1,1,1-Trimethylhydrazinium Iodide: A Novel, Highly Reactive Reagent for Aromatic Amination *via* Vicarious Nucleophilic Substitution of Hydrogen

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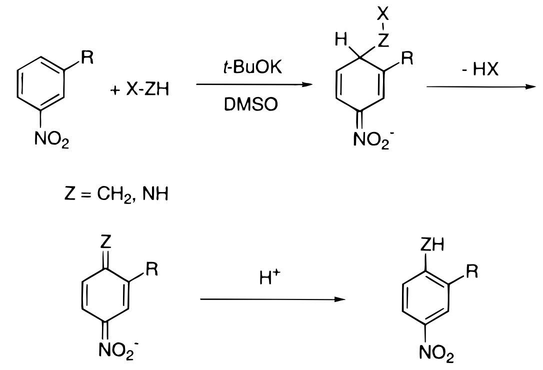
Vicarious nucleophilic substitution (VNS) of hydrogen is a well-established procedure for the introduction of carbon nucleophiles into electrophilic aromatic rings.[1,2] The reaction involves the addition of a carbanion bearing a leaving group (X) to an electrophilic aromatic ring and subsequent rearomatization by loss of the leaving group through elimination as HX (Scheme 1, Z = CH_2). This reaction has been applied to a wide variety of nitroarenes and nitro-substituted heterocycles.[2]

By analogy, VNS reactions can also take place with amine nucleophiles. Such reagents are of the common form XNH_2, where X is an auxiliary group capable of stabilizing a negative charge and of being eliminated as HX, thus driving rearomatization of the σ-intermediate adduct (Scheme 1, Z = NH). Meisenheimer and Patzig[3] reported in 1906 that 1,3-dinitrobenzene reacts with hydroxylamine in the presence of strong base to yield 2,4-dinitrophenylene-1,3-diamine, one of the first examples of amination by VNS of hydrogen. In more recent years, a number of reagents (including 4-amino-1,2,4-triazole[4] and substituted sulfenamides[5]) have been developed which facilitate the amination of nitroaromatic compounds by VNS of hydrogen under mild conditions. These reagents have proven to give regioselective amination under mild conditions in fair to high yields.

These results prompted us to investigate the use of 1,1,1-trimethylhydrazinium iodide (TMHI)[6] (**1**) as a VNS reagent for the introduction of amino groups into nitroaromatic substrates. We reasoned that TMHI (or its corresponding ylide, which may be produced upon reaction with strong base) should be sufficiently nucleophilic to attack nitro-substituted aromatic rings, with the neutral trimethylamine serving as an efficient leaving group. We have found that when TMHI reacts with various nitroarenes, the amino functionality is introduced in good to excellent yields.

The preparation of quaternized hydrazine halides, including TMHI, has been previously reported.[6−9] These compounds can be prepared by reaction of 1,1-disubstituted hydrazine with an alkyl halide, the alkylation generally occurring at the more substituted nitrogen.[7] Methyl iodide reacts with 1,1-dimethylhydrazine in THF at room temperature to give the desired 1,1,1-trimethylhydrazinium iodide (**1**) as white plates, mp 233−235 °C, in 81% yield after recrystallization from 95% EtOH (Scheme 2). The solid is stable at room temperature for at least several months in the absence of moisture.

Scheme 1



Scheme 2

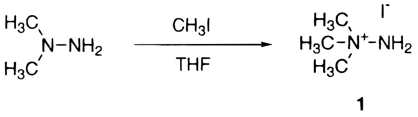
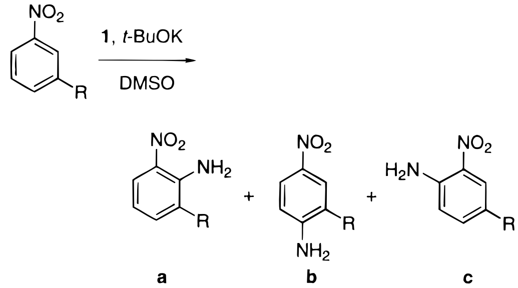


Table 1. Amination of 3-Substituted Nitrobenzenes with TMHI



compd	R	% yield	isomer ratios a	b	c
2	H	85	61	39	na
3	CH_3	84	38	35	27
4	Cl	82	32	49	19
5	COOH	95	0	71	29
6	OCH_3	66	90	10	0
7	F	84	45	47	8
8	I	76	45	38	17
9	CN	41	20	44	36

The efficacy of TMHI as a VNS aminating agent was tested by reaction with a variety of nitroarenes, including the 3-substituted nitroarenes used by Katritzky and Laurenzo in their study of 4-amino-1,2,4-triazole.[4a] In general, the reaction was conducted as follows: TMHI was dissolved in a solution of the nitroaromatic substrate in dry DMSO. Solid alkoxide base (potassium *tert*-butoxide or sodium methoxide) was then added in one portion with stirring, after which the solution turned deep red and the odor of trimethylamine was noted. After 4−17 h of stirring at room temperature, the reaction was quenched with 10% HCl. Precipitated solids were collected by suction filtration. The remaining solution was extracted with ethyl acetate, and the products were isolated by silica gel chromatography (9:1 petroleum ether/acetone). As all the products in this study are known compounds, their identity was con-

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(1) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.

(2) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic: San Diego, 1994; pp 59−66.

(3) Meisenheimer, J.; Patzig, E. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2533−42.

(4) (a) Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039. (b) Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1988**, *53*, 3978.

(5) Makosza, M.; Bialecki, M. *J. Org. Chem.* **1992**, *57*, 4784.

(6) Omietanski, G. M.; Sisler, H. H. *J. Am. Chem. Soc.* **1956**, *78*, 1211.

(7) Sisler, H. H.; Omietanski, G. M.; Rudner, B. *Chem. Rev.* **1957**, *57*, 1021.

(8) (a) Westphal, O. *Ber. Dtsch. Chem. Ges. B* **1941**, *74*, 759. (b) Westphal, O. *Ber. Dtsch. Chem. Ges. B* **1941**, *74*, 1365.

(9) Harries, C.; Haga, T. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 56.

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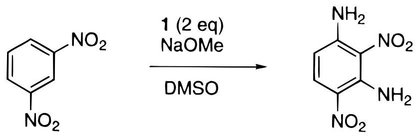
Scheme 3



firmed by reference to published melting points and/or comparison of ^{1}H NMR spectra with those of authentic material. Results are summarized in Table 1.

As indicated by these results, product yield with TMHI is generally good. Amination occurs both *ortho* and *para* to the nitro group, in contrast with the exclusive *para*-amination seen with 4-amino-1,2,4-triazole.[4a] Although we could discern no trends in regioselectivity of TMHI in this series, it is interesting to note that 2-amination varies from 90% (R = OCH_3) (**6a**) to 0% (R = COOH) (**5a**).

The reactivity of TMHI with 1,3-dinitrobenzene, a more highly activated ring system, was examined. In a reaction with 2 equiv of TMHI, 1,3-dinitrobenzene is converted in good yield (76% after recrystallization) to 2,4-dinitro-1,3-phenylenediamine (Scheme 3). Even when only 1 equiv of TMHI is used, substantial (10−15%) diamination takes place, indicating the very reactive nature of the reagent.

In summary, TMHI has been shown to be a novel VNS aminating reagent. It can be used to obtain isomers not produced by reaction with other nucleophilic aminating reagents. It is easily prepared from 1,1-dimethylhydrazine[8,9] or directly from hydrazine.[9] Further studies on the use of TMHI and related quaternary hydrazines as nucleophilic aminating reagents are in progress.

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Supporting Information Available: Experimental details for the preparation of **1** and its reaction with various substrates, including melting point and ^{1}H NMR spectral data (6 pages).

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