

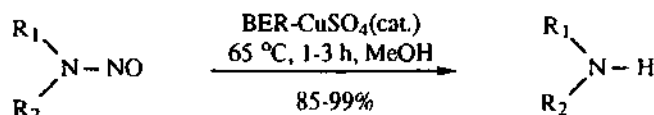
Selective Reduction of N-Nitrosoamines Using Borohydride Exchange Resin (BER)-CuSO₄ in Methanol

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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 TiCl₄/NaBH₄⁵ have been used, and BF₃-THF/NaHCO₃⁶ was also demonstrated to be an excellent alternative reagent for the purpose. Recently we have studied the reducing characteristics of borohydride exchange resin (BER)-CuSO₄(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.

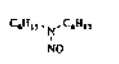
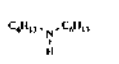


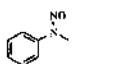
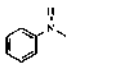
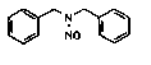
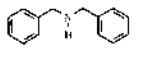
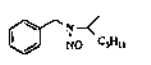
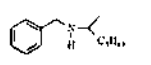
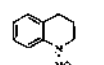
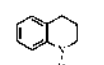
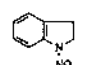
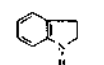
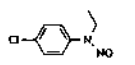
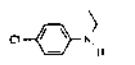
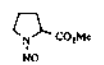
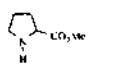


Scheme 1.

Nine representative N-nitrosoamines were reduced to the corresponding amines using BER (5 equiv)-CuSO₄ (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 CuSO₄ (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 Ni⁹ or the reduction with TiCl₄/NaBH₄.⁵ And present method gives a better yield (85-99%) than BF₃-THF/NaHCO₃⁶ method (68-84%).

In conclusion, the reduction of N-nitrosoamines can be performed conveniently using BER-CuSO₄(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

Table 1. Selective Reduction of Nitrosoamines Using Borohydride Exchange Resin-CuSO₄ in Methanol at 65 °C^c

Entry	Substrate	CuSO ₄ (eq.)	Time (h)	Product	Yields (%) ^b
1		0.3	3		92
2		0.1	1		99
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).

simple work-up. Therefore the heterogeneous catalyst, BER-CuSO₄(cat.) in methanol is an excellent alternative reagent for the reduction of N-nitrosoamines.

Experimental

General Procedure. The denitrosation of N-nitroso-N-methyl aniline is representative. BER⁸ (5.18 g, 15 mmol) was added to a methanol solution (10 mL) of CuSO₄·5H₂O (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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- Spectral data: ¹H NMR (200 MHz, CDCl₃): 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 C₇H₉N: N, 13.07; C, 78.46; H, 8.47. Found: N, 13.12; C, 78.43; H, 8.46.

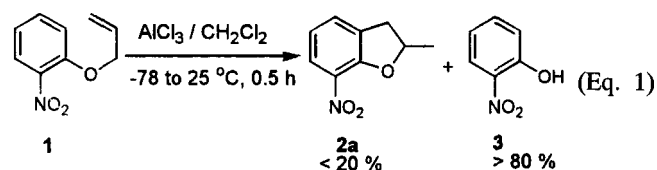
A Facile Synthesis of 7-Nitro-2,3-dihydrobenzo[b]furans

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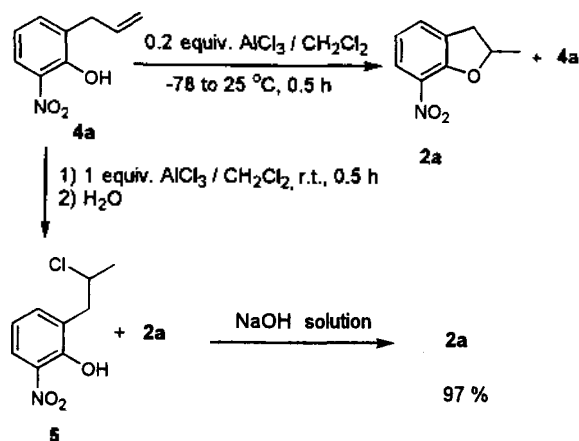
2,3-Dihydrobenzo[b]furan derivatives are very important intermediates for the preparation of pharmaceutical¹⁻³ and agricultural⁴⁻⁶ agents. The 2,3-dihydrobenzo[b]furans were generally synthesized by acid-mediated cyclization such as strong acids,⁷⁻¹² AlCl₃,¹³⁻¹⁴ MgCl₂,¹ TiCl₄,¹⁵ and ZnCl₂.¹⁶ The procedures 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 AlCl₃¹⁴ and I₂¹⁷ 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 AlCl₃-mediated cyclization of various allyl 2-nitrophenyl ethers with 0.1-1.0 equiv. of AlCl₃. 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).



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 AlCl₃ 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 AlCl₃ to cleave the tight intramolecular hydrogen bonding between phenolic hydrogen and oxygen of nitro group. The reaction using 1.0 equiv. of AlCl₃ provided a mixture of compounds 5 and 2a (9:1) in quantitative yield. The treatment of the mixture of compounds 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.