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SUGGESTION OF UNEXPECTED SULFUR DIOXIDE MECHANISM FOR DEOXYGENATIONS OF PYRIDINE *N*-OXIDES WITH ALKANESULFONYL CHLORIDES AND TRIETHYLAMINE

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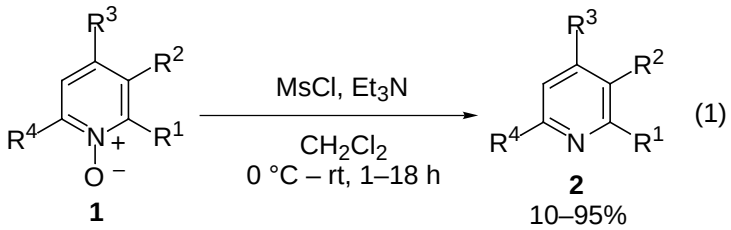
Abstract- The reaction mechanism for unusual deoxygenations of pyridine *N*-oxides with alkanesulfonyl chlorides and triethylamine was explored. Some experimental facts suggested that sulfur dioxide generated in the reaction system might be responsible for the deoxygenations without chlorinations of the pyridine nucleus.

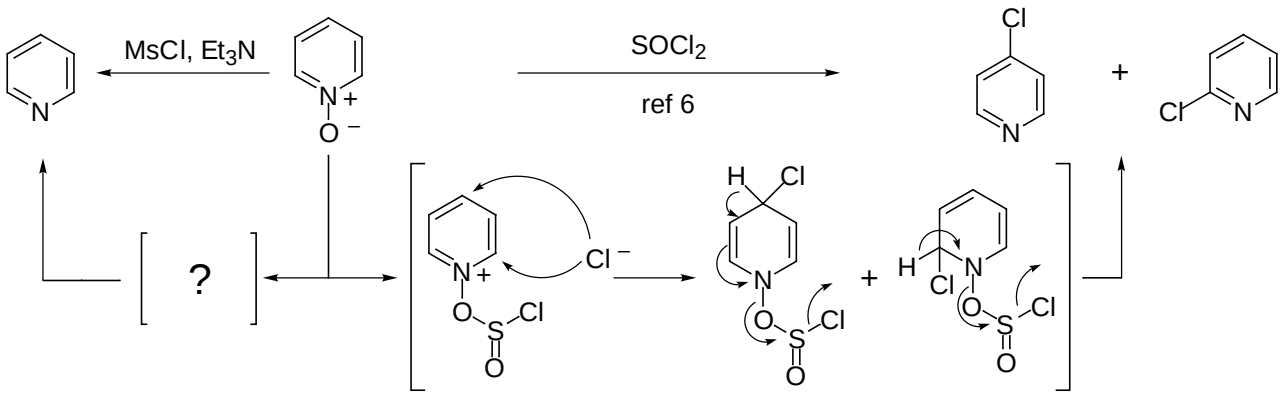
Methanesulfonyl chloride (MsCl) is one of the usual reagents most frequently used in organic synthesis. It is principally employed for the conversion of a hydroxyl group into a methylsulfonyloxy group, which is highly reactive as a leaving group in nucleophilic substitution and elimination reactions to be removed as methanesulfonate anion.[1] It is also useful for protection of hydroxyl and amino groups, though to a smaller extent.[2] The utilization of MsCl appears to be practically restricted to these two objects to the best of our knowledge. In the course of our synthetic studies of a marine macrocyclic alkaloid haliclamine,[3] we found that MsCl in the presence of triethylamine (Et_3N) is a novel deoxygenation system of pyridine *N*-oxides (eq 1).[4] The reaction mechanism of the deoxygenations, however, remains to be solved.



1 **2** 10–95% (1)

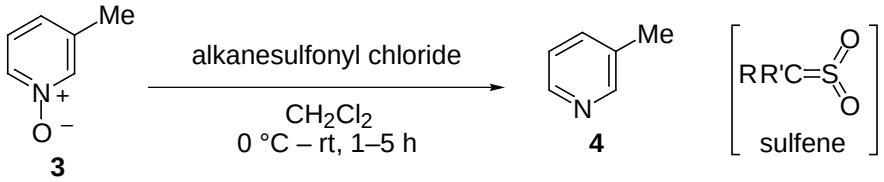
It is well known that reactions of pyridine *N*-oxides with chlorinating agents such as PCl_5, $POCl_3$, SO_2Cl_2, $SOCl_2$, *etc*. produce α- or γ-chloropyridines accompanied by the deoxygenation of the *N*-oxide function through the reaction pathway shown by the reaction with $SOCl_2$ in Scheme 1.[5] On the contrary, the deoxygenation by MsCl and Et_3N proceeds without such chlorination of the pyridine nucleus. Thus, the unusual behavior of familiar MsCl encouraged us to elucidate the reaction mechanism of this deoxygenation. In this communication, we report sulfur dioxide generated in the reaction system might be the real active species responsible for the unusual deoxygenation of pyridine *N*-oxides.

Scheme 1



Firstly, some preliminary studies were carried out in order to explore the essential features of this novel reaction (Table 1). Treatment of 3-methylpyridine *N*-oxide (**3**) with MsCl or (phenylmethane)sulfonyl chloride in the presence of excess Et_3N afforded the deoxygenation product, 3-methylpyridine (**4**), in 84 or 59% yield, respectively (entries 1 and 2). On the other hand, treatment with the same alkanesulfonyl chlorides in the absence of Et_3N resulted in recovery of the starting material (**3**) (entries 3 and 4). From the reaction with *p*-toluenesulfonyl chloride and Et_3N **4** could not be obtained, although **3** was consumed under the conditions giving a complicated mixture (entry 5). These results show that the sulfonyl chloride possessing an α-hydrogen and Et_3N are essential for the deoxygenation of **3**. This suggests the possibility that sulfenes are implicated as intermediates in this deoxygenation process, because the easy generation of sulfenes from alkanesulfonyl chlorides possessing an α-hydrogen and Et_3N is a well-established process in sulfene chemistry.[7]

Table 1. Deoxygenations of 3-Methylpyridine *N*-Oxide (**3**) with Alkanesulfonyl Chlorides under Various Conditions



entry	alkanesulfonyl chloride (equiv.)	base (equiv.)	product (yield%)[a]
1	$MeSO_2Cl$ (9)	Et_3N (12)	**4** (84)
2	$PhCH_2SO_2Cl$ (5)	Et_3N (8)	**4** (59)[b]
3	$MeSO_2Cl$ (9)	—[c]	**3** (91)
4	$PhCH_2SO_2Cl$ (5)	—[c]	**3** (94)
5	*p*-TsCl (5)	Et_3N (8)	—[d]

[a] Isolated yield. [b] 1,2-Diphenylethene (*trans*:*cis* = 65:35) was isolated in 32% yield as a by-product. [c] Without base. [d] Complex mixture.

Furthermore, we isolated 1,2-diphenylethene (*trans*:*cis* = 65:35) in 32% yield as a by-product in addition to **4** in the reaction with (phenylmethane)sulfonyl chloride and Et_3N (entry 2); this finding appears to be very informative for the reaction mechanism. It is known that *trans*- and *cis*-1,2-diphenylethenes are produced

from (phenylmethane)sulfonyl chloride and Et_3N through sulfene (**5**) (R = Ph), zwitterions (**6** and **7**), and episulfone (**8**) accompanying extrusion of sulfur dioxide (Scheme 2).[8] The same reaction sequence *via* **5** (R = H), **6**, and **7** is also invoked to explain some oligomeric products from MsCl and Et_3N.[9] Moreover, the redox exchange between *N*-oxide (**1**) and sulfur dioxide has already been described.[10] Thus, we assumed that in the above-mentioned deoxygenation of pyridine *N*-oxides the nascent sulfur dioxide generated in the reaction system might act as the reactive species in the presence of Et_3N (Scheme 2).

Scheme 2. Plausible Mechanism for the Deoxygenations of Pyridine *N*-Oxides with Alkanesulfonyl Chlorides and Triethylamine

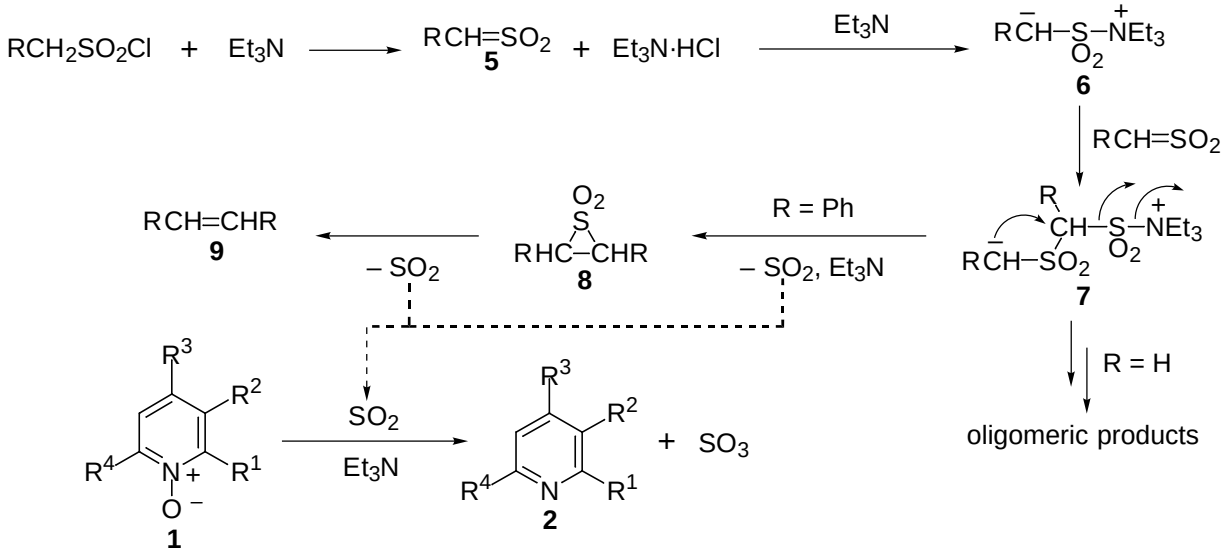
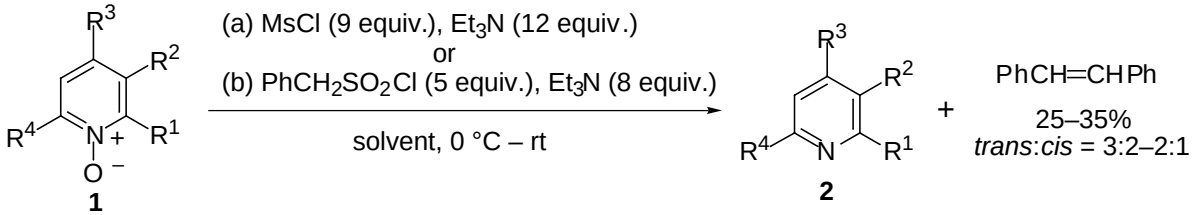


Table 2. Comparison of Our Deoxygenations with the Known Sulfur Dioxide Methods



1	yield% of **2**[a]					
	SO_2·NEt_3 (2 equiv.) dioxane, reflux[b]	atmospheric SO_2 dioxane, reflux[c]	reagents (a) dioxane	reagents (a) CH_2Cl_2	reagents (b) dioxane	reagents (b) CH_2Cl_2
R^1 = Me, R^2 = R^3 = R^4 = H	78	34	59	89	64	79
R^2 = Me, R^1 = R^3 = R^4 = H	76	—[d]	87	84	50	59
R^3 = Me, R^1 = R^2 = R^4 = H	75	31	48	59	55	53
R^1 = R^4 = Me, R^2 = R^3 =H	83	67	87	89	57	24[e]

[a] Isolated yield. [b] Cited from ref 10 (a). [c] Cited from ref 10 (b). [d] Not tested. [e] *N*-Oxide (**1**) (R^1 = R^4 = Me, R^2 = R^3 = H) was recovered in 57% yield.

For comparison with the previous results using sulfur dioxide as reducing agent, several pyridine *N*-oxides (**1**) were subjected to our deoxygenation procedure, and the satisfactory results were obtained, no formation of chloropyridines being noticed (Table 2). In reagent system (b), 1,2-diphenylethene (*trans*:*cis* = 3:2–2:1)

was always isolated in 25–35% yields along with **2**. Although there are a few differences in yields between the previous procedures[10] and ours, probably because of different reaction conditions, it appears that these results support the sulfur dioxide mechanism for the deoxygenations of pyridine *N*-oxides with alkanesulfonyl chlorides and Et_3N (Scheme 2). Thus, the reason why our deoxygenations do not experience chlorinations of the pyridine nucleus may be due to the sulfur dioxide mechanism different from the conventional pathway shown in Scheme 1.

This mild deoxygenation procedure of pyridine *N*-oxides using the inexpensive and accessible MsCl and Et_3N is apparently more favorable than that using commercially unavailable sulfur dioxide-triethylamine complex[10a] and that using intractable gaseous sulfur dioxide.[10b] The more detailed reaction mechanism is under investigation.

ACKNOWLEDGMENTS

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