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(71) Applicant (for all designated States except US): **THE SECRETARY OF STATE FOR DEFENCE** [GB/GB]; Whitehall, London SW1A 2HB (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GOLDING, Peter** [GB/GB]; La Villeta, The Street, Bramley, Hampshire RG26 5BP (GB). **MACCUISH, Alistair, J.** [GB/GB]; 13 Matheson Place, Portree, Isle of Skye IV51 9JA (GB). **BELLAMY, Anthony, John** [GB/GB]; 16 Martens Close, Shrivenham, Swindon SN6 8BA (GB).

(74) Agent: **BECKHAM, Robert, William**; D/IPR Formalities Section, Poplar 2, MOD Abbey Wood #2218, Bristol BS34 8JH (GB).

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(54) Title: PROTECTION OF AMINE AND HYDROXYL GROUPS USING FLUOROACYLATION

(57) Abstract: The invention describes the novel use of trifluoroacylation to generate protecting groups for amine and hydroxyl groups in strong nitrolysing media. Trifluoroacyl compounds not only provide excellent protection from media such as nitric acid/oleum but in turn may be readily de-protected by alcoholic solvents. In particular the invention describes how trifluoroacetylation may be used to selectively protect secondary amine groups and hydroxyl groups.

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PROTECTION OF AMINE AND HYDROXYL GROUPS USING FLUOROACYLATION

The present invention relates to the use of fluoroacylation for the protection of nitrogen and oxygen molecular sites and in particular
5 amine and hydroxyl groups against strong nitrolysing reagents.

As is well known in the art nitrolysis is a frequently used technique in organic synthesis often necessitating the use of strong nitrolysing reagents such as nitric acid, sulphuric acid and oleum. Such reagents
10 are highly effective at introducing the nitro group into organic compounds but tend to be indiscriminate in their reactivity. This poses a problem in relation to the development of selective synthetic pathways where nitration is required at some stage in the design of the reaction sequence.

The problem of indiscriminate nitrolysis is particularly acute for free amine or oxygen containing organic compounds. Previous research has only revealed compounds which bind irreversibly to the compound. Removal of the protecting group can be achieved but only at the
20 expense of breaking apart the underlying molecular structure.

Hitherto and as far as the applicant is aware there has been no method of reversibly protecting either nitrogen or oxygen molecular sites against nitrolysing reagents.

Accordingly there is provided use of a fluoroacylating reagent to protect a molecular site against nitrolysis. The fluoroacylating agent may be a trifluoroacetylating reagent.

The fluoroacylated derivative may be readily deprotected under mild conditions such as by solvolysis using alcohol or alcohol in conjunction with a carboxylic acid salt.

There is provided the use of a fluoroacylating reagent to protect a
35 nitrogen molecular site from nitrolysis. The nitrogen molecular site may be any primary or secondary amine.

In a specific embodiment the fluoroacylating reagent may be used to protect the secondary amine group(s) of an hexaazaisowurtzitane derivative.

5

The fluoroacylating reagent may be any trifluoroacetylating reagent such as for example trifluoroacetic anhydride or may be a mixture of trifluoroacetic acid and trifluoroacetic anhydride or trifluoroacetyl chloride. In the latter case the mixture may be used to selectively
10 provide protection for two secondary amine groups.

In a specific embodiment a mixture of trifluoroacetic anhydride and trifluoroacetic acid may be used to selectively protect only one secondary amine of a hexaazaisowurtzitane derivative.

15

The fluoroacylating reagent can be used to protect against strong nitrolysing solvents such as for example nitric acid/oleum.

Solvolysis may be used to fully deprotect the fluoroacylating group or
20 to selectively deprotect the fluoroacylating group. The deprotection of the fluoroacetyl group can be achieved using mild conditions with an alcohol such as for example methanol.

In two specific embodiments mild conditions in relation to using an
25 alcohol (such as ethanol, but also other alcohols such as for example methanol or propanol could be used) have been shown to selectively deprotect only one fluoroacyl protecting group from a di-amine hexaazaisowurtzitane derivative. Whereas, stronger de-protection conditions using ethanol in conjunction with sodium acetate have been
30 shown to remove both of the fluoroacyl protecting groups.

There is further provided the use of a fluoroacylating reagent to protect an oxygen molecular site from nitrolysis. The oxygen containing group may be a hydroxyl group.

35

The fluoroacylating reagent may be any fluoroalkylcarboxylic anhydride or halide. In specific embodiments the fluoroacylating reagent may be a trifluoroacetylating reagent such as trifluoroacetic anhydride.

- 5 The trifluoroacetylating reagent may be a mixture of trifluoroacetic acid and trifluoroacetic anhydride, or trifluoroacetyl chloride.

The fluoroacyl protecting group can provide protection to a hydroxy group under strong nitrolysing conditions such as for example nitric acid/oleum, sulphuric acid and N_2O_5 and may be readily removed from the oxygen containing group by reacting with an alcohol such as for example methanol.

15 In a specific embodiment the trifluoroacetyl group has been found to be an effective protecting group for hydroxyl groups in the nitrolysis of an oxetane using a nitrolysing reagent of nitric acid/oleum. Deprotection being effected under mild conditions using methanol.

The invention will now be described by way of the following synthetic examples and with reference to the figures of which:

Figure 1 shows use of trifluoroacetic anhydride for the protection of free amine for a tetra-acetyl-hexaazaisowurtzitane derivative against nitric acid and oleum. The fluoroacetyl group may be deprotected by the use of an alcohol in conjunction with the salt of a carboxylic acid. In this particular example sodium acetate with ethanol is used.

Figure 2 shows use of trifluoroacetic anhydride for the protection of free mono-amine for a penta-acetyl hexaazaisowurtzitane derivative against nitric acid and oleum. Mild conditions using ethanol is shown to remove the fluoroacetyl protecting group.

Figure 3 shows use of trifluoroacetic anhydride to trifluoroacetylate both the amine groups of a tetra-acetyl hexaazaisowurtzitane di-amine derivative. The trifluoroacetyl groups subsequently protect the nitrogen atom from nitrolysis using nitric acid and oleum.

Figure 4 shows use of a mixture of trifluoroacetic anhydride and trifluoroacetic acid to selectively mono fluoroacetylate one of the secondary amine groups of a tetra-acetyl hexaazaisowurtzitane di-amine derivative. The trifluoroacetylated groups subsequently protects the nitrogen atom from nitrolysis using nitric acid and oleum. Mild conditions using ethanol alone is shown to remove the trifluoroacetylate group.

Figure 5 shows use of trifluoroacetic anhydride for the protection of hydroxyl group for a hydroxyl oxetane derivative against dinitrogen pentoxide (N_2O_5). The fluoroacetate protecting group is shown to be removed using mild conditions with methanol.

Examples

(a) Trifluoracylation as protection for an amine

(a) Synthesis of 2,4,6,8,12-tetranitro-2,4,6,8,10,12-hexa aza isowurtzitane

The reaction comprises three steps:

(1) the preparation of 2,6,8,12-tetraacetyl-4,10-bis(trifluoroacetyl)-2,4,6,8,10,12-hexaazaiso wurtzitane (B) from 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (A),

(2) the nitration of 2,6,8,12-tetraacetyl-4,10-bis(trifluoroacetyl)-2,4,6,8,10,12-hexaazaiso wurtzitane (B) to form 2,,6,8,12-tetranitro-4,10-bis(trifluoroacetyl)-2,4,6,8,10,12-hexaazaisowurtzitane (C) and

(3) the removal of the two trifluoroacetyl groups from 2,6,8,12-tetranitro-4,10-bis(trifluoroacetyl)-2,4,6,8,10,12-hexaazaisowurtzitane (C) to form 2,6,8,12-tetranitro-2,4,6,8,10,12-hexaazaisowurtzitane (D).

(1) Preparation of 2,6,8,12-tetraacetyl-4,10-bis (tri fluoro acetyl)-2,4,6,8,10,12-hexaazaisowurtzitane (B)

Compound A (6.0 g) was suspended in trifluoroacetic anhydride (30 ml) and stirred at 38 °C for 48 hours. An aliquot removed and analysed after 24 hours indicated that the reaction was complete at that stage. Excess anhydride was removed on a rotary evaporator to leave a pink-white solid. The solid was dissolved in chloroform and evaporated to dryness, this process then being repeated. The resulting solid was dried under vacuum at 50 °C for 8 hours, giving 9.62 g, 102 % crude yield.

NMR and IR analysis indicated that the resulting solid was compound (B).

¹H NMR (DMSO-d₆): δ 2.06 (broad s, 12.4H, 4xCOCH₃), 6.63-7.00ppm (m, 6.0H, 6xCH).

¹⁹F NMR: δ 66.52 and 66.88ppm.

(2) Preparation of 2,6,8,12-tetranitro-4,10-bis (tri fluoro acetyl)-2,4,6,8,10,12-hexaazaiso wurtzitane (C)

A nitrating acid was prepared by the dropwise addition of 30% SO₃ fuming sulphuric acid (5.0 ml) to 99.5 % nitric acid (30.0 ml). An ice/water bath was used to keep the temperature of the reaction mixture below 15 °C during the addition process. The mixed acid was then cooled to 5 °C before the rapid addition with vigorous stirring of crude compound B (7.0 g) via a solids funnel. When all of compound B had dissolved, the solution was heated to 50 °C for 4 hours. TLC analysis of a sample at this point indicated the presence of un-nitrated products, so heating was continued at 60 °C for a further 1.5 hours. The solution was removed from the heat and drowned in 500 ml of an ice/water mixture. The precipitate that formed was removed by filtration, washed with water until washings were neutral, then dried

overnight in a vacuum dessicator to leave a fine white solid (6.59 g, 92 % crude yield).

NMR and IR analysis indicated that the resulting solid was compound C.

¹H NMR (DMSO-d₆): δ 7.31-7.41 (m, 3.6H, 4xCH), 8.01ppm (s, 2.0H, 2xCH)

¹⁹F NMR: δ 67.24 to 66.7ppm (m).

(3) Preparation of 2,6,8,12-tetranitro-2,4,6,8,10,12-hexa aza isowurtzitane (D)

Crude compound (C) (0.8 g) was added to a pre-prepared solution of sodium acetate (140 mg) in dry ethanol (14 ml). A precipitate formed immediately after the crude compound (C) had dissolved, and a yellow colouration was observed in the mixture. Stirring was continued for a further 10 minutes, then the precipitate was filtered off, washed with water and dried in a vacuum dessicator overnight to leave a white solid (303 mg, 58.7 % yield)

NMR and IR analysis indicated that the resulting solid was compound (D). DSC (10 K/min) indicated onset of decomposition at 183 °C. There was no explosive exotherm using these DSC conditions. This indicates that compound (D) is a thermally stable explosive, relative to CL-20.

¹H NMR (DMSO-d₆): δ 5.44 (s, 1.9H, 2xNH), 6.28 (s, 4.1H, 4xCH), 7.57ppm (s, 2.0H, 2xCH).

¹³C NMR (acetone-d₆): δ 72.48, 72.98ppm.

¹H-¹³C correlation: 5.44ppm (H-4, H-10) uncoupled, 6.28 (H-3, H-5, H-7, H-9) coupled to 72.48 9C-3, C-5, C-7, C-9), 7.57ppm 9H-1, H-11) coupled to 72.98 (C-1, C-11).

Reaction Scheme 2

(b) Synthesis of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexa aza isowurtzitane

5 The reaction comprises four steps:

(1) the preparation of 2,6,8,10,12-pentaacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (E) from 2,6,8,12-tetraacetyl-2, 4, 6, 8, 10, 12-hexaazaisowurtzitane (A);

10

(2) the preparation of 2,6,8,10,12-pentaacetyl-4-tri fluoro acetyl-2,4,6,8,10,12-hexaazaiso wurtzitane (F) from 2,6,8,10,12-pentaacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (E);

15 (3) the nitration of 2,6,8,10,12-pentaacetyl-4-tri fluoro acetyl-2,4,6,8,10,12-hexaazaiso wurtzitane (F) to form 2,6,8,10,12-pentanitro-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaiso wurtzitane (G) and

20 (4) the removal of the trifluoroacetyl group from 2, 6, 8, 10,12-pentanitro-4-trifluoroacetyl-2,4,6,8,10,12-hexa azaisowurtzitane (G) to form 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexaazaisowurtzitane (H).

(1) Preparation of 2,6,8,10,12-pentaacetyl-2,4,6,8,10,12-hexaazaisowurtzitane from 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane

A suspension of compound A (1.0 g) in a mixture of glacial acetic acid (15 ml) and acetic anhydride (10 ml) was stirred at 60 °C for 12
30 hours. Excess acetic acid/anhydride mixture was removed on a rotary evaporator at 60 °C. The remaining reaction mixture was dried under vacuum at 60 °C for 6 hours to leave a white solid. This solid was slurried in methanol (200 ml) at 60 °C and filtered hot. The remaining solids in the filter were recovered and extracted in a
35 similar manner with two further portions of hot methanol. The extracts were combined and the methanol was removed on the rotary

evaporator and the remaining off-white solid dried under vacuum at 50 °C (6.7 g, 99.5% crude yield, 302-304 °C melting point (DSC, ex methanol)).

5 NMR and IR analysis indicated that the resulting solid was compound (E).

¹H NMR (DMSO-d₆): δ1.90-2.04 (m, 12.0H, 4xCOCH₃), 2.18-2.31 (m, 3.1H, COCH₃), 4.66-4.85 (m, 0.8H, NH), 5.55-5.58 (m, 1.9H, 2xCH), 6.21-
10 6.77ppm (m, 4.0H, 4xCH).

(2) Preparation of 2,6,8,10,12-pentaacetyl-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaiso wurtzitane from 2,6,8,10,12-pentaacetyl-2,4,6,8,10,12-hexaazaisowurtzitane.

15

Crude compound (E) (3.0 g) was stirred in trifluoroacetic anhydride (12 ml) at 38 °C for 48 hours. The resulting clear solution was evaporated to dryness, the resulting solid being redissolved in chloroform and evaporated to dryness twice more. The solid was dried
20 under vacuum at 50 °C to leave a pinkish-white solid (3.3.8 g, 90 % crude yield).

NMR and IR analysis indicated that the resulting solid was compound (F).

25

¹H NMR (DMSO-d₆): δ1.94-2.09 (m, 12.5H, 4xCOCH₃), 2.28-2.36 (m, 3.6H, 1xCOCH₃), 6.45-7.08ppm (m, 6.0H, 6xCH).

¹⁹F NMR: δ67.66 and 66.86ppm.

30

(3) Preparation of 2,6,8,10,12-pentanitro-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaiso wurtzitane from 2,6,8,10,12-penta acetyl-4-trifluoroacetyl-2,4,6,8,10,12-hexa aza iso wurtzitane

35 A nitrating mixture was formed by the dropwise addition of 30 % SO₃ fuming sulphuric acid (6.0 ml) to 99.5 % nitric acid (13.0 ml). The

temperature was kept below 15 °C during the addition by immersion of the reaction vessel in a water/ice bath. The mixed acid was cooled to 5 °C before the rapid addition, with vigorous stirring, of crude compound F (2.0 g) via a solids funnel. When the solid had completely dissolved, the flask was heated at 60 °C for 3 hours. The reaction mixture was allowed to cool before being drowned in an ice/water mixture (200 ml). The flask was washed out with two portions of water (2 x 50 ml). The dense white precipitate was filtered off, washed with water until the washings were neutral, and dried overnight in a vacuum dessicator (1.2 g, 58 % crude yield).

MNR and IR analysis indicated that the resulting solid was compound (G).

¹H NMR (DMSO-d₆): 87.54-7.97 (m, 2.0H, 2xCH), 8.12 (s, 1.6H, 2xCH), 8.29ppm (d, J=7Hz, 1.4H 2xCH).

¹⁹F NMR: 67.99ppm.

TLC analysis of the crude material indicated that CL 20 was a major contaminant. NMR studies indicated that approximately 37 % of the crude product was CL-20.

(4) Preparation of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexaazaisowurtzitane (H) from 2,6,8,10,12-pentanitro-4-tri fluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (G).

25

Crude compound (G) (2.0 g) was dissolved in dry ethanol (2 ml) and stirred at room temperature for 48 hours, during which time the solution developed a yellow colouration. The solvent was removed by rotary evaporation and the resulting solid dried under vacuum at 50 °C to leave a yellow solid (1.2 g). TLC analysis of the solid suggested that it consisted of two major components, one of which was CL-20. A portion of the product was resolved by column chromatography, using a 40 cm nylon column of 2 cm diameter packed with silica gel (Merck Kieselgel 60 F₂₅₄), using a 3:2 mixture of n-heptane/ethyl acetate as eluent. After development, the column was cut-up and the products extracted from the silica gel.

MNR and IR analysis indicated that the purified solid was compound (H).

¹H NMR (DMSO-d₆): δ5.99 (broad s, 0.8H, NH), 6.67-6.72 (m, 2.0H, 2xCH), 7.88 (s, 1.9H, 2xCH), 7.94ppm (d, J=8Hz, 2H, 2xCH).

¹³C NMR: 71.19, 73.25, 74.21ppm.

¹H-¹H correlation (COSY45): 5.99 (H-4) coupled to 6.67-6.72 (H-3, H-5), 6.67-6.72 coupled to 7.94 (H-9, H-11).

¹H-¹³C correlation: 6.67-6.72 coupled to 73.25, 7.88 coupled to 74.21ppm, 7.94 coupled to 71.19.

DSC (10 K/min) of the purified solid recorded the onset of an explosive decomposition exotherm at 168 °C, indicating that compound (H) is an explosive compound.

Reaction Scheme 3

(c) Synthesis of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexaazaisowurtzitane

(1) the preparation of 2,6,8,12-tetraacetyl-4,10-bis (tri fluoroacetyl)-2,4,6,8,10,12-hexaazaiso wurtzitane (B) from 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (A);

(2) the preparation of 2,6,8,12-tetranitro-4,10-(bis) tri fluoroacetyl-2,4,6,8,10,12-hexaazaiso wurtzitane (C) from 2,,6,8,12-tetraacetyl-4,10-bis(trifluoroacetyl)-2,4,6,8,10,12-hexaazaiso wurtzitane (B);

(3) the preparation of 2,6,8,12-tetranitro-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (J) from 2,,6,8,12-tetranitro-4,10-(bis)trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (C);

(4) the preparation of 2,6,8,10,12-pentanitro-4-tri fluoro acetyl-2,4,6,8,10,12-hexaazaiso wurtzitane (G) from 2,6,8,12-tetranitro-4-trifluoroacetyl-2,4,6,8,10,12-hexa aza iso wurtzitane (J), and

(5) the preparation of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexaazaisowurtzitane (H) from 2,6,8,10,12-pentanitro-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (G).

5

Steps (1) and (2) above correspond to steps (1) and (2) of the method described in relation to reaction scheme 1 above.

(3) Preparation of 2,6,8,12-tetranitro-4-trifluoroacetyl-
10 2,4,6,8,10,12-hexazaiso wurtzitane from 2,6,8,12-tetranitro-4,10-(bis)trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane.

Compound (C) (2.0 g) was dissolved in dry ethanol (10 ml) and stirred at room temperature for 48 hours. The excess ethanol was removed by
15 rotary evaporation to leave a yellow solid which was dried under vacuum at 50 °C for 6 hours (1.73 g, 105 %).

NMR and IR analysis indicated that the solid was compound J.

20 (2) Preparation of 2,6,8,10,12-pentanitro-4-trifluoroacetyl-2, 4, 6, 8, 10, 12-hexaazaiso wurtzitane from 2,6,8,12-tetra nitro-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane.

Compound (J) (1.0 g) was added quickly with vigorous stirring to an
25 ice-cooled mixture of 30 % SO₃ fuming sulphuric acid (0.2 ml) and 99.5 % nitric acid (3.0 ml). The mixture was allowed to warm slowly to room temperature and then stirred for 4 hours. The reaction mixture was then drowned in an ice/water mixture (100 ml) and the white precipitate which formed was removed by filtration and washed with
30 several large portions of water before being dried overnight in a vacuum dessicator (0.96 g, crude yield 87 %).

NMR and IR analysis indicated that the solid was compound (G).

¹H NMR (d₆-acetone): 7.70-7.87 (m, 2.6H, 2xCH), 8.15 (s, 2.1H, 2xCH),
35 8.26ppm (d, J=7Hz, 2.0H, 2xCH)

¹³C NMR (d₆-acetone): 71.21, 73.26, 74.22ppm.

¹⁹F NMR (d₆-acetone): 68.41ppm.

(3) Preparation of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexa aza isowurtzitane from 2,6,8,10,12-pentanitro-4-trifluoro acetyl-
5 2,4,6,8,10,12-hexaazaisowurtzitane.

Compound (G) (0.50 g) was dissolved in dry ethanol (10.0 ml) and stirred at room temperature for 48 hours. The solution was then evaporated to dryness and the resulting yellowish solid was dried
10 under vacuum at 50 °C for 6 hours (0.45 g).

NMR analysis of the solid indicated that the solid was predominantly compound (H).

¹H NMR (acetone-d₆): 5.96 (s, 0.8H, NH), 6.66-6.71 (m, 2.0H, 2xCH),
15 7.84 (2.1H, 2xCH), 7.93ppm (d, J=8Hz, 2H, 2xCH).

TLC and NMR studies indicated that the main contaminants were CL 20 (about 10% of the final product) and compound (J).

20 The reaction method of Figure 2 was found to be reagent inefficient, especially the preparation of compound (E) from compound (A) and the subsequent preparation of compound (F). The final nitration product was found to contain almost 40 % CL 20 as an impurity.

25 It was discovered that nitration of compound (B), conducted in an identical manner to the nitration used in relation to the reaction scheme of Figure 2, gives a product which is almost entirely free of the two over-nitration products CL-20 and pentanitro-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane. This suggests that the N-COCF₃
30 group is stable under the harsh nitration conditions employed and that the COCF₃ group is an effective protecting group in nitration reactions. It seems likely that the CL 20 contaminant in the nitration product of compound (F) is a result of the presence of compound (E) in the crude starting material (B).

35 Reaction Scheme 4

(D) Synthesis of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexa aza isowurtzitane from 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexa aza isowurtzitane.

5

The reaction comprises three steps:

(1) the preparation of 2,6,8,12,tetraacetyl-4-tri fluoro acetyl-2,4,6,8,10,12-hexaazaisowurtzitane (K) from 2,6,8,12-tetraacetyl-2, 4, 6, 8,10,12-hexaazaisowurtzitane (A).

10

(2) Preparation of 2,6,8,10,12-pentanitro-4-trifluoro-2, 4, 6, 8, 10, 12-hexaazaisowurtzitane (G) from 2,6,8,12-tetraacetyl-2, 6, 8, 12 - tetraacetyl-4-trifluoroacetyl-2, 4, 6,8,10,12-hexa aza isowurtzitane (K).

15

(3) Preparation of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexa azaisowurtzitane (H) from 2,6,8,10,12-pentanitro-2,4,6,8,12-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (G).

20

(1) the preparation of 2,6,8,12,tetraacetyl-4-tri fluoro acetyl-2,4,6,8,10,12-hexaazaisowurtzitane from 2,6,8,12,tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane.

25 Compound (A) (3.0 g) was stirred in trifluoroacetic acid (25 ml) before the addition of trifluoroacetic anhydride (10 ml). The reaction mixture was stirred at room temperature for 24 hours. The excess of trifluoroacetic acid/anhydride mixture was removed on the rotary evaporator to leave a viscous liquid. Methanol (5 ml) was
30 added dropwise to the liquid, and then the volatile components were removed on the rotary evaporator to leave a white solid. This solid was dissolved in methanol (10 ml) and refluxed for 4.5 hours; a white solid precipitated from the solution as the reflux progressed. The methanol was then evaporated from the suspension and the resulting
35 solid dried under vacuum at 50 °C [2.85 g, 74.0 % crude yield, 292 °C melting point (DSC, ex methanol)].

NMR and IR analysis indicated that the resulting solid was compound (K).

- 5 (2) Preparation of 2,6,8,10,12-pentanitro-4-trifluoro-2,4,6,8,10,12-hexaazaisowurtzitane from 2,6,8,12-tetraacetyl-2,6,8,12-tetraacetyl-4-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane.

A nitrating mixture was prepared by the dropwise addition of 30 % SO₃ fuming sulphuric acid (0.4 ml) to 99.5 % nitric acid (3.0 ml). The temperature was kept below 15 °C during the addition by immersion of the reaction vessel in an ice/water bath. The reaction vessel was kept in the ice/water bath during the rapid addition, with vigorous stirring, of crude compound K (500 mg). The reaction mixture was then heated at 70 °C for 3 hours (after which time TLC analysis indicated that the reaction was complete). The reaction mixture was allowed to cool before being drowned in an ice/water (100 ml) bath. The precipitate was filtered off, washed with water until the washings were neutral and dried overnight in a vacuum dessicator (390 mg, 69 % yield).

TLC analysis indicated that the resulting solid was compound (G).

- (3) Preparation of 2,6,8,10,12-pentanitro-2,4,6,8,10,12-hexa aza isowurtzitane from 2,6,8,10,12-pentanitro-2,4,6,8,12-trifluoroacetyl-2,4,6,8,10,12-hexaazaisowurtzitane.

Crude compound (G) was dissolved in dry ethanol (10 ml) and stirred at room temperature for 48 hours. The solution was evaporated to dryness and the resulting yellowish solid was dried under vacuum at 50 °C for 6 hours (331 mg, 105 % crude yield).

TLC and NMR analysis indicated that the solid was predominantly compound (H), with CL-20 as the main contaminant.

(b) Trifluoroacylation as protection for oxygen

Trifluoroacetylation of 3-methyl-3-(hydroxymethyl)oxetane: 3-methyl-3-(hydroxymethyl)oxetane trifluoroacetate (4)

5 3-methyl-3-(hydroxymethyl)oxetane (2.0 g) was dissolved in CH_2Cl_2 (7.0 ml). The solution was cooled in an ice/water bath before and during dropwise addition of trifluoroacetic anhydride (2.0 ml). Stirring was continued in the ice bath for 1 h after completion of the addition, and the excess anhydride was then removed on the rotary evaporator.
10 The liquid which remained was washed into a separating funnel with CH_2Cl_2 (2x5 ml), then water (20 ml). The organic phase was removed and the aqueous phase was extracted with CH_2Cl_2 (3x10 ml). All of the organic extracts were combined and washed with water (10 ml), then dried over magnesium sulphate. The solution was filtered and
15 evaporated on the rotary evaporator to leave a colourless oil (3.79 g, 97 %).

NMR (CDCl_3): ^1H δ 1.38 (s, 3.0H) and 4.42-4.51 ppm (m, 6.0H - this multiplet can be resolved into a singlet (2.0H) and a quartet (4.0H, AA'BB' system) by acidification of the NMR sample);
20 ^{13}C δ 20.66, 39.23, 72.15, 79.08, 114.61 (q, $J=286\text{Hz}$, COCF_3) and 157.64 ppm (q, $J=42\text{Hz}$, COCF_3);
 ^{19}F δ -75.38 ppm (s).
IR (thin film): 1787.9 cm^{-1} (CO stretch).

25

Nitrolysis of 3-methyl-3-(hydroxymethyl)oxetane tri fluoro acetate with N_2O_5 ; 2,2-bis(nitratomethyl)propan-1-ol tri fluoroacetate ester

A solution of the ester (1.0 g) in CH_2Cl_2 (25.0 ml) was cooled in an
30 ice/water bath before the addition of N_2O_5 (2.5 g, approx. 5 eq) in CH_2Cl_2 (20 ml). Stirring was continued in the ice bath for 30 min, then at rt for a further 16h. The solution was then washed into a separating funnel with CH_2Cl_2 (50 ml) and washed with saturated NaHCO_3 solution (50 ml). The organic phase was removed, and the aqueous
35 phase was extracted with CH_2Cl_2 (1x50 ml and 1x20 ml). All the organic extracts were combined and washed with water (30 ml), then dried over

magnesium sulphate. Evaporation of the solvent gave a yellowish oil (1.28 g, 83 %).

NMR (CDCl₃): ¹H δ 1.20 (s, 3.0H), 4.32 (s, 2.2H) and 4.44 (s, 4.5H);

5 ¹³C 17.00, 38.75, 68.24, 72.54, 114.35 (q, J=285 Hz) and 156.90 ppm (q, J=43Hz) ¹⁹F δ -75.24ppm.

IR (thin film): 1791.7 (CO stretch), 1278.1 (-ONO₂ symmetric stretch) and 1643.2 cm⁻¹ (-ONO₂ asymmetric stretch).

10 Two phase Nitrolysis of 3-methyl-3-(hydroxymethyl)oxetane tri fluoroacetate with Mixed Acid: 2,2-bis(nitratomethyl)propan-1-ol trifluoroacetate ester

A solution of the ester (300 mg) in CH₂Cl₂ was cooled in an ice/water
15 bath before and during the addition of a previously prepared mixture of 99.5 % nitric acid and 98 % sulphuric acid (90/10 w/w, 2.0 ml). The reaction mixture was removed from the ice bath after the addition was completed, and stirred rapidly at room temperature for 3h. The reaction mixture was washed into a separating funnel with CH₂Cl₂ (5 ml)
20 and washed successively with water (20 ml), saturated NaHCO₃ (20 ml) and water (20 ml). The organic phase was removed and dried over magnesium sulphate. Filtration and evaporation of the solvent gave a yellowish oil (290 mg, 62 %). The ¹H NMR spectrum of this material was
25 almost identical to that produced by the procedure above, but no peaks due to MTN were apparent. (An aliquot was removed after 2h, worked up as above and analysed said analysis suggesting that the reaction was complete at that point).

30 Solvolysis of 2,2-bis(nitratomethyl)propan-1-ol tri fluoro acetate: 2,2-bis(nitratomethyl)propan-1-ol

2,2-Bis(nitratomethyl)propan-1-ol trifluoroacetate (153 mg) was dissolved in MeOH (5.0 ml). K₂CO₃ (30 mg) in water (0.50 ml) was added and the solution was extracted with CH₂Cl₂ (4x10 ml). The organic
35 extracts were combined, washed with water (10 ml) and dried over

magnesium sulphate. Evaporation of the solvent gave a yellowish oil (88 mg, 84 %).

NMR (CDCl₃): ¹H δ1.10 (s, 3.0H), 3.61 (s, 2.2H, CH₂OH) and 4.40-4.48ppm (m, 4.5H, CH₂ONO₂); ¹³C δ16.80, 39.89, 64.58 and 73.70ppm.
IR (thin film): 1276.8 (-ONO₂ symmetric stretch) and 1632.8 cm⁻¹ (-ONO₂ asymmetric stretch).

Solvolysis in MeOH alone at 40 °C for 24h (1000 mg in 10 ml) gave a quantitative yield of lower quality product following removal of the volatile products on the rotary evaporator. Washing a solution of the product in CH₂Cl₂ with saturated NaHCO₃ and water gave a material of similar quality to that produced by hydrolysis with K₂CO₃.

Nitration of 2,2-bis(nitratomethyl)propan-1-ol:meritol trinitrate (to confirm the structure of the end product of the previous step)

2,2-Bis(nitratomethyl)propan-1-ol (61 mg) was dissolved in CH₂Cl₂ (0.50 ml) and cooled in an ice/water bath before and during the addition of N₂O₅ (approx. 125 mg, 4eq) in CH₂Cl₂ (1.0 ml). Stirring was continued in the ice bath for 5 min after completion of the addition, then at rt for a further 1h. The solution was then washed into a separating funnel with CH₂Cl₂ (3x3 ml) and washed with saturated NaHCO₃ solution (20 ml). The organic phase was removed and the aqueous layer was extracted with CH₂Cl₂ (2x3 ml). All of the organic extracts were combined and washed with water (20 ml), then dried over magnesium sulphate. Evaporation of the solvent gave a colourless oil (58 mg, 74%).

NMR: ¹H 1.22 (s, 3.0H), 1.30 (s, 0.3H) and 4.44ppm (s, 6.4H);
¹³C 17.21, 38.54 and 72.68ppm.
IR (thin film): 1278.0 (-N)₂ symmetric stretch) and 1644.8 cm⁻¹ (-ONO₂ asymmetric stretch).

CLAIMS

1. Use of fluoroacylating reagent to protect a molecular site against nitrolysis.

5

2. Use of a fluoroacylating reagent to protect a molecular site against nitrolysis by strong nitrolysing reagents such as nitric acid or N_2O_5 .

10 3. Use according to claim 1 or 2 wherein trifluoroacylating reagent comprises trifluoroacetylating reagent.

4. Use according to any preceding claim wherein the molecular site is a nitrogen molecular site.

15

5. Use according to claim 4 wherein the nitrogen molecular site comprises an amine group.

20 6. Use according to claim 5 wherein the amine group comprises a secondary amine.

7. Use according to claim 6 wherein the secondary amine comprises a secondary amine residing at the N-4 and/or N-10 positions of a tetra or penta acylated hexaazaisowurtzitane derivative.

25

8. Use of a trifluoroacetylating reagent according to claims 3 to 6 wherein the trifluoroacetylating reagent comprises trifluoroacetic anhydride.

30 9. Use of a trifluoroacetylating reagent according to claims 3 to 6 wherein the trifluoroacetylating reagent comprises a mixture of trifluoroacetic anhydride and trifluoroacetic acid.

35 10. Use according to any preceding claim further comprising deprotection of the fluoroacylating group by a solvolysis reagent.

11. Use according to claim 10 wherein the solvolysis reagent comprises an alcohol.

12. Use according to claim 11 wherein the alcohol comprises methanol
5 ethanol or propanol.

13. Use according to claims 1 to 3 wherein the molecular site comprises an oxygen molecular site.

10 14. Use according to claim 13 wherein the oxygen molecular site comprises a hydroxyl group.

15. Use according to claim 14 wherein the trifluoroacetylating reagent comprises trifluoroacetic anhydride.

15

16. Use according to claim 15 wherein the trifluoroacetylating reagent comprises a mixture of tri fluoroacetic anhydride and acetic acid.

20 17. Use according to claim 13 to 16 further comprising deprotection of the fluoroacylating reagent by a solvolysis reagent.

18. Use according to claim 17 wherein the solvolysis reagent comprises an alcohol.

25

19. Use according to claim 18 wherein the alcohol comprises ethanol, methanol or propanol.

20. Use of a mixture of a fluorocarboxylic acid and a fluorocarboxylic
30 anhydride to selectively protect a di-amine containing compound.

21. Use according to claim 20 trifluoroacetic acid and tri fluoro acetic anhydride to selectively protect a di-amine.

22. Use of a mixture of trifluoroacetic acid and tri fluoro acetic anhydride to selectively protect the secondary amines of a tetraacylated-hexaazaisowurtzitane.

- 5 23. Use of a fluoroacylating reagent as substantially herein before described with reference to the examples and the drawings.

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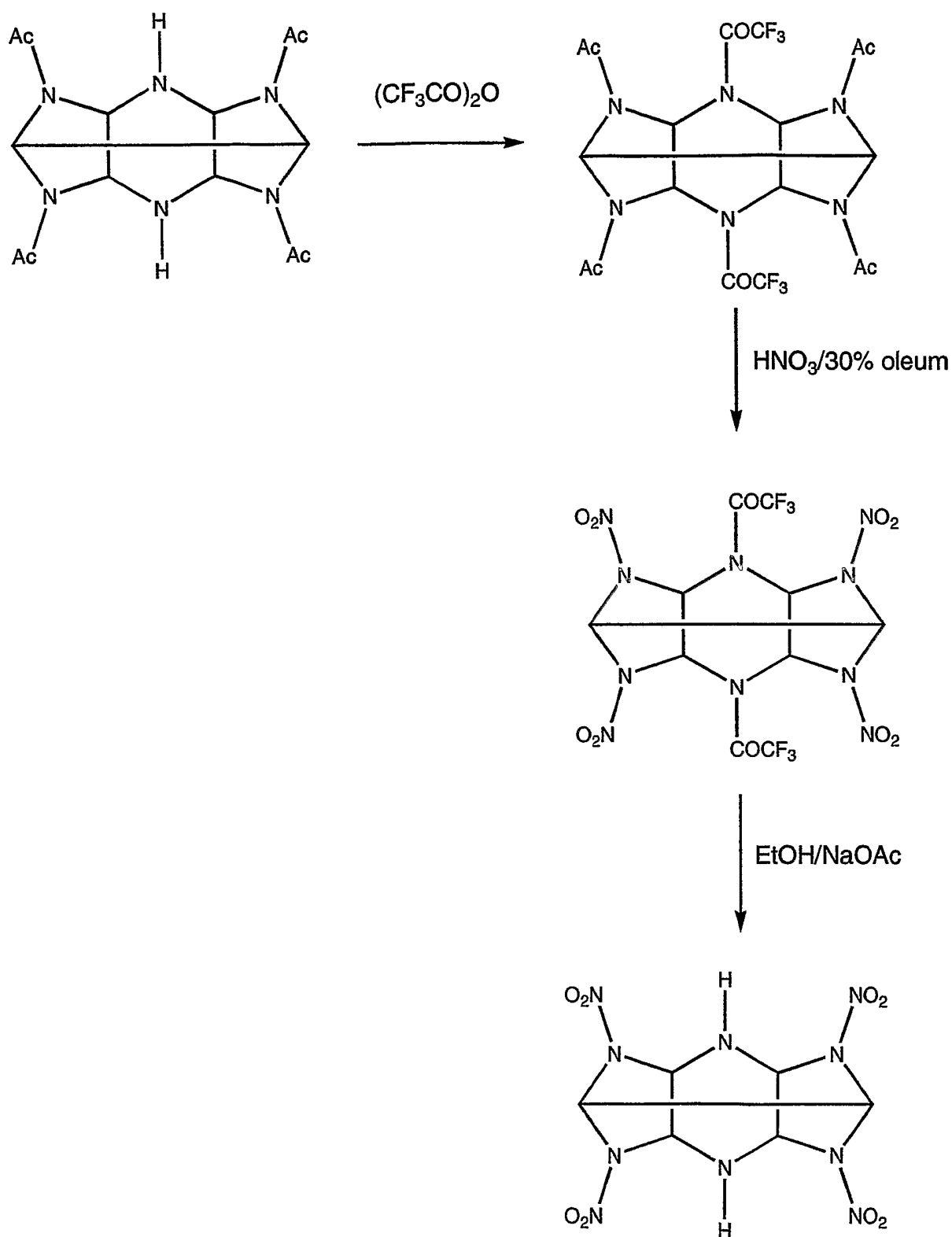


Figure 1

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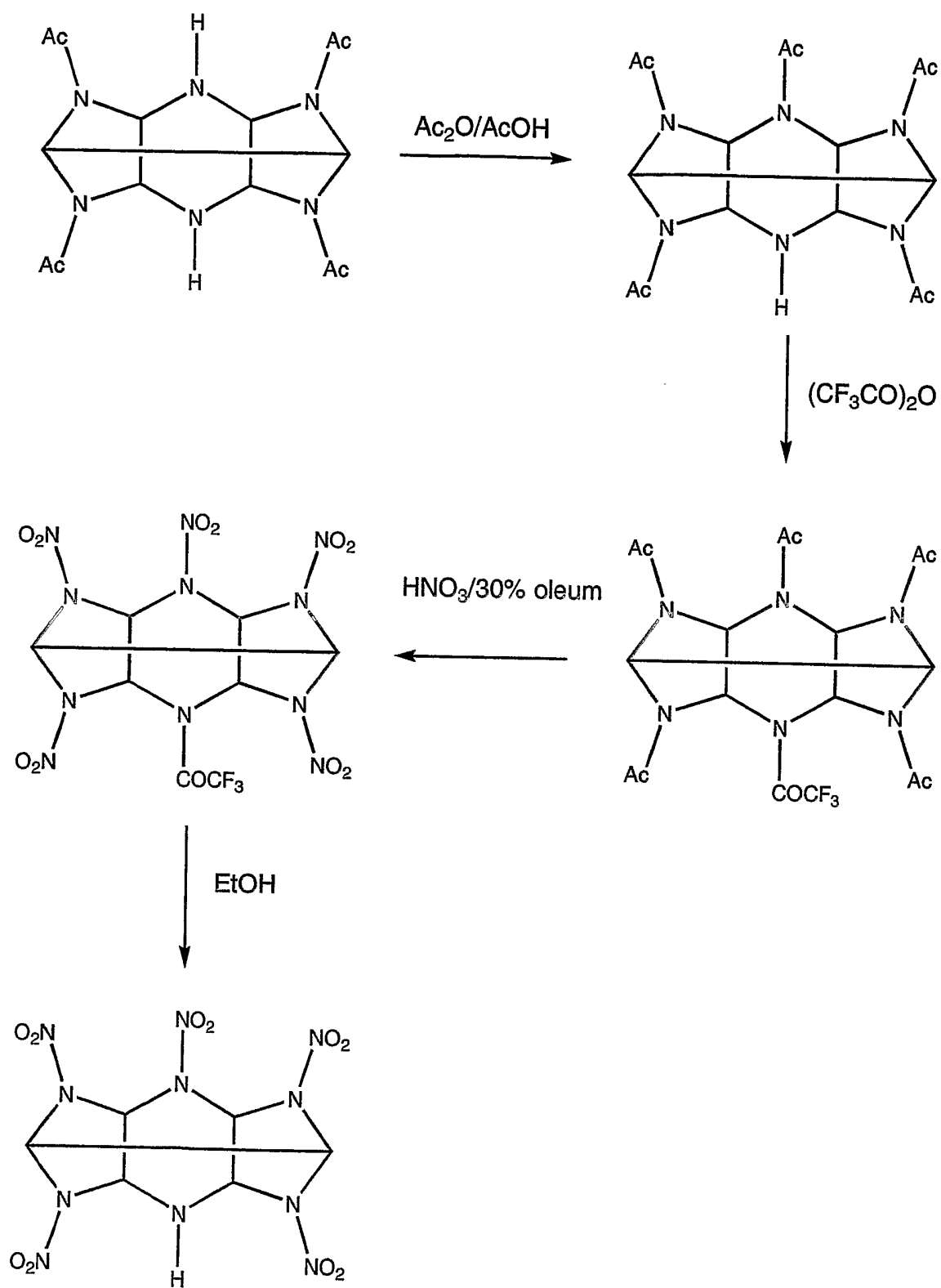


Figure 2

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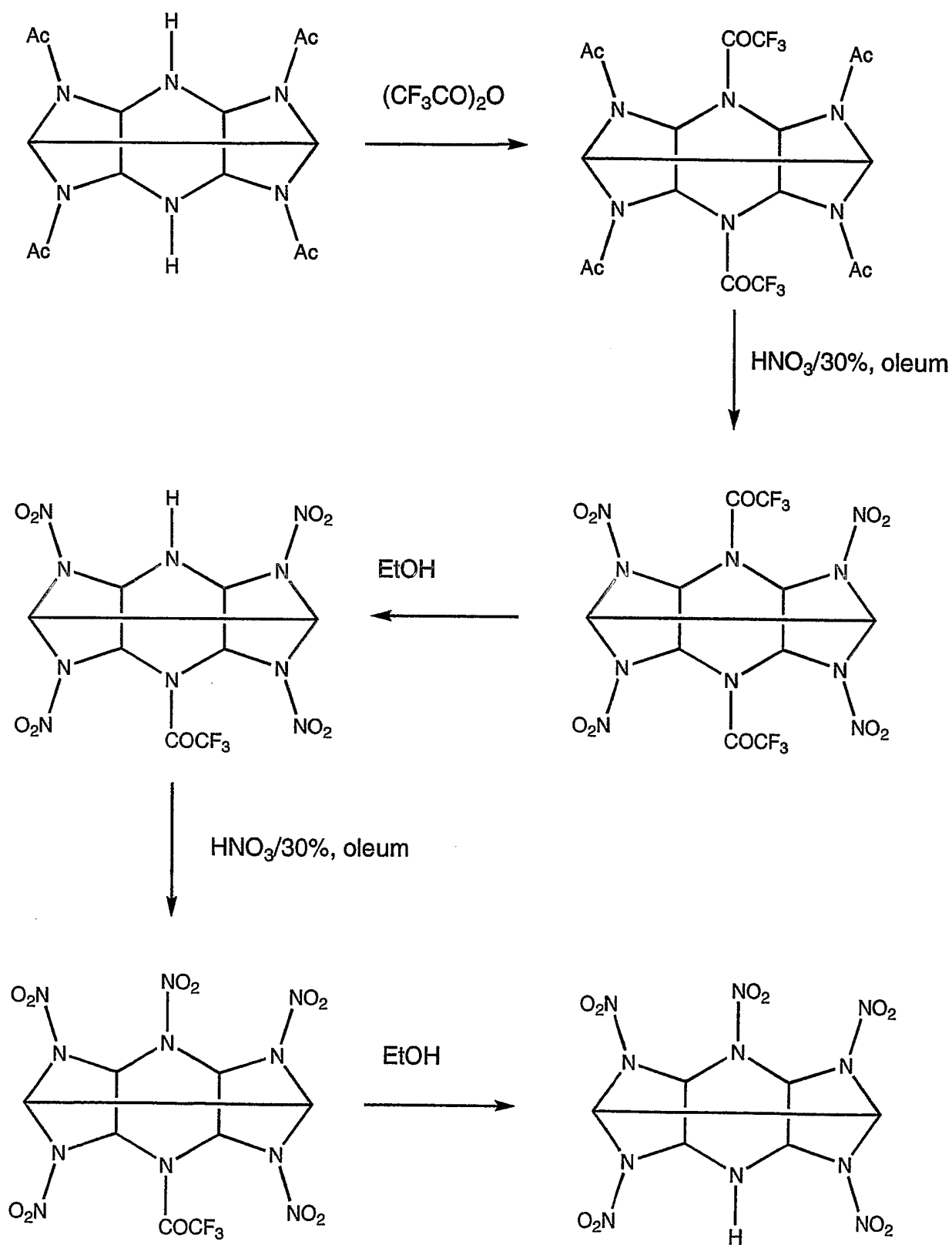


Figure 3

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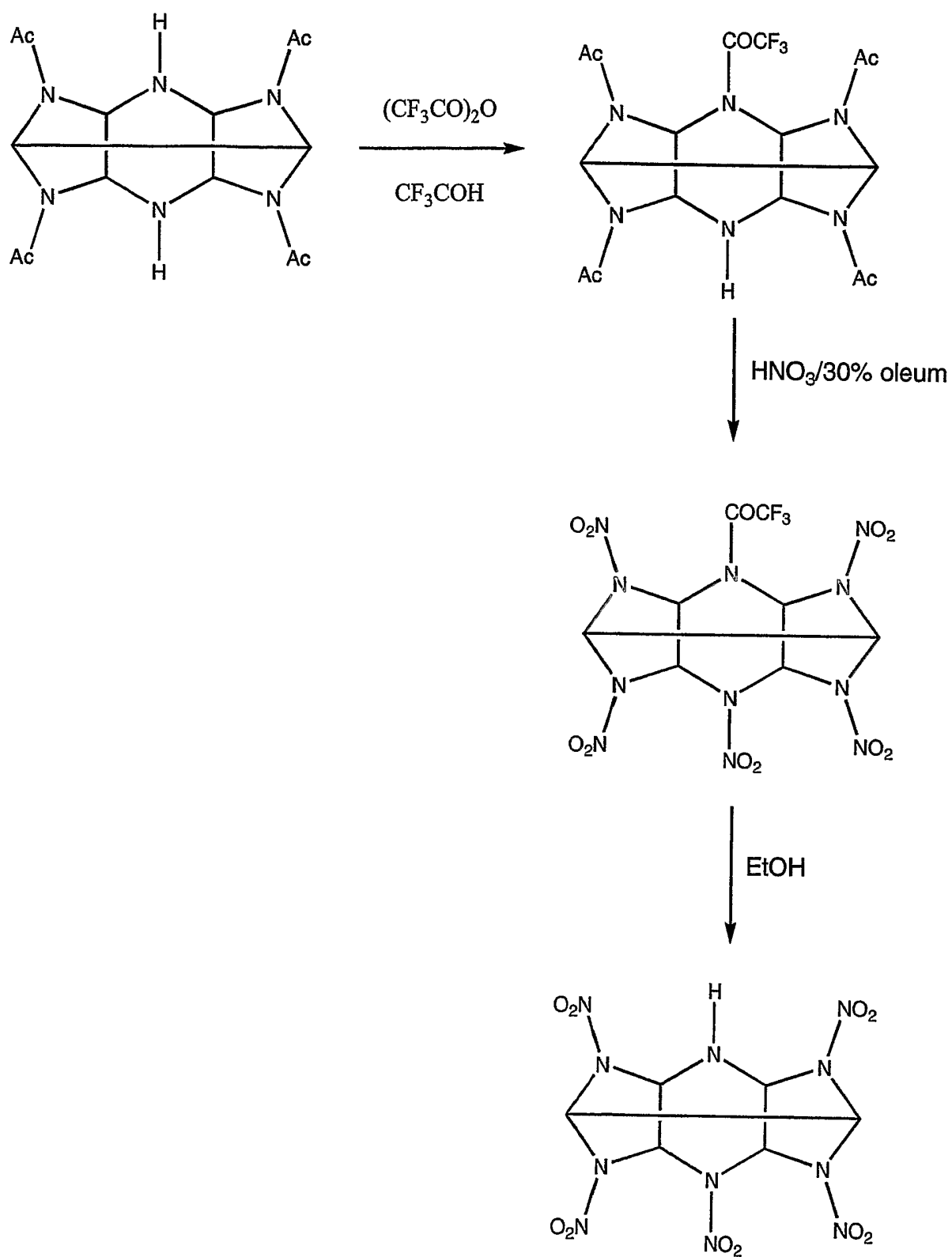


Figure 4

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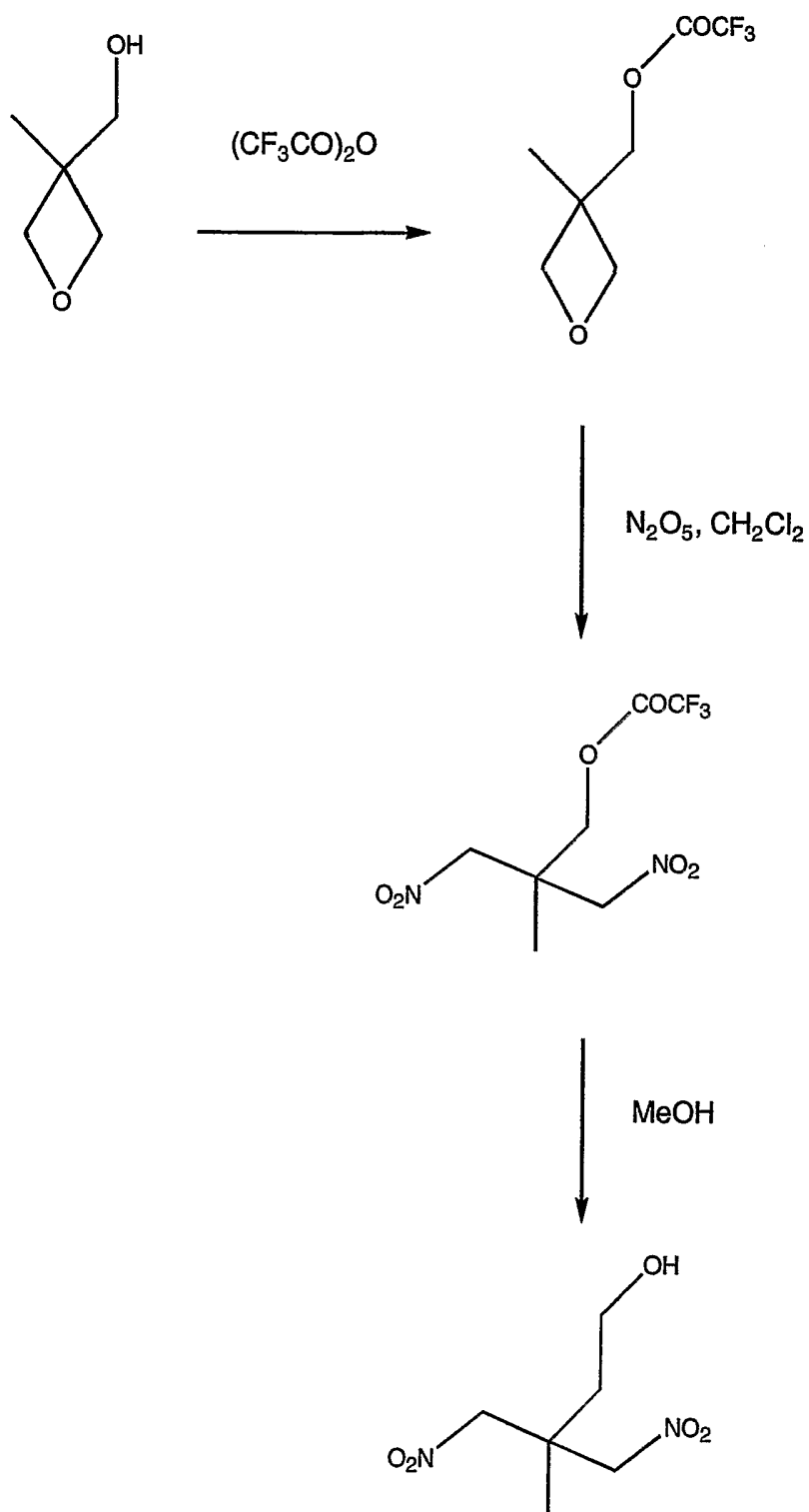


Figure 5