Pyrolysis of 2-Bis(methylthio)methylpyridine *S*-Oxides. Synthesis of Substituted Pyridinecarbaldehydes

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Summary A convenient preparation of pyridinecarbaldehydes by pyrolysis of 2-bis(methylthio)methylpyridine *S*-oxides is described.

In connection with other studies, we needed to prepare substituted pyridine-2-carbaldehydes. We herein report: (i) use of the carbanion of methyl methylsulphinylmethyl sulphide (**1**) to prepare heterocyclic aldehydes from the corresponding halide and (ii) the unexpected thermal rearrangement of the intermediate aldehyde dithioacetals.

Ogura and Tsuchihashi[1] first described the use of reagent (**1**) for the preparation of alkyl aldehydes and Schlessinger, *et al.*,[2] have extended this work. Heterocyclic aldehydes have been prepared from the corresponding halide *via* an organometallic intermediate and ethyl orthoformate[3] or *NN*-dimethylformamide,[4] but this route is limited. Since attempts to prepare pyridine-2-carbaldehyde *via* 1,3-dithians[5] failed, we investigated nucleophilic attack of the anion of (**1**) on simple 2-halogenopyridines. Reaction of (**1**) with sodium hydride in dimethoxyethane at 30° for 30 min followed by addition of 2-bromopyridine and stirring for 24 h at 30—35° gave (100%) the *S*-oxide (**2**; R = H), δ (CDCl$_3$) 2·28 and 2·32 (s, MeS), 2·51 (s, MeSO), 8·6 (d, [6-H, *J* 5 Hz), and 7·1—8·8 (m, py-H)]. Attempted purification of (**2**) by distillation did not afford the expected protected aldehyde but rather the free aldehyde (**4**; R = H) (74% overall yield), b.p. 181—182°, and dimethyl disulphide (70%), b.p. 116—117°, δ (CCl$_4$) 2·39 (s, MeS). Typical results are summarised in the Table.

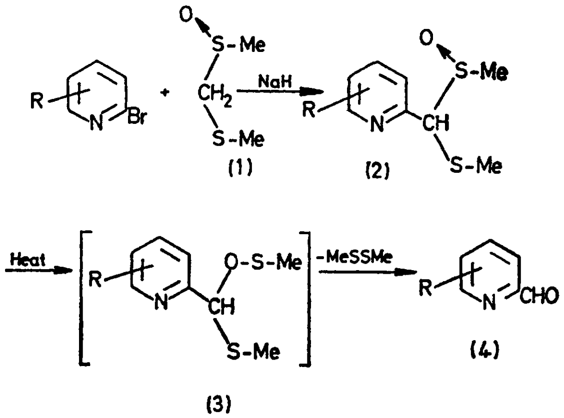
Alternatively, thioacetals such as (**2**; R = H) can be hydrolysed by treatment with concentrated hydrochloric acid in tetrahydrofuran at room temperature for several hours. Addition of HgCl$_2$ facilitates the work-up by eliminating disulphide contaminants. Thus, after 2 h under these conditions, the crude thioacetals afforded aldehydes (*e.g.* **4**; R = H) in *ca.* 60—70% yield. Hydrolytic work-up procedures have no apparent advantage, unless the resultant aldehyde is thermally labile.

Table

2-Halogenopyridine R	X	Reaction time /h	Temp. /°C	Yield of (2) (%)[a]	Rearr. temp. /°C	Compound (4) (%)[a]	m.p. (b.p./mmHg)
H	2-Br	24	30	~100	200	74	(181—182°/760)
H	2-Cl	48	30	b	200	12	
6-Br	2-Br	24	30	b	150	45[c]	77—78°[d]
6-Br	2-Br	24 1	30 reflux	64	150	61	
6-Cl	2-Cl	24 1	30 reflux	b	150	42	69—70°[d]
H	3-Br	48 1	30 reflux	b	240	10[e]	(95—97°/15)
H	4-Cl	48	30	b	200	43	(77—78°/12)

[a] Yield data were not optimized. [b] Detected by n.m.r., but not isolated. [c] Isolation of aldehyde was by bisulphite extraction. [d] Satisfactory analyses were obtained. [e] Yield estimated by n.m.r. analysis of the mixture.

Nucleophilic substitution of the halogen of the 2-halogenopyridine with the protected formyl function proceeds



smoothly at 25—85° to give compound (**2**), which is stable under the mild reaction conditions. In general, we find that: (i) Br^- is displaced more rapidly than Cl^-, (ii) only one halogen per pyridyl ring is easily substituted, and (iii) the 2- and 4-positions are more reactive than the 3-position. Upon heating to 150°—200°, compound (**2**- cleanly rearranged to compound (**4**) and dimethyl disulphide in reasonable yields, which were not maximized. We suggest that a thermal sulphur to oxygen 1,2-migration occurs [(**2**) → (**3**)] probably proceeding *via* ionic decomposition followed by elimination of dimethyl disulphide.[6] A similar rearrangement of methoxymethyl phenyl sulphoxide to give exclusively the *OO*-acetal has been recently reported.[7]

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