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ABNORMAL NUCLEOPHILIC SUBSTITUTION OF 3-TRICHLOROMETHYLPYRIDINES BY METHOXIDE

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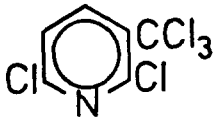
3-Trichloromethylpyridine and its α-chlorinated derivatives behave as ambident electrophilic substrates towards methoxide which attacks an α-position and the trichloromethyl group.

Aromatic or heteroaromatic trichloromethyl groups do not easily react with nucleophiles. Thus piperidine or methoxide in methanol replace only the ring chlorine atoms in 2,6-dichloro-4-trichloromethyl- or in other α-chlorinated 2- or 4-trichloromethyl-pyridines even under vigorous conditions[1,2]. By contrast 2,6-dichloro-3-trichloromethylpyridine (1) reacted rapidly under similar conditions with sodium methoxide to give the orthoester[3] or the methyl ester [2; R = $C(OMe)_3$ or (CO_2Me) under non-aqueous or aqueous work-up conditions respectively, in addition to the expected replacement of one of the α-chloro-atoms. With piperidine, only the amide (3; R = $CONC_5H_{10}$) was identified, but there was some n.m.r. evidence for the presence of the orthoamide [3; R = $C(NC_5H_{10})_3$].



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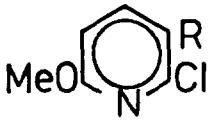

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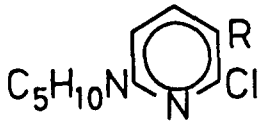
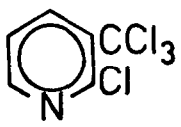


(3)

Methoxide also reacted with the mono-chlorinated derivatives (4,5; R = Cl and 6) converting the CCl_3-group into the acetal (or aldehyde on aqueous work-up) and substituting the non-chlorinated α-position. Thus 2-chloro-3-trichloromethylpyridine (4) gave the acetal

[2; R = $CH(OMe)_2$, 59%] but from a crude reaction mixture the aldehyde (2; R = CHO) and a little of the dimethoxyaldehyde (7) ws also isolated. On the other hand the 2-chloro-5-trichloromethylisomer (5; R = Cl) yielded under similar conditions the ester (8; R = CO_2Me, 60%) only, but with sodium methoxide in THF some aldehyde (9) was also obtained. From these preliminary results one can deduce that α-chlorine replacement by methoxide is accompanied by conversion of the 3-CCl_3-group into an orthoester [cf. 1 -> 2; R = $C(OMe)_3$]. By contrast methoxide attack on an unsubstituted α-position transforms the 3-CCl_3 into an acetal [cf. 4-> 2; R = $CH(OMe)_2$]. Further support for this view was obtained from a reaction between methoxide and 2-chloro-3,5-bis(trichloromethyl)pyridine (6) which offers the nucleophile a substituted and an unsubstituted α-position. The product (10) is the result of both types of reaction.



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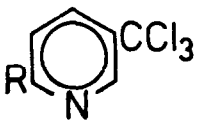

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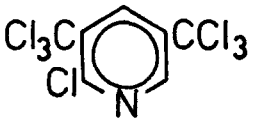

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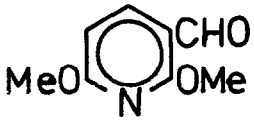

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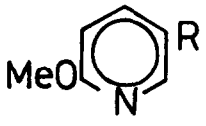

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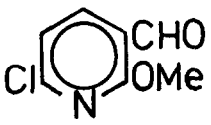

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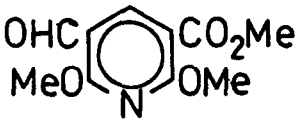
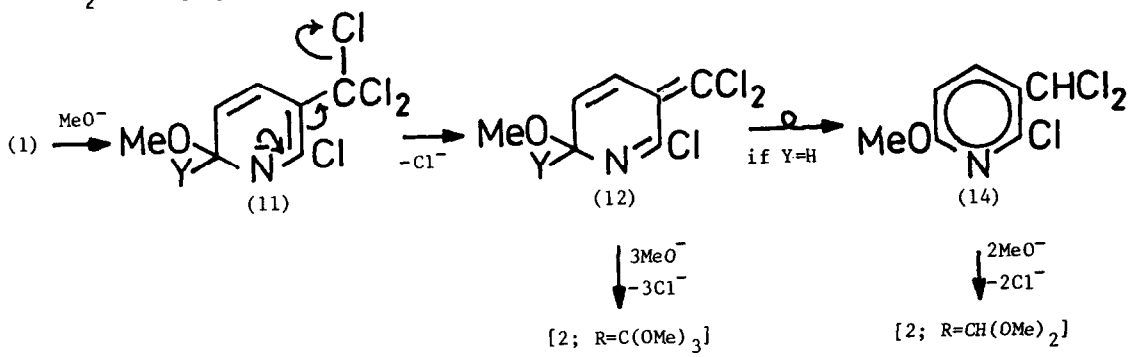


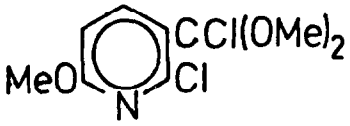
(10)

In order to ascertain whether an α-ring halogen is at all required for the above reactions 3-trichloromethylpyridine (5; R = H) prepared from nicotinic acid with phosphorus pentachloride[6] was made to react with sodium methoxide in methanol to give the acetal [8; R = $CH(OMe)_2$] in high yield.



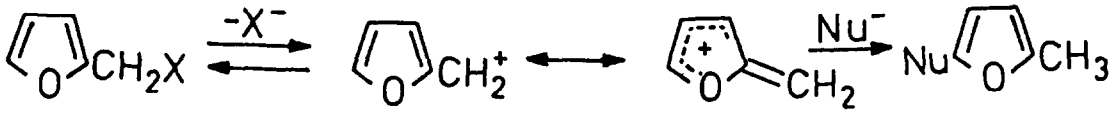
Scheme 1

A rational scheme to account for the ambident behaviour of 3-trichloromethylpyridines towards methoxide is outlined in scheme 1. The σ complex (11; Y = Cl) arises from an S_NAr process on (1) induced by the combined electronic effects of the CCl_3-group and the hetero-nitrogen. Elimination of Cl^- from the N-anion (11; Y = Cl) leads to intermediate (12; Y = Cl) which on attack at CCl_2 by the nucleophile (MeO^-) regains aromaticity and finally yields the orthoester [2; R = $C(OMe)_3$] by a repetition of similar sequences. Some evidence for these events was the isolation of the intermediate (13) from a quickly worked-up reaction



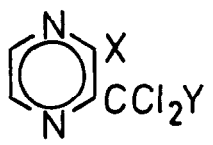
(13)

mixture. An analogous mechanism was in fact proposed to explain the unexpected reactivity of certain trifluoromethyl substituted quinolines [5] and imidazoquinolines.[6] Acetal (or aldehyde) formation following attack on an unsubstituted α-position could feasibly involve a [1,5]-H shift in the intermediate (12; Y = H) to give the dichloromethyl compound (14) which is subsequently converted by MeO into the acetal [2; R = $CH(OMe)_2$]. The alternative of a hydride ion migration from (12; Y = H), which was convincingly excluded recently for the remotely analogous vicarious substitution of hydrogen by nucleophiles[7], is equally unlikely in our system.



Scheme 2

Several examples are known in which benzylic halides ($-CH_2Cl$) undergo indirect (abnormal) replacement of the halogen by a nucleophile, especially cyanide in various 5-membered (π-rich) heterocyclic systems[8] e.g. furan, involving probably an ambident intermediate (cf. scheme 2). There are also reports of related reactions in nitrobenzylhalides.[9] We are, however, aware of only one example of a 6π-heteroaromatic system undergoing an abnormal nucleophilic substitution analogous to our case: the trichloromethyl pyrazine (15; X = H, Y = Cl) gave the acetal (16), while the 3-dichloromethyl compound (15; X = Cl, Y = H) yielded (17) with methoxide.[10]



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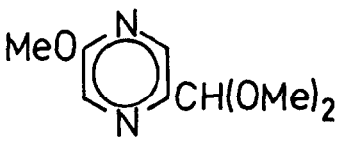

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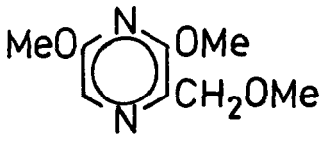

(17)

We are further investigating mechanistic and synthetic aspects of these novel pyridine reactions.

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3. All new compounds gave acceptable elemental analyses [except (13), which could not be adequately purified]. M.p.s. and selected i.r. and n.m.r. data: (2), R = $C(OMe)_3$, m.p. 69°C, δ3.98 (s, 3H), 3.16 (s, 9H); (2), R = CO_2Me, m.p. 68.5°C, ν 1725 cm^{-1}, δ 4.0 (s, 3H), 3.9 (s, 3H); (2), R = $CH(OMe)_2$, oil, δ 5.55 (s, 1H), 3.9 (s, 3H), 3.35 (s, 6H); (2), R = CHO, m.p. 118-120°C, ν 1690 cm^{-1}, δ 10.4 (s, 1H); (3), R = $CONC_5H_{10}$, m.p. 158-160°C, ν 1620 cm^{-1}; (7), m.p. 64-66°C, ν 1680 cm^{-1}, δ 10.25 (s, 1H); (8), R=CO_2Me, m.p. 50°C [Lit. 48-49°C: R.J. Dummel and H.S. Mosher, J. Org. Chem., 24, 1007 (1959)]; (8), R=$CH(OMe)_2$, oil, δ 5.4 (s, 1H), 4.0 (s, 3H) 3.35 (s, 6H); (9), m.p. 62-64°C, ν 1680 cm^{-1}, δ 10.15 (s, 1H); (10), m.p. 143-144°C, ν 1685 and 1705 cm^{-1}, δ 10.2 (s, 1H), 4.1 (s, 6H), 3.9 (s, 3H).
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