

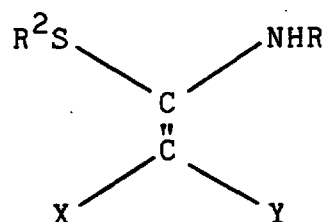
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Preparation of Amine Derivatives

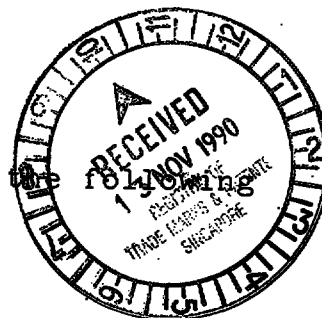
The present invention relates to the preparation of amine derivatives. N-Methyl-1-alkylthio-2-nitroethenamine derivatives are useful as intermediates for the preparation of ranitidine and other histamine H_2 -antagonists containing the $-NHC(=CHNO_2)NHCH_3$ end group, such as nizatidine.

Such intermediates have previously been prepared by direct displacement of a single alkylthio group in 2,2-bisalkylthio-1-nitroethene derivatives by reaction with methylamine. However this reaction suffers from a lack of selectivity and provides N-methyl-1-alkylthio-2-nitroethenes contaminated with both unreacted starting material and the bis-aminated side product 2,2-bismethylamino-1-nitroethene.

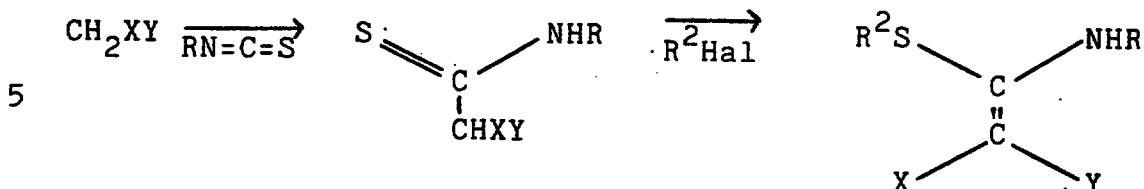
British Patent Specification 1421792 discloses the preparation of compounds of formula



in which X and Y, which may be the same or different, each represent hydrogen, nitro, cyano, or SO_2Ar (where Ar is optionally substituted phenyl), except that X and Y cannot both represent hydrogen, R represents lower alkyl and R^2



represents lower alkyl or aralkyl, by the following reaction sequence:



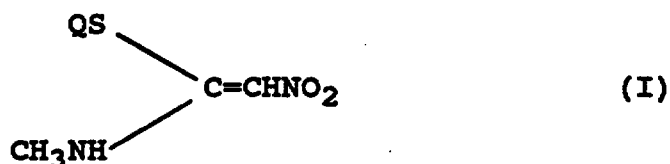
The substituted methane CH_2XY is said to be reacted with the isothiocyanate ester after treatment with a strong base such as sodium hydride or sodium hydroxide. In the only specific example of this reaction which is disclosed, methyl isothiocyanate is reacted with malononitrile in the presence of sodium hydride and dimethylformamide. The second stage of the reaction is carried out by adding methyl iodide in dimethylformamide.

Chem. Ber. 100 591-604(1967) discloses the reaction of phenyl isothiocyanate with nitromethane and also discloses that the reaction should be carried out in the presence of sodium hydride in dimethylformamide. The reaction is followed by methylation with methyl iodide to produce N-phenyl-1-methylthio-2-nitroethenamine.

The use of sodium hydride in dimethylformamide as taught by the documents referred to above is unsuitable for large scale preparations in view of the known hazards associated with the combination of these reagents.

The present invention provides a process for the preparation of a compound of formula (I)

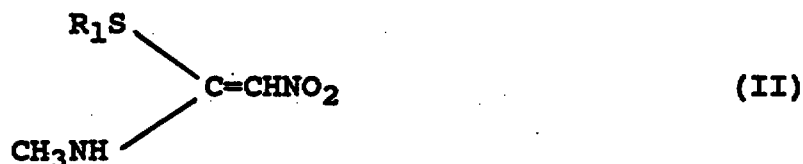
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wherein Q is hydrogen or a cation derived from a suitable base which comprises reacting methyl isothiocyanate with the carbanion of nitromethane in the presence of dimethyl sulphoxide as solvent, optionally in the presence of a co-solvent. The carbanion of nitromethane is generated in situ from nitromethane by reaction with the base. The compound of formula (I) wherein Q is a hydrogen atom may be prepared from the compound of formula (I) in which Q is a cation by addition of one equivalent of a suitable acid.

The compound of formula (I) may be treated with an appropriate alkylating agent such as an alkyl halide (e.g. methyl bromide or methyl iodide) or a dialkyl sulphate (e.g. dimethyl sulphate), to produce an N-methyl-1-alkylthio-2-nitro-ethenamine derivative of formula (II)

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wherein R_1 is a C_{1-4} alkyl group, preferably methyl

It has now surprisingly been found that formation of the compound of formula (I) and thus production of the N-methyl-1-alkylthio-2-nitroethanamine derivatives of formula (II) takes place in particularly good yield, provided that the reaction between methyl isothiocyanate and the carbanion of nitromethane is carried out in dimethyl sulphoxide as a solvent, optionally in the presence of a co-solvent. Thus when the reaction of methyl isothiocyanate with nitromethane is carried out in the presence of sodium hydride as base the yield increases from 22% when dimethylformamide is used as solvent to 59% when dimethyl sulphoxide is used as solvent.

Preferably the compound of formula (I) is reacted in situ with the alkylating agent and in this case the reaction will also generally be carried out in the same solvent medium.

A preferred process according to the invention for preparing N-methyl-1-alkylthio-2-nitroethanamine derivatives of formula (II) comprises reacting methyl isothiocyanate with the carbanion of nitromethane to give the compound of formula (I) in situ followed by alkylation with an appropriate alkylating agent as referred to above, the reaction being carried out in the presence of dimethyl sulphoxide as solvent, optionally in the presence of a co-solvent. Suitable co-solvents, the choice of which depends on the base used, include aprotic solvents (such as dimethylformamide and N-

methylpyrrolidinone) and water.

A particular embodiment of this process involves methylation of the compound of formula (I) prepared in situ using a suitable methylating agent such as methyl iodide or
5 dimethyl sulphate to give N-methyl-1-methylthio-2-nitroethenamine, i.e. the compound of formula (II) where R_1 is methyl.

The compounds of formula (I) can exist in tautomeric forms and formula (I) is intended to include all such forms.

10 The process of the present invention gives N-methyl-1-alkylthio-2-nitroethenamines of formula (II) in good yield and in a form that may be used to prepare compounds such as ranitidine without further purification. This, process, which uses cheap simple and commercially available starting
15 materials, may in general be carried out safely on a large scale and under mild conditions. The process of the invention is particularly applicable to the preparation of N-methyl-1-methylthio-2-nitroethenamine.

Conveniently the carbanion of nitromethane is prepared
20 in situ by treating nitromethane with a suitable base. Particularly suitable bases include alkali metal hydrides, alkali metal hydroxides or alkali metal alkoxides, for example sodium hydride, sodium hydroxide, potassium hydroxide, sodium ethoxide, sodium isopropoxide and potassium
25 tert-butoxide. Alkali metal hydroxides are preferred and when the base is an alkali metal hydroxide it may be added as an aqueous solution.

Where subsequent reaction with the alkylating agent is carried out on the compound of formula (I) prepared in situ then the same solvent medium will generally be used for the alkylation reaction.

The temperature of the reaction is conveniently within the range 0-50°C, and the reaction is preferably carried out at room temperature.

According to a further aspect, the invention provides a process for the preparation of compounds, particularly histamine H₂ antagonists, containing an -NHC(=CHNO₂)NHCH₃ end group which comprises reacting an N-methyl-1-alkylthio-2-nitroethenamine derivative of formula (II), prepared as described above, with an appropriate amine. Thus, in accordance with this aspect of the invention, ranitidine may be prepared from 2-[5-(N,N-dimethylaminomethyl)-2-furanmethylthio]ethylamine as the amine, preferably using N-methyl-1-methylthio-2-nitroethenamine as the compound of formula (II). The reaction may be carried out in a solvent such as water, optionally with heating.

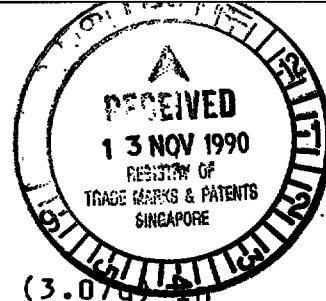
The invention is illustrated but in no way limited by the following Examples:

Example 1

N-Methyl-1-methylthio-2-nitroethenamine

5 (i) Nitromethane (1.25g) was added over 1 min. to a
suspension of flake potassium hydroxide (1.15g) in di-
methyl sulphoxide (containing 7.5% water) (18ml). A
solution of methylisothiocyanate (1.5g) in dimethyl
sulphoxide (containing 7.5% water) (2.5ml) was added over
10 2 min. keeping the temperature at 20-26°. The solution
was stirred for a further 0.5h at room temperature and
methyl iodide (3.19g) added dropwise over 2 min. keeping
the temperature at 22-24°. Stirring was continued for 1h.
at room temperature, and the solution was then diluted
with water (200ml) and extracted with dichloromethane.
15 The combined extracts were washed with water, evaporated
to dryness, and the residue was crystallised from
2-propanol to give the title compound (1.5g), Y49.4% m.p.
113-116.5°.

20 (ii) Nitromethane (1.32g) in dimethyl sulphoxide
(containing 7.5% water) (5ml) was added over 5 min. at
0-5° to sodium hydride (0.52g) in dimethyl sulphoxide
(containing 7.5% water) (20ml). The mixture was allowed to
warm to room temperature and after a further 30 min.
25 methyl isothiocyanate (1.58g) in dimethyl sulphoxide
(containing 7.5% water) (5ml) was added over 5 min.



The mixture was treated with methyl iodide (3.07g) in dimethyl sulphoxide (containing 7.5% water). (5ml) keeping the temperature below 30⁰, and the resulting solution was stirred overnight. The solvent was removed, water (50ml) was added to the residue and the mixture was worked up according to the procedure in Example 1(i) to give the title compound (1.88g), Y58.7%. m.p. 112-114⁰.

(iii) Nitromethane (0.62g) was added dropwise over 2 min. to a suspension of potassium tert-butoxide (1.1g) in dry dimethyl sulphoxide (9ml) under an atmosphere of nitrogen with the temperature kept at 20-25⁰. The mixture was stirred for 10 min. and a solution of methyl isothiocyanate (0.715g) in dimethyl sulphoxide (containing 7.5% water) (3ml) was added dropwise over 2 min. Stirring was continued for 0.5h at room temperature and then methyl iodide (1.52g) was added dropwise over 2 min. with the temperature kept at 20-25⁰. The solution was stirred at room temperature for 2h., diluted with water (100ml) and worked up according to the procedure in Example 1(i) to give the title compound (0.96g), Y66.1%. m.p. 113-115.5⁰.

(iv) According to the procedure in Example 1(iii), but replacing potassium tert-butoxide with sodium hydroxide (1.6g), nitromethane (2.44g) in dimethyl sulphoxide (containing 7.5% water) (35ml) and methyl isothiocyanate (2.92g) in dimethyl sulphoxide (containing 7.5% water) (5ml) followed by alkylation with methyl iodide (6.25g) gave the title compound (2.64g), Y44.5%. m.p. 113-116°.

Example 2

N-Methyl-1-methylthio-2-nitroethenamine

Potassium hydroxide (20.88g) in water (12.4ml) was added to a stirred solution of methyl isothiocyanate (27.22g) and nitromethane (22.75g) in dimethyl sulphoxide (185ml), keeping the temperature at 10-15°. Stirring was continued for 60 min. at 10-15° then the solution was divided into 2 equal portions (each 120ml).

(i) The first portion was stirred at 10-15° while dimethyl sulphate (17.62ml) was added over 15 min. Stirring was continued for 30 min. then water (90ml) was added and the mixture was worked up according to the procedure in Example 1(i) to give the title compound (12.45g), Y45.1%. m.p. 112.5 - 114°.

(ii) The second portion was treated with methyl iodide (11.66ml) and worked up in the same manner to give the title compound (14.61g), Y52.9%. m.p. 112.5 - 114°.

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Example 3

N-Methyl-1-methylthio-2-nitroethenamine

10 Nitromethane (1.05g) and methyl isothiocyanate (1.26g) in dry dimethyl sulphoxide (6.71g) was added over 70 min. to a stirred suspension of sodium hydride (0.41g) in dimethylformamide (4.3ml) with the temperature kept below 25°. Stirring was continued for 3h. then methyl iodide
15 (2.45g) was added over 15 min. keeping the temperature below 30°. The resulting solution was stirred for 30 min., water (9ml) was added and the solution was worked up according to the procedure in Example 1(i) to give the title compound. (1.30g), Y50.8%. m.p. 113.5-115.5°.

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Example 4

N-Methyl-1-methylthio-2-nitroethenamine

Nitromethane (22.7g) was added over 8 min. to a stirred
25 suspension of flake potassium hydroxide (20.86g) in

dimethyl sulphoxide (157.5ml) and water (6.4ml) keeping the temperature at 15-20°. A solution of methyl isothiocyanate (27.19g) in dimethyl sulphoxide (27ml) and water (1ml) was added dropwise over 20 min. keeping the temperature at 15-25°. Stirring was continued for a further 1h. at room temperature and methyl iodide (52.78g) was added over 10 min. keeping the temperature at 15-20°. The resulting mixture was stirred for a further 1h. at room temperature then water (178ml) was added and the mixture was worked up according to the procedure in Example 1 (i) to give the title compound (25.68g), Y46.6%. m.p. 113-116°.

Example 5

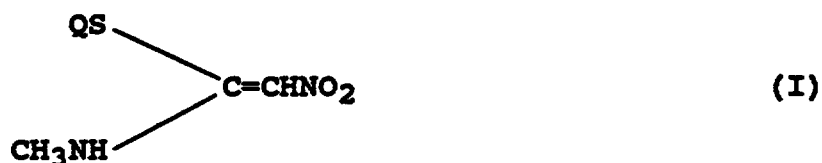
N-[2-[5-(Dimethylamino)methyl-2-furanylmethylthio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine

A solution of 2-[5-(N,N-dimethylaminomethyl)-2-furan-methylthio]ethylamine (32.1g) in water (25ml) was added dropwise over 4h. to a stirred solution of N-methyl-1-methylthio-2-nitroethenamine (23g) in water (40ml) at 50°. The reaction mixture was heated at 50° for a further 2h. and then heated to 90°. Methyl isobutyl ketone (150ml) was added to the solution and the water removed by azeotropic distillation. The solution was cooled at 60°

and charcoal (1.5g) added. The mixture was filtered, the charcoal residue washed with methyl isobutyl ketone (50ml) and the combined filtrate and washings were cooled to 0°. The title compound (39g) m.p. 68-70° crystallised and was filtered off.

CLAIMS

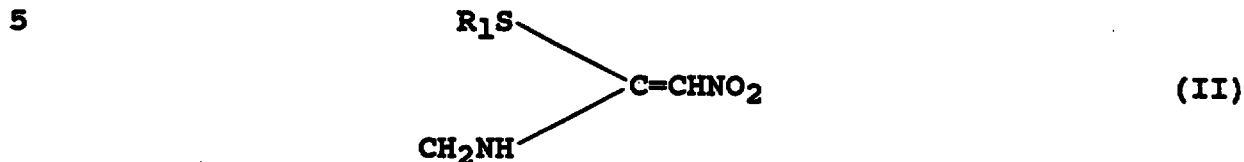
- 5 1. A process for the preparation of a compound of formula (I)



- 10 wherein Q is a hydrogen or a cation derived from a suitable base which comprises reacting methyl isothiocyanate with the carbanion of nitromethane in the presence of dimethyl sulphoxide as solvent, the carbanion of nitromethane having been generated in situ from nitromethane and the base, and
15 optionally treating the compound in which Q is a cation with a suitable acid to generate the compound in which Q is hydrogen.
2. A process as claimed in claim 1, wherein dimethyl sulphoxide is used together with a co-solvent.
- 20 3. A process as claimed in claim 1 or 2, wherein the base is an alkali metal hydroxide.
4. A process as claimed in claim 3 wherein the base is an alkali metal hydroxide used as an aqueous solution.
5. A process as claimed in claim 3 or 4 wherein the
25 alkali metal hydroxide is potassium hydroxide.
6. A process as claimed in claim 1 or 2, wherein the base is an alkali metal hydride or an alkali metal alkoxide.
7. A process as claimed in claim 6, wherein the base is sodium hydride or potassium tert-butoxide.



8. A process for the preparation of an N-methyl-alkylthio-2-nitroethenamine derivative of formula (II)



wherein R_1 is a C_{1-4} alkyl group, which comprises preparing a compound of formula (I) as defined in claim 1 by a process as
10 claimed in any of claims 1 to 7 and subsequently reacting the compound of formula (I) with a suitable alkylating agent to produce the N-methyl-1-alkylthio-2-nitroethenamine derivative of formula (II).

9. A process as claimed in claim 8 wherein the reaction
15 with the alkylating agent is carried out on the compound of formula (I) prepared in situ.

10. A process as claimed in claim 8 or 9, wherein the alkylating agent is an alkyl halide or a dialkyl sulphate.

11. A process as claimed in any of claims 8 to 10 for the
20 preparation of the compound of formula (II) in which R_1 is methyl, wherein the alkylating agent is methyl iodide or dimethyl sulphate.

12. A process for the preparation of a compound containing an $-\text{NHC}(=\text{CHNO}_2)\text{NHCH}_3$ end group which comprises
25 preparing an N-methyl-1-alkylthio-2-nitroethenamine derivative of formula (II) as defined in claim 8 by a method as claimed in any of claims 8 to 11, and subsequently reacting the derivative of formula (II) with a suitable amine.



13. A process as claimed in claim 12, wherein the compound containing an $\text{-NHC(=CHNO}_2\text{)NHCH}_3$ end group is 5 ranitidine and the amine is 2-[5-(N,N-dimethylaminomethyl)-2-furanmethylthio]ethylamine.

14. A process as claimed in claim 13, wherein the compound of formula (II) is N-methyl-1-methylthio-2-nitroethenamine.

