Selective Reduction of N-Nitrosoamines Using Borohydride Exchange Resin (BER)-$CuSO_4$ in Methanol

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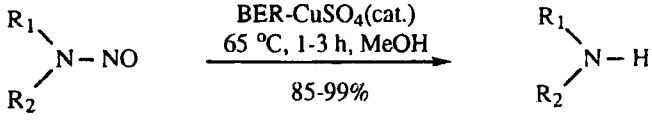
Nitrosoamines have been used for the introduction of alkyl groups at the α-position of secondary amines, and by this method a variety of secondary amines have been synthesized.[1-4] A key step for this synthetic operation is the removal of the nitroso group.[3-6] Of the methods presently available for the denitrosation, catalytic hydrogenation over Raney Ni[3,4] and $TiCl_4/NaBH_4$[5] have been used, and BF_3-THF/$NaHCO_3$[6] was also demonstrated to be an excellent alternative reagent for the purpose. Recently we have studied the reducing characteristics of borohydride exchange resin (BER)-$CuSO_4$(cat.) in methanol, and found nitro compounds and amine oxides are readily reduced with this reducing system.[7,8] Therefore we thought this system might be a convenient selective reagent for the reduction of nitrosoamines to the corresponding secondary amines. we report here a simple and general procedure for the denitrosation.

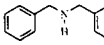
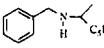
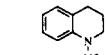
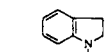
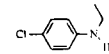
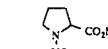
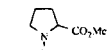


Scheme 1.

Nine representative N-nitrosoamines were reduced to the corresponding amines using BER (5 equiv)-$CuSO_4$ (0.1 equiv) in methanol at 65 °C. The results are summarized in Table 1. As shown in Table 1, the yields are excellent in all cases. In the case of sterically hindered N-nitrosoamine (entry 5), increased amounts of BER (7 equiv) and $CuSO_4$ (0.5 equiv) were required. Aromatic chloro substituents and ester groups were inert to this reagent. Thus N-nitrosoamines of 4-chloro-N-ethylaniline and proline methyl ester were selectively reduced to the corresponding secondary amines in quantitative yields (entries 8 and 9). Other groups, such as epoxides, amides and nitriles are also expected to be inert to this reducing system.[7] Several methods are available for the reduction of N-nitroso secondary amines to the corresponding derivatives.[3-6] However a considerably long time is required (14 h) either for the preparation of Raney Ni[9] or the reduction with $TiCl_4/NaBH_4$.[5] And present method gives a better yield (85-99%) than BF_3-THF/$NaHCO_3$[6] method (68-84%).

In conclusion, the reduction of N-nitrosoamines can be performed conveniently using BER-$CuSO_4$(cat.) in methanol. This method gives excellent yields of the corresponding amines, and tolerates many functional groups such as aromatic chloro substituent and ester, and has another advantage of simple work-up. Therefore the heterogeneous catalyst, BER-$CuSO_4$(cat.) in methanol is an excellent alternative reagent for the reduction of N-nitrosoamines.

Table 1. Selective Reduction of Nitrosoamines Using Borohydride Exchange Resin-$CuSO_4$ in Methanol at 65 °C[a]

Entry	Substrate	$CuSO_4$ (eq.)	Time (h)	Product	Yields (%)[b]
1		0.3	3		92
2		0.1	1		99[c]
3		0.1	1		90
4		0.1	1		91
5[d]		0.5	1		95
6		0.3	3		85
7		0.3	3		90
8		0.1	3		93
9[e]		0.1	3		90

[a] Reduction was carried out with 5 equiv of BER. [b] Isolated yields. [c] Isolated as hydrochloride salt. [d] BER (7 equiv) was used. [e] Racemic mixture (1 : 1).

Experimental

General Procedure. The denitrosation of N-nitroso-N-methyl aniline is representative. BER[8] (5.18 g, 15 mmol) was added to a methanol solution (10 mL) of $CuSO_4$-$5H_2O$ (0.075 g, 0.3 mmol) and the mixture was stirred slowly at room temperature. Immediately, a black coating of copper was observed. A methanol solution (10 mL) of N-methyl-N-nitrosoaniline (0.41 g, 3 mmol) was added and reacted at 65 °C. After 1h, the resin was removed by filtration, and

methanol was evaporated under reduced pressure. The crude residue was chromatographed on a silica gel (eluent; Hexane/EtOAc 10 : 1) to give 0.29 g (90%) of the pure N-methylaniline.[10]

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10. Spectral data: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.85 (S, 3 H), 6.61-6.76 (m, 3 H), 7.17-7.26 (m, 2 H); IR (neat) 3433 cm^{-1}; GCMS m/z (relative intensity) (EI, 70 eV) 107 (M^+ 82), 106 (100), 77 (29); Anal. Calcd for C_7H_9N: N, 13.07; C, 78.46; H, 8.47. Found: N, 13.12; C, 78.43; H, 8.46.

A Facile Synthesis of 7-Nitro-2,3-dihydrobenzo[*b*]furans

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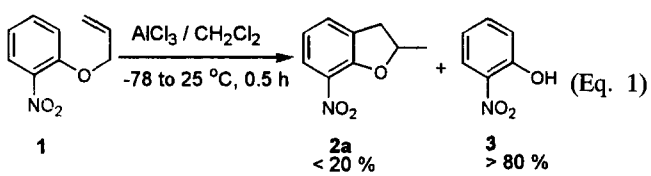
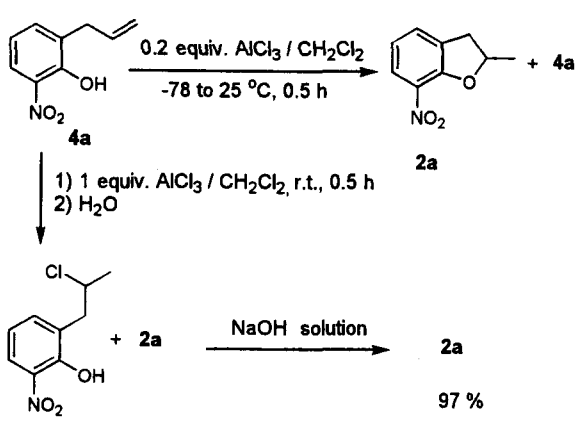
2,3-Dihydrobenzo[*b*]furan derivatives are very important intermediates for the preparation of pharmaceutical[1-3] and agricultural[4-6] agents. The 2,3-dihydrobenzo[*b*]furans were generally synthesized by acid-mediated cyclization such as strong acids,[7-12] $AlCl_3$,[13-14] $MgCl_2$,[1] $TiCl_4$,[15] and $ZnCl_2$.[16] The procedures were usually consisted of two steps: Claisen rearrangement of allyl phenyl ether to 2-allylphenol and the acid-mediated cyclization of the 2-allylphenol to 2,3-dihydrobenzo[*b*]furan. Recently, a convenient synthesis of 2,3-dihydrobenzo[*b*]furans with catalytic amount of $AlCl_3$[14] and I_2[17] was reported by Ryu and coworkers. However, the reactions of allyl phenyl ethers substituted with electron-withdrawing group provided low yields of desired benzo[*b*]furans. It was specifically noted that the cyclization of 2-allylnitrophenol did not give any desired product.[17] To investigate pharmaceutically useful benzo[*b*]furan analogues, we have been interested in synthesizing nitro substituted benzo[*b*]furans. Initially, we examined $AlCl_3$-mediated cyclization of various allyl 2-nitrophenyl ethers with 0.1-1.0 equiv. of $AlCl_3$. However, the reactions provided desired benzo[*b*]furans in low yields (<20%) and 2-nitrophenol which came from cleavage of allyl 2-nitrophenyl ether (Eq. 1).



(Eq. 1)

We employed 2-allyl-6-nitrophenol instead of allyl 2-nitrophenyl ether to improve the cyclization. The reaction of 2-allyl-6-nitrophenol, which was prepared by thermal Claisen rearrangement of allyl 2-nitrophenyl ether was treated with 0.1-0.2 equiv. of $AlCl_3$ at − 78 °C and followed by warming to room temperature over 0.5 h. The reaction gave less than 20% of benzo[*b*]furan and the starting material. We assumed that the reaction required 1.0 equiv. of $AlCl_3$ to cleave the tight intramolecular hydrogen bonding between phenolic hydrogen and oxygen of nitro group. The reaction using 1.0 equiv. of $AlCl_3$ provided a mixture of compounds **5** and **2a** (9 : 1) in quantitative yield. The treatment of the mixture of compouds **5** and **2a** with aqueous sodium hydroxide gave 7-nitro-2,3-dihydrobenzo[*b*]furan **2a** in 97% yield (Scheme 1).

With the optimized reaction conditions at hand, we in-



Scheme 1.