reaction step which would require strict technical monitoring consists of synthetizing the intermediate nitro-imidazole derivative which is subsequently subject to condensation with 4-mercaptomethyl-phenol, i.e. 1-methyl-2-chloromethyl-5-nitro-imidazole as referred to in US 4,042,705. This disclosure, however, remains silent concerning the preparation of the said intermediate 2-chloromethyl derivative or its equivalents (alkyl, aryl, etc.).

In some instances moreover, trials performed have shown that specific intermediate 2-chloro-alkyl or aryl-derivatives, although quite attractive in theory, proved poorly stable if not dangerous to handle. It was further observed that the condensation reactions are leading, as usual, to substantial amounts of secondary material (impurities) and eventually to a modest overall reaction yield hardly acceptable for the industry. Last but not least some reaction steps required different solvents and/or catalysts and could not therefore allow an easy integration of all the reaction steps.

The invention avoids all the technical drawbacks observed until now and provides the skilled technician with a method which affords fexinidazole with a high grade of purity and which is definitely simpler and easier to implement in a dedicated factory. The invention is defined in the attached claims.

Summary

The disclosure refers to a method for preparing 1-methyl-2-(4-methlymercapto-phenyloxymethyl)-5-nitro-imidazole (compound I) which comprises the following steps:

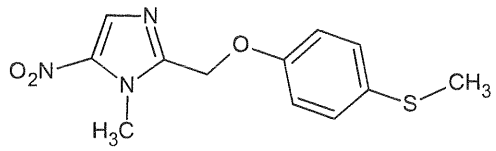
a) reacting 1-methyl-2-hydroxymethyl-5-nitro-imidazole with methanesulfonyl chloride in the presence of a suspension of powdered alkaline carbonate in an anhydrous organic solvent suitable for performing nucleophile substitution reactions, while monitoring the reaction conditions in such a way to afford less than 3 % area per cent of each of the secondary compounds of formula II and III, wherein the methanesulfonyl chloride, in the form of a solution in the organic solvent, is progressively added to 1-methyl-2-hydroxymethyl-5-nitro-imidazole while keeping the reaction medium at a temperature not exceeding 20° C, wherein the organic solvent suitable for performing nucleophile substitution reactions is a polar aprotic organic solvent; b) adding to the resulting reaction medium a solution of 4-methylmercapto-phenol in the same organic solvent as referred to in step a) while monitoring the reaction conditions in such a way to avoid dimerization of compound I into compound of formula V;

c) separating compound I from the reaction mixture as its hydrochloride salt and

d) converting said hydrochloride salt into compound I and, optionally, purifying the latter.

CLAIMS

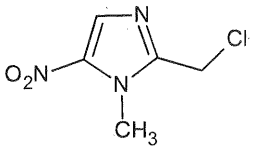
1. A method for preparing 1-methyl-2-(4-methlymercapto-phenyloxymethyl)-5-nitro-imidazole having the formula

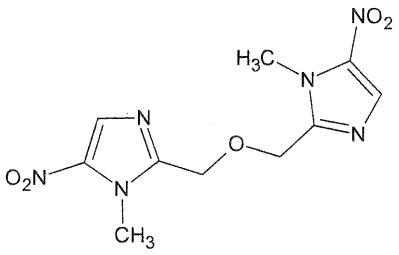


(I)

which comprises the steps of

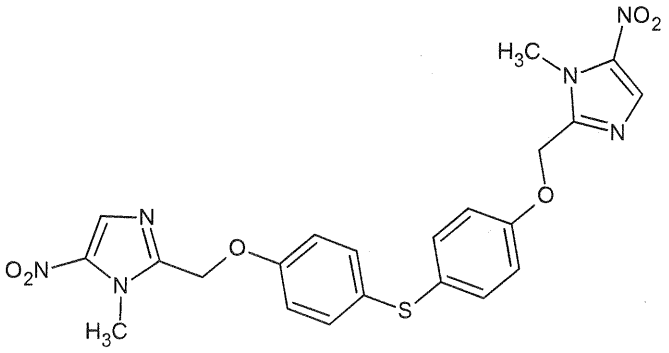
a) reacting 1-methyl-2-hydroxymethyl-5-nitro-imidazole with methanesulfonyl chloride in the presence of a suspension of powdered alkaline carbonate in an anhydrous organic solvent suitable for performing nucleophile substitution reactions while monitoring the reaction conditions in such a way to afford less than 3 area per cent of each of the following secondary compounds of formula





(II) and (III), wherein the methanesulfonyl chloride, in the form of a solution in the organic solvent, is progressively added to 1-methyl-2-hydroxymethyl-5-nitro-imidazole while keeping the reaction medium at a temperature not exceeding 20° C;

b) adding to the resulting reaction medium a solution of 4-methylmercapto-phenol in the organic solvent referred to in step a) while monitoring the reaction conditions in such a way to avoid dimerization of compound I into the compound of formula



(V);

c) separating compound of formula I from the reaction mixture as its hydrochloride salt and

d) converting said hydrochloride salt into compound of formula I and, optionally, purifying the latter.

~~2. The method of claim 1~~ wherein the organic solvent suitable for performing nucleophile substitution reactions is a polar aprotic organic solvent.

~~3.~~2. The method of claim ~~2~~ 1 wherein the polar aprotic organic solvent is an aliphatic ketone, especially a C3 to C5 aliphatic ketone and preferably acetone, or acetonitrile.

~~4.~~3. The method of any of claims 1 to ~~3~~ 2 wherein powdered alkaline carbonate is potassium carbonate.

~~5. The method of any of claims 1 to 4 which comprises progressively adding methanesulfonyl chloride, in the form of a solution in the same solvent as referred to in step a) to 1-methyl-2-hydroxymethyl-5-nitro-imidazole while keeping the reaction medium at a temperature not exceeding 20° C.~~

~~6.~~4. The method of any of claims 1 to ~~5~~ 3 which comprises adding 4-methyl-mercapto-phenol, in the form of a solution in the same solvent as referred to in step a), to the reaction mixture resulting from step a) while keeping the reaction medium at a temperature not exceeding 25° C and heating thereafter the resulting reaction mixture up to 40° C.

~~7.~~5. The method of any of claims 1 to ~~6~~ 4 which comprises adding preheated water to the reaction mixture resulting from step b) prior to transforming compound of formula I into its hydrochloride salt according to step c).

~~8.~~6. The method of any of claims 1 to ~~7~~5 which comprises filtering off the said hydrochloride from the reaction mixture resulting from step c) and subsequently subjecting said hydrochloride salt to alkalinisation by means of ammonia in an aqueous organic media.

~~9. 1-Methyl-2-(4-methlymercapto-phenyloxymethyl)-5-nitro-imidazole as obtained by means of the method according to claims 1 to 8.~~

~~10. Use of 1-Methyl-2-(4-methlymercapto-phenyloxymethyl)-5-nitro-imidazole according to claim 9 in the manufacture of a medicament for treating parasitic diseases and in particular Chagas disease and human African trypanosomiasis.~~