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REACTIONS OF 4-ALKYLPYRIDINE N-OXIDES WITH DIMETHYL SULFOXIDE

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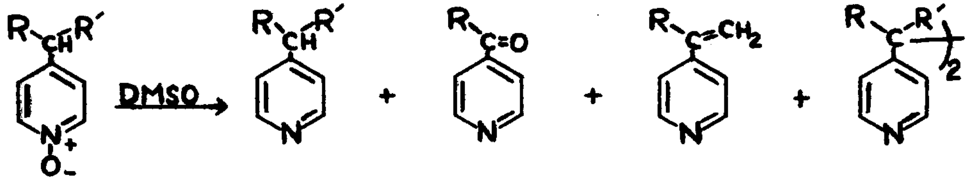
In the course of our mechanistic studies of the reaction of aromatic N-oxides with acid anhydrides, we explored the use of dimethyl sulfoxide (DMSO) as a substitute for the acid anhydride in reactions with 4-alkylpyridine N-oxides. The recent report by Biffin, Miller and Paul (1) on the deoxygenation of pyridine N-oxide by DMSO described a reaction which we also observed in part and thus leads us to communicate the results of our experiments.

When a solution of 4-picoline N-oxide (**1a**) and DMSO (1:5 mole ratio) was refluxed for 4 hrs. under nitrogen, 4-picoline (**2a**, 35%) and 4-pyridinecarboxaldehyde (**3a**, < 1%) were isolated along with unreacted **1a** (35%). However, when a solution of 4-benzylpyridine N-oxide (**1b**) and DMSO (1:10 mole ratio) was refluxed under nitrogen, the reaction was more rapid than with **1a** and was complete after one hour. The products isolated were 4-benzylpyridine (**2b**, 29%), 4-benzoylpyridine (**3b**, 41%) and 1,2-diphenyl-1,2-di(4-pyridyl)ethane (**5a**, 9%) which consisted of two diastereomers, m.p. 219.5-221° and m.p. 270-272° (predominant isomer). In a similar manner the reaction of 4-*p*-nitrobenzylpyridine N-oxide (**1c**) and DMSO was complete in one hour and produced 4-*p*-nitrobenzoylpyridine (**3c**, 51%) and 1,2-di(*p*-nitrophenyl)-1,2-di(4-pyridyl)ethane (**5b**, 6%). On the other hand the reaction of 4-isopropylpyridine N-oxide (**1d**) and DMSO (1:8 mole ratio) provided 4-isopropylpyridine (**2c**, 16%), 4-isopropenylpyridine (**4**, 14%), 2,3-dimethyl-2,3-di(4-pyridyl)butane (**5c**, 9%) and unreacted **1d** (8%).

The products isolated from these reactions were separated by distillation and/or column chromatography and identified by physical constants, ir and nmr spectra, elemental analysis (for new compounds) and/or preparation of solid derivatives.



1
a) R=R'=H
b) $R=C_6H_5$, R'=H
c) $R=\underline{p}NO_2C_6H_4$, R'=H
d) $R=R'=CH_3$

2
a) R=R'=H
b) $R=C_6H_5$, R'=H
c) $R=R''=CH_3$

3
a) R=H
b) $R=C_6H_5$
c) $R=\underline{p}NO_2C_6H_4$

4
$R=CH_3$

5
a) $R=C_6H_5$, R'=H
b) $R=\underline{p}NO_2C_6H_4$, R'=H
c) $R=R'=CH_3$

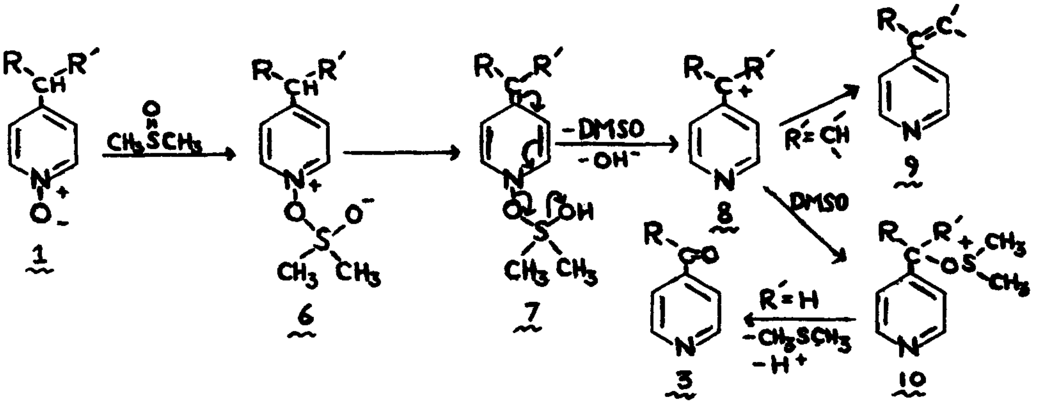
The alkylpyridine (**2a**, **2b**, **2c**) formed in these reactions, in most instances was not the major product. Although the mechanism proposed by Biffin and coworkers (1) for the acid catalyzed deoxgenation of pyridine N-oxides in DMSO may be operative here, one must also consider another pathway namely, the hydrogen abstraction reaction of 4-pyridylmethyl radicals (**12**). The presence of radicals in these reactions is suggested by the formation of the dimeric products **5a**, **5b** and **5c**. An independent preparation of 2,3-dimethyl-2,3-di(4-pyridyl)butane (**5c**) was achieved from the reaction of 4-isopropylpyridine (**2c**) and ammonium peroxydisulfate in DMSO. The reaction after 2.5 hrs. under nitrogen gave **5c** (20%), **4** (trace) and recovered starting material **2c** (40%). Dimerization reactions similar to the peroxydisulfate conversion of **2c** to **5c** have been attributed to a radical coupling process (2).

The alkylpyridines (**2a**, **2b**, and **2c**) were shown to be stable under the reaction conditions thus excluding them as precursors to the other products (**3**, **4**, **5**). A consideration of radical intermediates in the formation of carbonyl compounds (**3**) via oxidation to the corresponding 4-pyridylcarbinols and subsequent conversion of the alcohol by DMSO to carbonyl compounds (3) is rejected because alcohols were absent in the reaction mixture and the attempted conversion of 4-pyridylmethanol, phenyl-4-pyridylmethanol and p-nitrophenyl-4-pyridylmethanol to the corresponding carbonyl compounds (**3**) by DMSO failed under the reaction conditions.

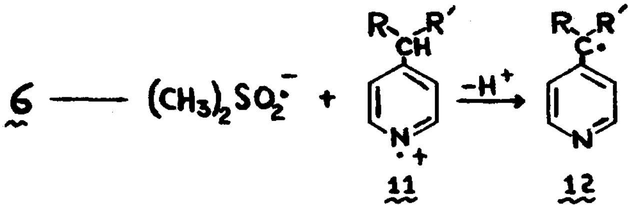
Also, the generation of olefin **4** from radical precursors was excluded by the results of the reaction of 4-isopropylpyridine (**2c**) and ammonium peroxydisulfate in DMSO. When one compares the yield ratios of the olefin **4** to the dimeric product **5c** (14/9 vs trace/20) between the reaction of 4-isopropylpyridine N-oxide (1d) with DMSO and the reaction of 4-isopropylpyridine (2c) with peroxydisulfate, respectively, it seems reasonable to conclude that the olefin 4 in the reaction of 1d with DMSO does not arise from radical intermediates.

On the other hand the formation of olefins by proton loss from carbonium ions is common place. Accordingly, the generation of a significant amount of 4-isopropenylpyridine (4) in the reaction of 1d with DMSO is suggestive of the presence of the 2-(4-pyridyl)-2-propyl cation. Furthermore, carbonium ions can also account for the origin of carbonyl compounds through the intermediacy of the alkoxydimethylsulfonium ion (vide infra).

Thus the mechanism proposed to account for the ketonic and olefinic products resembles the mechanism of the 4-alkylpyridine N-oxide acid anhydride reaction (4). Nucleophilic attack of the N-oxide oxygen on the sulfur atom of DMSO provides an oxypridinium ion (6) which upon removal of an α-proton from the 4-alkyl group leads to the anhydrobase 7. The heterolytic cleavage of the N-O bond in 7 produces a carbonium ion 8 which upon proton transfer may form olefin 9 or can be captured by DMSO to provide an alkoxydimethylsulfonium ion 10. Alkoxydimethylsulfonium ions have been established as intermediates in the formation of carbonyl compounds in the Pfitzner Moffat reaction (5) and thus support the transformation of 10 to 3. Also 10 may undergo an elimination reaction to provide olefin 9. The early steps in the proposed reaction pathway closely parallel the mechanism for the reaction of 4-alkylpyridine N-oxide and acid anhydrides. Enhanced reaction with increased acidity of the α-hydrogen of the 4-alkyl group in the conversion of 1 to 3 is also consistent with the proposed mechanism.



The origin of radical species in the N-oxide (1)-DMSO reaction is not clear; however, one attractive possibility may be the homolytic cleavage of the N-O bond in 6 to form the 4-pyridylmethyl radical cation (**11**) which upon deprotonation forms the pyridylmethyl radical (**12**). A similar mode of cleavage of the N-O bond has been proposed by Oae (6) in the reaction of pyridine N-oxides with p-nitrobenzenesulfinyl or sulfenyl chlorides.



The above discussion leads one to the conclusion that both ionic and radical species are generated in the reaction of 4-alkylpyridine N-oxides (**1**) with DMSO and that the former gives carbonyl (**3**) and olefinic (**4**) products while the latter provides the dimeric products (**5**) and possibly the deoxygenated alkylpyridines (**2**).

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