Synthesis of Acetamides by the Reactions of Alcohols with Sulphuryl Chloride in Acetonitrile

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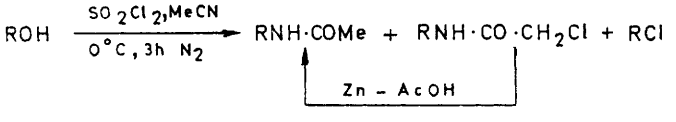
The reactions of primary, secondary, and tertiary alcohols with sulphuryl chloride in acetonitrile afforded the corresponding acetamides in moderate to good yields. 7,7-Dimethylnorbornan-1-ol afforded 7,7-dimethylnorbornan-1-yl chlorosulphate in 71% yield.

THE preparation of amides by the reaction of carbocations with nitriles (the Ritter reaction [1]) occupies an important position in synthetic chemistry because of its wide applicability and the usefulness of the resulting amides as a source of the corresponding amines. A problem in its use is the need for a strong acid to generate the carbocation, which may cause isomerization and polymerization. Another limitation is that *N*(primary alkyl)acetamides cannot be prepared by this method. Recently ethyl and methyl fluorosulphates were found to alkylate acetonitrile to form nitrilium ions.[2] This method is attractive because the reaction medium is almost neutral, but only simple primary and secondary alkyl fluoro- and chloro-sulphates were isolable.[3,4]

In the light of these results we have studied the reactions of alcohols with sulphuryl chloride in acetonitrile, expecting to generate alkyl chlorosulphates *in situ* and, after hydrolysis, to obtain the corresponding acetamides.

RESULTS AND DISCUSSION

The reactions of primary, secondary, and tertiary alcohols with sulphuryl chloride in acetonitrile were



performed at 0 °C with nitrogen bubbling through the solution to remove hydrochloric acid. The products were the corresponding acetamide, chloroacetamide, and alkyl chloride, as shown by g.l.c. and mass spectroscopic analysis. After reduction of the chloroacetamide by zinc–acetic acid,[5] the acetamide was isolated by column chromatography and characterized by comparing the physical data with those of authentic samples.

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Alcohol	Acetamide	Yield (%)	M.p. (°C)
Hexan-1-ol	*N*-Hexyl [a]	12	*g*
4-Methylpentan-2-ol	*N*-1,3-Dimethylbutyl [b]	19	83—85
Norbornan-2-*endo*-ol	*N*-Norbornan-2-*exo*-yl [c]	22	140—141
Norbornan-2-*exo*-ol	*N*-Norbornan-2-*exo*-yl	33	
Bornan-2-*endo*-ol	*N*-Bornan-2-*exo*-yl [d]	59	134—135
Bornan-2-*exo*-ol	*N*-Bornan-2-*exo*-yl	66	
1,1-Dimethylheptyl	*N*-1,1-Dimethylheptyl [e]	58	39—41
1-Methyl-4-t-butylcyclohexanol	*N*-1-Methyl-4-t-butylcyclohexyl [f]	72	140—143

[a] H. E. Baumgarten, F. A. Bower, R. A. Setterquist, and R. E. Allen, *J. Amer. Chem. Soc.*, 1958, **80**, 4588. [b] δ 0.88 (6 H, d), 1.07 (3 H, d), 1.89 (3 H, s), 3.78—4.10 (1 H, m), and 7.68br (1 H, d). [c] J. A. Berson and D. A. Benpefraim, *J. Amer. Chem. Soc.*, 1969, **81**, 4094. [d] M. O. Foster, *J. Chem. Soc.*, 1898, **73**, 386. [e] δ 0.80 (3 H, t), 1.24 (6 H, s), 1.81 (3 H, s), and 6.64 (1 H, s). [f] P. J. Beeby and S. Sternhell, *Austral. J. Chem.*, 1971, **24**, 809. [g] B.p. 134° at 2 mmHg.

From hexan-1-ol, *N*-hexylacetamide was obtained in low yield. 4-Methylpentan-2-ol afforded only unrearranged product. Since *N*-(1-ethyl-2-methylpropyl)-acetamide was a by-product of the Ritter reaction in

[1] L. I. Krimen and D. J. Cota, 'Organic Reactions,' vol. 17, ed. by W. G. Dauben, John Wiley and Sons, New York, 1969, p. 213.

[2] M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, *Chem. Comm.*, 1968, 1533.

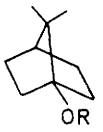
[3] E. Buncel, *Chem. Rev.*, 1970, **70**, 323.

[4] G. A. Olah, J. Nishimura, and Y. K. Mo, *Synthesis*, 1973, 661.

[5] P. A. Levene, *Org. Synth.*, Coll. Vol. II, 1943, p. 320.

sulphuric acid–acetonitrile, formation of the rearrangement product appears to be depressed more in the sulphuryl chloride–acetonitrile system. From norbornan-2-*exo*- and -*endo*-ols, *N*-(norbornan-2-*exo*-yl)acetamide was obtained selectively. The same behaviour was also found in the reactions of bornan-2-*endo*- and -*exo*-ols. Selective axial attack of acetonitrile was also observed in the reaction of 1-methyl-4-t-butylcyclohexanol.

The inertness of the bridgehead position of bicyclo-[2.2.1]heptanes to carbocation formation [6] prompted us to examine the reaction of 7,7-dimethylnorbornan-1-ol (1) with sulphuryl chloride. 7,7-Dimethylnorbornan-1-yl chlorosulphate (2), the first example to be reported of a tertiary chlorosulphate stable even at room temperature,[3] was isolated in 71% yield. The chlorosulphate was inert (2) towards silver nitrate at high temperature. Its behaviour with sodium ethoxide also differs from that of other chlorosulphates, which yield alkyl ethyl ethers; [3] the chlorosulphate (2) afforded the alcohol (1)



(1) R = H

(2) R = SO_2Cl

quantitatively. This result suggests attack of ethoxide ion on the sulphur atom followed by elimination of ethyl chlorosulphate. Rear-side attack by the nucleophile on the sterically hindered 1-carbon atom is considered unlikely. In the aluminium chloride-catalysed reaction of the salt (2) with benzene, 7,7-dimethyl-1-phenylnorbornane was the sole product.

EXPERIMENTAL

General Procedure for the Reaction of Alcohols with Sulphuryl Chloride in Acetonitrile.—To a solution of sulphuryl chloride (0.06 mol) in acetonitrile (15 ml) was added the alcohol (0.02 mol) in acetonitrile (15 ml) during 30 min at −30 °C, while a current of nitrogen was bubbled through. Then the mixture was warmed to 0 °C, and bubbling was continued with stirring for a further 2 h. The mixture was poured into ice-cold aqueous sodium hydroxide, and extracted with three portions of ether. The combined extracts were dried (Na_2SO_4) and evaporated. The products were treated with zinc (0.5 g) in acetic acid (30 ml) under reflux for 5 h. After conventional work-up the final products were separated by column chromatography on alumina. Elution with ether–methanol (10 : 1) afforded the pure acetamide.

7,7-*Dimethylnorbornan*-1-*yl Chlorosulphate* (2).—The reaction of 7,7-dimethylnorbornan-1-ol [6] (1.4 g, 10 mmol) with sulphuryl chloride (4.1 g, 30 mmol) in acetonitrile (45 ml) was performed as above. Recrystallization of the product from ethanol–water gave the *chlorosulphate* (2) (1.7 g, 71%), m.p. 58—59 °C (Found: Cl, 15.0; S, 13.4. $C_9H_{15}ClO_3S$ requires Cl, 14.85; S, 13.45%), $\nu_{max.}$ 1 400, 1 190, and 910 cm^{-1}, δ 1.10 (6 H, s) and 1.30—2.40 (9 H, m). The chlorosulphate (2) was unaffected by refluxing in acetonitrile for 5 h with silver nitrate (1 mol. equiv.).

Reaction of the Chlorosulphate (2) *with Sodium Ethoxide.*—A mixture of the chlorosulphate (2) (200 mg, 0.84 mmol) and sodium ethoxide (100 mg, 1.4 mmol) in ethanol (15 ml) was refluxed for 3 h, then extracted with ether. Evaporation of the extract gave the alcohol (1) (104 mg, 53%), m.p. 159—161 °C, *m/e* 140, δ 0.90 (6 H, s) and 1.10—2.00 (9 H, m).

Reaction of the Chlorosulphate (2) *with Benzene in the Presence of Aluminium Chloride.*—A solution of the chlorosulphate (2) (230 mg, 1.0 mmol) and aluminium chloride (100 mg, 0.75 mmol) in benzene (15 ml) was refluxed for 4 h. 7,7-Dimethyl 1-phenylnorbornane was isolated by sublimation as a viscous liquid (190 mg, 95%), identical (i.r., n.m.r., and mass spectra, and g.l.c. retention times) with an authentic sample.[6]

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[6] P. Beak, R. J. Trancik, and D. A. Simpson, *J. Amer. Chem. Soc.*, 1969, **91**, 5073.