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FACILE DENITROSATION OF CYCLIC N-NITROSAMINES WITH BORON TRIFLUORIDE

Ramasubbu Jeyaraman* and Thiruvenkadam Ravindran

Department of Chemistry, Bharathidasan University, Tiruchirapalli-620 024

Tamil Nadu, India

Abstract: A facile method for denitrosation of cyclic N-nitrosamines employing BF_3-Furan, BF_3-Thiophene, or BF_3-THF, in the presence of $NaHCO_3$ is described. Carbonyl groups are not affected in this method.

As part of our investigations on the stereochemistry of cyclic N-nitrosamines we tried the BF_3-catalyzed cycloaddition of furan to N-nitroso-2,6-diphenylpiperidines. The corresponding free amines were obtained as the exclusive products. Denitrosation was found to occur in a facile manner when furan was replaced by thiophene and THF. Several cyclic N-nitrosamines were subjected to this denitrosation process. Representative examples are given in Table 1. This method is synthetically useful, since treatment of the N-nitrosamines with metallating agents such as LDA followed by alkylation and denitrosation will lead to alpha alkylated amines.[1]

In a typical reaction, a mixture of N-nitroso-2,6-diphenylpiperidin-4-one (2.8g, 0.010 mol) dissolved in dry benzene (100 mL), THF (2.2 mL, 0.030 mol) and 48 % boron trifluoride etherate (7.85 mL, 0.03 mol) was stirred at room temperature for an hour. The mixture was then washed with saturated aqueous $NaHCO_3$ solution until effervescence subsided. The benzene layer was separated, washed with water, dried over Na_2SO_4 and the solvent stripped off. The solid obtained was recrystallized from ethanol. When furan or thiophene was used in the place of THF, the benzene- insoluble BF_3-Furan or BF_3-Thiophene complex was filtered off. The filtrate was washed with bicarbonate solution, benzene layer was separated and passed through a short column of silica gel. The solvent was evaporated to get the denitrosated product.[2]

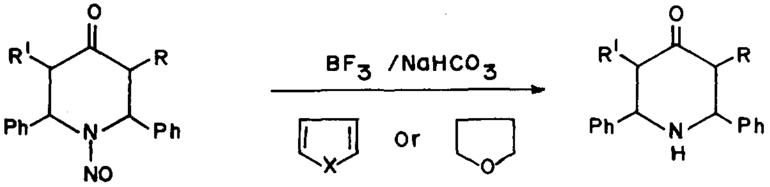
Denitrosation occurred neither with BF_3 or $NaHCO_3$ alone nor with a mixture of both. Many other control reactions have also been carried out and the combination of THF (furan or thiophene), BF_3 etherate and $NaHCO_3$ solution was found to be necessary to exhibit the denitrosation.

The nitrosamine, BF_3 and THF first form a solid adduct which could be separated from the benzene solution by cooling the reaction mixture to about 0°C overnight. The separated adduct, when destroyed with saturated aqueous $NaHCO_3$ solution, gave the free amine. However, the adduct could not be characterized.

Gaseous HCl in aprotic solvents, which was used for denitrosation several years ago has been replaced by reagents such as $TiCl_2$-$NaBH_4$, $NiCl_2$-$NaBH_4$ and chlorosulphonyl isocyanate.[3] Denitrosation can also be done by treatment with LAH followed by Raney Ni.[4] However, all these methods employ either strong acidic conditions or conditions in which some functional groups would be reduced.

The reagents reported herein, namely BF_3/THF, BF_3/furan, BF_3/thiophene are mild and the reaction conditions, workup, and purification are simple. Above all side reactions are absent atleast in the cases studied. For instance, the carbonyl group present in the N-nitrosopiperidin-4-ones was not affected.

Table 1. Denitrosation of nitrosamines with BF_3



No.	R	R'	Yields of the denitrosated products (in %) BF_3/THF $NaHCO_3$	 BF_3/furan $NaHCO_3$	 BF_3/thiophene $NaHCO_3$
1	H	H	81	52	50
2	Me	H	77	42	51
3	Et	H	68	38	36
4	i-Pr	H	76	46	49
5	Me	Me	84	58	56
6	$-(CH_2)_3-$		73	49	48

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