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Abnormal Nucleophilic Substitution in 3-Trichloromethylpyridine, its *N*-Oxide and 3,5-Bis(trichloromethyl)pyridine

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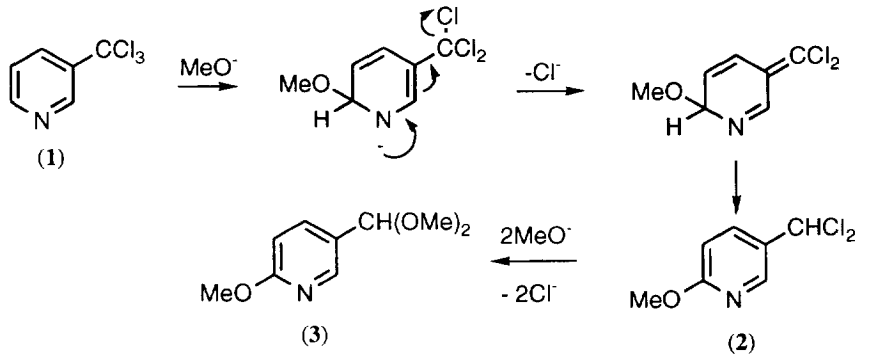
Dedicated to Hans Suschitzky, with affection and respect, on the occasion of his eightieth birthday

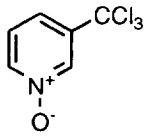
Abstract: The scope of abnormal reactions of nucleophiles with β-trichloromethylazines is further explored: reactions of 3-trichloromethylpyridine with nucleophiles other than methoxide, and reactions of 3-trichloromethylpyridine *N*-oxide and 3,5-bis(trichloromethyl)pyridine with methoxide. Attack at a ring carbon, followed by hydrogen migration to the side-chain, occurred in most cases, though attack at the trichloromethyl carbon was also sometimes observed.

We have reported that the reaction of methoxide with 3-trichloromethylpyridine (**1**) proceeds *via* attack at the 6-position, elimination of chloride ion, and migration of hydrogen, leading to 2-methoxy-5-dichloromethylpyridine (**2**) and thence to the acetal (**3**) as shown in Scheme 1.[1]

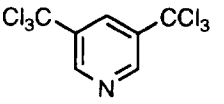


Scheme 1

We now report further studies on this type of interesting, and potentially useful, reaction. These involved reactions of 3-trichloromethylpyridine (**1**) with nucleophiles other than methoxide, comparative reactions of 3-trichloromethylpyridine-*N*-oxide (**4**), and reactions of 3,5-bis(trichloromethyl)pyridine (**5**) with methoxide.

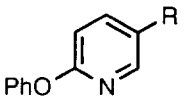


(4)

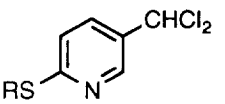


(5)

'Abnormal nucleophilic substitution' of 3-trichloromethylpyridine (**1**) appeared to be fairly general, although a strong nucleophile was required, and the use of strongly basic nucleophiles led to complications. Thus, while reactions with sodium methoxide proceeded under mild conditions, reaction with sodium phenoxide required the use of *N,N*-dimethylformamide (DMF) as solvent, and even after 2.5 h at 110° the products (after aqueous work-up) (**6**) and (**7**) were obtained in only low yield.



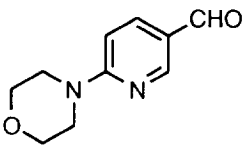
(**6**) R = CHO
(**7**) R = $CH(OPh)_2$



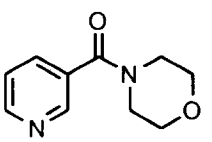
(**8**) R = Ph
(**9**) R = CH_2COOMe

On the other hand, a reaction of 3-trichloromethylpyridine with thiophenol and triethylamine in tetrahydrofuran (THF) under reflux gave the dichloromethyl compound (**8**) in 37% isolated yield and with methyl thioglycolate and triethylamine the dichloromethyl compound (**9**) was obtained in high yield even at room temperature. No reaction was observed with thiocyanate, even in the presence of crown ether, or thioacids.

Reactions of 3-trichloromethylpyridine with nitrogen nucleophiles were very sensitive to the conditions used. For example, with morpholine in acetonitrile under reflux the aldehyde (**10**) was obtained, whereas a reaction at room temperature gave the amide (**11**), *via* attack at the trichloromethyl carbon followed by hydrolysis. Sodium azide failed to react.



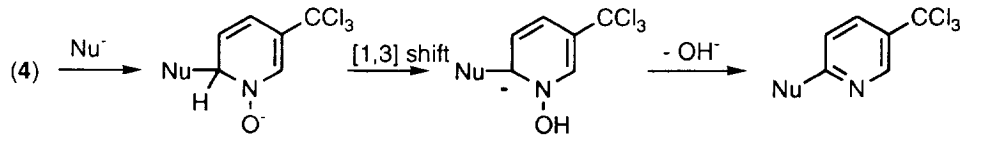
(**10**)



(**11**)

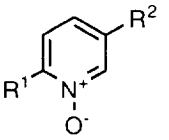
Experiments with carbon nucleophiles and phosphorus nucleophiles proved disappointing. No reaction was observed with cyanide, even in the presence of crown ether, and reactions with stabilised carbanions (e.g. from ethyl acetoacetate), organolithium compounds, Grignard reagents, triethyl phosphite or triphenylphosphine (*cf.* ref. [2]) failed to give identifiable products.

In the light of these results, analogous reactions of 3-trichloromethylpyridine-*N*-oxide (**4**) were of interest. Not only would *N*-oxidation increase the reactivity of the ring towards nucleophiles, but we predicted that the reactions might take a different course, involving substitution of the ring without reduction of the trichloromethyl group, as outlined in Scheme 2. In the event, our first expectation was fulfilled, but the second was not. The *N*-oxide (**4**) was prepared by oxidation of 3-trichloromethylpyridine (**1**) with 3-chlorophenoxybenzoic acid. On reaction with 1.5 eq. of sodium methoxide in THF at 0° for only 15 min, it gave a mixture from which the 'abnormal substitution' product (**12**) was isolated; the mixture obtained from a similar reaction with 4.5 eq. of sodium methoxide was shown by nmr and ms to contain the dichloromethyl compound (**13**), the acetal (**12**) and the orthoester (**14**). Similarly, reactions with methyl thioglycolate or



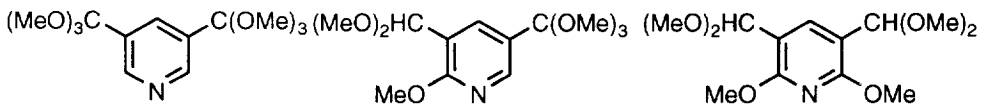
Scheme 2

2-mercaptoethanol and triethylamine at room temperature gave the dichloromethyl compounds (**15**) and (**16**) respectively. Likewise, although the reaction between the *N*-oxide (**4**) and morpholine in THF did not give clear-cut results, reaction in the presence of triethylamine gave the aldehyde (**17**) in 71% yield. It is remarkable that in these reactions the 1,5 hydrogen shift, which can not be concerted, took precedence over the 1,3 shift shown in Scheme 2, which could have been.

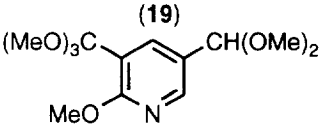


(**12**) R^1 = MeO, R^2 = $CH(OMe)_2$
(**13**) R^1 = MeO, R^2 = $CHCl_2$
(**14**) R^1 = MeO, R^2 = $C(OMe)_3$
(**15**) R^1 = $MeOCOCH_2S$, R^2 = $CHCl_2$
(**16**) R^1 = $HOCH_2CH_2S$, R^2 = $CHCl_2$
(**17**) R^1 = morpholino, R^2 = CHO

Further information was sought from reactions of 3,5-bis(trichloromethyl)pyridine (**5**)[3]. In the reactions of this compound with methoxide, attack at the ring α-positions[4] competed with direct attack on trichloromethyl groups, to give a mixture of products. With an excess of methoxide, the four products (**18** - **21**) could not be quantitatively separated, but samples were obtained and characterised by nmr spectroscopy, and the mixture was analysed by gas chromatography-mass spectrometry.



(**18**) (**19**) (**21**)



(**20**)

Compound (**18**) is formed by attack only at the trichloromethyl groups; compound (**19**) is formed *via* attack at a ring α-position followed by a 1,3 hydrogen shift, together with attack at a trichloromethyl group; compound (**20**) is formed *via* attack at a ring α-position followed by a 1,5 hydrogen shift, together with attack at a trichloromethyl group; and compound (**21**) is formed *via* attack at both ring α-positions. The reactions were

carried out under two conditions: (A) with sodium methoxide in boiling methanol for 19 h, and (B) with sodium methoxide in diglyme under reflux for 2.5 h. The proportions of the products obtained are shown in the Table. Note that the identities of compounds (**19**) and (**20**) have not been unambiguously determined. Their nmr spectra are inconclusive, but formation of (**20**), requiring the (intermolecular) 1,5-shift would be disfavoured by the aprotic conditions (B). Compound (**18**), formed without 'abnormal substitution' was a minor product in both cases.

Table. Reactions of 3,5-Bis(trichloromethyl)pyridine (**5**) with sodium methoxide

Reaction conditions	Proportions of products (%)			
	(**18**)	(**19**)	(**20**)	(**21**)
A	11	23	48	14
B	3	35	9	40

EXPERIMENTAL

M.p.s are uncorrected. I.r. spectra were recorded on a Perkin Elmer 1710 FT instrument. N.m.r. spectra were recorded at 90 MHz (Perkin Elmer R-32) referenced to internal TMS, 270 MHz (Bruker AC270), 300 MHz (Bruker AC300), or 400 MHz (Bruker AMX-400) referenced to deuteriochloroform. Mass spectra were obtained by use of Finnigan 4500 (low resolution) or Kratos Concept (high resolution or FAB) instruments, using chemical ionisation (NH_3); data are given for ions containing ^{35}Cl only: appropriate isotope patterns were observed. Gas chromatographs were run on a Perkin Elmer 8320 Capillary Gas Chromatograph, using a BP1 column (0.25 mm x 25 m, hydrogen carrier gas). Combined gc -ms measurements were made using a Varian 3400 Capillary Gas Chromatograph coupled with a Finnigan 4500 mass spectrometer. Analytical t.l.c was carried out on Camlab Polygram SIL G/UV_{254} plates. Preparative 'flash' column chromatography was carried out using Merck 9385 silica gel.
'Light petroleum' refers to the fraction b.p. 40-60°.

Reactions of 3-trichloromethylpyridine:- (a) with sodium phenoxide. To a solution of phenol (2.35 g, 25 mmol) in dry THF (30 ml) was added sodium (0.58 g, 25 mmol) and the mixture was stirred for 1 h. The solvent was evaporated and replaced by dry DMF (20 ml). A solution of 3-trichloromethylpyridine (1.0 g, 5 mmol) in dry DMF (5 ml) was added and the resulting mixture was heated at 110° for 3 h. The mixture was cooled and added to water (120 ml) and the resulting mixture was extracted with ether (3 x 25 ml). Conventional work-up and flash chromatography (eluant 1 ethyl acetate: 12 light petroleum) to give 2-phenoxypyridine-5-carbaldehyde (**6**), (80 mg, 4%), oil, δ 10.4 (not analytically pure) and *5-diphenoxymethyl-2-phenoxypyridine* (**7**) (400 mg, 21%), oil, δ 6.64 (1H, s; CH), 6.9-7.4 (16H, m; Ph, H-3), 7.90 (1H,dd; H-4), 8.40 (1H, d; H-6); M - OPh at *m/z* 276 (Found: C, 78.3; H, 5.3; N, 3.8 $C_{24}H_{19}NO_3$ requires C, 78.0; H, 5.2; N, 3.8%). A fraction containing phenol (190 mg) was also collected.
b) with sodium thiophenoxide. A mixture of 3-trichloromethylpyridine (1.0g, 5 mmol), thiophenol (0.51 ml, 5 mmol), triethylamine (1.0 ml, 7.5 mmol) and dry THF (30 ml) was heated under reflux for 5 h.. The mixture was cooled and filtered and the solvent was evaporated to leave a dark oil. Flash chromatography (eluant 1 ethyl acetate: 19 light petroleum) gave diphenyldisulfide (0.31 g) followed by *5-dichloromethyl-2-phenylthio)pyridine* (**8**) (0.51 g, 37%), oil, δ 6.65 (1H, s; $CHCl_2$), 6.9 (1H, d, J = 8 Hz; H-3), 7.4-7.8 (5H,

m; Ph, H-4),8.45 (1H, d, J = 3 Hz; H-6), $(M + 1)^+$ at *m/z* 269.9905; $C_{12}H_9Cl_2NS$ requires 269.9911.

c) with methyl thioglycolate. To a solution of 3-trichloromethylpyridine (1.0g, 5 mmol) in dry THF was added methyl thioglycolate (0.50 ml, 5 mmol) and triethylamine (1.0 ml, 7.5 mmol), and the mixture was stirred under argon for 1 week. The resulting suspension was filtered and the filtrate was evaporated to dryness. Flash chromatography of the residue (eluant 1 ethyl acetate: 25 toluene) gave 5-dichloromethyl-2-(methoxycarbonylmethylthio)pyridine (**9**) (1.01 g, 87%), m.p. 52-53°, δ 3.73 (3H,s; OMe), 3.98 (2H, s; CH_2), 6.65 (1H, s; $CHCl_2$), 7.27 (1H, d, J = 8.6 Hz; H-3), 7.76 (1H, dd, J = 8.4, 2.3 Hz; H-4), 8.45 (1H, d, J = 2.5 Hz; H-6), M^+ at *m/z* 265. (Found: C, 40.55; H, 3.5; N, 5.0 $C_9H_9Cl_2NO_2S$ requires C, 40.6; H, 3.4; N, 5.2%)

d) with morpholine

i) A mixture of 3-trichloromethylpyridine (1.0g, 5 mmol), freshly distilled morpholine (1.74 g, 20 mmol) and dry acetonotrile (40 ml) was heated under reflux under argon for 3 h. The solvent was evaporated and the residue was suspended in dichloromethane. The suspension was filtered and the filtrate was evaporated. Flash chromatography of the oily residue (eluant ethyl acetate) gave *2-morpholinopyridine-5-carbaldehyde* (**10**) (0.30 g, 31%), m.p. 88-89° (from cyclohexane), δ 3.8 (8H,m; morpholino), 6.65 (1H, d, J = 9 Hz; H-3), 7.95 (1H, dd, J = 9,33 Hz; H-4), 8.6 (1H, d, J = 3 Hz; H-6), 9.8 (1H, s; CHO), ν_{max} 1680 cm^{-1}, M^+ at *m/z* 192. Found: C, 62.85; H, 6.3; N, 14.6 $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 14.6%

ii) A mixture of 3-trichloromethylpyridine (0.30 g, 1.5 mmol), freshly distilled morpholine (0.26 ml, 3 mmol) and dry THF (15 ml) was stirred under argon at room temperature for 1 week. The solvent was evaporated. Flash chromatography of the residue (eluant ethyl acetate, then 1 ethyl acetate: 1 methanol) gave *N*-(3-pyridinoyl)morpholine (**11**) (0.12 g, 38%), oil (lit.[5]: liquid), δ 3.4-3.8 (8H, m; morpholino), 7.38 (1H, m; H-5), 7.75 (1H, ddd; H-4), 8.68 (2H, m; H-2,6)

3-Trichloromethylpyridine-1-oxide (**4**):- To a stirred solution of 3-trichloromethylpyridine (0.50 g, 2.5 mmol) in dry chloroform (20 ml) was added in small portions 3-chloroperoxybenzoic acid (0.6 g, 3 mmol), and the mixture was heated under reflux for 5 h. The mixture was cooled and extracted with 10% aq. sodium hydroxide, and the organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (1 ethyl acetate: 1 methanol) gave *3-trichloromethylpyridine-1-oxide* (0.41 g, 76%), m.p. 68-70°; δ 7.36 (1H, m; H-5), 7.73 (1H, m; H-4), 8.23 (1H, dd; H-6), 8.78 (1H, d; H-2); ν_{max} 1270 cm^{-1}; M^+ at *m/z* 212. Found: C, 34.0; H, 2.0; N, 6.4 $C_6H_4Cl_3NO$ requires C, 33.9; H, 1.9; N, 6.6%

Reactions of 3-trichloromethylpyridine-1-oxide:- (a) with methoxide. A solution of 3-trichloromethylpyridine-1-oxide (0.30 g, 1.4 mmol) in dry THF (10 ml) was stirred under argon at 0° as a solution of sodium methoxide (0.11 g, 2.1 mmol) in dry THF (5 ml) was added dropwise, and stirring was continued for 15 min. The mixture was filtered, the solvent was evaporated from the filtrate under reduced pressure, and the residue was recrystallised from diethyl ether to give *5-dimethoxymethyl-2-methoxypyridine-1-oxide* (**12**) (30 mg, 11%), m.p. 93-95°; δ 3.19 (9H, s; 3 x OMe), 5.23 (1H, s; CH), 6.80 (1H, d, J = 8.8 Hz; H-3), 7.25 (1H, d, J = 8.8 Hz; H-4), 8.24 (1H, s; H-6); M + 1 at *m/z* 200.0930 $C_9H_{13}NO_4$ requires 200.0923.

(b) with methyl thioglycolate. A mixture of 3-trichloromethylpyridine-1-oxide (0.30 g, 1.4 mmol), methyl thioglycolate (0.14 ml, 1.5 mmol) and triethylamine (0.31 ml, 2.2 mmol) in dry THF (25 ml) was stirred under argon at room temperature for 4 d. The mixture was filtered and the filtrate evaporated under reduced pressure to leave a residue which on flash chromatography (eluant ethyl acetate) gave *5-dichloromethyl-2-(methoxycarbonylmethylthio)pyridine-1-oxide* (**15**) (0.32 g, 81%), m.p. 83-85°, δ 3.73 (3H, s; Me), 3.77 (3H, s; Me), 6.60 (1H, s; $CHCl_2$), 7.40 (1H, d, J = 8.8 Hz; H-3), 7.44 (1H, d, J = 8.8 Hz; H-4), 8.44 (1H, s; H-6); ν_{max} 1740, 1210 cm^{-1}; $(M + 1)^+$ at *m/z* 282 Found: C, 38.6; H, 3.5; N, 4.9 $C_9H_9Cl_2NO_3S$ requires C, 38.3; H, 3.2; N, 5.0%

(c) with 2-mercaptoethanol. A mixture of 3-trichloromethylpyridine-1-oxide (0.30 g, 1.4 mmol), 2-mercaptoethanol (0.11 ml, 1.6 mmol) and triethylamine (0.30 ml, 2.1 mmol) in dry THF (25 ml) was stirred under argon at room temperature for 24 h. The mixture was filtered and the filtrate evaporated under reduced pressure. Water (30 ml) was added to the residue and the mixture was extracted with dichloromethane (3 x 15 ml). Conventional work-up of the combined extracts, followed by flash chromatography (eluant ethyl acetate) gave 5-dichloromethyl-2-(2-hydroxyethylthio)pyridine-1-oxide (**16**) (not analytically pure) (90 mg, 25%), oil , δ 3.7-3.8 (4H, m; CH_2CH_2), 4.3 (1H, br s, exch; OH), 6.70 (1H, s; $CHCl_2$), 7.40 (1H, d, J = 8.5 Hz; H-3), 7.60 (1H, d, J = 8.6 Hz; H-4), 8.50 (1H, s; H-6); ν_{max} 3300, 1220 cm^{-1}; $(M+1)^+$ at *m/z* 254. $C_8H_9Cl_2NO_2S$ requires 254.

(d) with morpholine. A mixture of 3-trichloromethylpyridine-1-oxide (0.30 g, 1.4 mmol), morpholine (0.12 ml, 1.4 mmol) and triethylamine (0.30 ml, 2.1 mmol) in dry THF (25 ml) was stirred under argon at room temperature for 24 h. The mixture was filtered and the filtrate evaporated under reduced pressure. Flash chromatography of the residue (eluant ethyl acetate) gave *2-morpholino-1-oxidopyridine-5-carboxaldehyde* (**17**) (0.27 g, 71%), oil, δ 3.63-3.65 and 3.93-3.95 (8H, m; morpholino), 6.93 (1H, d, J = 8.8 Hz; H-3), 7.71 (1H, dd, J = 8.6,2 Hz; H-4), 8.62 (1H, d, J = 3 Hz; H-6), 9.84 (1H, s; CHO); ν_{max} 1760, 1210 cm^{-1}, $(M - 16 + 1)^+$ (deoxygenates in MS) at *m/z* 193.0987. $C_{10}H_{13}N_2O_2$ requires 193.0977

Reaction of 3,5-bis(trichloromethyl)pyridine with methoxide:- Sodium (1.11 g, 47 mmol) was dissolved in dry methanol (60 ml) in a flask containing 4Å molecular sieves, under an inert atmosphere. 3,5-bis(trichloromethyl)pyridine (1.5 g, 4.7 mmol) was added and the mixture was stirred and heated under reflux for 19 h. The mixture was cooled and poured into water, and the resulting mixture was extracted with ethyl acetate (3 x 100 ml). The extract was dried ($MgSO_4$) and the solvents were evaporated. Gas-chromatography - mass spectrometry of the residue showed four components, each with *m/z* 287 ($C_{13}H_{21}NO_6$). Flash chromatography (eluant 1 ethyl acetate: 9 light petroleum) gave the following samples.

3,5-Bis(trimethoxymethyl)pyridine (**18**), δ 3.25 (18H, s; OCH_3), 8.15 (1H, t; H-4), 8.90 (2H, d; H-2,6)

3-Dimethoxymethyl-2-methoxy-5-trimethoxymethylpyridine (**19**), δ 3.10 (9H, s; $(OCH_3)_3$), 3.35 (6H, s; $(OCH_3)_2$), 4.0 (3H, s; OCH_3), 5.4 (1H, s; CH), 8.05 (1H, d; H-4), 8.25 (1H, d; H-6)

5-Dimethoxymethyl-2-methoxy-3-trimethoxymethylpyridine (**20**), δ 3.20 (9H, s; $(OCH_3)_3$), 3.45 (6H, s; $(OCH_3)_2$), 4.1 (3H, s; OCH_3), 5.65 (1H, s; CH), 8.0 (1H, d; H-4), 8.4 (1H, d; H-6)

3,5-Bis(dimethoxymethyl)-2,6-dimethoxypyridine (**21**), δ 3.4 (12H, s; $(OCH_3)_2$), 4.05 (6H, s; OCH_3), 5.6 (2H, s; CH), 8.0 (1H, s; H-4)

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REFERENCES

1. Dainter, R.S.; Jackson, T.; Omar, A.H.H.; Suschitzky, H.; Wakefield, B.J.; Hughes, N.; Nelson, A.J.; Varvounis, G. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 283
2. Kato, T.; Katagiri, N.; Takashi, T.; Katagiri, Y. *J. Heterocycl. Chem.* **1979**, *16*, 1575; Konno, S.; Sato, Y.; Sakamoto, T.; Katagiri, N.; Yamanaka, H. *Heterocyvcles* **1984**, *22*, 1332
3. Cartwright, D.; Ferguson, J.R.; Wakefield, B.J.; Giannopoulos, T.; Varvounis, G. *J. Chem. Soc., Perkin Trans. 1*, in press.
4. Attack at the γ-position was regarded as unlikely in the face of steric hindrance, and none was observed.
5. Parfenov, E.A.; Fomin, V.A. *J. Gen. Chem. USSR* **1981**, *51*, 1129

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