Facile Preparation of Hydrazones by the Treatment of Azides with Hydrazines Catalyzed by $FeCl_3 \cdot 6H_2O$

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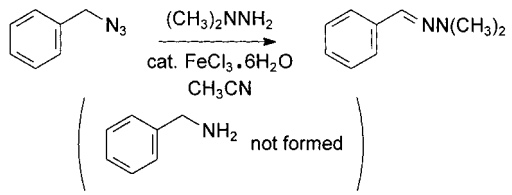
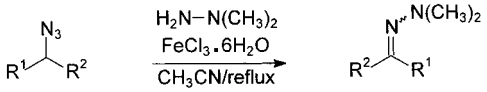
Introduction

Recently, we reported that the reduction of aromatic nitro compounds was effected in high yields by treatment with *N*,*N*-dimethylhydrazine in the presence of catalytic ferric chloride hexahydrate.[1] While unsure of the exact mechanism of that reduction, we were curious as to whether this system would be effective in reducing other nitrogen functional groups, particularly the conversion of azides to amines, a commonly used and valuable transformation. To that end we began an investigation in which a series of simple azides were treated with *N*,*N*-dimethylhydrazine/ferric chloride. Coincident with the outset of our research, a report by Kamal and co-workers appeared in which a series of azides, when treated with virtually the same reagent/catalyst system, produced the corresponding amines in reasonable yields.[2] While initially disappointed, we soon realized that our initial results were in stark contrast to those of Kamal.[3] Using benzyl azide as a substrate, we isolated the benzaldehyde *N*,*N*-dimethylhydrazone as the sole product and not benzylamine as reported. We have found this to be a



general reaction of azides with a variety of hydrazines and believe this to be the only report of such a conversion—a net oxidation of the nitrogen-bearing carbon. Given the synthetic utility of hydrazones as protecting groups[4] and as metalation substrates,[5] we feel that this transformation will be of use to the synthetic chemist. The results of our investigation form the basis of this report.

Table 1. Synthesis of *N*,*N*-Dimethylhydrazones from Azides



entry	R^1	R^2	time (h)	yield (%)[a]
1	Ph-	H	8	100
2	*p*-BrPh-	H	7	98
3	*p*-NO_2Ph-	H	3	99
4	*p*-CH_3O_2CPh-	H	8	91
5	*p*-CH_3OPh-	H	21	95
6	*m*-CH_3OPh-	H	15	97
7	*o*-CH_3OPh-	H	23	98
8	Ph-	CH_3	11	87
9	$PhCH_2$-	H	17	89
10	*trans*-PhCHCH-	H	17	93
11	$CH_3(CH_2)_6$-	H	18	91
12	$CH_3(CH_2)_5$-	CH_3	34	81

[a] Yields refer to yields of homogeneous compounds isolated from the reaction mixture and which required no further purification.

Results and Discussion

A variety of azides (each prepared by simple treatment of the corresponding alkyl halides with sodium azide) were treated with *N*,*N*-dimethylhydrazine and 5−10 mol % ferric chloride hexahydrate in refluxing acetonitrile. The results are shown in Table 1.[6,7] It is noteworthy that the products (isolated by extractive workup) yielded the pure hydrazones which were homogeneous as recovered and needed no further purification. Note that the yields are uniformly high and that 1° and 2° benzylic, allylic, and 1° and 2° aliphatic azides reacted smoothly to give the corresponding hydrazones.

A variety of solvents (CH_3OH, THF, CH_2Cl_2, and CH_3CN) were screened; however, none were superior to acetonitrile in performance. A number of other potential catalysts ($BF_3 \cdot Et_2O$, $Yb(OTf)_3$, $Cu(OTf)_2$, $CuCl_2$, and TsOH) were ineffective in promoting the reaction, leaving ferric chloride hexahydrate as the catalyst of choice. The reaction failed to proceed in the absence of catalyst.

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(1) Boothroyd, S. R.; Kerr, M. A. *Tetrahedron Lett.* **1995**, 2411−2414.

(2) (a) Kamal, A.; Reddy, B. S. N. *Chem. Lett.* **1998**, 593−594. (b) Kamal, A.; Reddy, B. S. N.; Reddy, B. S. P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1825−1828.

(3) There are differences between our optimized reaction conditions and those of Kamal (acetonitrile rather than methanol as solvent, the presence of charcoal in their case). However, using the exact conditions (and substrates) of Kamal, we observed no reduction to the amines. The substrates remained unchanged for the most part; however, phenyl azide produced a small amount of aniline along with several other unidentified products when reacted for prolonged periods. While we do not dispute the findings of Kamal, we can offer no explanation at this time for this discrepancy.

(4) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.

(5) (a) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 34−35. (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3−6.

(6) Aside from the *p*-carbomethoxybenzyl hydrazone (Table 1, entry 4), all of the products are known compounds. The identity of the known products was confirmed by comparison of ^1H NMR to the published data. The identity of all of the products was confirmed by routine spectroscopic analysis (^1H NMR, ^{13}C NMR, and MS). In addition, several hydrazones (Table 1, entries 1 and 11) were synthesized for comparison from the aldehydes using known procedures.

(7) For published data on the *N*,*N*-dimethylhydrazones in Table 1, see: (a) (benzaldehyde, cinnamaldehyde, acetophenone) Sharma, S. D.; Pandhi, S. B. *J. Org. Chem.* **1990**, *55*, 2196−2200. (b) (*p*-bromobenzaldehyde) Said, S. B.; Skarzewski, J. M.; Mlochowski, J. *Synthesis* **1989**, 223−224. (c) (*p*-nitrobenzaldehyde, phenylacetaldehyde) Clark, L. F.; O'Sullivan, F.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1649−1652. (d) (*p*-methoxybenzaldehyde) Smith, R. F., Albright, J. A.; Waring, A. M. *J. Org. Chem.* **1966**, *31*, 4100−4102. (e) (*m*-methoxybenzaldehyde) Hwu, J. R.; Wang, N. *Tetrahedron* **1988**, *44*, 4181−4196. (f) (*o*-methoxybenzaldehyde, octanal) Wiley, R. H.; Slaymaker, S. C.; Kraus, H. *J. Org. Chem.* **1957**, *22*, 204−207. (g) (2-octanone) Yamashita, M.; Matsumiya, K.; Hiroko, M.; Rikisaku, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1668−1670.

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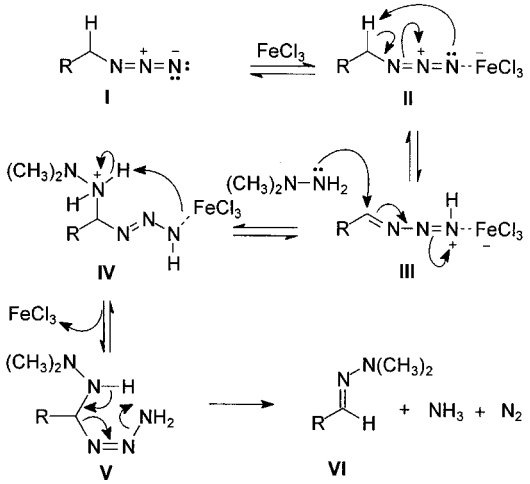
Scheme 1

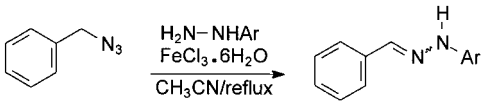


While we were initially surprised and puzzled by this transformation, we believe we can provide a plausible explanation (Scheme 1).[8] Presumably the Lewis acid can promote a tautomerization of azido species **I**, via **II**, to an imino type compound **III** which, when complexed with the Lewis acid, provides a good electrophilic substrate for the nucleophilic hydrazine. The hydrazine adduct **IV** after a proton transfer to yield **V** can collapse to the product hydrazone **VI** with the expulsion of nitrogen and ammonia. Both the rate of tautomerization and the nucleophilic attack on **III** should be enhanced by electron-withdrawing groups on the aromatic ring of the benzyl azides. Although detailed kinetic studies were not performed, this can be qualitatively observed by noting the reaction times in Table 1. The reaction of *p*-nitrobenzyl azide (Table 1, entry 3) was complete in 3 h compared to 8 h for benzaldehyde (Table 1, entry 1). The *o*- and *p*-methoxybenzyl azides (Table 1, entries 7 and 5) were the slowest to react while the *m*-methoxybenzyl azide was slightly faster. The bromo and carbomethoxy substituents had little effect on the rate. The cinnamyl substrate (Table 1, entry 10), which had the possibility of undergoing alternate modes of attack as a result of the allylic moiety, afforded the expected product in excellent yield. The 1° aliphatic and both 2° azides were well behaved and produced the hydrazones in excellent yields.

Surprisingly, the nitro group in entry 3 of Table 1 did not undergo reduction under the reaction conditions.[1] While long reaction times and an excess of hydrazine did eventually result in some reduction, formation of the hydrazone as the exclusive product was not difficult.

Table 2 illustrates the results of several experiments in which the above methodology was extended to the synthesis of phenyl hydrazones. Phenyl-, 4-nitrophenyl-, and 2,4-dinitrophenylhydrazine (Table 2, entries 1−3) afforded the corresponding hydrazones when treated with benzyl azide in the presence of $FeCl_3 \cdot 6H_2O$. The nitrophenylhydrazones were produced without concomitant reduction of the nitro groups. The use of *p*-methoxyphenylhydrazine hydrochloride was not successful and resulted only in decomposition. This is not unexpected since aryl hydrazines which contain electron-donating groups are unstable as the free base, decomposing upon exposure to air.[9]

Table 2. Synthesis of Arylhydrazones from Azides



entry	Ar	time (h)	yield (%)[a]
1	Ph-	13	88
2	*p*-NO_2Ph-	11	82[b]
3	2,4-$(NO_2)_2$Ph-	13	79[b]
4	*p*-CH_3OPh-[c]	21	dec.

[a] Yields refer to isolated, homogeneous compounds. [b] Yields after recrystallization. [c] Used as the hydrochloride salt.

In summary, we have described a novel and efficient preparation of hydrazones from azides. The method seems to be applicable to most 1° and 2° azides and is tolerant of a variety of functional groups.

Experimental Section

General Considerations. All reactions were performed in anhydrous acetonitrile as purchased from VWR (DriSolv). $FeCl_3 \cdot 6H_2O$ was purchased from Aldrich and used as received. *N*,*N*-Dimethylhydrazine was purchased from Alfa/AESAR and used without further purification. TLC analysis was performed on E Merck glass plates precoated with silica gel 60 F254. ^{1}H NMR spectra were recorded at 300 or 200 MHz on Varian Gemini 300 and Varian Gemini 200 spectrometers, respectively. ^{13}C NMR spectra were recorded on the same instruments at 75 or 50 MHz. Mass spectra (EI) were recorded on a Finnigan MAT 8200 spectrometer using an ionizing voltage of 70 eV.

General Procedure for the Conversion of Azides to *N*,*N*-Dimethylhydrazones. *p*-Carbomethoxybenzaldehyde *N*,*N*-Dimethylhydrazone. To a stirred solution of methyl 4-(azidomethyl)benzoate (578 mg, 3.02 mmol) in anhydrous acetonitrile (5 mL) was added iron(III) chloride hexahydrate (81 mg, 0.30 mmol). The reaction vessel, equipped with a reflux condenser, was purged with Argon, and *N*,*N*-dimethylhydrazine (1.0 mL, 13.1 mmol) was added via syringe. The reaction mixture was heated to reflux until TLC analysis indicated the consumption of the azide (8 h), at which time the reaction mixture was allowed to cool. Saturated sodium bicarbonate (10 mL) was added, and the reaction mixture was allowed to stir at room temperature for approximately 10 min and partitioned between methylene chloride (20 mL) and saturated aqueous sodium bicarbonate solution (25 mL). The organic phase was separated, and the aqueous layer was extracted with methylene chloride (15 mL) 3 times. The organic layers were then combined and washed with a saturated sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo to yield the pure hydrazone as a solid (564 mg, 91% yield): mp = 63−64 °C; R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR δ = 7.98 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.17 (s, 1H), 3.90 (s, 3H), 3.03 (s, 6H); ^{13}C NMR δ = 167.0, 141.4, 129.8, 129.7, 128.0, 124.9, 51.9, 42.5; HRMS *m*/*z* (M^+) calcd for $C_{11}H_{14}N_2O_2$ 206.1055, found 206.1059.

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(8) At this time we offer this only as a plausible explanation. We are currently exploring ways to elucidate the mechanistic nature of this reaction.

(9) Robinson, B. *The Fischer Indole Synthesis*; John Wiley and Sons: Chichester, 1982.