

The Reaction of Thionyl Chloride with Methyl-Substituted Heteroaromatic Compounds

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Abstract

Some heteroaromatic compounds with methyl substituents in the heterocyclic ring, such as 2-methylbenzothiazole, 2-methylbenzoxazole, and analogues, undergo rapid methyl group chlorination when heated with thionyl chloride. A mechanism for such reactions is proposed.

There are scattered reports in the chemical literature of unexpected side reactions, involving methyl groups, occurring in the otherwise commonplace thionyl chloride conversion of heterocyclic carboxylic acids into acid chlorides. For example, Boon¹ noted that the heating of 2,4-dimethylthiazole-5-carboxylic acid with thionyl chloride, and subsequent hydrolysis, afforded 4-methylthiazole-2,5-dicarboxylic acid.

4-Methylnicotinic acid^{2,3} and 6-methylnicotinic acid⁴ also suffer similar methyl group chlorination* on being heated with thionyl chloride. The presumed intermediate in these anomalous reactions is either a trichloromethyl derivative or, as in the case of the 4-methylnicotinic acid, a dichloromethanesulphenyl chloride compound.

It appeared initially that the original carboxylic acid function is not involved in the chlorination reaction, as such reactions have also been observed to occur with 2-methylchromone⁵ and with 3-methyl-2,1-benzisothiazole.⁶ In the latter case chlorination takes place rather rapidly, being complete in less than 1 h.

It seemed worthwhile to try the reaction of thionyl chloride with a representative range of methyl-substituted heteroaromatic compounds. We were interested in finding out what types of heterocyclic compounds were susceptible to this chlorination, and we also wanted to establish whether the reaction is a useful synthetic procedure.

Results

Some 23 methyl-substituted heterocyclic compounds were used in this study, together with three simple non-heterocyclic compounds. Five distinct reaction modes were observed.

* 'Chlorination' here includes the formation of other chlorine-containing oxidized species such as $-SCl$, $-SOCl$, etc., the product being at the oxidation level of a carboxylic acid.

¹ Boon, W. R., *J. Chem. Soc.*, 1945, 601.

² Preobrazhenskii, N. A., and Beer, A. A., *J. Gen. Chem. USSR*, 1945, 15, 667.

³ Wenkert, E., Haglid, F., and Mueller, S. L., *J. Org. Chem.*, 1969, 34, 247.

⁴ Graf, R., and Zettl, F., *J. Prakt. Chem.*, 1936, 147, 188.

⁵ Merchant, J. R., Bhat, A. R., and Rege, D. V., *Tetrahedron Lett.*, 1972, 2061.

⁶ Davis, M., Paproth, T. G., and Stephens, L. J., *J. Chem. Soc., Perkin Trans. I*, 1973, 2057.

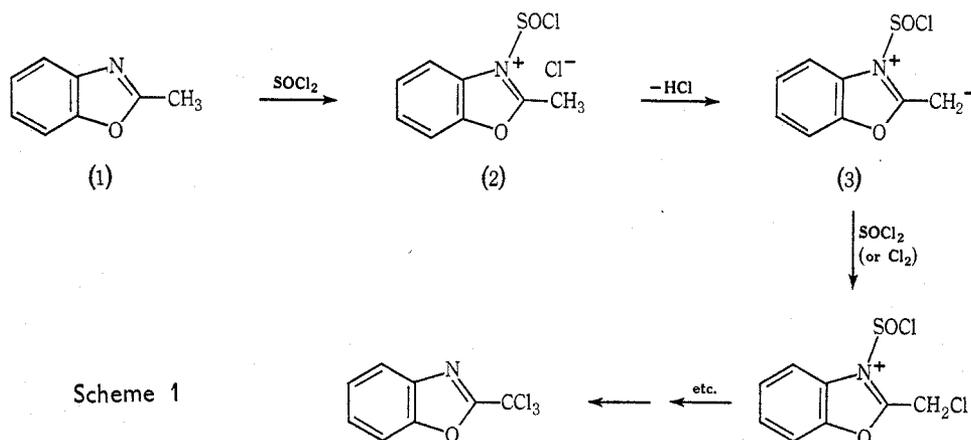
(1) Relatively rapid and complete chlorination of the methyl group in 2-methylbenzothiazole (1 h), 2-methylbenzoxazole (1 h), 2-methylbenzimidazole (72 h), 4-methylpyridine (24 h), 2-methylquinoline (24 h) and 2-methylquinoxaline (45 min). 2-Methylindole appeared to undergo chlorination but other reactions also occurred.

(2) Slow monochlorination of the methyl group in 1-methylnaphthalene (7 days) and 2-methylthiophen (30 h).

(3) Complete decomposition or formation of intractable tars in 2-methylimidazole, 2-methylpyrazine, 2-methylpyridazine and 4-methylpyrimidine.

(4) Other reactions (especially ring chlorination) in 2-amino-6-methylpyridine, 2-methylfuran, 3-methylisoxazole, 5-methylisoxazole, 3-methyl-1-phenyl-2-pyrazolin-5-one, 3-methylpyrazole and 3-methylthiophen.

(5) No observable reaction with 2-methylnaphthalene, 2-methylpyridine, 3-methylpyridine, 6-methylquinoline, 8-methylquinoline and 4-nitrotoluene.



Scheme 1

It is surprising that whilst 4-methylpyridine is chlorinated, the 2-methyl isomer under the same conditions is unaffected. As already noted, 6-methylnicotinic acid⁴ undergoes chlorination. Apart from this, rapid chlorination occurs with particular ease in bicyclic compounds in which the methyl group is attached *ortho* or *para* to a nitrogen atom in a multi-heteroatom ring. Such rings are strongly π -deficient. It seems possible that the reaction may involve electrophilic attack at a deprotonated species such as the compound (3) in the reaction sequence shown in Scheme 1. A similar intermediate (3) is probably involved in the known condensation reactions (such as with aldehydes) of certain methyl-substituted heteroaromatic compounds. There is a rough correspondence between the two reactions as far as ease of reaction is concerned.

The suggested sequence might also account for the observed formation of substituted sulphenyl and sulphinyl chlorides, the former arising from the latter by further reaction with thionyl chloride.⁷

In those cases where rapid and complete chlorination of the methyl group occurs, the present reaction provides a useful route to the corresponding icarboxylic acids.

The slow monochlorination, observed in a few cases, is probably a simple free radical reaction. Thionyl chloride slowly decomposes at reflux temperature into sulphur monoxide and chlorine.

⁷ Granoth, I., *J. Chem. Soc., Perkin Trans. I*, 1974, 2166.

Experimental

Reaction with Thionyl Chloride

The heterocyclic compound (1 g) and thionyl chloride (reagent grade, 7 ml) were mixed and heated under reflux. Samples were removed at intervals and examined by n.m.r. The time intervals were chosen according to the observed initial rate of disappearance of the methyl group signal, appearance of the chloromethyl signal, etc. A compound was categorized as 'no reaction' only if no change in the spectrum was observed after an initial heating period of at least 6 h. Chloromethyl derivatives were identified by n.m.r. and mass spectrometry, or direct isolation by distillation.

Isolation of Carboxylic Acids

In those cases where n.m.r. had indicated complete chlorination of the methyl group, the formation of trichloromethyl (or dichloromethanesulphenyl chloride, etc.) derivatives was confirmed by hydrolysis of the reaction product to the corresponding carboxylic acid by treatment with excess boiling sodium hydroxide solution (20 min) and subsequent acidification. The acids thus obtained were identified by their n.m.r. and mass spectra, and by direct comparison (mixed m.p.) with authentic samples. Although we have not attempted to optimize yields in every instance, the methyl group chlorinations and subsequent hydrolyses to carboxylic acids appear to proceed essentially quantitatively.

Acknowledgment

We thank Professor J. Zoltewicz for useful discussions.

Manuscript received 1 July 1976