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(54) Title: METHOD OF PREPARING 5– OR 8–BROMOISOQUINOLINE DERIVATIVES

(57) Abstract

The invention describes a novel process for the preparation of 5– or 8–bromoisoquinoline from isoquinoline. The process gives high yields and is suitable for large scale work.

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METHOD OF PREPARING 5- OR 8-BROMOISOQUINOLINE DERIVATIVES

Technical field.

The present invention is directed to a method of preparing bromoisoquinoline derivatives, in particular 5- or 8-bromoisoquinoline derivatives. Bromoisoquinoline derivatives, and in particular 5-bromoisoquinoline and 5-bromo-8-nitroisoquinoline derivatives, are key intermediates in the synthesis of pharmaceutical compounds.

Background art

Bromoisoquinoline derivatives, and in particular 5-bromoisoquinoline and 5-bromo-8-nitroisoquinoline derivatives, are key intermediates in the synthesis of pharmaceutical compounds.

Direct bromination of the rather electron poor isoquinoline system using elemental bromine can only be achieved by the co-use of catalysts. One such method has been described by Gordon and Pearson [see *Gordon M. & Pearson D.E.*, J. Org. Chem. 1964 **29** 329; and *Butler J.L., Bayer F.L. & Gordon M.*, Trans K.Y. Acad. Sci., 1977 **38** 15] by which 5-bromoisoquinoline was synthesised by the addition of liquid bromine to a melt of isoquinoline and aluminium chloride at 75°C, giving 43-46% yield of product after re-crystallisation. The method has been modified by *Mathison and Morgan* [*Mathison I.W. & Morgan P.H.*, J. Org. Chem., 1974 **39** 3210], who used gaseous bromine and obtained a yield of 42%. A similar method using liquid bromine and $AlBr_3$ has been described by Rey *et al.* [see *Rey M., Vergnani T. & Dreiding A.S.*, Helv. Chim. Acta., 1985 **68** 1828], giving a yield of 39%. Bromination using Br_2 and Ag_2SO_4 in H_2SO_4 could also be accomplished, however, only giving a yield of 23% [see *Rey M., Vergnani T. & Dreiding A.S.*, Helv. Chim. Acta., 1985 **68** 1828; *De La Mare P.B.D. Kiamud-din M. & Ridd J.H.*, J. Chem. Soc., 1960 561; and *De La Mare P.B.D. Kiamud-din M. & Ridd J.H.*, Chem. Ind. (London), 1958 361].

An indirect method for the synthesis of 5-bromoisoquinoline, makes uses of the fact, that nitration is much more easily achieved, *i.e.* nitration, reduction and finally diazotation gives 5-bromoisoquinoline [see *Butler J.L., Bayer F.L. & Gordon M.*, Trans K.Y. Acad. Sci., 1977 **38** 15; *Glyde E. & Talor R.*, J. Chem. Soc. Perkin Trans II, 1975 1783; *Robinson R.A.*, J.

Am. Chem. Soc., 1947 **69** 1942; and *Osburn A.R., Schofield K. & Short L.N.*, J. Chem. Soc., 1956 4191].

The direct bromination procedure tends to give mixtures of brominated products and in unsatisfactory yield, and none of the methods described are well suited for large scale work. The indirect method is not very suitable for large scale work especially due to the diazotation step.

Summary of the invention

In the present invention we describe a high yielding method for the synthesis of 5- or 8-bromoisoquinoline and its derivatives using cheap starting materials. The method of the invention is particularly well suited for large scale work operation and for accomplishing "one-pot" synthesis.

Detailed disclosure of the invention

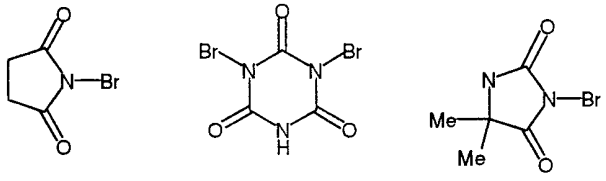
The present invention provides a method of preparing bromoisoquinoline and its derivatives. More particularly, the invention provides a high yielding method for the synthesis of 5- or 8-bromoisoquinoline and its derivatives, in particular 5-bromo-8-nitroisoquinoline.

Accordingly, in its most general aspect, the invention provides a process for the preparation of 5- or 8-bromoisoisoquinoline, or a derivative thereof, which process comprises the step of reacting isoquinoline, or a derivative thereof, with a brominating agent in the presence of a catalyst.

The Brominating Agent

The brominating agent used according to the present invention may be any suitable brominating agent. However, in a preferred embodiment, a suitable brominating agent is an agent of the general formula Z-Br, wherein Z represents a suitable leaving group.

In a most preferred embodiment the leaving group may be a secondary amino group of the general formula R_2N-Br, wherein R is alkyl, aryl, acyl or sulfonyl, or R_2N-Br describes a cyclic structure [e.g. *N*-bromosuccinimide (NBS), *N,N'*-dibromoisocyanuric acid (DBI) or *N,N'*-dibromohydantoin (DBH)]:



Catalyst and Catalytic Solvents

The catalyst contemplated in the method of the invention may be any suitable H^+ or a Lewis acid. The Lewis acid may in particular be a compound of the formula $M'_mX_{n'}$, where M' represents a metal, and X represents halogen. Preferred Lewis acids are e.g. BF_3, AlX_3, TiX_4, ZnX_2, MnX_2, FeX_3, FeX_2, SnX_2, PbX_2, SbX_3, and SbX_5.

The solvent is an acid with or without H_2O, e.g. FSO_3H, $ClSO_3H$, CF_3SO_3H, H_2SO_4, CH_3SO_3H, H_3PO_4, polyphosphoric acid, H_3PO_3, HXO_4, HXO_3, HXO_2, HXO, HX, CF_3COOH, CH_3COOH and others, where X represents halogen.

In a preferred aspect of the invention the solvent is an acid with or without H_2O i.e. HCl (0.1 N to conc.), CF_3SO_3H, H_2SO_4, CH_3SO_3H, CF_3COOH or CH_3COOH.

In another preferred aspect of the invention the solvent functions as a catalyst.

Nitrating Reagent

MNO3 is a nitrating reagent as known in the art, wherein M represents a metal or H^+. The active component being NO_2^+ formed *in situ* in the reaction mixture.

Process Conditions

The method of the invention may be conducted at temperatures ranging from -50 °C to 200 °C with the temperature range between -30 °C to -15 °C being the preferred for the preparation of the 5- or 8-bromoisoquinolines.

The method of the invention may be conducted from 0.1 g to 500 kg scale with the preferred scale being 1 g to 50 kg. Finally, the reaction may be conducted at 0.1 M to 5 M concentration with a preferred concentration of 0.5-1 M.

The method of the invention may be quenched after bromination giving 5-bromo or 8-bromoisoquinoline or continued by addition of metal nitrate, whereby 5-bromo-8-nitroisoquinoline or 8-bromo-5-nitroisoquinoline may be isolated from a "ONE POT" reaction.

The synthesis of 5-bromoisoquinoline and 5-bromo-8-nitroisoquinoline may in broad terms be described as a transformation of isoquinoline to 5-bromoisoquinoline using strong acid, preferably conc. H_2SO_4, and a brominating agent, preferably NBS. The bromination is preferably conducted at 0.5-1 M scale at a temperature of -30 °C to -15°C. 5-Bromoisoquinoline may be worked up and isolated as pure material or it may be further transformed, without prior isolation into 5-bromo-8-nitroisoquinoline by addition of potassium nitrate to the reaction mixture. Workup and recrystalization gives pure 5-bromo-8-nitroisoquinoline.

Examples

The invention is further illustrated with reference to the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

In the following we describe one selected set of optimised reaction conditions for both labscale and large scale production, making a compromise between yield (of the reaction), costs (of the solvent and the brominating agent) and availability (of the brominating agent).

5-Bromoisoquinoline.

Isoquinoline (15 ml; 128 mmol) was slowly added to a mechanically stirred solution of concentrated H_2SO_4 (130 ml) (Note 1) at -20 °C, at such a speed that the temperature did not exceed +8 °C. The reaction mixture was then re-cooled to -20 °C, and solid *N*-bromosuccinimide (27.29 g; 153 mmol) (Note 2 and 3) was added at such a speed that the reaction temperature did not exceed -15 °C (Note 4). The reaction mixture was stirred at -20 °C until all isoquinoline was consumed (Note 5). The reaction was then allowed to warm to -9 °C over 20 min. The reaction mixture was poured onto 300 g of crushed ice and pH adjusted to 10 using 25% NH_3 (aq.), while the temperature was kept below 50-60 °C. Extraction with diethyl ether (2x 250 ml) filtration through celite and evaporation to dryness gave a red-brown oil which crystalized upon cooling. The precipitate was suspended in boiling heptane (300 ml) under rapid stirring and decanted while warm. This procedure was repeated with hexane (2x 100 ml). The combined organic fractions was evaporated to dryness to give 18.2 g crude product as a slightly yellow powder. Recrystalization from heptane gave 15.2 g (59 % from 97% isoquinoline) of pure product as a slightly yellow powder.

M.p. 82-83 °C (Litt. 82-83 °C[4], 79.5-80.5 °C[1], 82-84 °C[3,9], 83.0-83.5 °C[2], 83-85 °C[5])

^{1}H-NMR (DMSO-d_6): δ 9.38 (d, J = 0.9 Hz); 8.67 (d, J = 5.9 Hz); 8.21 (d, J = 8.2 Hz); 8.16 (dd, J_A = 0.9 Hz, J_B = 7.5 Hz); 7.94 (d, J = 5.9 Hz); 7.64 (t†, J = 7.8 Hz). † A dd with J_A = 8.2 Hz and J_B = 7.5 Hz was expected.

5-Bromo-8-nitroisoquinoline.

Isoquinoline (15 ml; 128 mmol) was slowly added to a mechanically stirred solution of concentrated H_2SO_4 (130 ml) (Note 1) at -20 °C, at such a speed that the temperature did not exceed +8 °C. The reaction mixture was then re-cooled to -20 °C, and solid

N-bromosuccinimide (27.29 g; 153 mmol) (Note 2 and 3) was added at such a speed that the reaction temperature did not exceed -15 °C (Note 4). The reaction mixture was stirred at -20 °C until all isoquinoline was consumed (Note 5). Solid KNO_3 (13 g; 128 mmol) was added in one portion, whereby the reaction temperature warmed up to -12 °C to -10 °C. The reaction was stirred at -10 °C to -20 °C for 2 hours and then allowed to warm up to rt. The reaction mixture was poured onto 650 g of crushed ice and pH adjusted to 7.0 (Note 6) using 25% NH_3 (aq.), while the temperature was kept below +30 °C. The mixture was left for precipitation for 1 h at rt. The yellow precipitate was isolated by filtration, washed on the filter with H_2O (3x 500 ml) and then dried by suction followed by air drying to give 27.1 g crude product. (Note 7).

Purification was achieved by either recrystalisation from heptane (**A**) or heptane/toluene (**B**).

A. The crude product was suspended in heptane (1500 ml), heated to reflux, and then filtered warm through celite. The filtrate was evaporated until precipitation occured (appoximate when 900 ml was left). It was then heated to reflux again and heptane (250 ml) was added to give a clear solution, which was slowly cooled and left for precipitation over night. Filtration and air drying to constant weight gave 22.8 g (73 % from 97% pure isoquinoline) of pure 5-bromo-8-nitroisoquinoline as light yellow needles (Note 8).

B. The crude product was suspended in heptane/toluene (300 ml/150 ml) heated to reflux and then filtered warm through celite. The filtrate was evaporated until approximately 250 ml was left. The clear solution was slowly cooled and left for precipitation over night. Filtration and air drying to constant weight gave 21.7 g (69 % from 97% pure isoquinoline) of pure 5-bromo-8-nitroisoquinoline as light yellow needles (Note 8).

M.p. 137.5-139.5 °C (Litt. 138-139 °C[4], 138-140 °C[9], 139-141 °C[3])

^{1}H-NMR (DMSO-d_6): δ 9.81 (d, J = 0.6 Hz); 8.87 (d, J = 5.9 Hz); 8.39† (d, 8.1 Hz); 8.36† (d, 8.1 Hz); 8.16 (dd, J_A = 0.6 Hz, J_B = 5.9 Hz). † AB-system.

Notes

1. Different acids [HCl, CF_3SO_3H, H_2SO_4, CH_3SO_3H, CF_3COOH, CH_3COOH] were tested as solvents with or without the addition of H_2O. The reaction rate and 5- vs. 8-selectivity increases with acidity of the solvent. NBS decomposed in CF_3SO_3H. This was not the case with DBI. Isoquinoline decomposition increases with the amount of water present.

2. *N*-Bromosuccinimide was recrystalized (10 g in 100 ml H_2O) and air dried over night before use. Otherwise a substantial excess of NBS was needed to achieve fully conversion of isoquinoline with a concomitant increase in the amount of 5,8-dibromoisoquinoline.
3. The relative reactivity and selectivity of the brominating agents was DBI > NBS > DBH. NBS and DBH are commercially available and DBI is very easy to make from elemental bromine, lithium hydroxide and cyanuric acid according to the procedure of Gottardi.[10]
4. The reaction temperature is very important in order to achieve a high 5- vs. 8-selectivity and should not be above -15 °C during the bromination.
5. The reaction was monitored by TLC (CH_2Cl_2/EtOAc = 9/1). Isoquinoline was nearly or completely consumed after 4-5 h.
6. When pH was raised above 7.0 the reaction mixture started to darken.
7. The crude product was typically of the following composition:
   5-Bromo-8-nitroisoquinolin/5,8-dibromoisoquinoline/5-nitroisoquinoline/8-bromo-5-nitroisoquinoline:
   90-94%/2-5%/2-4%/0-1%.
8. The purified product was typically of the following composition:
   5-Bromo-8-nitroisoquinolin/5,8-dibromoisoquinoline/5-nitroisoquinoline/8-bromo-5-nitroisoquinoline:
   >97%/<1%/<1%/<1%.

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CLAIMS

1. A process for the preparation of 5- or 8-bromoisoquinoline, or a derivative thereof, which process comprises the step of

   (i) reacting isoquinoline, or a derivative thereof, with a brominating agent, Z-Br, wherein Z represents a leaving group, in the presence of a catalyst;

followed by isolation of the desired product.

2. The process according to claim 1, wherein the 5- or 8-bromoisoisoquinoline is subjected to the action NO_2^+ derived from a nitrating agent of the formula MNO_3, wherein M represents a metal or H^+, to obtain a 5-bromo-8-nitroisoisoquinoline or a 5-nitro-8-bromoisoisoquinoline.

3. The process according to either of claims 1-2 for the preparation of a 5- or 8-bromoisoisoquinoline derivative, which process comprises the steps of

   (i) reacting isoquinoline with a brominating agent in the presence of a catalyst to form a 5- or 8-bromoisoisoquinoline; and

   (ii) reacting the 5- or 8-bromoisoisoquinoline obtained according to step (i) with a nitrating agent;

followed by isolation of the 5- or 8-bromoisoquinoline derivative.

4. The process according to any of claims 1-3, wherein the leaving group Z is a secondary amino group of the general formula R_2N-Br,

   wherein R is alkyl, aryl, acyl or sulfonyl,

   or R_2N-Br describes a cyclic structure such as *N*-bromosuccinimide (NBS), *N,N'*-dibromoisocyanuric acid (DBI), or *N,N'*-dibromohydantoin (DBH).

5. The process according to any of claims 1-4, wherein the catalyst is H^+ or a Lewis acid.

6. The process according to claim 5, wherein the catalyst is an acid with or without H_2O, such as FSO_3H, $ClSO_3H$, CF_3SO_3H, H_2SO_4, CH_3SO_3H, H_3PO_4, polyphosphoric acid,

H_3PO_3, HXO_4, HXO_3, HXO_2, HXO, HX, CF_3COOH, and CH_3COOH, wherein X represents halogen.

7. The process according to claim 5, wherein the catalyst is a Lewis acid of the formula M'_mX_n, where M' represents a metal, and X represents halogen.

8. The process according to claim 7, wherein the Lewis acid is BF_3, AlX_3, TiX_4, ZnX_2, MnX_2, FeX_3, FeX_2, SnX_2, PbX_2, SbX_3, or SbX_5 wherein X represents halogen.

9. The process according to any of claims 1-8, which is carried out as a "one pot" process.