4 with concentrated HCl. The resulting orange/ yellow slurry was evaporated under reduced pressure at 80°C to remove DMF. Ethyl acetate (4.25ml/g) was added and the reaction mixture stirred for 10 minutes, after which time the reaction mixture was filtered. The cake obtained was washed with ethyl acetate (0.21ml/g) and the filtrate was washed with dilute brine (3.2ml/g) followed by two saturated brine washes (2.1ml/g). The end filtrate was then evaporated under

reduced pressure to obtain 527.7g of the product representing a yield of 77% of a dark brown / black oil. NMR (CDCl₃) data was consistent with the structure.

The methods exemplified above are applicable to the preparation of other $\alpha\beta$ -dicyanopropionate derivatives.

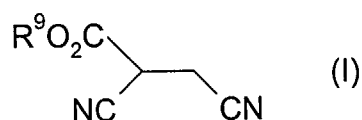
Example 3

Process for the preparation of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethyl-phenyl)pyrazole.

5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethyl-phenyl) pyrazole can be prepared from 2,6-dichloro-4-trifluoromethyl aniline and ethyl-2,3 dicyanopropionate as described in reference example 2 of EP 0295117. This compound is a useful starting material for the synthesis of 4-substituted -1- aryl pyrazoles which can be obtained by conventional synthetic methods from this material as described in, for example, EP 0946515.

Claims

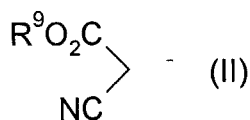
1. A process for preparing a compound of formula (I):



wherein

R^9 is selected from: C_{1-8} alkyl, C_{3-8} cycloalkyl, $(\text{CH}_2)_n\text{Ph}$ and $(\text{CH}_2)_n$ heteroaryl wherein $n = 0, 1$ or 2 , each of which groups may be optionally substituted on any carbon atom by one or more groups selected independently from: halogen, hydroxy, cyano, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkanoyl, C_{1-4} haloalkanoyl, C_{1-4} alkylsulphinyl, C_{1-4} haloalkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} haloalkylsulphonyl, C_{3-8} cycloalkyl and C_{3-8} halocycloalkyl; and R^9 can be hydrogen;

which process comprises the reaction of a cyanoacetate of formula (II):



wherein R^9 is as defined above, with formaldehyde cyanohydrin and an inorganic base in a polar solvent at a temperature not exceeding 20°C .