N-Methylation of Amino Alcohols and Amino Mercaptans

Asher Kaluszyner and Arjeh B. Galun

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The preparation of *N*-methylated amino alcohols and amino mercaptans is usually very cumbersome and employs devious routes.[1–13] Therefore, the possibility has been studied of methylating amino alcohols and amino mercaptans by means of formic acid and formaldehyde, a method which[14–16] has been recently used to methylate 3-amino-1-propanol[17] and 2-ethylaminoethanol.[18]

We modified this method and extended it to other amino alcohols and mercaptoethylamine and found that yields of 90–100% of the *N*,*N*-dimethyl derivatives are obtained in all cases by refluxing 1 mole of the amino alcohol (or amino mercaptan) with 2.5 moles of formic acid and 2.5 moles of formaldehyde for five hours. The methylated product is isolated from the reaction mixture by salting out with sodium or potassium hydroxide. Only the first member of this series, *N*,*N*-dialkylaminoethanol, has to be distilled after salting out. All others were found to be practically pure, containing at most traces of moisture.

EXPERIMENTAL

Starting materials. Yellow label 2-aminoethanol, 2-ethylaminoethanol, 3-amino-1-propanol, 1-amino-2-propanol, and 2-amino-2 methyl-1-propanol were purchased from Eastman Kodak Co. 4-Amino-1-butanol was synthesized by a recently published method[19] and 2-mercaptoethylamine was prepared from ethyleneimine and hydrogen sulfide.[20]

Methylations. To 30.5 g. (0.5 mole) of *2-aminoethanol* 65 g. (1.25 moles) of 88% formic acid and 108 g. (1.25 moles) of a 35% formaldehyde solution were added slowly and with cooling. The mixture was heated gently until the evolution of carbon dioxide ceased, and refluxed for 5 hr. The deeply colored solution was then cooled and saturated with solid sodium hydroxide. The organic layer was separated, treated with a few grams of solid sodium hydroxide, separated again, mixed with a large volume of benzene and distilled. The forerun, consisting of benzene and water, was discarded and a yield of 90–95% of *N*,*N*-dimethyl-2-aminoethanol distilling in the range of 129–134° was obtained.

N-Methyl-N-ethylaminoethanol was prepared entirely analogously in 96% yield from 2-ethylaminoethanol. B.p. 149–150°, n_D^{26} 1.4348 d_{26}^{26} 0.8824; MR, calcd., 30.53; MR, found, 30.51.

N,N-Dimethyl-3-amino-1-propanol. To 37.5 g. (0.5 mole) of 3-amino-1-propanol, 65 g. (1.25 moles) of 88% formic acid and 108 g. (1.25 moles) of a 35% formaldehyde solution was added with cooling. The mixture was first heated slowly and then refluxed for 5 hr. It was then cooled and saturated with potassium hydroxide. To the upper layer a few grams of solid potassium hydroxide was added, and this operation continued until no more stratification took place. A yield of 90–95% of a material which was quite pure was thus obtained. It was distilled for the determination of the physical properties. B.p. 163–164° (reported[21] b.p. 163–164°); n_D^{21} 1.4355 (reported[7] n_D^{25} 1.4349), d_{21}^{21} 0.8816; MR, calcd., 30.54; MR, found, 30.58.

Similarly from 37.5 g. of *1-amino-2-propanol*, 49 g. (95%) of the *N*,*N*-dimethyl derivative was obtained. B.p. 124–126° (reported[6,10] b.p. 122–126°); n_D^{23} 1.4218, d_{23}^{23} 0.8722; MR, calcd., 30.51; MR, found, 30.06.

The methylation of 8.9 g. of *4-amino-1-butanol* provided a quantitative yield of the *N*,*N*-dimethyl derivative. B.p. 186–189° (reported[22] b.p. 187–189°); n_D^{22} 1.4388, d_{27}^{27} 0.8758; MR, calcd., 35.18; MR, found, 35.18.

Analogously, 44.5 g. of *2-amino-2-methyl-1-propanol* gave a quantitative yield of *2-dimethylamino-2-methyl-1-propanol*, b.p. 160–161° (reported[23] b.p. 159–161°), n_D^{27} 1.4442, d_{27}^{27} 0.9007; MR, calcd., 35.15; MR, found, 34.57. This material should not be dried over solid potassium hydroxide, since salt formation occurs. Should this happen, a small amount of water will cause the free base to separate.

To 15.4 g. (0.2 mole) of *2-mercaptoethylamine* 13 g. of 88% formic acid and 21 g. of 35% formaldehyde was added and the mixture refluxed for 5 hr., made strongly alkaline and distilled almost to dryness. The distillate was acidified with hydrochloric acid, the water removed *in vacuo* and the hydrochloride recrystallized from a large volume of ethanol. The yield was nearly quantitative; m.p. 157° (reported[24] m.p. 157°).

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Israel Institute for Biological
Research, Ness-Zionah
Israel Atomic Energy Commission,
Tel-Aviv, Israel

Formation of Girard-T Derivatives[1]

Owen H. Wheeler,[2a] V. S. Gaind,[2d] and Oscar Rosado[2a]

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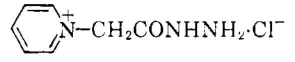
The Girard reagents,[3] Girard-T (I, *N,N,N*-trimethylammonium acetylhydrazine chloride) and Girard-P (II, pyridinium acetylhydrazine chloride), have been widely used for separating aldehydes and ketones from complex mixtures[4] since their introduction by Girard and Sandulesco in 1936, but no quantitative study has been made of the formation of Girard derivatives.

$(CH_3)_3\overset{+}{N}CH_2CONHNH_2\cdot Cl^-$

I



II

Semicarbazide can be titrated iodometrically[5] and it seemed probable that the Girard reagents could be titrated similarly. An aqueous solution of the Girard-T reagent (I) is strongly acidic (*p*H 2) and reacts very slowly with iodine (Table I). However in a neutral buffer solution the reaction with iodine is rapid and corresponds to the utilization of two moles (4 g.-atoms) of iodine per mole of Girard-T reagent. Titrations at different *p*H (Table I) showed that there was an optimum *p*H for the reaction (*p*H 7–8); below this the reaction was very slow and incomplete and in strongly alkaline solution the iodine was consumed by the base. The stoichiometry of the reaction[5] is presumably the following:

$$(CH_3)_3\overset{+}{N}CH_2CONHNH_2\cdot Cl^- + 2I_2 + H_2O \longrightarrow (CH_3)_3\overset{+}{N}CH_2CO_2H + N_2 + 4HI$$

Although the Girard-T reagent (I) can be readily determined in this manner, the Girard-P reagent (II) reacted incompletely with iodine in both acid and basic solution (Table II).

TABLE I

Titration of Girard-T Reagent

Buffer	*p*H	Ml. of $0.1N$ I_2 for 2 Ml. of $0.025M$ Girard	Ml. of $0.1N$ Thiosulfate for 2 Ml. of $0.1N$ I_2[a]
None	2	0.00	2.00
Chloride	2	0.00	
	3	0.04	
Acetate	4	1.00	
	5	1.02	
	6	1.05	
Phosphate	7	2.00	
	8	2.00	
	8.5	1.95	
	9	1.01	
Borate	9	0.60[b]	1.80
	10	0.40[b]	1.36

[a] With 10 ml. of buffer solution. [b] Corrected for blank.

TABLE II

Titration of Girard-P Reagent

Buffer	*p*H	Ml. of $0.05N$ I_2 for 2 Ml. of $0.04M$ Girard[a]	Same with 2½ × Excess I_2
Chloride	2	0.07	—
	3	0.13	0.37
Acetate	4	0.57	—
	5	0.55	—
	6	0.55	—
Phosphate	7	0.60	—
	8	0.65	1.58[b]
	9	0.78	—

[a] Solution titrated after 2–3 min. Theory 6.4 ml. [b] Used 2.95 ml. at 50°.

The kinetics of reaction of simple aldehydes and ketones with Girard-T reagent can be followed conveniently in 60% ethanol at 25° (Tables III and IV) by withdrawing samples at intervals, adding to an excess of iodine solution adjusted to *p*H 7 and titrating with thiosulfate in the usual manner. The reaction with cyclohexanone was essentially instantaneous in acid media at *p*H 3 and 25°, and measurements were accordingly made at *p*H 8 (Table III), where the reaction is much slower. The reactions showed good second order plots up to *ca.* 90%. The increases in rate in rate for cyclohexanone and cyclopentanone on increasing the temperature from 25° to 64° were only factors of 8 and 9, respectively, which corresponds to an energy of activation of 10.7 and 11.1 kcal/mole respectively.

TABLE III

Rates of Reaction with Cyclic Ketones[a]

	$k \times 10^4$ L. Mole^{-1} Sec.$^{-1}$ 25.0°	64.0°
Cyclohexanone	87	708
4-Methylcyclohexanone	55	—
Cyclopentanone	5.4	48
Cycloheptanone	5.8	—

[a] In 60% aqueous-ethanol at *p*H 8.5.

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[2] (a) University of Puerto Rico at Mayaguez; (b) National Research Council of Canada Post-doctorate Fellow at Dalhousie University. Present address: Department of Chemistry, Panjab University, Chandigarh, India.

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