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PERFLUOROALKYL DERIVATIVES OF NITROGEN. PART L [1]. SYNTHESIS OF THE AMPHETAMINE 2-AMINO-1-[(4-NN-BISTRIFLUOROMETHYLAMINO)-PHENYL]PROPANE

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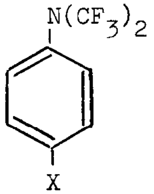
SUMMARY



(III) X=Br ; (IV) X=CHO (n.c.) ;
(V) X=CH=CMeNO$_2$ (n.c.) ; (VI) X=CH$_2$CHMeNH$_2$ (n.c.)

Treatment of the Grignard reagent derived from the bromo-compound (III) with dimethyl formamide affords the corresponding aldehyde (IV) which undergoes ready condensation with nitroethane to give the nitropropene (V). Reduction of compound (V) with an excess of lithium aluminium hydride gives the amphetamine (VI) in reasonable yield.

INTRODUCTION

A number of routes to amphetamine PhCH$_2$CHMeNH$_2$ (I) and its derivatives have been reported, e.g. [2].

A new synthesis of NN-bistrifluoromethylaniline (II) was recently developed in this Department [3] and the availability of this compound and its reported exclusive bromination in the 4-position [4] prompted an investigation of the following possible route to the amphetamine (VI).

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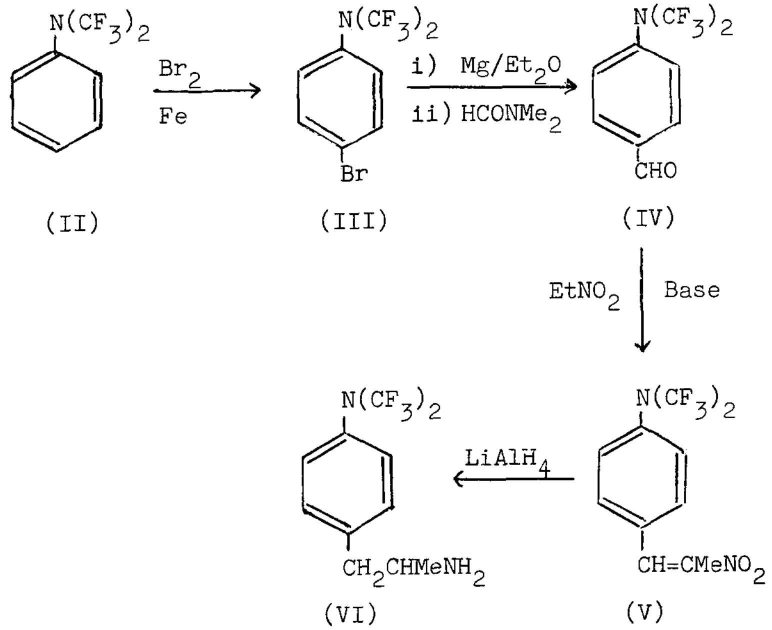

RESULTS AND DISCUSSION

Bromination of aniline (II) with bromine and iron powder as reported [4], gave the 4-bromoaniline (III) (61%, reported yield 66%). The formylation of the Grignard reagent derived from the bromo-compound (III) by the Bouveault Synthesis [5,6], *i.e.* treatment with dimethyl formamide followed by aqueous ammonium chloride work up, went smoothly and the aldehyde (IV) was isolated in good yield (65%).

The Hass modification [7] of the Knoevenagel reaction, involving treatment of the aldehyde (IV) with nitroethane using diethylamine as the basic catalyst under reflux in petroleum ether (b.p. 100-120 °C) with azeotropic removal of the water formed, gave the desired nitropropene (V) in high yield (89%).

Lithium aluminium hydride reduction of the nitropropene $PhCH{=}CMeNO_2$ (VII) has been reported [8,9] to give the amphetamine (I), the nitroalkane $PhCH_2CHMeNO_2$, the oxime $PhCH_2CMe{=}NOH$, and the hydroxylamine $PhCH_2CHMeNHOH$ in various ratios depending on the conditions used. However, a control experiment in which the nitropropene (VII) was treated with an excess of the reducing agent under reflux in diethyl ether [a higher temperature than that reported (-70 to +30 °C)] afforded the amphetamine (I) in good yield (84%). This procedure was repeated using the nitropropene (V) and the desired amphetamine (VI) was obtained in reasonable yield (56%).

The amphetamine (VI) was thus obtained in 20% overall yield from aniline (II).

EXPERIMENTAL

Spectroscopy

I.r., n.m.r. [references ext. TMS (^{1}H) and CF_3CO_2H (^{19}F); shifts to low field of references designated positive] and mass spectroscopic analyses, respectively, were carried out with a Perkin-Elmer spectrophotometer model 257, a Perkin-Elmer R10 instrument (^{19}F at 56·46 and ^{1}H at 60 MHz) and a G.E.C.-A.E.I. MS902 spectrometer (electron beam energy 70eV).

Starting Material

NN-bistrifluoromethylaniline

This was obtained by the reaction of N-bromobistrifluoromethylamine with cyclohexa-1,3-diene to give a mixture of 1,2- and 1,4-adducts which were dehydrobrominated (KOH) to a mixture of 1- and 2-(NN-bistrifluoromethylamino)cyclohexa-1,3-dienes followed by dehydrogenation [3]. Chloranil in 1,2,4-trichlorobenzene at 150 °C was used in the dehydrogenation step rather than Pd/C previously reported [3] and gave a mixture of benzene (27%) and the aniline (55%) from which the latter compound was isolated pure by distillation.

Preparation of 4-(NN-bistrifluoromethylamino)benzaldehyde

A crystal of iodine followed by a small portion of a solution of 4-bromo-NN-bistrifluoromethylaniline (3·50 g, 11·4 mmol) in anhydrous diethyl ether (10 cm^3) was added to a stirred slurry of magnesium turnings (0·29 g, 12·0 mmol) in ether (25 cm^3) under an atmosphere of nitrogen. The mixture was heated under reflux (10 min) to initiate reaction and the remainder of the aniline solution was added slowly (15 min). Reflux was maintained (2·5h) during which time the solution darkened and the majority of the magnesium dissolved. A solution of anhydrous dimethyl formamide (0·83 g, 11·4 mmol) in ether (5 cm^3) was added dropwise (10 min) to the stirred solution, stirring was continued (1h), then ether (50 cm^3) was added and the resulting mixture kept at room temperature (12h). The mixture was poured into saturated aqueous ammonium chloride (100 cm^3), extracted with ether (3 x 25 cm^3) and the ether extracts were dried (Na_2SO_4). Removal of the ether by evaporation gave a liquid residue (2·34 g) which was shown by g.l.c. (2m PEGA at 130 °C) to consist of four components in the ratio 4:10:81:5; the first two components having identical retention times to those of NN-bistrifluoromethylaniline and the reactant bromo compound, respectively.

The major component was separated by g.l.c. (as before) and identified as 4-(NN-bistrifluoromethylamino)benzaldehyde (1·90 g, 7·4 mmol, 65%)(Found: C, 41·8; H, 1·7; N, 5·6%. $C_9H_5F_6NO$ requires C, 42·0; H, 1·9; N, 5·4%), $\upsilon_{max.}$ 3058 (aromatic C-H str.), 2853 and 2740 (aldehydic C-H str.) and 980[C-N str. in $(CF_3)_2N$] cm^{-1}, δ_F (neat solution) +20·0 [$(CF_3)_2N$] p.p.m. and δ_H +7·15 (AA'BB'; aromatic 4H) and + 9·45 (s; CHO) p.p.m., m/e 257 (79%, M^+), 256 [100, $(M-H)^+$], 238 [22, $(M-F)^+$], 140(33, $C_7H_4F_2N^+$) and 69(56, $CF_3{}^+$).

Condensation of 4-(NN-bistrifluoromethylamino)benzaldehyde with nitroethane

A mixture of the aldehyde (1·70 g, 6·6 mmol), nitroethane (0·50 g, 7·0 mmol) and diethylamine (ca. 0·1 g) in petroleum ether (b.p. 100-120 °C, 35 cm^3) was heated under reflux and the water formed was removed azeotropically. The reaction was monitored by g.l.c. (2m PEGA at 135 °C) and reflux was continued until the reaction was complete (35h). Removal of the solvent under reduced pressure (20 mmHg) gave a dark brown oil (2·1 g) which was purified by reduced pressure distillation in a molecular still to afford 1-[(4-NN-bistrifluoromethylamino)phenyl]-2-nitroprop-1-ene (2·0 g, 5·9 mmol, 89%) (Found: C, 41·8; H, 2·9; N, 8·5; F, 36·3%. $C_{11}H_8F_6N_2O_2$ requires C, 42·0; H, 2·5; H, 8·9; F, 36·3%), $\upsilon_{max.}$ 1522 (conj. NO_2 and C=C) and 980 [C-N str. in $(CF_3)_2N$] cm^{-1}, δ_F(neat solution) +21·1 [$(CF_3)_2N$] p.p.m. and δ_H +1·96 (s; CH_3), +7·0 (AA'BB'; aromatic 4H) and +7·50 (s, CH=) p.p.m., *m/e* 314 (7%, M^+), 256[100,$(M-CNO_2)^+$] and 69(87, CF_3^+).

Reduction of 1-[(4-NN-bistrifluoromethylamino)phenyl]-2-nitroprop-1-ene

A solution of the nitro compound (2·0 g, 5·9 mmol) in diethyl ether (30 cm^3) was added dropwise (30 min) to a stirred slurry of lithium aluminium hydride (1·10 g, 29·1 mmol) in ether (30 cm^3) under reflux and heating was continued (1·5 h). Water (1·5 cm^3) was added cautiously to the cooled material followed by aqueous sodium hydroxide (1·5 cm^3, 15% solution) and a further amount of water (7 cm^3). The resulting solution was extracted with ether (3 x 25 cm^3) and the ether solution was further extracted with dilute hydrochloric acid (3 x 15 cm^3, 7% solution). The acid extract was basified [(15% NaOH aq), extracted with ether (3 x 25 cm^3) and the ether extracts were dried ($MgSO_4$). Removal of the ether *in vacuo* gave a liquid residue (1·05 g) which was purified by vacuum distillation in a molecular still to afford 2-amino-1-[(4-NN-bistrifluoromethylamino)phenyl]propane (0·90 g, 3·2 mmol, 56%) (Found: C, 45·9; H, 4·5; N, 9·4%. $C_{11}H_{12}F_6N_2$ requires C, 46·1; H, 4·2; N, 9·8%), b.p. (Siwoloboff) 202 °C at 760 mmHg, $\upsilon_{max.}$ 3185 (N-H str.), 1580 (N-H bend) and 972 [C-N str. in $(CF_3)_2N$] cm^{-1}, δ_F(neat solution) +20·4 [$(CF_3)_2N$] p.p.m. and δ_H 0·70 (d; CH_3; *J* 6·0 Hz), 1·92 (broad; NH_2), 2·25 (d; CH_2; *J* 6·0 Hz), 2·72 (mult; CH) and 6·90 (AA'BB'; aromatic 4H) p.p.m.

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