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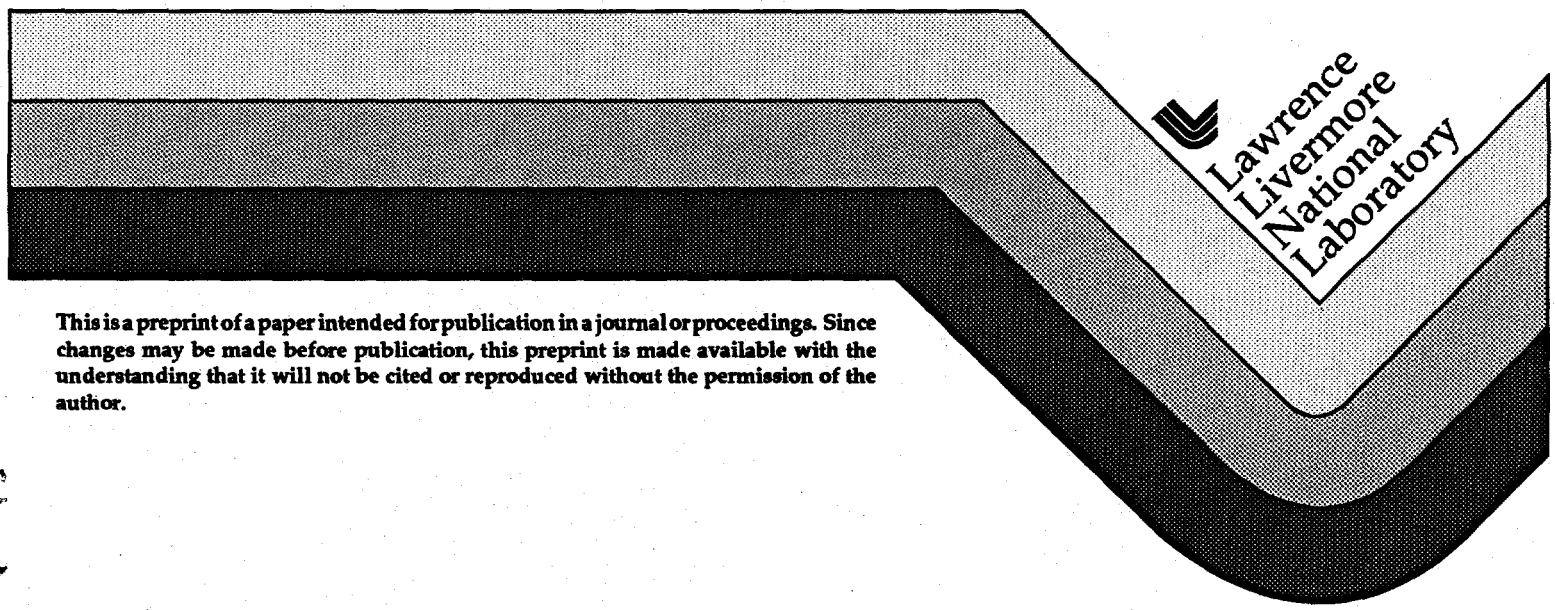
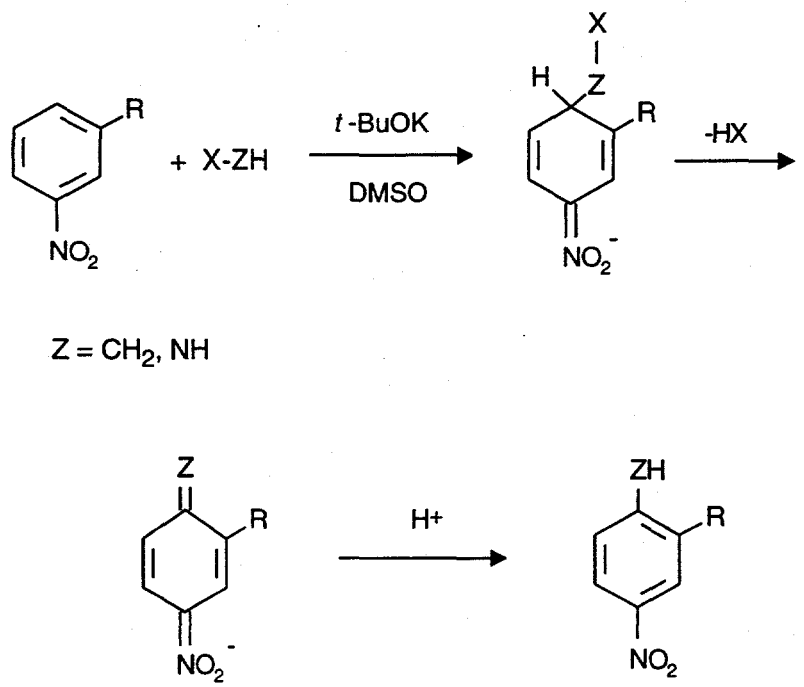


VICARIOUS AMINATION OF NITROARENES WITH TRIMETHYL-HYDRAZINIUM IODIDE Philip F. Pagoria,* Alexander R. Mitchell, and Robert D. Schmidt, *Lawrence Livermore National Laboratory, Mail Stop L-282, P.O. Box 808, Livermore, California, 94551*

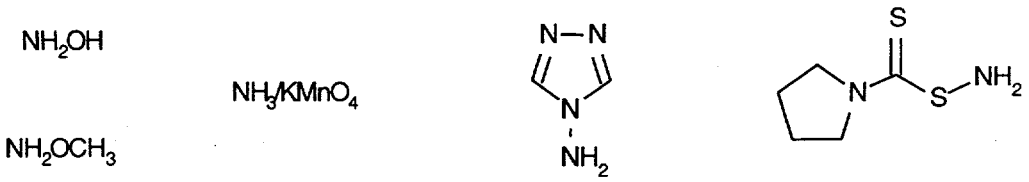
Vicarious nucleophilic substitution (VNS) of hydrogen is a well-established procedure for the introduction of carbon nucleophiles onto electrophilic aromatic rings.[1,2] The reaction involves the addition of a carbanion bearing a leaving group (X) to an electrophilic aromatic ring and subsequent rearomatization 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]



Scheme 1

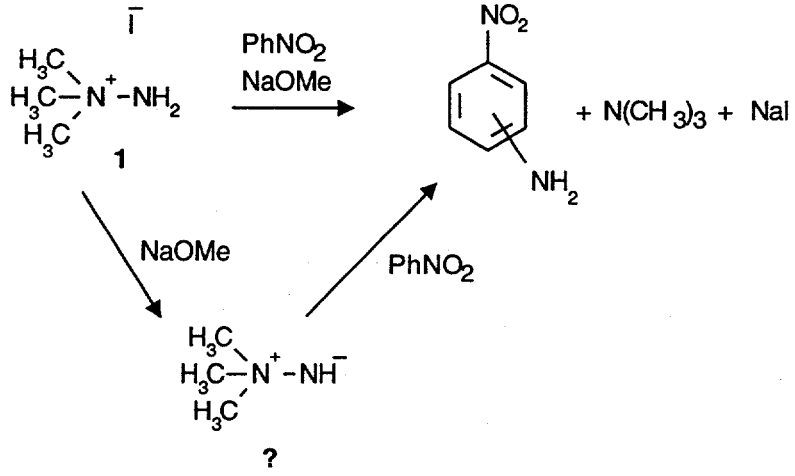
By analogy, VNS reactions can also take place with amine nucleophiles. Such reagents are of the common form X-NH_2, where X is an auxiliary group capable of stabilizing a negative charge and eliminating as HX, thus driving rearomatization of the σ-intermediate adduct (Scheme 1, Z=NH). Meisenheimer and Patzig[3] reported in 1906 that *m*-dinitrobenzene reacts with hydroxylamine in the presence of strong base to yield 2,4-dinitrophenylene-1,3-diamine, one of the first examples of a VNS amination reaction. 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 vicarious amination of nitroaromatic

compounds under mild conditions (Scheme 2). These reagents have proven to give regioselective amination under mild conditions and with fair to high yields.



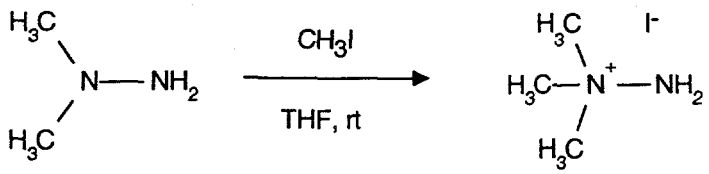
Scheme 2

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 onto nitroaromatic substrates. 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 (Scheme 3). We have found that when TMHI is reacted with various nitroarenes, the amino functionality is introduced in good to excellent yields.



Scheme 3

The preparation of quaternized hydrazine halides, including TMHI, has been previously reported.[6-9] These compounds can be prepared by reacting a 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[8,9] in THF at room temperature to give the desired 1,1,1-trimethylhydrazinium iodide **1** as white plates, mp 233-235C, in 81% yield after recrystallization from 95% EtOH (Scheme 4). The solid is stable at room temperature for at least several months in the absence of moisture.

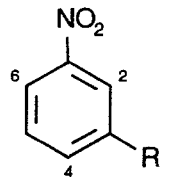


1

Scheme 4

The efficacy of TMHI as a VNS aminating agent was tested by reacting it with a variety of nitroarenes, including the 3-substituted nitroarenes **2a-f** used by Katritzky and Laurenzo in their study of 4-amino-1,2,4-triazole.[4a] See Experimental section for details. As indicated by the results summarized in Table I the yields with TMHI are good and, in general, multiple isomers result (**3-5**). This contrasts with the chemistry of 4-amino-1,2,4-triazole in which substitution in the 4-position is observed exclusively.[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) to 0% (R=COOH).

Table I. Amination of 3-Substituted Nitrobenzenes

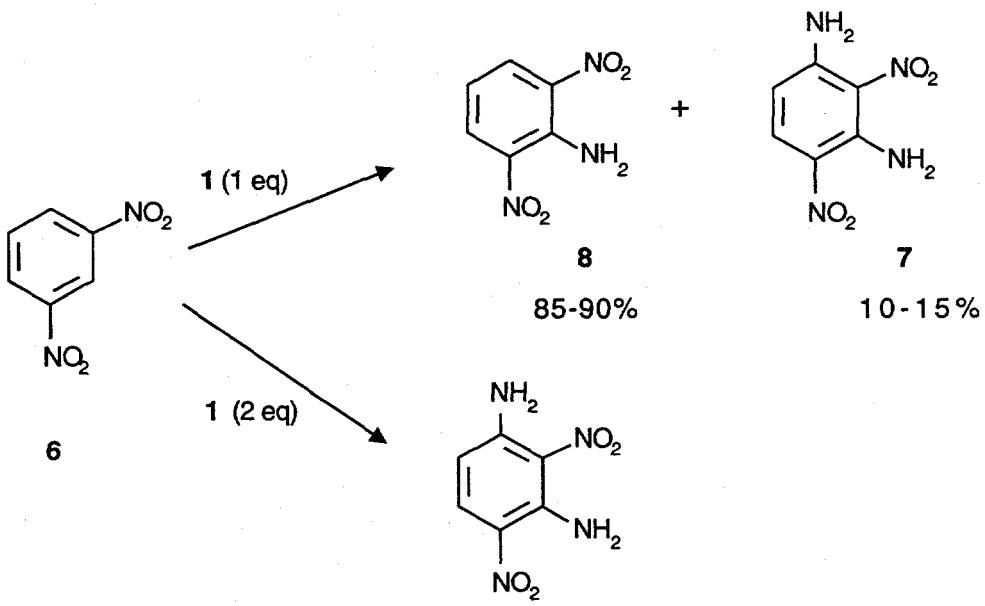


2a-f

(amination position numbering scheme used in table)

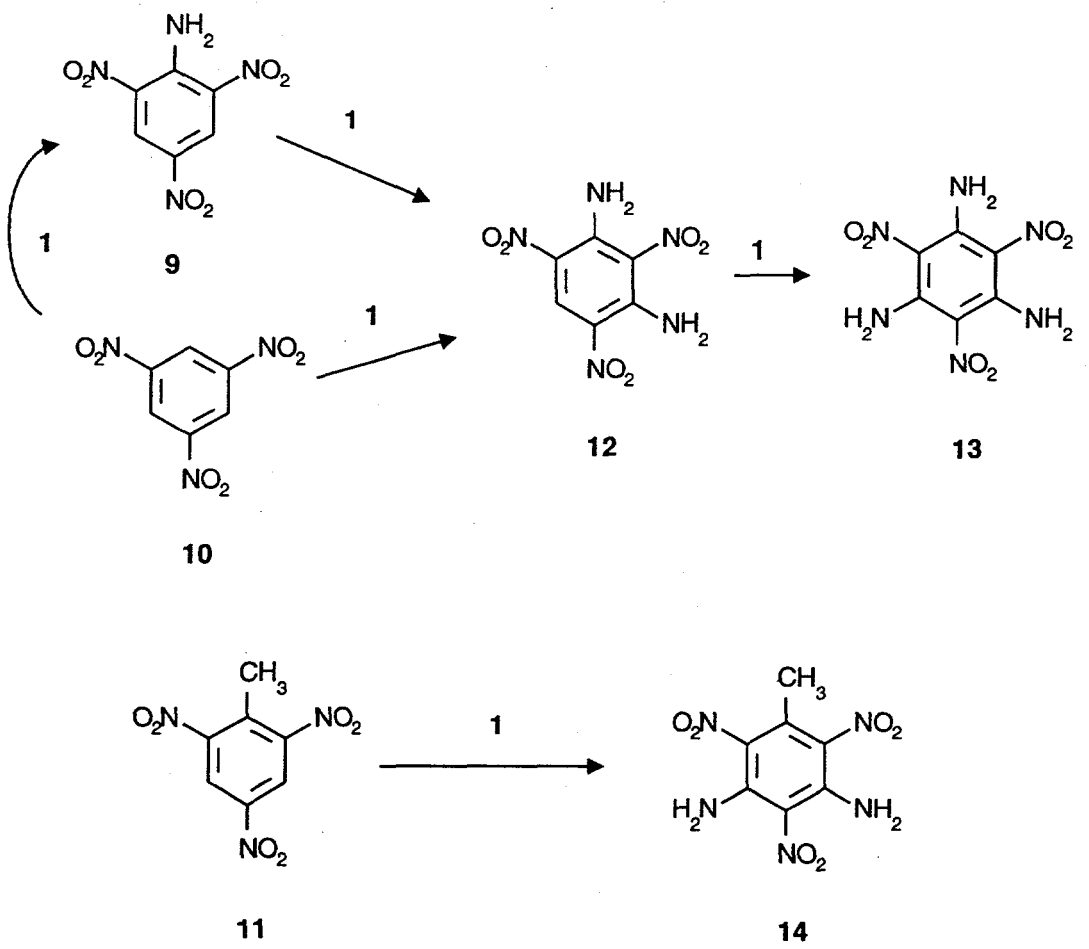
R	Total Yield (%)	position of NH_2	% isomer
H	85	2	61
		4	39
CH_3	84	2	38
		4	35
		6	27
Cl	82	2	32
		4	49
		6	19
COOH	95	4	71
		6	29
OCH_3	66	2	90
		4	10
F	84	2	45
		4	47
		6	8
I	76	2	45
		4	38
		6	17
CN	41	2	20
		4	44
		6	36

In a similar fashion, TMHI was reacted with several polynitrobenzenes to test its reactivity toward more highly activated ring systems. In general, product yields were excellent, and some diamination was noted even when only 1 equivalent of **1** was used. When reacted with 2 equivalents of TMHI, *m*-dinitrobenzene (**6**) is converted in good yield (76% after recrystallization) to 2,4-dinitro-1,3-phenylenediamine (**7**)(Scheme 5).



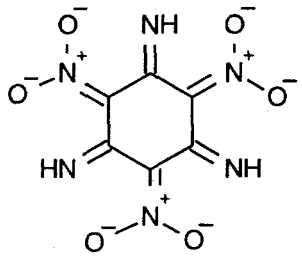
Scheme 5

The reaction was also tried on 2,4,6-trinitroaniline (picramide, **9**), 1,3,5-trinitrobenzene (**10**), and 2,4,6-trinitrotoluene (**11**); these energetic compounds are of interest as high explosives, and it is well-known that replacement of ring hydrogen atoms with NH_2 groups substantially reduces their sensitivity to impact. In each case, high yields of the desired aminated polynitroarenes (**12-14**) resulted (Scheme 6).



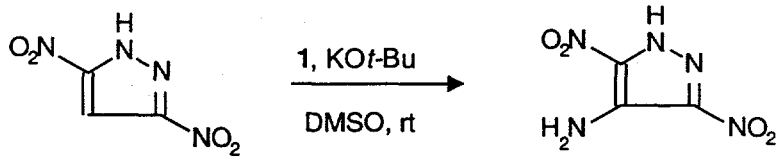
Scheme 6

It is interesting to note that a mechanism for this one-pot polyamination suggests that it proceeds through a completely dearomatized, highly charged intermediate (Scheme 7), which demonstrates the strong stabilizing power of the nitro groups as well as the high reactivity of TMHI. We have found that, in general, the number of amino groups which may be added is equal to the number of nitro groups on the aromatic substrate.



Scheme 7

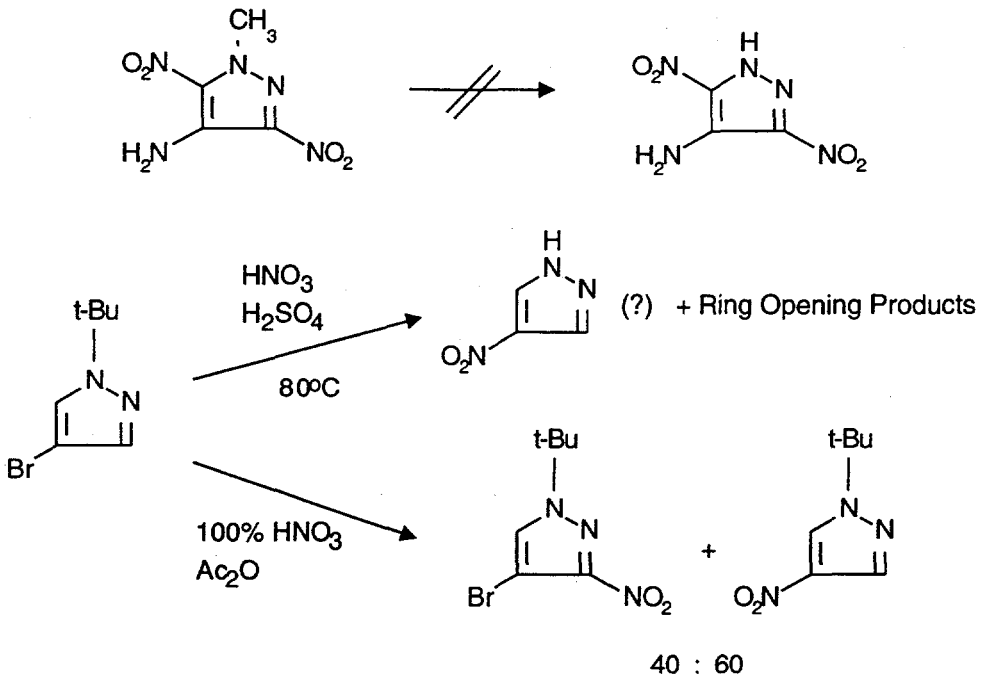
To test this reaction on other ring systems, **1** was reacted with 3,5-dinitropyrazole (**15**)[10], resulting in what we believe to be the first reported synthesis of 4-amino-3,5-dinitropyrazole (**16**) (Scheme 8).



15 **16**

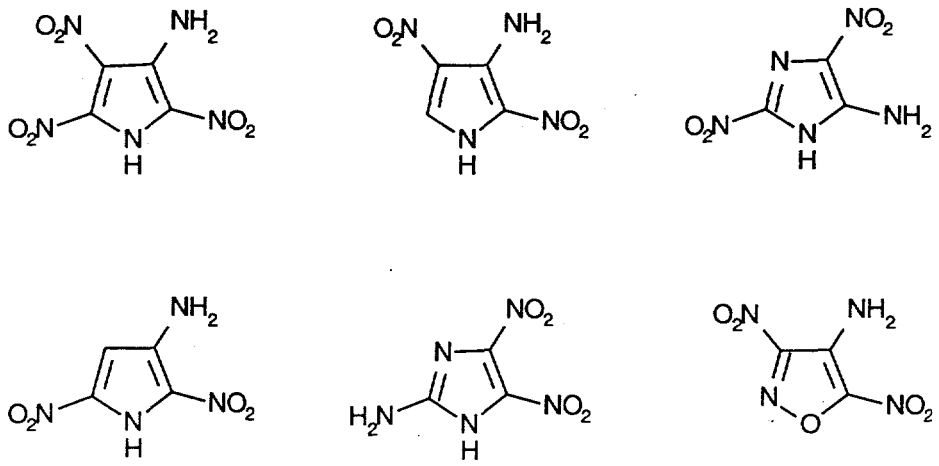
Scheme 8

It is perhaps surprising that this should work, since the removal of the acidic ring proton (pK = 3.14)[11] might be expected to deactivate the ring to nucleophilic attack. Nevertheless, the reaction proceeds with 82% yield, to give the desired product solvated by one molecule of DMSO (which proved difficult to remove). It is postulated that, although the base abstracts the acidic ring proton to form the pyrazolate anion, which is stabilized by one of the nitro- groups, the second nitro group stabilizes the charge from the reaction with TMHI. In this manner proton removal may actually stabilize the ring system from undergoing unwanted ring opening reactions. Earlier attempts at synthesizing **16** were based on an approach by Coburn[12] in which an *N*-protecting group is used. However, none of these were succcessful; either the protecting group could not be removed, or the substrate decomposed during nitration (Scheme 9). The use of TMHI obviates the need for a protecting group on the ring nitrogen, thus giving direct access to **16**.



Scheme 9

We are currently investigating the general utility of this approach of aminating dinitro-substituted heterocyclic systems containing an acidic proton. Studies on the reaction of **1** with other nitroazoles to obtain the corresponding aminated compounds (Scheme 10) is currently underway and will be reported when complete.



Scheme 10

Acknowledgements. This work was performed under the auspices of the U. S. Department of Energy by the Lawrence Livermore National Laboratory (LLNL) under

contract No. W-7405-ENG-48. The authors wish to thank Dr. Richard Gilardi (Naval Research Laboratory, Washington, D.C.) for performing X-ray crystallographic work, and Dr. Ray Ward (LLNL) for 300 MHz NMR spectra. We gratefully acknowledge Dr. Jeffrey Bottaro of SRI International, Menlo Park, CA, for informative discussions on this and related topics.

Experimental. DMSO (Aldrich, 99.9%, ACS Spectrophotometric Grade) was stored over 4A molecular sieves prior to use. All other reagents were used as received.

Synthesis of 1,1,1-Trimethylhydrazinium Iodide (TMHI). 1,1-dimethylhydrazine (4g, 5.1 mL, 67 mmol) was dissolved in 60 mL of THF, and the reaction vessel was cooled in an ice-water bath. To this was added dropwise with mechanical stirring methyl iodide (9.4g, 4 mL, 67 mmol). (A slurry forms immediately upon addition which becomes very thick with time, so efficient mechanical stirring is required. Diluting the reaction mixture with additional THF also allows for easier stirring.) The addition was exothermic. The mixture was allowed to stir at room temperature for 2h and the resulting white solid was collected by suction filtration. Recrystallization from 100 mL of EtOH yielded 11.6g (86%) of white plates; m.p. 233-35 ^{0}C (with decomposition; softening begins at 226 ^{0}C)(lit[7]: 235 C) ^{1}H NMR (90MHz, D_2O) δ (ppm) 3.42 (d, 9H, CH_3), 4.55 (broad s, 2H, NH_2 exchangeable).

Reaction of TMHI with 3-Substituted Nitrobenzenes (Typical Procedure). To a 25 mL oven-dried round bottomed flask were added nitrobenzene (0.133 mL, 0.159 g, 1.29 mmol) , 7.0 mL dry DMSO, and **1** (0.283 g), and the mixture was stirred until dissolved. The flask was protected from moisture with a $CaSO_4$ drying tube. Next was added, in one portion, potassium *tert*-butoxide (0.348 g, 3.10 mmol), and the mixture was stirred to dissolve. Of note, the solution immediately changed from clear to intense red-orange (almost black), and the odor of trimethylamine was noted, upon addition of base. Stirring was continued for 4 hours at room temperature, after which the reaction mixture was poured over 5 g ice, and acidified to about pH 3 with 10% HCl. The acidified solution was a clear orange. It was stirred for 30 m.and extracted with ethyl acetate (3 x 20 mL) (20 mL aq. NH_4Cl was added to break up the emulsion). The combined organic layers were washed once with 25 mL distilled water, dried over $MgSO_4$, and solvent evaporated to yield 0.221g of a slightly damp yellow-brown solid. The solid was subjected to chromatography (Chromatotron, 9:1 petroleum ether/acetone), yielding 3 products which were identified by melting point and by comparison of ^{1}H NMR with standard spectra.

In some cases (most notably with 3-nitroanisole), solid products resulted after acidifying the reaction mixture. These were separated by suction filtration prior to ethyl acetate extraction. Solid products (either from direct precipitation or chromatography) were recrystallized as necessary to achieve satisfactory melting points).

In the case of 3-nitrobenzoic acid, additional base was used (3 equivalents) and the reaction was run for 17 hours. Separation of isomers by esterification and chromatography was unsuccessful. However, by controlling pH at 5, one isomer could be collected as a solid precipitate, followed by the second isomer at about pH 4.

Also, in a few cases, isomers could not be completely separated by chromatography for melting point determination and/or product quantification. In these cases, identification was made by comparing NMR to authentic spectra, and estimating isomer ratios by integration.

Reaction of TMHI (1 equivalent) with 1,3-Dinitrobenzene. To 7 mL of dry DMSO were added 1,3-dinitrobenzene (0.230g, 1.31 mmol) and **1** (0.380 g, 1.38 mmol) , and the mixture was stirred to dissolve. To this solution was added in one portion solid sodium methoxide (0.380 g, 2.76 mmol) , and the mixture was stirred at room temperature under a dry atmosphere overnight. The reaction mixture was poured into 20 mL water, acidified with concentrated HCl, extracted with ethyl acetate (3 x 15 mL), dried over $MgSO_4$, and the solvent removed to yield 0.190 g (83%) of a yellow-orange solid. Comparison of ^1H NMR to standard spectra and integration revealed a 7:1 mixture of 2,4-dinitroaniline and 2,4-dinitro-1,3-phenylenediamine.

Reaction of TMHI (2 equivalents) with 1,3-Dinitrobenzene. 1,3 dinitrobenzene (0.230g, 1.31 mmol) was dissolved in 5.0 mL dry DMSO. To this was added dropwise a slurry of **1** (0.580 g, 2.88 mmol) and sodium methoxide (0.310 g, 5.76 mmol) in 6.0 mL dry DMSO. The mixture was stirred at room temperature under a dry atmosphere overnight, after which it was poured into 20 mL water, acidified with concentrated HCl to pH 4. The resulting solid was collected by suction filtration, washed with cold water, and air dried to yield 0..260 g (100%) of an orange solid. Recrystallization from EtOH yielded 0.190 g (76%) orange needles, m.p. 250-252 C(lit[3]: 253-254 C).

Reaction of TMHI with Nitroarenes 9, 10, and 11. These were conducted as with the 1,3-dinitrobenzene reactions, with the appropriate number of equivalents of TMHI and base. Products were identified by comparison of m.p., NMR and IR spectra with authentic standards.

Reaction of TMHI with 3,5-Dinitropyrazole. Reaction was conducted as with the 3-R-nitrobenzenes, with 0.266g (1.68 mol) 3,5-dinitropyrazole[10], 9.0 mL DMSO, 0.368 g (1.81 mol) **1**, and 0.571 g (5.09 mol) potassium t-butoxide. The reaction mixture was stirred at room temperature for 4 hours, after which it was poured over 7 g ice, and acidified to pH 3 with 10% aq. HCl. After 20 min. of stirring, a yellow precipitate formed, which was recovered by suction filtration, washed with water, and dried to yield 0.197 g of a yellow powder. The filtrate was extracted with ethyl acetate (3 x 25 mL), washed with water, dried over $MgSO_4$, and evaporated to yield a brown-yellow solid. Recrystallization from dimethylformamide yielded fine, yellow-orange needles, m.p. 160-162 C (uncorrected), with decomposition occurring above 161 C. ^{13}C NMR (300 MHz; DMSO-d_6) δ 137.8 (br s), 128.8 (s), 39.5 (septet) (**16:DMSO complex**); ^1H NMR (300 MHz; DMSO-d_6) δ 7.13 (br s, 2H), 2.51 (s, 6H). X-ray crystallography demonstrated structure as **16**·DMSO.

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