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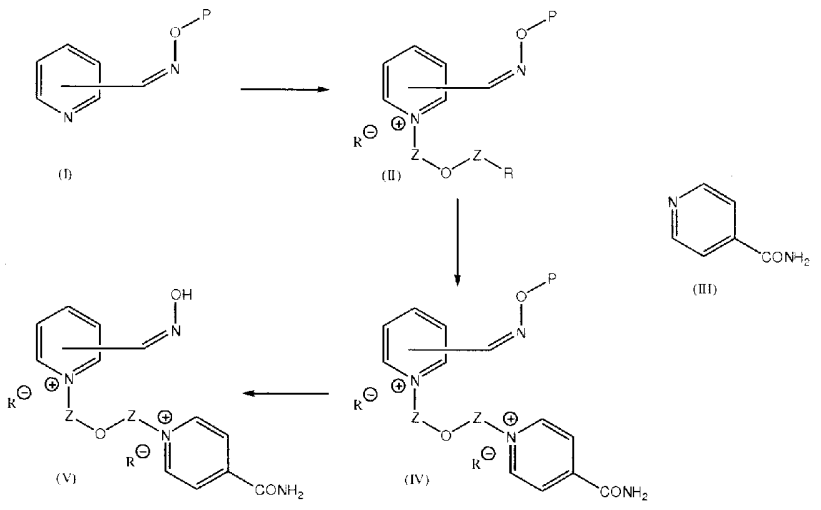
(56) Documents Cited:
US 2924604 A
Chemical Journal of Chinese Universities, 1984, Vol. 5(5), page 683-685.
Arzneimittel Forschung, 1976, Vol. 23, page 1273-1275.
Journal of Labelled Compounds and Radiopharmaceuticals, 1993, Vol. 33(1), pages 19-32.

(58) Field of Search:
Other: **CAS ONLINE**

(54) Abstract Title: **1-([(4-Aminocarbonylpyridinio)methoxy]methyl)-2-(hydroxyiminomethyl)pyridinium salts (HI 6), homologues & regioisomers from O-protected pyridine aldoximes**

(57) A process for the manufacture of HI 6, or a homologue or regioisomer thereof, of formula (V)
wherein: -Z- is an alkylene group, and
R is such that R^- is a suitable counterion,
or both Rs, taken together, correspond to a divalent counter-anion,
comprises contacting an O-protected pyridine aldoxime compound of formula (I), wherein P is a protecting group, with an ether R-Z-O-Z-R in a suitable solvent to form an intermediate compound of formula (II), contacting the latter with isonicotinamide (III) to form an O-protected HI 6 type compound of formula (IV), and de-protecting the latter to form the required product of formula (V).
Preferably, -Z- is $-CH_2-$; -P is -Et, -CO-Me and -SiEt3; and R^- is $Me-SO_3^-$.
O-Protection facilitates the quaternization reaction to give higher yields of the required products than conventional non-protected routes. It also affords new solubility properties to the O-protected quaternized intermediates that allows for convenient removal of impurities and subsequent enhancement of purities, as well as easier processing in scaled up industrial manufacture.



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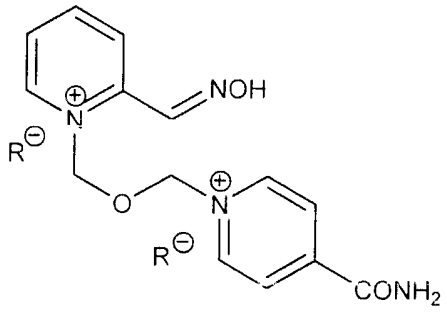
PROCESS

The present invention relates to a process for the manufacture of HI-6, and to certain novel intermediate compounds in the process

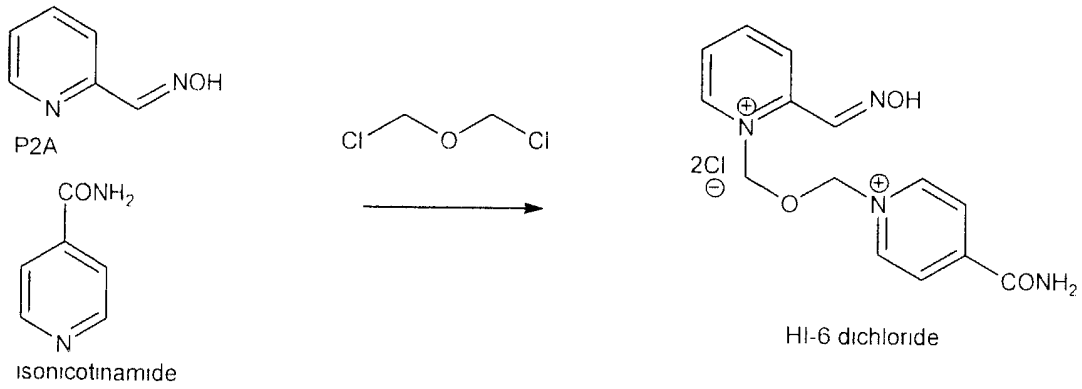
HI-6 is a bis-pyridinium oxime antidote to certain organophosphate nerve agents HI-6 has the chemical formula I



I

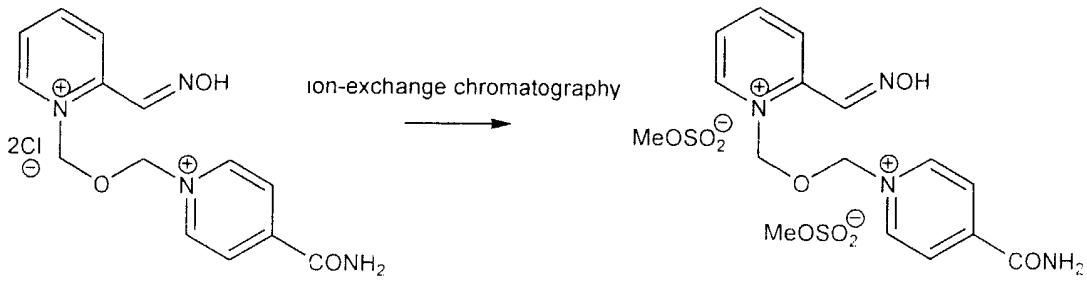
Wherein R is a suitable counterion. Suitable counterions include chloride and methanesulphonate

HI-6 with chloride as the counterion has the chemical name (1-(((4-(aminocarbonyl)pyridinio)methoxy)-methyl)-2-((hydroxyimino)methyl) pyridinium dichloride monohydrate (CAS 34433-31-3), and has been known for many years as a suitable antidote for organophosphate nerve agents Known regimens for producing HI-6 dichloride (2Cl) have involved the use of bis(chloromethyl) ether as a quaternization reagent for the pyridinium moieties pyridine-2-aldoxime (P2A) and isonicotinamide (INA) The reaction scheme proceeds as follows.



This conventional method for manufacturing HI-6 has the disadvantage that the reagent bis(chloromethyl) ether is itself highly toxic A medicament used as antidote against a nerve toxin will preferably be free from highly toxic materials, even incidental amounts thereof left over from a starting reagent Even if the end product can be guaranteed free of the carcinogenic bis(chloromethyl) ether, it is highly undesirable for this compound even to be used in the manufacturing process because of the potential health hazard to personnel involved in its manufacture and use

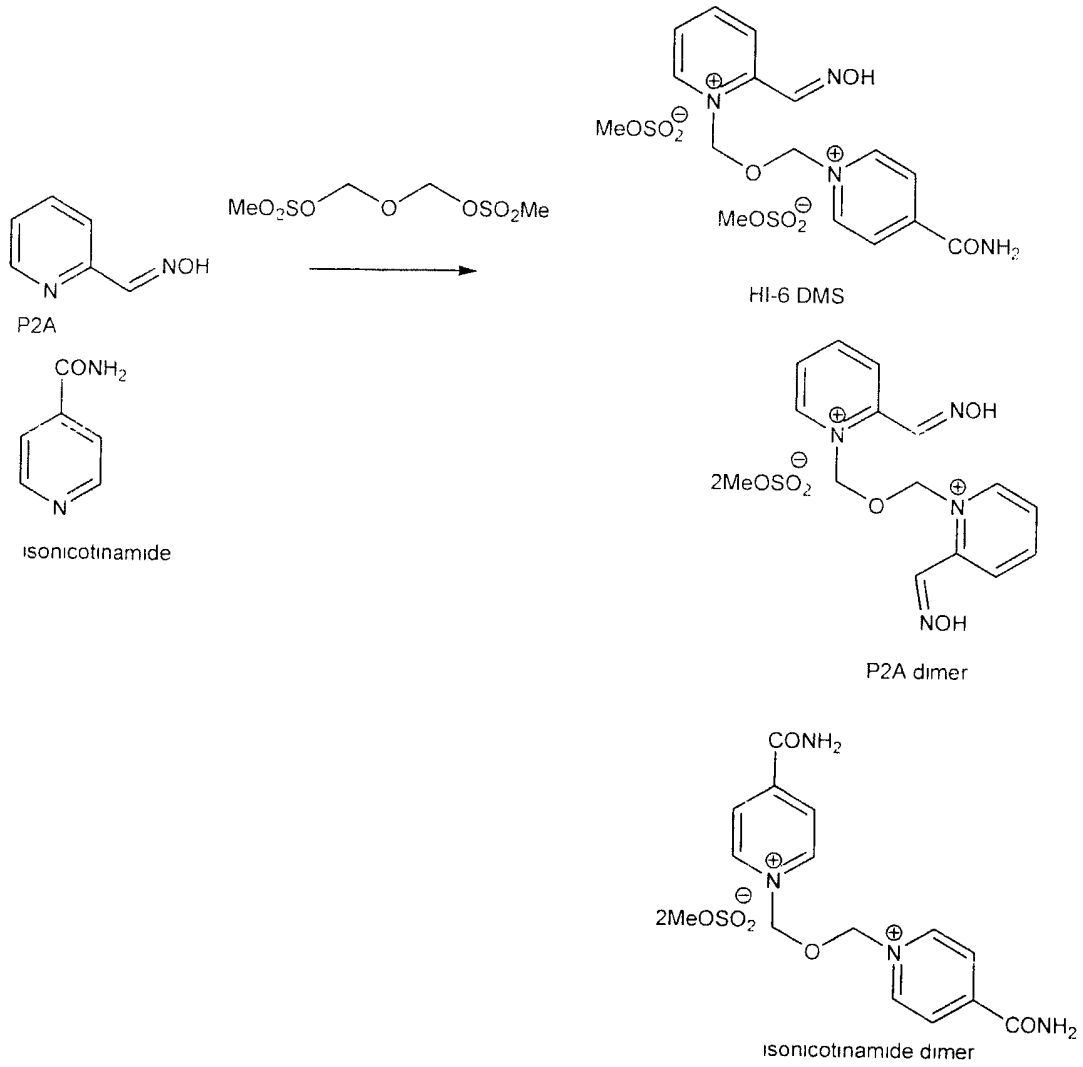
Another recognised HI-6 antidote is HI-6 in which the counterion is methanesulfonate, HI-6 dimethanesulfonate (DMS) Some studies (eg Thiermann et al , International Journal of Pharmaceutics, 137 (1996) 167-176) have reported advantageous properties of HI-6 DMS compared to HI-6 2Cl HI-6 DMS can be obtained from HI-6 2Cl by an ion exchange chromatography process



HI-6 dichloride HI-6 DMS

However, this manufacturing route for HI-6 DMS still has the disadvantage that the highly toxic bis(chloromethyl) ether is used in the synthesis, with the attendant risk that traces of this material may be present as a contaminant in any end product medicament comprising HI-6 DMS, or that the reagent used in the manufacturing process may affect adversely the health of any person involved in its manufacture, storage, transport or use.

There have been proposed alternative routes to HI-6 DMS, directly from the starting oxime, and using bis(methylsulfonoxymethyl) ether (BSME) as an alternative quaternization agent Yang et al. have proposed, in Bull Korean Chem. Soc. 2003 Vol 24, No 9, 1368-1370, such a route but with very poor yields of the product material Similar problems attend the disclosure of US Patent No 5,130.438 of Hsiao et al In both cases HI-6 DMS yields of 11% (with respect to P2A) are quoted after multiple fractional recrystallisations. The scheme for these prior art syntheses may be summarised as:



Wherein the pyridine-2-aldoxime and isonicotinamide dimers are unwanted side products, present in the product mixture in unsatisfactorily high proportions. These unwanted side products have similar solubility properties to HI-6 DMS and are difficult to remove from the product. Thus it is difficult to obtain HI-6 DMS of satisfactory purity using such synthetic routes

It is an object of the present invention to provide a synthetic route to HI-6 which overcomes or ameliorates some of the aforesaid disadvantages of previous routes In particular, it is an object of the invention to provide a

process for HI-6 production which avoids the use of highly toxic and/or carcinogenic reagents It is a further object of the invention to provide a convenient industrial scale process for HI-6 manufacture in which product yields and/or purities are commercially satisfactory, and improved with respect to the prior art

According to the present invention there is provided a process for the manufacture of HI-6 R, wherein R is a suitable counterion or counterion pair, comprising contacting an O-protected pyridine aldoxime compound with an (R'-alkyl) ether, wherein R' corresponds to the counterion or one counterion of the pair, in a suitable solvent to form an intermediate compound, contacting said intermediate compound with isonicotinamide to form an O-protected HI-6 product precursor, and de-protecting the precursor to form HI-6 R.

It will be appreciated that the HI-6 cation is divalent and that R in this case necessarily comprises a divalent anion or two univalent anions Preferably, it will be two univalent anions, each univalent anion corresponding to R' and the (R'-alkyl) ether is in this case being a bis-(R' alkyl) ether In the case of R being a divalent anion, R will correspond with R' in this case

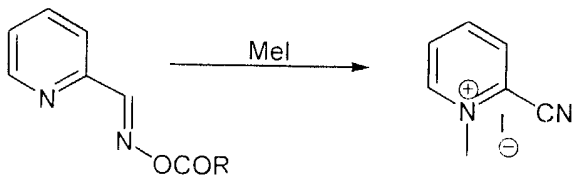
The process proceeds via the quaternization of the pyridine aldoxime. Preferably the pyridine aldoxime is a pyridine-2-aldoxime. Therefore the invention provides a process for the manufacture of HI-6 R, (wherein R is a suitable counterion or counterion pair) comprising the quaternization of an O-protected pyridine-2-aldoxime compound with a bis(R'-alkyl) ether, wherein R'

corresponds to the counterion or one counterion of the pair, in a suitable solvent to form an intermediate compound, contacting said intermediate compound with isonicotinamide to effect quaternization of the isonicotinamide to form an O-protected HI 6 product precursor, separation of said O-protected HI-6 from unwanted impurities and de-protecting the O-protected HI6 to form HI-6 R

Preferably, the counterion is methanesulfonate.

Preferably, the alkyl group is a short chain alkyl (alkylene) group, for example C_{1-4} Preferably it is methyl (methylene).

Hagedorn has previously reported quaternization of O-methyl pyridine-2-aldoxime in Arzneimittel Forschung vol 27. 1976, 1273 However, O-alkyl protecting groups are not readily removed Attempted quaternizations of a number of O-substituted species with more readily removed protecting groups such as O-benzoyl pyridine-2-aldoxime derivatives with methyl iodide has been disclosed previously in the Chemical Journal of Chinese Universities 1984,Vol 5, No 5, pp 683 by Zhou Xirui In this work it was found that O-benzoyl pyridine-2-aldoxime derivatives did not form the normal quaternized products rather β-elimination of the aldoxime functional group occurred to give quaternized 2-cyanopyridine derivatives Thus the desired oxime function was destroyed during the quaternization process



We have prepared a number of O-substituted pyridine-2-aldoximes and we have found that quaternization of these derivatives is possible and that β-elimination does not occur to any significant extent. In fact it has been found that in many instances O-protection greatly facilitates the quaternization reaction to give much higher yields of the desired products than conventional non-protected routes Additionally and of great benefit, O-protection affords new solubility properties to these intermediate O-protected quaternized species that allows for the convenient removal of impurities and the subsequent enhancement in purities and yields

Thus, the present invention provides a process for the manufacture of HI 6 DMS comprising contacting an O-protected pyridine aldoxime compound with bis(methylsulfonoxymethyl) ether (BSME) in a suitable solvent to form an intermediate quaternized compound. contacting said intermediate compound with isonicotinamide in a suitable solvent to allow quaternization of isonicotinamide to form an O-protected HI-6 product precursor, separation of unwanted impurities from the O-protected HI-6 product precursor and de-protecting the precursor to form HI-6 DMS

The protecting group is preferably an ester group, more preferably an acetate group

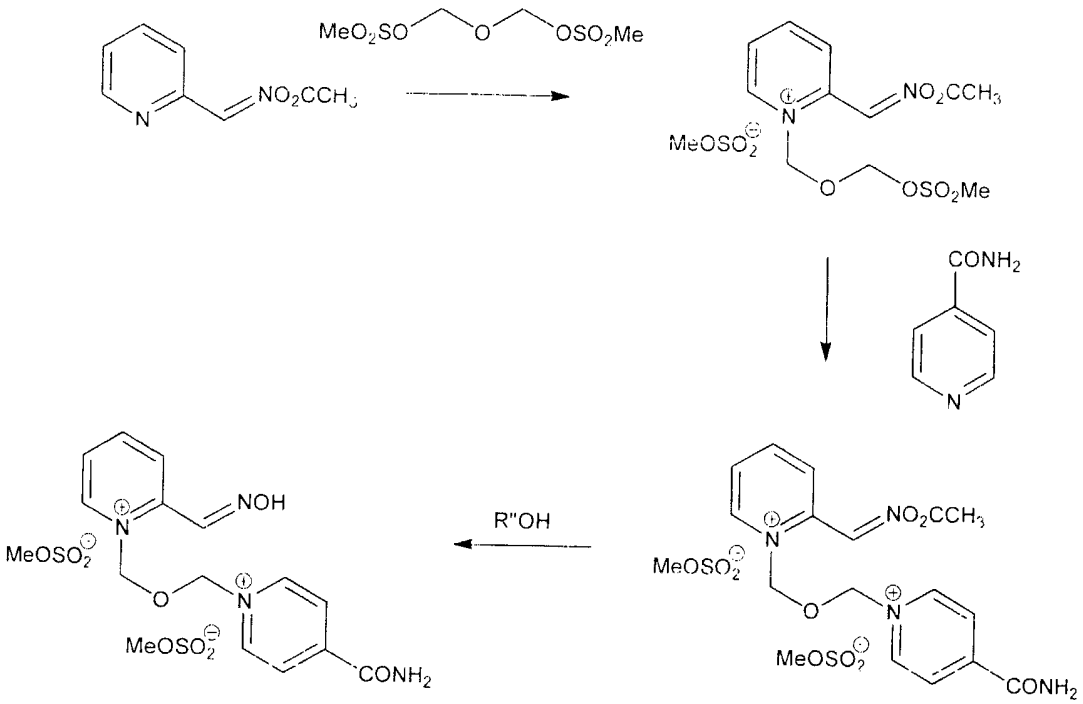
Suitable solvents for the quaternization of O-protected pyridine aldoxime with BSME include· chlorinated hydrocarbons, acetonitrile, ethers such as tetrahydrofuran, dioxane and dimethoxyethane

Suitable solvents for the quaternization of isonicotinamide with the O-protected intermediate include dimethylformamide, dimethylacetamide, dimethylsulfoxide acetonitrile, N-methylpyrrolidinone

The unwanted isonicotinamide containing impurities are separated from the O-protected HI-6 product precursor by trituration of the reaction mixture with a suitable solvent mixture such that precipitation/crystallisation of the unwanted impurities occurs These are then removed by filtration leaving in the filtrate the O-protected HI-6 product precursor. Suitable solvents for such a process include aqueous alcohols (preferably methanol, ethanol), acetone. Other suitable solvents will be apparent to those skilled in the art

The protected product precursor may be de-protected for example by contacting the precursor with a de-protecting agent comprising a solvent and/or reagent suitable for removing the protecting group. Suitable de-protecting agents include protic solvents or solvent mixtures containing labile protons, combinations of solvent mixtures containing labile protons and acylation catalysts such as 4-dimethylaminopyridine Examples of such de-protecting agents are solvents such as ethanol or water or combinations thereof

One preferred process according to the invention proceeds according to the following scheme.



HI-6 DMS

Wherein R"OH is an alcoholic and/or protic solvent or a mixture of two or more therof

Also provided in accordance with the invention is a protected HI-6 product precursor Preferably the precursor is protected by an ester group

This route to HI-6 DMS from BSME using protected P2A species offers a number of advantages over the non-protected P2A chemistry The protected route offers more facile operability for scaled up industrial manufacture. For example in the non-protected chemistry and on lab scale the reaction of P2A with BSME leads to a tar-like paste and a supernatant, this supernatant is

decanted off and the paste taken through the process This decantation step is difficult to achieve on manufacturing scale and such pastes are difficult to stir and mix with further reagents. Advantageously the changed solubility properties imparted by the protecting group mean that no pastes and decantation steps are required during this route This allows for easier processing

The protected route allows for greatly enhanced yields of HI-6 DMS Reported yields of HI-6 DMS from the non-protected routes are in the region of 10% after multiple fractional recrystallisation steps We have found the non-protected route to be quite irreproducible, with the best results obtained when using elevated mole equivalent amounts of BSME relative to P2A (2-3 mole equivs relative to P2A). In any event yields obtained using non-protected routes were never greater than 10-12% The protected route will reproducibly give crude HI-6 DMS in 50-60% yield (relative to P2AOAc) of 85-95% purity. This material can be recrystallised to pure HI6 DMS in 70-80% yield leading to an overall yield reproducibly in the range of 35-42% (relative to P2AOAc).

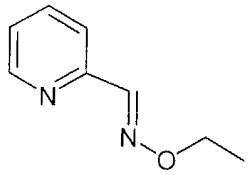
Direct comparison of yields and purities of crude HI-6DMS derived from protected and non-protected routes

Route	*Substrate*	*Yield of isolated solid (%) wrt to starting P2A species*	*Purity (area %)*
Protected	P2AOAc	55	88
Non-Protected	P2A	43	4

The invention will now be more particularly described with reference to the following examples

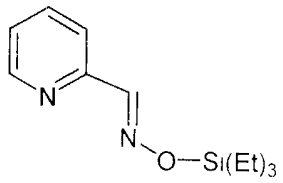
Synthesis of O-Protected pyridine-2-aldoxime substrates

O-Ethyl pyridine-2-aldoxime (P2AOEt)



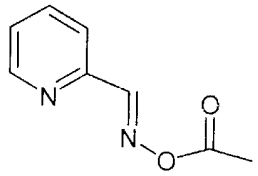
To sodium hydroxide (33 5g of a 10%w/w aqueous solution, 83 8 mmol) with overhead stirring was charged solid P2A (10g, 81.9mmol) under a blanket of N_2 Toluene (144g), tetrabutylammonium bromide (1 3g, 4 1mmol) and ethyl bromide (10.6g, 97 5mmol) were added to give two phases The mixture was heated to 80 °C with good stirring. After 3 hours, sampling and analysis by HPLC revealed that >90% conversion had occurred The mixture was cooled to 23°C and the brown organic phase was isolated, dried over anhydrous magnesium sulphate ($MgSO_4$), and filtered. The solvent was removed under reduced pressure (40mbar) to yield 7 44g of a brown oil (60 5% yield) Analysis by ^1H nmr indicated trace quantities of ethyl bromide, toluene and P2A This oil was then distilled (81°C, 2mbar) to give a colourless oil, ^1H NMR ($CDCl_3$, 250MHz) δ 1 35 (t, 3H,J = 7.1Hz), 4 28 (q, 2H, J = 7.1), 7.25 (m, 1H), 7 70 (m, 1H). 7 80 (m, 1H), 8.17 (s, 1H), 8 61 (m, 1H)ppm ^{13}C NMR ($CDCl_3$, 63MHz): δ 14 61, 70 36, 120 99, 123.85, 136.43, 148 89, 149 68, 151 88ppm.

O-Triethylsilyl pyridine-2-aldoxime (P2AOTES)



To a vessel was charged solid P2A (2g, 16 4mmol) under a blanket of N_2 Anhydrous methylene chloride (MDC 10 6g), triethylamine (1 8g, 17 9mmol) and 4-dimethylaminopyridine (4-DMAP, 4mg, 0 3mmol) were added and the mixture stirred. Triethylsilyl chloride (2.5g, 16 6mmol) in MDC (10 6g) was added dropwise and with good stirring, an exotherm was noted (26 to 31°C). At the end of the addition a white suspension resulted The mixture was stirred at 23°C for 12hours and then MDC (106g) was added The mixture was then washed with ice cold water (3 x 100g), the organic phase isolated, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 3 24g of a pale yellow oil (83 7% yield), ^1H NMR ($CDCl_3$, 250MHz) δ 0 83 (q, 6H,J = 7 1Hz), 1.06 (t, 2H, J = 7 1), 7.25 (m, 1H), 7 68 (m, 1H), 7 88 (m, 1H), 8.31 (s, 1H), 8 59 (m, 1H)ppm. ^{13}C NMR ($CDCl_3$, 63MHz). δ 4.33, 6 64, 120.57, 123.88, 136.34, 149 42, 152.36, 154.23ppm

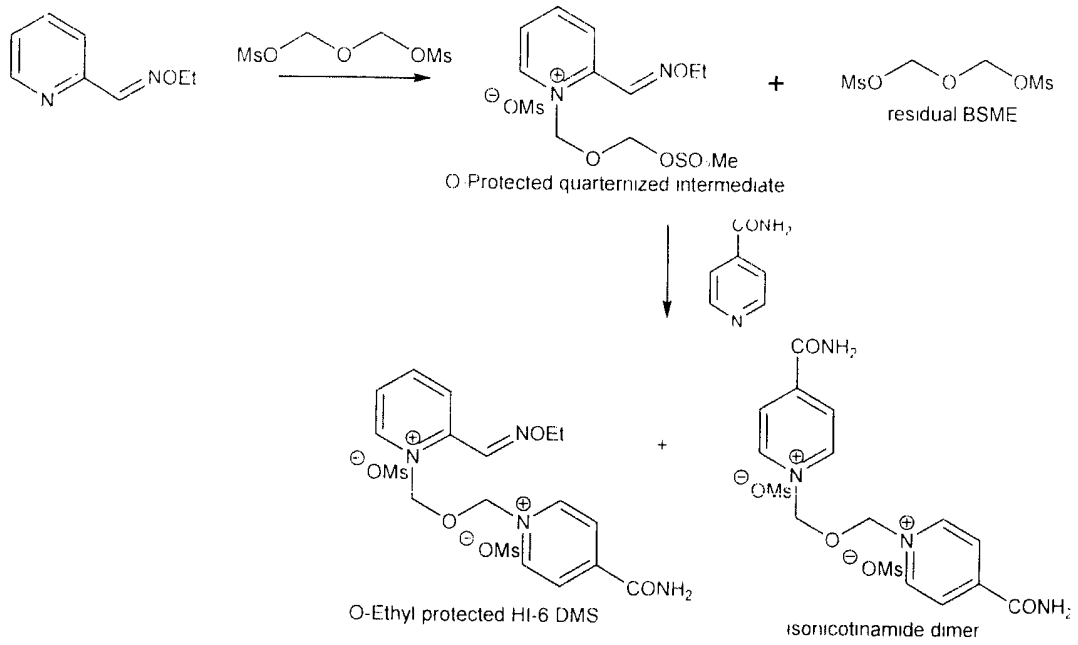
O-Acetyl pyridine-2-aldoxime (P2AOAc)



A 14%w/w solution of acetic anhydride (1moleq) in MDC was slowly charged to a 14%w/w solution of P2A (10g, 81 9mmol), triethylamine (8.27g, 81 9mmol) and catalytic 4-DMAP (0 004g) in MDC at room temperature under N_2. After stirring the reaction mixture for 14hours the mixture was quenched into ice water (150g), the organic phase was washed with ice water (150g), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford 12 2g (91% yield) of a pale yellow transparent oil, which crystallised to a white solid on standing, ^1H NMR ($CDCl_3$, 250MHz) δ 2 2 (s, 3H), 7.3 (m, 1H), 7 8 (t, 1H), 8 0 (d, 1H), 8 4 (s, 1H), 8.7 (d, 1H)ppm ^{13}C NMR ($CDCl_3$, 63MHz) δ 19 54 ($OC(O)CH_3$), 122.00, 125.51, 136.70, 149 87, 149.93, 156 57, 168 31ppm

Quaternization Reactions

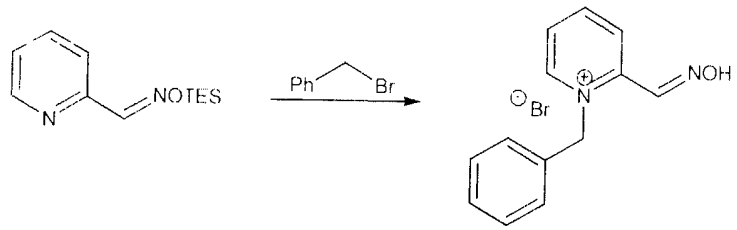
Reaction of O-Ethyl pyridine-2-aldoxime (P2AOEt) with BSME and isonicotinamide



Solid BSME (1 4g, 5.9mmol) was placed in a vessel under a slow stream of N_2 Acetonitrile (2 1g) was added and the resulting mixture stirred P2AOEt (0 9g, 5 9mmol) in acetonitrile (4.8g) was added at 23°C and the resulting mixture stirred for 22 hours Solid isonicotinamide (0 69g, 5 6mmol) was added and the mixture stirred for 5 hours and then held at -20°C for 4 days The resulting heterogeneous slurry was warmed to 23°C and then filtered. The filter cake/paste was then stirred in ethanol (15 8g) for 1 hour and filtered to give a dry solid HPLC and ^{1}H nmr analysis indicated it to be the dimethanesulfonate salt of isonicotinamide dimer The filtrates were combined and the solvent was removed under reduced pressure to give a brown oil that crystallised on standing to yield 1 4g of solid ^{1}H NMR (d_6-DMSO, 250MHz) δ 1.30 (t, 3H, OCH_2CH_3), 2 34 (s, 6H, OSO_2CH_3), 4 40 (q, 2H, OCH_2CH_3), 6 24 (s, 2H, CH_2OCH_2), 6 39 (s, 2H, CH_2OCH_2), 7 25 (m, 1H),

7 70 (m, 1H), 7 80 (m, 1H), 8.23 (m, 1H), 8 32 (s, 1H, N*H*), 8 52 (m, 3H), 8 75 (m, 3H, 2 x C*H*, 1 x N*H*), 9 25 (m, 1H) 9.36 (m, 2H) ppm.

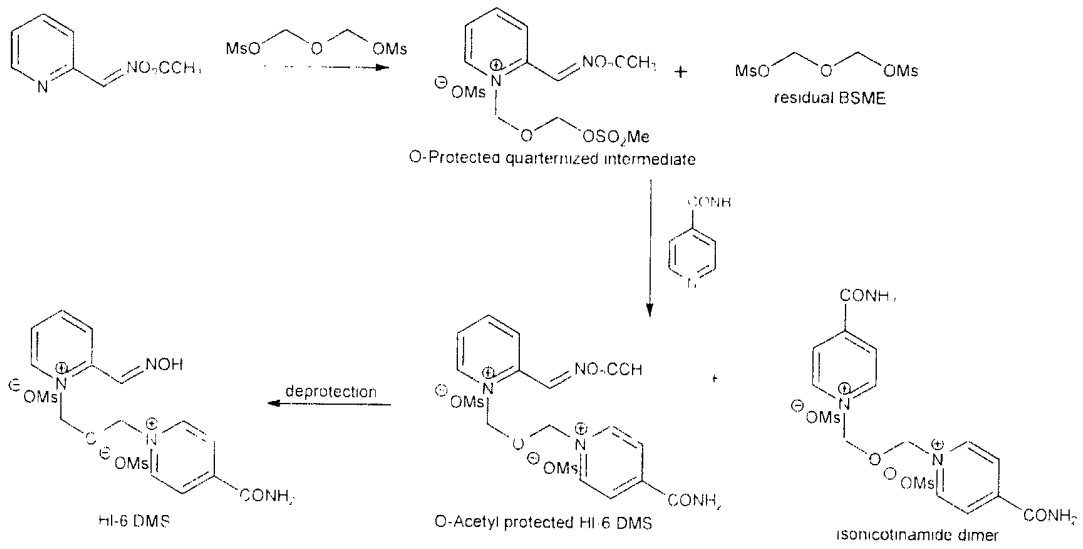
Reaction of O-Triethylsilyl pyridine-2-aldoxime (P2AOTES) with benzyl bromide



To a solution of P2AOTES (0 12g, 0 50mmol) in MDC/ acetonitrile (4g/ 3 5g) was added benzyl bromide (0.17g, 1 0mmol, 2 0moleq) The mixture was refluxed for 2 days to give a heterogeneous slurry The mixture was filtered and the cake was rinsed with acetonitrile (2.5g) and dried using air-flow Analysis of the cake by HPLC indicated >98% (area) purity ^{1}H NMR (D_2O, 250MHz) δ 5 88 (s, 2H, CH_2Ph), 7.14 (m, 2H), 7.34 (m, 3H); 7 95 (m, 1H), 8.27 (m, 1H), 8.46 (m, 1H), 8 5 (s, 1H), 8.80 (m, 1H)ppm. ^{13}C NMR (D_2O, 63MHz): δ 61 64 (CH_2Ph), 127 16, 127.45, 128.00, 129 41, 129 46, 132 43, 141.99, 145.94, 146.00, 147 14ppm.

Example 1

Preparation of HI-6 DMS



To a solution of BSME (2 89g) and acetonitrile(11 3g) was slowly added a solution of P2A (2.03g) in chilled (-20°C) tetrahydrofuran (71 2g) over 30 minutes under nitrogen The solvent was partially evaporated over 2 hours and acetonitrile (11.3g) and tetrahydrofuran (71 2g) was added to form a gum The supernatant liquid was decanted and acetonitrile (14ml) added to the gum Isonicotinamide (1.2g) was added and the mixture stirred at room temperature for 20 hours The solvent was removed under reduced pressure and the residue triturated with ethanol (49 5g) The slurry was filtered to remove isonicotinamide dimer. The filtrate was stirred overnight The solid was collected by filtration and the cake washed with ethanol to yield HI-6 DMS (1.9g, 90% area by HPLC, 29% th yield)

Example 2

Preparation of HI-6 DMS

To a solution of BSME (2.89g) and acetonitrile (11 3g) was slowly added a solution of P2A (2.03g) in acetonitrile (17 8g) over 1 5 hours under nitrogen

and the mixture stirred for 20 hours Isonicotinamide (1.2g) and acetonitrile (3 95g) was added and the mixture stirred at room temperature for 20 hours The solvent was removed under reduced pressure and the residue triturated with ethanol (49.5g) The slurry was filtered to remove 'isonicotinamide dimer'. The homogeneous filtrate was stirred overnight The solid was collected by filtration and the cake washed with ethanol to yield HI 6 DMS (2g, 85% area by HPLC. 30% th yield) The crude HI-6 DMS was recrystallised form aqueous ethanol to give 1 2g HI-6 DMS (>98% area by HPLC) This is a 21% overall yield from P2AOAc.

Example 3

Preparation of HI-6 DMS

Solid BSME (20g. 84 0mmol, 1 2moleq.) was charged to a dry vessel under N_2 and a solution of P2AOAc (11.6g, 70.0mmol, 1 0moleq) in MDC/ acetonitrile (85 3g/ 9 2g) was added The mixture was stirred for 6 hours and then isonicotinamide (11.4g. 93.3mmol) in dimethylformamide (25 8g) was added. The mixture was stirred out for 17 hours. Ethanol (370g) was added and the mixture was stirredfor ca 6 hours The resulting slurry was filtered. The homogeneous filtrate was then placed in a vessel and stirred until deprotection was complete. The resulting slurry was then filtered to give 17 8g (53% yield based on P2AOAc) of an off-white powder (HPLC 95% by area) 5g of this cake was then re-crystallised from aqueous ethanol (44.4g) to give 3 9g of a white solid, HPLC (>99% by area); ^{1}H NMR (D_2O. 250MHz) δ 2 67 (s. 6H) 6.22 (s 2H) 6 34 (s, 2H); 8 03 (m, 1H), 8 42 (m, 3H), 8 60 (m, 2H), 8 98 (d, 1H), 9.14 (d, 2H)ppm ^{13}C NMR (D_2O, 63MHz). δ 38 48

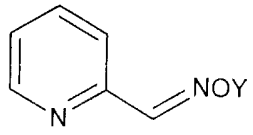
($OS(O)_2CH_3$), 85 58, 86 86, 126.70, 127 57, 127.95, 141 89, 144.54, 145 17, 146.97, 148 18, 150 79, 166 26 ($C(O)NH_2$)ppm Found C, 40 24, H, 4 59; N, 11 68 Calculated for $C_{16}H_{22}N_4O_9S_2$, C, 40.16, H, 4 63, N, 11.71

CLAIMS

1. A process for the manufacture of HI-6 R, wherein R is a suitable counterion or counterion pair, comprising contacting an O-protected pyridine aldoxime compound with an (R'-alkyl) ether, wherein R' corresponds to the counterion or one counterion of the pair, in a suitable solvent to form an intermediate compound, contacting said intermediate compound with isonicotinamide to form an O-protected HI-6 product precursor, and de-protecting the precursor to form HI-6 R.

2 A process according to claim 1 wherein R comprises two univalent anions, each univalent anion corresponding to R', and the (R'-alkyl) ether is a bis(R'-alkyl) ether

3 A process according to claim 1 or claim 2 wherein the O-protected pyridine aldoxime compound has the formula:



wherein Y is a protecting group

4 A process according to claim 3 wherein the protecting group comprises an ester group

5 A process according to claim 4 wherein the protecting group comprises an acetate group

6. A process according to any one of claims 1 to 5 wherein the alkyl group is a short chain alkyl (alkylene) group

7 A process according to claim 6 wherein the alkyl group is a C_{1-4} alkyl(ene) group.

8 A process according to claim 7 wherein the alkyl group is methyl(ene).

9 A process according to any one of claims 1 to 8 wherein R' is methanesulphonate.

10 A process according to claim 9 for the manufacture of HI-6 dimethanesulfonate comprising contacting an O-protected pyridine aldoxime compound with bis(methylsulphonoxymethyl) ether in a suitable solvent to form an intermediate compound, contacting said intermediate compound with isonicotinamide to form an O-protected HI-6 product precursor, and de-protecting the precursor to form HI-6 dimethanesulfonate

11 A process according to claims 1 to 10 wherein an O-protected HI-6 product precursor is separated from impurities by contacting the reaction mixture with a solvent effective for dissolving the O-protected HI-6 product precursor, precipitating said impurities and removing the impurities by filtration

12 A process according to claim 11 wherein the impurities comprise isonicotinamide dimer.

13 A process according to any one of claims 1 to 12 wherein the protected product precursor is de-protected by contacting the precursor with a de-protecting agent

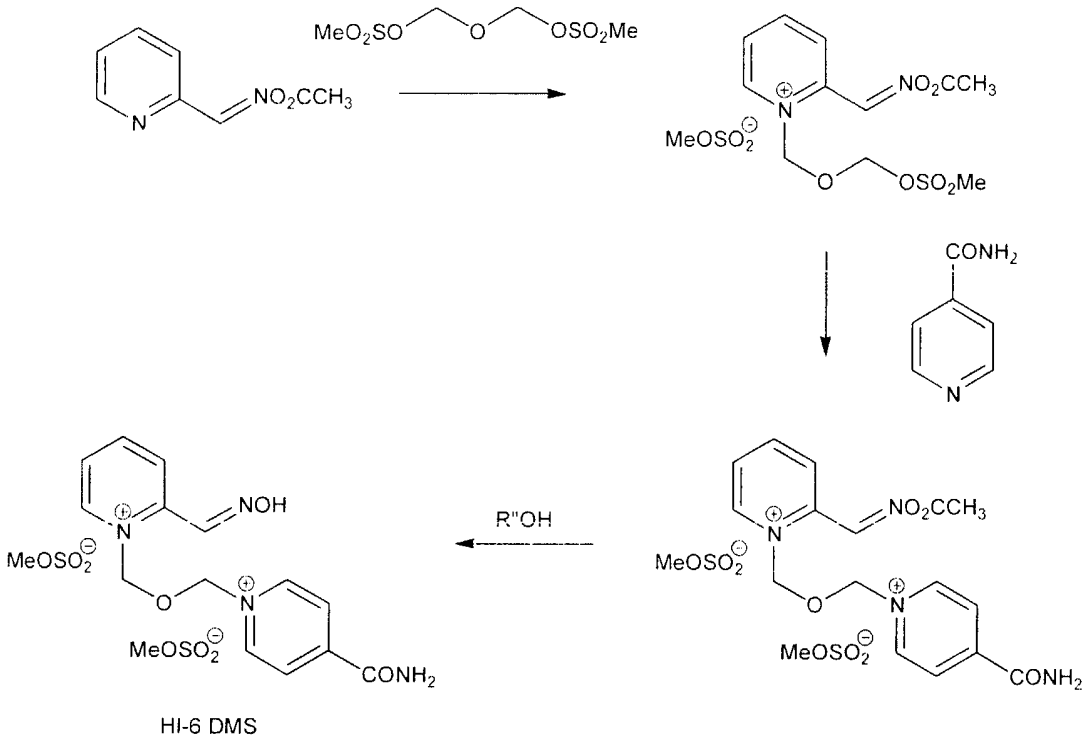
14 A process according to claim 13 wherein the de-protecting agent comprises a solvent and/or reagent suitable for removing the protecting group

15. A process according to claim 13 or claim 14 wherein the precursor is triturated with the de-protecting agent to effect the de-protection

16 A process according to any one of claims 13 to 15 wherein the de-protecting agent comprises an alcoholic solvent and/or a protic solvent

17 A process according to claim 16 wherein the solvent comprises ethanol or water or combinations thereof.

18 A process according to any one of claims 1 to 17 to which proceeds according to the following scheme



wherein R"OH is an alcoholic and/or protic solvent or a mixture of two or more thereof.

19 A protected HI-6 product precursor

20. A precursor according to claim 19 protected by an ester group.

21. A precursor according to claim 20 protected by an acetate group.

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Application No: GB0716349 6 **Examiner:** Stephen Quick

Claims searched: 1-21 **Date of search:** 3 April 2008

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	19 & 20	Chemical Journal of Chinese Universities, 1984, Vol. 5(5), page 683-685. See page 685 (English language abstract, four optionally substituted O-benzoyl derivatives of each of the two pyridine-aldoximes) and corresponding formulae on page 683; acknowledged in this application.
X	19	Arzneimittel Forschung, 1976, Vol. 23, page 1273-1275. See page 1274 (table 1, all entries) and 1275 (LH column, 3rd paragraph, headed "alkyl aether...."); acknowledged in this application.
X	19	US 2924604 A (DR F RASCHIG). See especially examples 1-4, 6, 7 & 10-12
X	19	Journal of Labelled Compounds and Radiopharmaceuticals, 1993, Vol. 33(1), pages 19-32. See paragraph bridging pages 26 & 27 (compound 3, 1H-isotope) and page 27 (1st complete paragraph, compound 4, 1H-isotope) in context of page 27 (2nd complete paragraph) & page 28 (both complete paragraphs); c.f. also, re 3H-isotope, page 22 (scheme 2) & page 29 (top half).

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[X]:

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report

CAS ONLINE

International Classification:

24

Subclass	Subgroup	Valid From
C07D	0213/81	01/01/2006