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REDUCTIVE METHYLATION OF SECONDARY AMINES CONTAINING REDUCIBLE, HYDROLYZABLE AND STERICALLY HINDERED GROUPS

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Abstract: Aliphatic secondary amines, including those that are sterically hindered, undergo reductive methylation under mild conditions in high yield using formaldehyde and sodium phosphite solution without reducing or hydrolyzing ethynyl, ester or cyano groups.

As part of a study of the antiapoptotic properties of some aliphatic secondary amines and their N-methyl analogues, we required an efficient, simple and mild method of N-methylation of the secondary amines which contained sterically hindered, reducible and/or hydrolyzable functional groups. Methylation of sterically hindered amines has been achieved with dimethyl sulfate but only at high temperature and in low yield[1]. Conventional lithium aluminum

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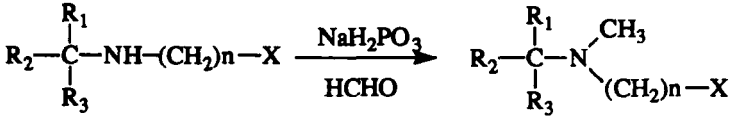
hydride reduction of an intermediate such as a carbamate or formamide[2] is unsuitable for amines possessing reducible functional groups. Milder reductive methylation methods using formaldehyde/formic acid under microwave irradiation[3], paraformaldehyde/sodium borohydride/trifluoroacetic acid[4] or sodium triacetoxyborohydride[5] appear to have more potential, although their methylating properties with sterically hindered amines and effect on sensitive functional groups was not explored. It has previously been demonstrated that arylalkyl and alicyclic secondary amines can be reductively methylated in a very simple procedure by means of formaldehyde in a solution of sodium phosphite in 10 minutes at 60°C[6].



where R_1 and R_3 are H, methyl or ethyl, R_2 is alkyl and X is ethynyl, carboxylate or cyano, and n is 1 or 2.

Scheme

We have investigated this method for its applicability to aliphatic secondary amines in which the aliphatic group may sterically hinder the site of reaction, while the other group contains a reducible (ethynyl, ester or cyano) or hydrolyzable (ester, cyano) moiety (Scheme). The effects of branching and chain length of the aliphatic group, the type of functional group, and the reaction time and temperature have been investigated.

Table 1: Reductive Methylation of Aliphatic Secondary Amines Containing Ethynyl, Cyano or Ester Groups

Aliphatic Group	n	Functional Group X	% Yield*
2-propyl	1	C≡CH	82
1-pentyl	1	C≡CH	93
2-pentyl	1	C≡CH	95
3-pentyl	1	C≡CH	86
t-amyl	1	C≡CH	86
2-heptyl	1	C≡CH	80
2-propyl	2	C≡N	90
1-pentyl	2	C≡N	90
2-pentyl	2	C≡N	92
3-pentyl	2	C≡N	91
t-amyl	2	C≡N	87
2-heptyl	2	C≡N	85
2-propyl	2	$COOCH_3$	83
2-heptyl	2	$COOCH_3$	96

* Yield of isolated hydrochloride salt

The standard reaction conditions described by Loibner et al[6] were modified to take account of the susceptibility of esters to hydrolysis in base during workup and the significant solubility in aqueous solution of some of the relatively low molecular weight products. Under the modified standard reaction conditions of 60°C for 15 minutes at pH 6, the yields of crude product were nearly quantitative and of the isolated hydrochloride salts typically greater than 80% (Table 1). The ethynyl (X

Table 2: Effect of Reaction Temperature and Time on Methylation of N-(2-Pentyl)propargylamine

Reaction Time	Reaction Temperature	% Yield*
15 min	60°C	95
15	20°	20
30	20°	36
60	20°	72
7 hrs	20°	95
24 hrs	20°	96

* % of starting material in product was assessed by NMR

= -C≡CH), cyano (X = C≡N) and ester groups (X = -COOR) were not reduced or hydrolyzed under the reaction conditions, although yields of the N-methylated amino esters were appreciably lower unless basification and extraction of the reaction mixture were carried out rapidly at low temperature (less than 10°C) from solutions saturated with sodium chloride. Reductive methylation occurred readily even for sterically hindered amines such as N-(t-amyl)propargylamine and 3-t-amylaminopropionitrile.

A limitation of the method was observed for compounds in which conjugation of an electron-withdrawing group with the nitrogen non-bonded electron pair was possible. Thus, when n = 1 and X is cyano or carboxylate, significant amounts (up to 40%) of a byproduct are formed. The mass spectra and NMR spectra of the product mixtures were consistent with N-methylation as well as addition of methanol across the nitrile triple bond or carbonyl double bond. The elucidation of the structures of these by-products was not further pursued.

The reductive methylation occurs much more slowly at room temperature (Table 2), but even for the sterically hindered t-amyl-propargylamine, methylation is 70% complete after 19 hours.

In conclusion, our results demonstrate that aliphatic secondary amines possessing sterically hindered substituents and substituents sensitive to heat and reducing or hydrolyzing agents undergo reductive methylation in high yield using formaldehyde and sodium phosphite solution.

Experimental Section

Phosphorous acid, propargyl bromide, methyl acrylate, acrylonitrile, ethyl bromoacetate and bromoacetonitrile were purchased from Lancaster Synthesis Inc, and 37% formaldehyde and diethyl ether from BDH. The aliphatic primary amines were purchased from Lancaster Synthesis Inc, except for 2-propylamine and t-amylamine which were obtained from the Aldrich Chemical Co. ^{1}H NMR spectra were recorded in deuterium oxide on a Bruker AM300 NMR instrument (300 MHz), mass spectra were obtained by electron impact at 70 eV on a VG 7070F instrument, and elemental analyses were performed in the Analytical Laboratory, Chemistry Department, University of Saskatchewan.

The secondary amine starting materials were synthesized, isolated as their hydrochloride salts and characterized as described previously[7,8]. Briefly, the propargylamines, amino acetates and aminoacetonitriles were synthesized by reaction of a two-fold excess of primary amine with propargyl bromide, ethyl bromoacetate and

bromoacetonitrile in diethyl ether, respectively; and the aminopropionitriles and aminopropionates by addition of the primary amine across the olefinic double bond of acrylonitrile or methyl acrylate.

General Procedure:

The secondary amine (5.0 mmoles) was dissolved in 1N sodium phosphite (25 ml) [prepared by the addition of a solution of sodium hydroxide (8.0 g diluted to 100 ml water) to a solution of phosphorous acid (16.4 g diluted to 100 ml with water) followed by the addition of NaOH pellets to pH 6]. If the reaction solution was cloudy, sufficient dioxan was added to clarify it (necessary only for the 2-heptyl analogues). Aqueous formaldehyde (37%)(2.4 ml, 2.7 mmol) was added and the reaction solution was heated with stirring at 60°C for 15 min in an oil bath or stirred at room temperature for 7 to 24 hours. The reaction flask was cooled in ice water and basified to about pH 10 with cold 20% NaOH. The mixture was saturated with NaCl and extracted immediately with ether (3 x 15 ml). The combined extracts were dried over sodium sulfate, treated with methanolic HCl and evaporated to give crude tertiary amine hydrochlorides which were purified by recrystallization from methanol/ether. The relative amount of starting material in the crude and purified products was assessed by comparing the integrated NMR signals for the propargyl, cyanoalkyl or alkyl carboxylate methylene protons which have different chemical shifts for the N-methyl and desmethyl compounds. For example, for N-(2-pentyl)propargylamine the methylene protons of the propargyl group appear at 3.78 ppm and at 3.90 ppm for the N-methylated

product. The percent of starting material in the product was further verified by comparing these areas to that of the terminal methyl group.

The physical and spectral properties of the hydrochloride salts of the products are:

N-(2-Propyl)-N-methylpropargylamine: m.p. 158.5-159°C (lit. 155-6°C; MS, NMR, elemental analysis)[7].

N-(1-Pentyl)-N-methylpropargylamine: m.p. 102-103°C (oxalate). (MS, NMR, elemental analysis)[7].

N-(2-Pentyl)-N-methylpropargylamine: m.p. 93.5-94.5°C (lit 94-5°C; MS, NMR, elemental analysis)[7].

N-(3-Pentyl)-N-methylpropargylamine: m.p. 125-6°C (lit 119-120°C; MS, NMR, elemental analysis)[7].

N-(t-Amyl)-N-methylpropargylamine: m.p. 148-150°C. ^{1}H NMR (D_2O): δ 0.89 (t, 3H, propyl CH_3); δ 1.29 (s, 6H, α–CH_3); δ 1.69 (q, 2H, β-CH_2); δ 2.99 (s, 1H, propargyl CH); δ 3.81, 4.10 (broad d, 2H, propargyl CH_2). Elemental analysis: Calculated (found): %C = 61.52 (61.24); %H = 10.33 (10.24); %N = 7.97 (7.83). Mass spectrum (EI): m/z 139 (M^+), 124 (M - CH_3), 110 (M - C_2H_5).

N-(2-Heptyl)-N-methylpropargylamine: m.p. 126-127C (lit 115-116°C; MS, NMR, elemental analysis)[7].

3-(2-Propylmethylamino)propionitrile: m.p. 121-121.5°C. ^{1}H-NMR (D_2O): δ 1.23 (d, 6H, propyl CH_3); δ 2.73 (s, 3H, N-CH_3); δ 2.97 (t, 2H, N-CH_2); δ 3.52 (broad s, 2H, CH_2-CN); δ 3.60 (m, 1H, αCH). Elemental analysis: Calculated (found): %C = 51.69 (51.72); %H = 9.30 (9.13); %N = 17.22 (17.30). Mass spectrum (EI): m/z: 126 (M^+); 111 (M-CH_3); 86 (M-CH_2CN).

3-(1-Pentylmethylamino)propionitrile: m.p. 130°C. ^{1}H NMR (D_2O): δ

0.88 (t, 3H, terminal CH_3), δ 1.31 (broad s, 4H, γ, δCH_2), δ 1.71 (m, 2H, βCH_2), δ 2.91 (s, 3H, N-CH_3), δ 3.07 (t, 2H, N-CH_2, pentyl group), δ 3.20 (t, 2H, N-CH_2, cyanoethyl group), δ 3.55 (t, 2H, CH_2-CN). Elemental analysis: Calculated (found): %C = 56.68 (56.73); %H = 10.04 (10.08); %N = 14.69 (14.60). Mass Spectrum (EI): m/z 154 (M^+), 114 (M - CH_2CN), 97 (M - C_4H_9).

3-(2-Pentylmethylamino)propionitrile: m.p. 141.5-142°C. ^1H NMR (D_2O): δ 0.83 (t, 3H, terminal CH_3), δ 1.22 (d, 3H, α-CH_3), δ 1.25 -1.65 (2m, 4H, β, γ CH_2), δ 2.73 (s, 3H, N-CH_3), δ 2.96 (t, 2H, N-CH_2), δ 3.41 (broad s, 3H, α–CH plus CH_2-CN). Elemental analysis: Calculated (found): %C = 56.68 (56.81); %H = 10.04 (9.82); %N = 14.69 (14.65). Mass spectrum (EI): m/z 154 (M^+), 139 (M -CH_3), 111 (M - C_3H_7).

3-(3-Pentylmethylamino)propionitrile: m.p. 145-146°C. ^1H NMR (D_2O): δ 0.91 (d, 6H, 2 x terminal CH_3), δ 1.53-1.73 (m, 4H, 2 x β CH_2), δ 2.76 (s, 3H, N-CH_3), δ 2.98 (t, 2H, N-CH_2), δ 3.12, (m, 1H, αCH), δ 3.30-3.60, (broad s, 2H, CH_2-CN). Elemental analysis: Calculated (found): %C = 56.68 (56.79); %H = 10.04 (10.21); %N = 14.69 (14.59). Mass spectrum (EI): m/z 154 (M^+), 125 (M - C_2H_5), 114 (M - CH_2CN).

3-(t-Amylmethylamino)propionitrile: m.p. 137-138°C. ^1H-NMR (D_2O): δ 0.87 (t, 3H, terminal CH_3); δ 1.25 (s, 6H, 2 x α-CH_3); δ 1.67 (q, 2H, β CH_2); δ 2.73 (s, 3H, N-CH_3); δ 2.94 (t, 2H, N-CH_2), δ 3.1-3.8 (broad d, 2H, CH_2-CN). Elemental Analysis: Calculated (found): %C = 56.68 (56.62); %H = 10.04 (10.12); %N = 14.69 (14.62). Mass spectrum (EI): m/z: 154 (M^+); 139 (M - CH_3); 125 (M - C_2H_5).

3-(2-Heptylmethylamino)propionitrile: m.p. 98-98.5°C. ^1H-NMR (D_2O): δ 0.77 (t, 3H, terminal CH_3), δ 1.20 (d, 3H, α-CH_3); δ 1.15-1.35 (m, 6H, β, γ, ε CH_2); δ 1.50/1.62 (2m, 1H each, β CH_2); δ 2.73 (s, 3H, N-CH_3); δ 2.95 (t,

2H, N-CH_2); δ 3.40 (m, 3H; α-CH and CH_2CN). Elemental Analysis: Calculated (found): %C = 60.39 (60.55); %H = 10.60 (10.29); %N = 12.80 (12.67). Mass spectrum (EI): m/z 182 (M^+); 167 (M-CH_3); 142 (M-CH_2CN); 111 (M-C_5H_{11}).

3-(2-Propylmethylamino)acetonitrile: m.p. 130-135°C. ^1H NMR (D_2O) δ 1.29 (d, 6H, propyl CH_3), δ 2.89 (s, 3H, N-CH_3), δ 3.71, (m, 1H, αCH), δ 4.35 (s, 2H, N-CH_2). Elemental analysis: Calculated (found): %C = 48.48 (48.50); %H = 8.82 (8.68); %N = 18.85 (18.80).

Methyl 3-(2-propylmethylamino)propionate: viscous oil. ^1H NMR (D_2O): δ 1.22 (d, 6H, 2 propyl CH_3), δ 2.67 (s, 3H, N-CH_3), δ 2.72-2.81 (m, 2H, N-CH_2), δ 3.14 (m, 1H, α–CH), δ 3.37-3.57 (m, 2H, CH_2-$COOCH_3$), δ 3.63 (s, 3H, OCH_3). Mass spectrum (EI): m/z 159 (M^+), 144 (M - α-CH_3), 86 (M - CH_2COOCH_3).

Methyl 3-(2-heptylmethylamino)propionate: viscous oil. ^1H NMR (D_2O): δ 0.73 (t, 3H, terminal CH_3), δ 1.08-1.31 (m, 9H, γ,δ,ε CH_2 and α-CH_3), δ 1.47, 1.57 (2m, 2H, β CH_2), δ 2.64 (d, 3H, N-CH_3), δ 2.73 (q, 2H, N-CH_2), δ 3.12 (m, 1H, α–CH), δ 3.25-3.47 (m, 2H, CH_2-$COOCH_3$), δ 3.60 (s, 3H, OCH_3). Mass spectrum (EI): m/z 215 (M^+), 200 (M - α-CH_3), 144 (M - C_5H_{11}).

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