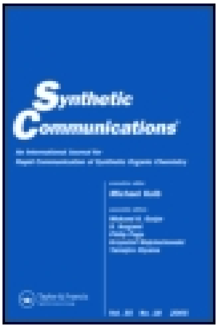

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Reduction of Azobenzenes to Diphenylhydrazines

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REDUCTION OF AZOBENZENES TO DIPHENYLHYDRAZINES

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Abstract: A selective, rapid and simple reduction of azobenzenes to diphenylhydrazines using borane-THF is described.

As a part of our ongoing program directed toward the development of radiolabeled agents[1] for potential use in evaluating Alzheimer's disease, we required access to a variety of substituted diphenylhydrazines. Azo compounds are readily reduced to the corresponding diphenylhydrazines, but they are often over-reduced to form anilines. Azobenzenes have been successfully reduced by catalytic hydrogenation,[2] sodium amalgam,[3] aluminum amalgam,[4] zinc in alcoholic ammonia[5] and stannous chloride[6] in ethanolic sodium hydroxide. These methods are not generally applicable to azo derivatives containing functionality such as the nitro, iodo and ester groups since they do not survive the reduction conditions. Brown and Subba Rao[7] reported that azobenzene was reduced to aniline by borane. However, they employed excess reagent under refluxing conditions. We wish to report

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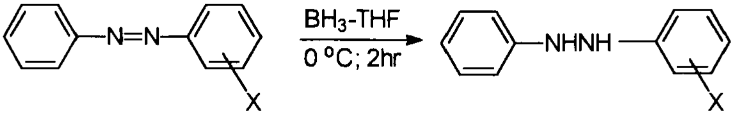
Entry	X	Yield%[a]	mp(lit.)°C
1	hydrogen	88	120-121(123-126[9])
2	methyl	75	99-101(102-103[10])
3	2,4-dimethyl	68	76-77(78-79[11])
4	2,6-dimethyl	60	gummy solid[b]
5	2-methoxy	81	81-83(84-85[8])
6	2-fluoro	82	56-58
7	2-chloro	79	74-76
8	2-bromo	68	71-72
9	2-iodo	71	98-99
10	3-iodo	75	92-94
11	4-nitro	48	110-112(114-115[12])
12	3-carboethoxy	74	56-58

[a] Isolated yield. [b] Converted to benzidine and characterized

	δ	Calculated			Found	
		C	H	N	C	H
2,6-Dimethyl	2.22 (*s*, 6H), 5.43 (*s*, 2H), 6.75-6.95 (*m*, 4H), 7.00 (*d*, 2H) and 7.31 (*m*, 2H)	79.20	7.60	13.20	78.96[a]	7.68
2-fluoro	550 (*s*, 1H), 5.85 (*s*, 1H), 6.65-6.85 (*m*, 5H), 6.90-7.15 (*m*, 3H) and 7.22-7.32 (*dd*, 1H, $J_{F,H} = J_{3,4} = 7.2$ Hz)	71.72	5.48	13.85	71.62	5.48
2-Chloro	5.62 (*s*, 1H), 6.15 (*s*, 1H), 6.70-6.87 (*m*, 4H), 7.05-7.15 (*m*, 2H) and 7.20-7.30 (*d*, 1H, $J_{3,4} = 7.5$ Hz)	65.91	5.07	12.81	65.93	5.04
2-Bromo	5.25 (*s*, 1H), 6.05 (*s*, 1H), 6.60-6.85 (*m*, 4H), 7.95 (*d*, 1H, $J_{6,5} = 7.24$) 7.15-7.25 (*m*, 3H) and 7.42 (*d*, 1H, $J_{3,4} = 7.4$ Hz)	54.97	4.21	10.65	55.48	4.37
2-Iodo	5.65 (*s*, 1H), 5.95 (*s* 1H), 6.55 (*m*, 1H), 6.81-6.90 (*m*, 3H), 6.95 (*d*, 1H, $J_{6,5} = 7.5$ Hz), 7.12-7.30 (*m*, 3H), 7.70 (*d*, 1H, $J_{3,4} = 7.44$ Hz)	46.65	3.58	9.03	46.49	3.59
3-Iodo	5.43 (*s*, 1H), 5.64 (*s*, 1H), 6.71-6.99 (*m*, 5H) and 7.09-7.31 (*m*, 4H)	46.65	3.58	9.03	46.39	3.62
3-carbo-methoxy	1.34 (*t*, 3H), 4.23 (*q*, 2H), 5.60 (*s*, 1H), 5.76 (*s*, 1H), 6.74-6.87 (*m*, 3H), 6.95-7.06 (*m*, 1H), 7.09-7.31 (*m*, 3H), 7.47 (*d*, 1H, $J_{4,5} = 7.2$ Hz) and 7.55 (*s*, 1H)	70.29	6.29	10.93	70.16	6.29

tial decomposition of product (to starting azobenzene) precluded the acquisition of satisfactory analytical data. T
was rearranged to 3,5-dimethylbenzidine and elemental analysis was obtained.

a selective, rapid and simple reduction of azobenzenes to diphenylhydrazines using borane-THF as the reducing agent.



The preparation of *N*-phenyl-*N'*-2-methoxyphenylhydrazine was representative: 2-methoxyazobenzene (3.9 mmol, 0.64 g) was dissolved in 10 mL of THF at 0°C. Borane in THF (7.0 mmol, 7.0 ml of a 1.0 *N* solution) was added at a rate sufficient to maintain the temperature below 5 °C. The mixture is then stirred at 0 °C for 2h and the reaction monitored by TLC. The reaction was quenched with methanol to destroy excess borane and the solvent removed. Potassium hydroxide (2 ml of a 20% solution) was added and the mixture refluxed for 0.5 hr. The solvent was then evaporated, the residue extracted with ether (3X20 mL) and the extract dried (Na_2SO_4). After removing the ether, the product was isolated by column chromatography (neutral alumina; pet. ether/ethyl acetate = 3/1) to yield= 0.59 g (81%) of *N*-phenyl-*N'*-2-methoxyphenyl hydrazine; mp. 81-83 lit.[8] mp. (84-85 °C).

As summarized in Table I, borane is an efficient and selective reagent for reducing substituted azobenzenes. The nitro group is unaffected (entry 11), but the reaction must be conducted at -15 °C to prevent over-reduction. Halogenated substrates (entries 6-10) yield the desired products without dehalogenation. In most of the earlier methods, partial dehalogenation occured. Hindered substrates such as 2,6-dimethylazobenzene (entry 4) and the ester analogue (entry 12) are also conveniently reduced to the desired products. The analytical data for all new compounds is summarized in Table II.

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