ORGANIC LETTERS

2007
Vol. 9, No. 9
1789−1792

Diazo Preparation via Dehydrogenation of Hydrazones with "Activated" DMSO

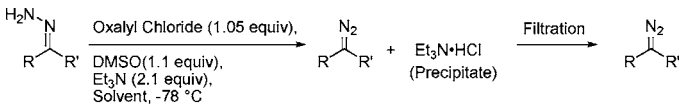
Muhammad I. Javed and Matthias Brewer*

The University of Vermont, Department of Chemistry, 82 University Place, Burlington, Vermont 05405

matthias.brewer@uvm.edu

Received February 28, 2007

ABSTRACT



We report that "activated" dimethyl sulfoxide efficiently dehydrogenates hydrazones to the respective diazo species at −78 °C. Under optimized conditions, triethylamine hydrochloride is removed quantitatively by vacuum filtration to provide solutions of diazo compounds. Stable diazo species can be isolated in high yield, or alternatively, the direct treatment of these solutions with carboxylic acids provides esters.

Diazo compounds have a rich history in organic synthesis as carbene and carbenoid precursors,[1] as components of 1,3-dipolar cycloadditions,[2] and as reagents for carbonyl homologation[3] and acid esterification.[4] In a small number of cases, diazo compounds have been isolated from natural sources.[5] The preparation of diazo compounds is often achieved by the dehydrogenation of hydrazones with stoichiometric quantities of toxic heavy-metal salts (i.e., mercury(II) oxide, lead(IV) acetate).[4,6−9] Not only are these reagents hazardous and environmentally unfriendly, but the isolation and purification of the resulting diazo product can also be problematic and can involve potentially hazardous manipulations of the diazo solution. Herein, we wish to report conditions for the preparation of diazo compounds via dehydrogenation of hydrazones with "activated" DMSO.[10] In this operationally simple and mild method, solutions of diazo compounds are easily isolated by simply filtering the reaction mixture.

While conducting research on the conversion of N-unsubstituted hydrazones to alkyl chlorides by treatment with chlorodimethylsulfonium chloride,[11] we noted that when benzophenone hydrazone was the substrate a short-lived and localized red coloration would occasionally appear. We reasoned that this red coloration might be due to the transient formation of diphenyldiazomethane in the reaction mixture and sought to develop this into a useful method for diazo preparation. Our initial studies focused on preparing the isolable and relatively stable diphenyldiazomethane (**2**, Scheme 1) from commercially available benzophenone hydrazone (**1**).

When a solution of benzophenone hydrazone in CH_2Cl_2 containing 2.1 equiv of triethylamine was added to a −78 °C solution of chlorodimethylsulfonium chloride in CH_2Cl_2, the color of the reaction immediately changed to dark red. IR spectroscopy of this clear red solution showed the characteristic diazo stretch. In an attempt to utilize the diazo compound directly in an esterification reaction, excess

(1) (a) Bethell, D.; Parker, V. D. *Acc. Chem. Res.* **1988**, *21*, 400−407. (b) Doyle, M. *Acc. Chem. Res.* **1986**, *19*, 348−356. (c) Padwa, A. *J. Organomet. Chem.* **2001**, *617*, 3−16.

(2) Mass, G. In *Heterocyclic Compounds: 1,3-Dipolar Cycloaddition*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons, Inc.: New York, 2002; Vol. 59, pp 541−621.

(3) (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364−429. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725−4726.

(4) Regitz, M.; Mass, G. *Diazo Compounds Properties and Synthesis*; Academic Press, Inc.: Orlando, 1986.

(5) Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002**, *124*, 1854−1855.

(6) Heydt, H. In *Science of Synthesis Houben-Weyl Methods of Molecular Transformations: Heteroatom Analogues of Aldehydes and Ketones*, 5th ed.; Padwa, A., Ed.; Thieme: Stuttgart, 2004; Vol. 27, pp 843−935.

(7) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725−4729.

(8) For recent nonheavy-metal-mediated hydrazone dehydrogenation methods, see: (a) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222−12223. (b) McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **2002**, *43*, 8425−8427.

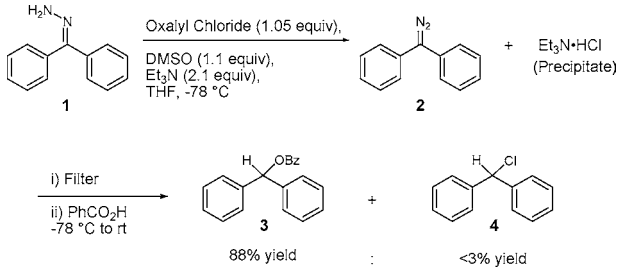
(9) For a summary of other oxidants that effect this conversion but find less use, see ref 7.

(10) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

(11) Brewer, M. *Tetrahedron Lett.* **2006**, *47*, 7731−7733.

10.1021/ol070515w CCC: $37.00
Published on Web 04/05/2007

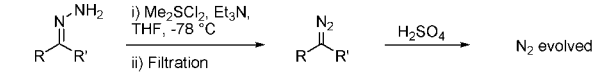
Scheme 1

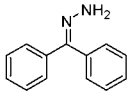
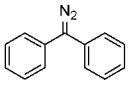
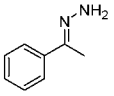
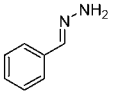
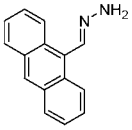
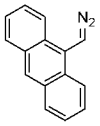


benzoic acid was added and the solution was warmed to room temperature. The resulting product mixture contained diphenylmethyl benzoate (**3**) and chlorodiphenylmethane (**4**) in a 5:1 ratio as determined by NMR. The reactions of diphenyldiazomethane with triethylamine hydrochloride and benzoic acid were clearly competitive. We reasoned that alkyl chloride formation might be suppressed by changing the solvent to one in which triethylamine hydrochloride is insoluble. This was ultimately realized by using THF as the reaction solvent.[12] Dropwise addition of a mixture of benzophenone hydrazone and triethylamine in THF to a solution of preformed chlorodimethylsulfonium chloride in THF at −78 °C provided a red solution containing copious amounts of white precipitate. Filtration of the cold solution provided a clear red solution of diphenyldiazomethane and a quantitative yield of solid triethylamine hydrochloride.[13] Addition of benzoic acid to the red solution and warming to room temperature provided diphenylmethyl benzoate (**3**) in 88% yield after purification by chromatography; less than 3% of chlorodiphenylmethane (**4**) was observed.

The yield of diazo compounds is difficult to establish due to their high reactivity. Yields are most commonly estimated either by conversion of the diazo compound to an isolable ester on treatment with a carboxylic acid or by measuring the volume of N_2 gas evolved upon treatment of the diazo solution with acid.[14,15] Due to competitive side reactions (azine formation, elimination reactions, etc.), neither of these procedures is ideal, and the actual yield of the diazo compound has been estimated to be as much as 20% higher than the observed yield determined by these methods.[16] In our studies, we determined the yield of the diazo product by both gas evolution[17] (Table 1) and esterification (Table 2) methods.

Table 1. Yield of Diazo Compounds as Determined by Gas Evolution Measurements



hydrazone	diazo	N_2 yield
		99
		97
		87
		88
		51
		5 - 42

As seen from the results in Table 1, gas evolution studies show uniformly good yields for the formation of α-aryl diazo compounds.[18] Benzophenone hydrazone provided diphenyldiazomethane in 99% yield, whereas acetophenone hydrazone, benzaldehyde hydrazone, and 9-anthraldehyde hydrazone returned their respective diazo products in 97%, 87%, and 88% yield. As observed in all previous methods of diazo preparation, the yields of nonstabilized secondary and primary α-alkyl diazo compounds were significantly lower. For example, pivaldehyde hydrazone provided *tert*-butyldiazomethane in 51% yield. The yield of diazocyclohexane, as determined by gas evolution experiments, was highly variable with results ranging from 5% to 42% yield. We attribute this variability to the instability of diazocyclohexane, which we suspect decomposes during filtration.

Alternatively, stable diazo compounds were easily isolated from the reaction mixture. For example, dehydrogenation of benzil monohydrazone (**5**, Scheme 2) followed by a simple extractive workup provided 2-diazo-1,2-diphenylethanone[19] (**6**) in 97% isolated yield. In the case of diphenyldiaz-

(12) The activation of DMSO with oxalyl chloride in THF was initially problematic. When DMSO was added to a precooled solution of oxalyl chloride in THF, the DMSO solidified and only slowly dissolved and reacted. This was circumvented by changing the order of addition: oxalyl chloride was added to a cold solution of DMSO in THF.

(13) ***Caution***: Diazo compounds are known to be explosive, and ground glass is thought to catalyze the explosive decomposition of diazomethane. Although we had no explosions while working with these compounds, suitable safety precautions were taken and all manipulations were conducted behind safety blast shields.

(14) Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N−N Bonds*; The Benjamin/Cummings Publishing Co.: Reading, MA, 1983.

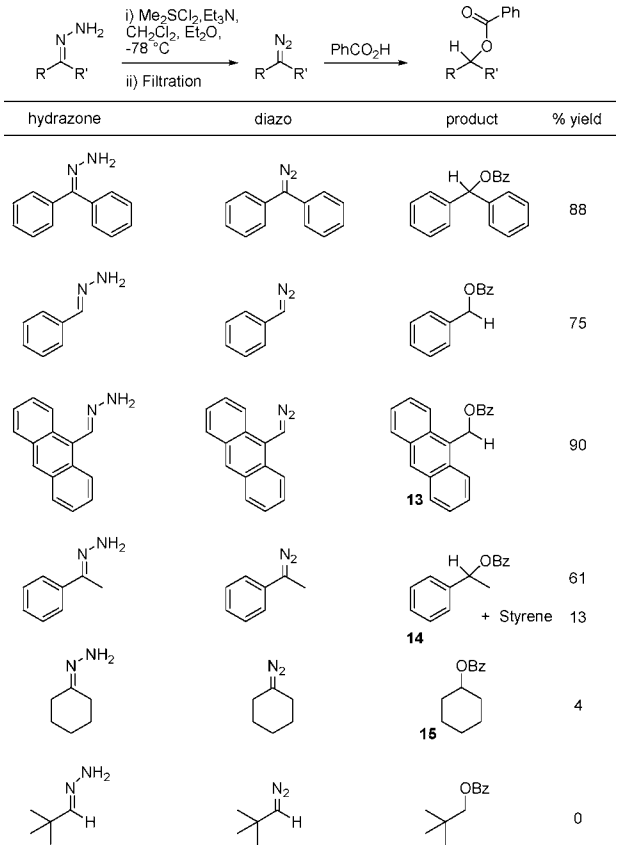
(15) Cheronis, N. D.; Ma, T. S. *Organic Functional Group Analysis*; Interscience Publishers: New York, 1964.

(16) Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Organic Syntheses*; Coll. Vol. 6, p 392 (1988); Vol. 50, p 50 (1970).

(17) The apparatus and procedure we used to measure nitrogen gas evolution was based on that described by: (i) Holton, T. C. The Synthesis of Diazo Compounds by Low-Temperature Oxidation of Hydrazones with Lead Tetraacetate. Ph.D. Thesis, The Ohio State University, 1971, 98−102. (ii) McGuiness, M. J. Synthesis of Diazo Compounds with Azidotris-(diethylamino)phosphodium Bromide. Ph.D. Thesis, The Ohio State University, 1991, 242−245. (iii) Holton, T. C.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725.

(18) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989−1003.

Table 2. Isolated Yield of Esters Derived from Diazo Intermediates



omethane, simply removing the triethylamine hydrochloride salt by filtration and removing the solvents in vacuo provided diphenyldiazomethane[20] in 99% yield as a viscous red oil that solidified on cooling. Proton NMR of this material showed only trace contaminants that were readily removed by crystallization from pentane.

Scheme 2

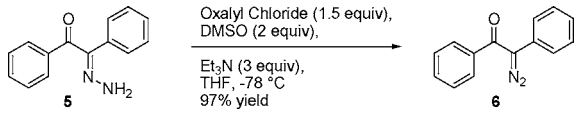
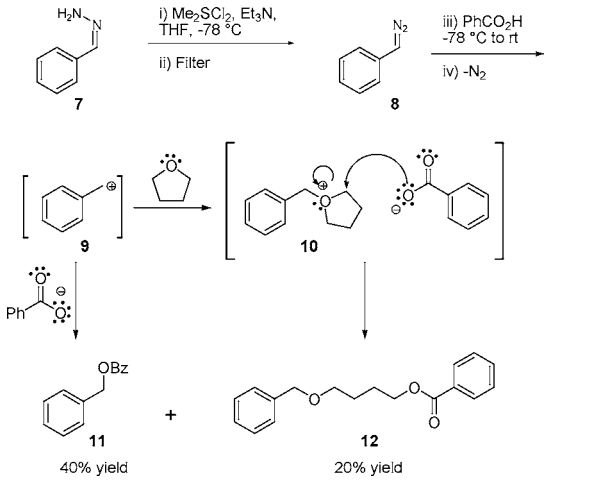


Table 2 shows the yields of benzoate esters obtained for the two-step sequence of diazo formation and subsequent reaction with excess benzoic acid. Interestingly, treating the THF solution of phenyldiazomethane (**8**, Scheme 3) with benzoic acid returned a mixture of the expected benzyl benzoate (**11**) in 40% yield and an additional 20% yield of

(19) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192−5201.

(20) Smith, L. I.; Howard, K. L. *Organic Syntheses*; Coll. Vol. 3, p 351 (1955); Vol. 24, p 53 (1944).

Scheme 3



4-(benzyloxy)butyl benzoate (**12**).[21] Ester **12** is likely derived by solvent participation as shown in Scheme 3.[22] Initial protonation of phenyldiazomethane by benzoic acid would provide the corresponding diazonium that could lose nitrogen to provide benzylic cation **9**. Reaction of THF with the benzylic cation would provide oxonium ion **10**, which in turn would be attacked by the benzoate anion to provide ester **12**. Solvent participation was also noted to a lesser extent in the reaction of 1-phenyldiazoethane with benzoic acid. In this case, 1-phenylethyl benzoate and 4-(1-phenylethoxy)-butyl benzoate were isolated in a 16:1 ratio. On the basis of these results, it appears that the degree of solvent participation reflects the stability of the cation intermediate.

To circumvent the problem of solvent participation, we sought an alternative reaction medium. The primary difficulty in establishing a good solvent for diazo preparation lay in balancing the solubility of chlorodimethylsulfonium chloride to that of triethylamine hydrochloride. Ultimately, a 9:1 mixture of diethyl ether and dichloromethane provided the right solvent characteristics, and no solvent participation was noted in any of the esterification reactions shown in Table 2. Due to the high vapor pressures of diethyl ether and dichloromethane, this solvent system did not provide reproducible results in gas evolution measurements; all gas evolution measurements were conducted using THF as solvent.

Subjecting benzylic hydrazones to the two-step process of diazo formation and subsequent esterification with excess benzoic acid provided good yields of benzoate esters. For example, benzophenone hydrazone provided diphenylmethyl benzoate[23] in 88% yield, whereas benzaldehyde hydrazone

(21) Suzuki, T.; Ohashi, K.; Oriyama, T. *Synthesis* **1999**, 1561−1563. The ^{13}C NMR data for this compound are identical to those described in the literature. The ^{1}H NMR data are also identical except for the chemical shift of one set of protons that appears to have been reported in error. We observed the methylene protons on the carbon bearing the ester as a triplet at 4.38 ppm. We believe the reported shift of 4.85 ppm is in error as it is presented out of numerical order in the original publication.

(22) Song, F. H.; Darbeau, R. W.; White, E. H. *J. Org. Chem.* **2000**, *65*, 1825−1829.

(23) Strazzolini, P.; Giumanini, A. G.; Verardo, G. *Tetrahedron* **1994**, *50*, 217−254.

and 9-anthraldehyde hydrazone provided benzyl benzoate[24] and 9-anthracenylmethyl benzoate in 75% and 90% yield, respectively. Acetophenone hydrazone provided a mixture of 1-phenylethyl benzoate[24] and styrene in 61% and 13% yield. Unstabilized alkyl diazo compounds are typically not synthetically useful in esterification reactions due to their high acid lability and propensity to undergo elimination or rearrangement reactions.[4] Not surprisingly, our attempts to isolate esters derived from unstabilized alkyl diazo compounds returned little to no product. Cyclohexanone hydrazone provided only 4% yield of cyclohexyl benzoate,[25] whereas pivaldehyde hydrazone failed to yield any neopentyl benzoate.

The dehydrogenation of hydrazones with activated DMSO in the presence of at least two equivalents of triethylamine offers a new method for the synthesis of diazo compounds. Significantly, this method avoids the use of the toxic heavy-metal salts used in previous diazo preparations. A simple filtration provided α-aryl diazo compounds in high yields as determined by gas evolution measurements and esterification reactions.

(24) Chen, C. T.; Munot, Y. S. *J. Org. Chem.* **2005**, *70*, 8625−8627.
(25) Werner, T.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 4302−4304.

Acknowledgment. We thank John Greaves (University of California, Irvine) for obtaining mass spectral data on 9-anthracenylmethyl benzoate. Financial support from the University of Vermont is gratefully acknowledged. Support from the Vermont Experimental Program to Stimulate Competitive Research (grant no. EPS0236976) is gratefully acknowledged. Amgen is gratefully acknowledged for financial support of this research in the form of an Amgen new faculty award. The project described was supported by the Vermont Genetics Network through Grant No. P20 RR16462 from the INBRE Program of the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR or NIH.

Supporting Information Available: Complete experimental details for the preparation of diazo compounds, the formation of esters from diazo compounds, and the method used to determine yield based on gas evolution and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070515W