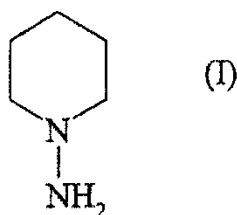


METHOD FOR PREPARING N-AMINOPIPERIDINE
AND ITS SALTS

A subject-matter of the present invention is
a novel process for the preparation of
5 N-aminopiperidine of formula



Several processes for the preparation of
N-aminopiperidine are known in the literature:

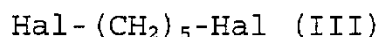
- 10 - Raschig process using piperidine and chloramine;
- process via hydrazine and N-acetylamino-
piperidine;
- process via N-nitrosopiperidine (Lunn, Keefer,
J. Org. Chem., 1984, 49 (19), 3470);
- 15 - process via glutaraldehyde and benzotriazole
(Katritzky A.R., Wei-Quiang Fan, J. Org. Chem., 1990,
55, 3205-3209).

The process for the preparation of
N-aminopiperidine (I) and its salts according to the
20 present invention is characterized in that:

a) a carbazate of formula:

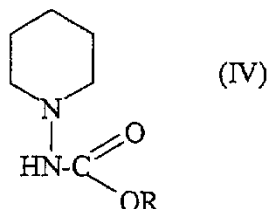


in which R represents a (C₁-C₆)alkyl group, a phenyl or
a benzyl, is treated with a 1,5-dihalopentane of
25 formula:



in which Hal represents a halogen atom;

b) the piperidin-1-ylcarbamate thus obtained of formula:



5

in which R represents a (C₁-C₆)alkyl group, a phenyl or a benzyl, is treated in acidic medium or in basic medium to produce the expected N-aminopiperidine.

If appropriate, a salt of N-aminopiperidine
10 (I) can be prepared by the action of an inorganic or organic acid.

The term "halogen atom" is understood to mean a bromine, chlorine or iodine atom.

Stage a) is carried out in a solvent, such as
15 acetonitrile or toluene, at a temperature between ambient temperature and the reflux temperature of the solvent.

Stage b) is carried out either in acidic medium, for example in the presence of hydrochloric or
20 hydrobromic acid, or in basic medium, for example in the presence of potassium hydroxide or sodium hydroxide, in a solvent such as water or ethanol and at a temperature between ambient temperature and the reflux temperature of the solvent.

25

According to a preferred embodiment of the

present invention, in stage a), a compound of formula (II) in which R represents an ethyl radical is treated with a compound of formula (III) in which Hal represents a bromine atom, in acetonitrile, by heating
5 at reflux of the solvent.

According to a preferred embodiment of the present invention, in stage b), the compound of formula (IV) in which R represents an ethyl radical is treated with sodium hydroxide in water by heating at reflux of
10 the solvent.

Preferably, an N-aminopiperidine salt, such as the hydrobromide, the hydrochloride or the oxalate, is prepared. For example, N-aminopiperidine hydrobromide can be prepared in a solvent such as
15 methyl tert-butyl ether (MTBE).

EXAMPLE

A - Ethyl piperidin-1-ylcarbamate

A mixture of 565.3 g of ethyl carbazate in 373 ml of acetonitrile is prepared. 415.4 g of
20 1,5-dibromopentane are run onto the preceding mixture brought to reflux. Reflux is maintained for 3 hours. The acetonitrile is removed by concentrating under vacuum. The residue thus obtained is dissolved in a toluene/water mixture. The two-phase mixture is brought
25 to pH = 5 by addition of 30% NaOH. The aqueous phase is separated by settling and re-extracted with toluene. Water and 36% HCl are added to the combined toluene

phases. The "rich" aqueous phase is washed 3 to 4 times with methyl tert-butyl ether (MTBE) to remove the neutral materials (impurities, diethyl carbazate, residual dibromopentane). The acidic aqueous phase is
5 basified with NaOH and then NaHCO₃ in the presence of toluene. The aqueous phase is re-extracted with toluene. The toluene phases are washed separately with water in order to deplete in residual ethyl carbazate. The toluene phases are concentrated to dryness. 252 g
10 of the expected product are obtained in the form of a white powder which is purified by recrystallization from methylcyclohexane.

¹H NMR spectrum at 300 MHz: δ (ppm): 1.23: t: 3H; 4.14: qd: 2H; 2.70: t: 4H; 1.66: qt: 4H; 1.36: qt: 2H; 5.54: bs: 1H.
15

B - N-Aminopiperidine

A mixture of 160 g of compound obtained in the preceding stage, 214 ml of water and 120 g of sodium hydroxide beads is brought to reflux for 3 hours
20 while flushing with argon. After cooling, 640 ml of MTBE are introduced before filtering off the inorganic materials present. A crude N-aminopiperidine solution in MTBE is thus obtained.

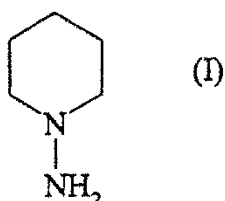
C - Preparation of crude N-aminopiperidine 25 hydrobromide

Approximately 1 volume of a 36% w/w solution of hydrobromic acid in ethanol is run, at 25°C and over

0.5 hour, onto the solution of N-aminopiperidine in MTBE obtained in the preceding stage. The formation of a precipitate is observed and the mixture is kept stirred for 1 hour. The hydrobromide is filtered off at
5 20°C and washed with ethanol and then with MTBE. It is subsequently dried under vacuum at 45-50°C and 156 g of the expected compound are obtained.
M.p. = 177-177.5°C (literature 174-175°C).

CLAIMS

1. Process for the preparation of
N-aminopiperidine of formula:



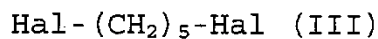
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and its salts with an inorganic or organic acid,
characterized in that:

a) a carbazate of formula:

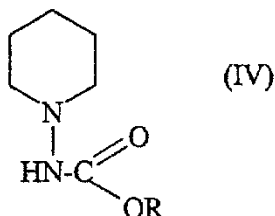


10 in which R represents a (C₁-C₆)alkyl group, a phenyl or
a benzyl, is treated with a 1,5-dihalopentane of
formula:



in which Hal represents a halogen atom;

15 b) the piperidin-1-ylcarbamate thus obtained of
formula:



in which R is as defined above, is treated in acidic
20 medium or in basic medium to produce the compound of
formula (I).

2. Process according to Claim 1,

characterized in that, in stage a), the reaction is carried out in a solvent chosen from acetonitrile or toluene at a temperature between ambient temperature and the reflux temperature of the solvent.

5 3. Process according to Claim 1 or 2, characterized in that, in stage b), the reaction is carried out using either an acid chosen from hydrochloric acid or hydrobromic acid or a base chosen from potassium hydroxide or sodium hydroxide in a
10 solvent such as water or ethanol and at a temperature between ambient temperature and the reflux temperature of the solvent.

 4. Process according to any one of Claims 1 to 3, characterized in that, in stage a), a compound of
15 formula (II) in which R represents an ethyl radical is treated with a compound of formula (III) in which Hal represents a bromine atom, in acetonitrile, by heating at reflux of the solvent.

 5. Process according to any one of Claims 1
20 to 4, characterized in that, in stage b), the compound of formula (IV) in which R represents an ethyl radical is treated with sodium hydroxide in water by heating at reflux of the solvent.

 6. Process according to any one of Claims 1
25 to 5, characterized in that a salt of the compound of formula (I) chosen from the hydrobromide, the hydrochloride or the oxalate is prepared.

7. Process according to any one of Claims 1 to 6, characterized in that the hydrobromide of the compound of formula (I) is prepared in methyl tert-butyl ether.