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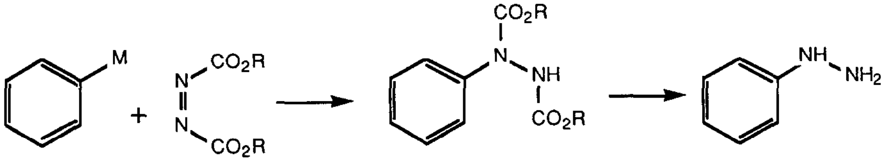
ADDITION OF ARYLMETALLICS TO AZODICARBOXYLATES: A NOVEL SYNTHESIS OF ARYLHYDRAZINES BY AROMATIC HYDRAZINATION

James P. Demers and Dieter H. Klaubert

Research Laboratories, Ortho Pharmaceutical Corporation
P.O. Box 300, Raritan, NJ 08869-0602

Summary: *Aryllithiums and arylmagnesium bromides add to the N=N bond of di-t-butyl azodicarboxylate, and subsequent acid deprotection provides the arylhydrazine.*

Recent work in these laboratories required access to a wide variety of arylhydrazines, some of which were not readily available by the usual routes[1]. In particular, there are no generally useful syntheses that do not require the corresponding aniline as a starting material. Since the addition of organometallic reagents to azo compounds has been demonstrated in a few cases[2-4], we sought a suitable diazo substrate that would add cleanly to arylmetallic reagents, and be readily convertible to a hydrazine in a subsequent operation. Azodicarboxylate esters seemed to be ideal candidates[5] (scheme below), but a search of the literature revealed only a single example[6], in which *t*-butylmagnesium chloride was found to add to the N=N bond of di-*t*-butyl azodicarboxylate. Since the completion of this work, several workers have reported the addition of enolates to azodicarboxylate esters.[7-10]



Initial experiments demonstrated that addition of phenyllithium or phenylmagnesium bromide to diethyl azodicarboxylate in THF at -78° provided, after hydrolytic workup and flash chromatography, the expected N,N'-bis(ethoxycarbonyl)phenylhydrazine in quantitative yield. From 3,4-dimethoxyphenylmagnesium bromide, the adduct was obtained in 96% yield. The conditions required to generate arylhydrazine by hydrolysis, however, turned out to be quite vigorous (KOH in refluxing methanol or isopropanol), and led to extensive decomposition of the products.

Di-*t*-butyl azodicarboxylate promised to provide a more readily cleaved bis-carbamate, and this proved to be the case. Addition of arylmetallics to a slurry of di-*t*-butyl azodicarboxylate (commercially available from Lancaster Synthesis) in THF at -78° resulted in rapid and clean formation of the bis(*t*-butoxycarbonyl) arylhydrazines. The latter materials could be purified by chromatography and/or recrystallization, but better overall yields of the desired arylhydrazines were obtained by carrying out the next step on crude product.

Removal of the *t*-BOC groups was accomplished by saturating an isopropanol solution of the bis-carbamate with hydrogen chloride gas, and allowing the resulting hot mixture to cool, or by adding 10 equivalents of HCl as a dioxane solution and refluxing briefly. The arylhydrazine hydrochlorides precipitated directly from the solution, and were collected by filtration. Dilution with ethyl ether before filtration was helpful for the more soluble salts. Results of several experiments are presented below, and a typical experimental procedure is provided. The process failed to produce the very electron-rich 3,4-dimethoxyphenylhydrazine, generating dark unidentifiable tars even under mild conditions (CF_3SO_3H, CF_3CH_2OH, -20° [11]). All isolated materials exhibited satisfactory IR and NMR spectra, and chemical ionization mass spectra.

Aryl	Metal	Yield (mp) of bis(*t*-Bu-carbamate)	Yield, mp of arylhydrazine HCl		Lit. mp (ref) of arylhydrazine HCl	
3,4-dimethoxyphenyl	MgBr	96% (oil)	12%*	103-6°†	81°†	(12)
4-(methylthio)phenyl	MgBr	(not isolated)	75%	198-9°	-	(13)
phenyl	Li	60% (109-111°)	88%	248-50°	243-6°	(14)
2-(trifluoromethyl)phenyl	MgBr	81% (oil)	79%	241-2°(sub)	218°	(15)
6-methoxy-2-naphthyl	MgBr	47% (oil)	67%	207-8°	209°	(16)
4-(pentyloxy)phenyl	MgBr	(not isolated)	60%	177-8°	169-70°	(17)
4-(2,2,2-trifluoroethoxy)phenyl	Li	61% (140-141°)	43%	185-6°		

*by hydrolysis (KOH/isopropanol) of bis(ethoxycarbonyl) derivative
†free base

Typical procedure : A solution of the Grignard reagent prepared from 4-bromothioanisole (49 mmol) in THF (100 ml) is cooled in a dry ice bath, and added *via* cannula to a stirred slurry of di-*t*-butyl azodicarboxylate (49 mmol) in THF (100 ml), also in a dry ice bath. (We subsequently found inverse addition to be unnecessary; the solid azodicarboxylate can be added all at once to the cold arylmetallic solution.) The resulting homogeneous solution is stirred for 10 min, and acetic acid (50 mmol) is added. The mixture is warmed to 20°, and water (30 ml) and ether (100 ml) are added. The organic layer is washed with brine, dried ($MgSO_4$), filtered, and evaporated, leaving N,N'-bis-(*t*-butoxycarbonyl)-4-(methylthio)phenylhydrazine as a viscous yellow oil. This is dissolved in isopropanol (500 ml), and HCl in dioxane (100 ml of 4.8 M solution) is added. After 15 min at reflux, the mixture is cooled, diluted with ether (250 ml), and the precipitate collected by filtration and dried *in vacuo*, providing 7.0 g (75%) 4-(methylthio)phenylhydrazine hydrochloride, mp 198-199° (dec).

References and Notes

1. J. Timberlake, J. Stowell, *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, p. 69 (S. Patai, ed.), John Wiley & Sons, Ltd., London (1975)
2. E. Schmitz, R. Ohme, *Chem. Ber.* , **94**, 2166 (1961)
3. G. Coleman, H. Gilman, C. Adams, P. Pratt, *J. Org. Chem.*, **3**, 99 (1938)
4. S. Bozzini, A. Stener, *Annali di Chimica (Rome)*, **58**, 169 (1968)
5. E. Fahr, H. Lind, *Angew. Chem. Int. Ed. Engl.*, **5**, 372 (1966)
6. L. Carpino, P. Terry, P. Crowley, *J. Org. Chem.*, **26**, 4336 (1961)
7. C. Gennari, L. Colombo, G. Bertolini, *J. Amer. Chem. Soc.*, **108**, 6394 (1986)
8. D. Evans, T. Britton, R. Dorow, J. Dellaria, *ibid.* , 6395
9. L. Trimble, J. Vederas, *ibid.*, 6397
10. W. Oppolzer, R. Moretti, *Helv. Chim. Acta*, **69**, 1923 (1986)
11. J. Holcombe, T. Livinghouse, *J. Org. Chem.*, **51**, 111 (1986)
12. W. Perkin Jr., L Rubenstein, *J. Chem. Soc.*, 357 (1926)
13. H. Hodgson, F. Handley, *J. Chem. Soc.*, 1882 (1928)
14. Merck Index, 10th Ed., entry 7175 (1983)
15. E. Forbes, M. Stacey, J. Tatlow, R. Wragg, *Tetrahedron*, **8**, 67 (1960). An analytically pure sample, prepared from the commercially available free base, sublimed at 245°.
16. K. Boltze *et al*, German patent DE 2,740,836 (1979); *Chem. Abstr.*, **91**:91500f
17. E. Kosower, T. Miyadera, *J. Med. Chem.*, **15**, 307 (1972)

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