Direct N-Alkyl Azidonation of *N,N*-Dialkylarylamines with the Iodosylbenzene/Trimethylsilylazide Reagent Combination

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Received July 7, 1993

While exploring the scope of the β-azidonation of triisopropylsilyl (TIPS) enol ethers using the reagent combination PhIO/$TMSN_3$, we discovered that triethylamine completely suppressed the formation of the β-azido TIPS enol ether **1**, Scheme I.[1]

Presumably, the more basic triethylamine competes for the electrophilic intermediates more effectively and is oxidized[2] by the PhIO/$TMSN_3$ reagent.[3] To ascertain the fate of the amine in this reaction and to isolate the product(s), we treated 3-methoxy-*N,N*-dimethylaniline (**2**) with PhIO/$TMSN_3$ in deuteriochloroform at 0 °C. Following the reaction by ^1H NMR, we observed the rapid formation of the aminomethylene azide **3**, iodobenzene, and $(TMS)_2O$ in a very clean transformation! Table I lists the results for the reactions of a number of electron-rich *N,N*-dimethylarylamines (entries 1, 2, and 4–6), and in all cases the *N*-methyl group is converted into an *N*-azidomethylene functionality in high yield (>95%) as judged by NMR [^1H δ 4.85 (2H, s) and ^{13}C δ 70.5]. All of the conversions are complete within 5 min.

Surprisingly, even 4-(*N,N*-dimethylamino)pyridine (**6**) (DMAP) (entry 3) is converted into the azidomethylene adduct **7**, although it requires twice the amount of PhIO/$TMSN_3$. Only in the case of 1,4-bis-(*N,N*-dimethylamino)benzene (**14**) (entry 7) was the more normal electrophilic substitution to give **15** observed.[4] During the conversion of **14** into **15**, a fleeting blue color was observed (which changed to yellow), which is most probably due to the aminium radical cation, Wursters salt.[5] While the azidomethylene adducts were stable enough to be used in subsequent reactions, in general they were too labile to be purified by chromatography. The adduct **5** decomposed to **16** and **17** when treated with $NaHCO_3$/THF, and acidic conditions gave the adduct **18** (as a mixture of *p,p* and *o,p* isomers) (Scheme II). Similar modes of decomposition were seen for **3** and **9**.[6]

Scheme I

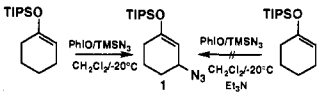

Table I. Reactions of *N,N*-Dimethylarylamines

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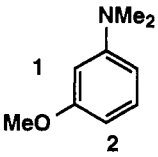
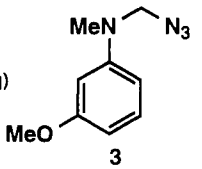
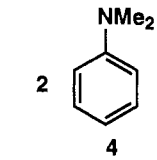
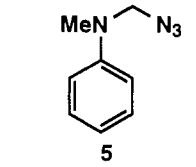
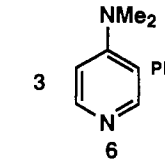
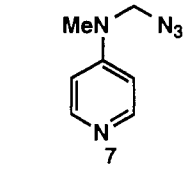
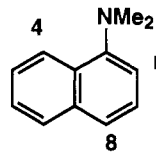
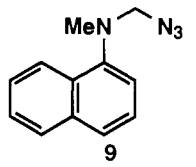
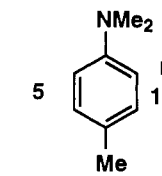
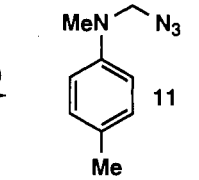
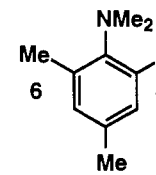
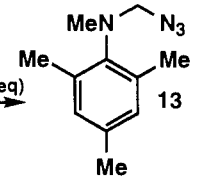
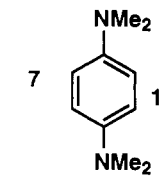
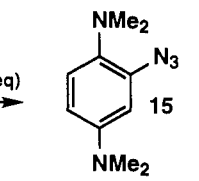
1		
2		
3		
4		
5		
6		
7		

[a] All reactions were carried out at −20 °C.

(1) Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767. Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 3993. Magnus, P.; Evans, A.; Lacour, J. *Tetrahedron Lett.* **1992**, 2933. $PhI(OAc)_2/NaN_3$ has been proposed as a source of N_3· radicals: Fontana, F.; Minisci, F.; Yan, Y. M.; Zhao, L. *Tetrahedron Lett.* **1993**, *34*, 2517. For a comprehensive survey of hypervalent iodine chemistry, see: Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992.

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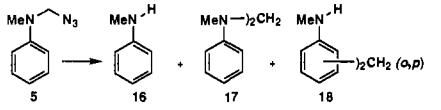
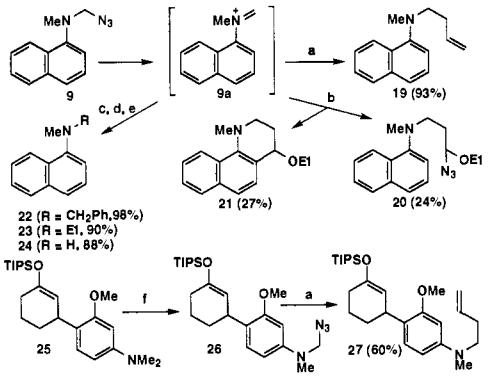
Scheme II



Scheme III[a]



[a] (a) Me_2AlCl/allyltributyltin. (b) Ethyl vinyl ether/$Me_2AlCl_2Cl_2$. (c) PhMgBr (4.0 equiv)/THF. (d) MeMgBr (4.0 equiv)/THF. (e) Aqueous $NaHCO_3$/THF. (f) $PhIO/TMSN_3/CH_2Cl_2$, –20 °C.

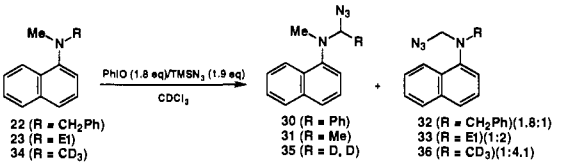
Treatment of **8** (1 mmol) with PhIO (1.8 mmol)/$TMSN_3$ (1.9 mmol)/THF (5 mL) at 0 °C for 5 min gave a solution of **9**, to which were added allyltri-*n*-butyltin (1.2 mmol) and zinc chloride (1.0 mmol in Et_2O). After 30 min, workup gave *N*-butenyl-*N*-methylnaphthylamine (**19**) (93%) (Scheme III).[7] In a similar fashion, solutions of **9** can be converted into the *N*-benzyl (**22**) (98%) and *N*-ethyl (**23**) (90%) derivatives by treatment with PhMgBr and MeMgBr, respectively.[8] Hydrolysis (aqueous THF/$NaHCO_3$) of the adduct **9** gave the secondary amine **24** (88%), thus providing a very mild monodemethylation procedure. Treatment of **9** with ethyl vinyl ether/Me_2AlCl/CH_2Cl_2 at 0 °C gave the adducts **20** and **21**. Prolonged reaction converted **20** into **21**.[9] A particularly vivid illustration of the selective reactivity is the conversion of **25** into **27** (60%) in a single reaction vessel!

Quite surprisingly we found that doubling the amount of PhIO/$TMSN_3$ converted **8** into the bis-azidomethylene adduct **28** (^1H NMR δ 4.83) (Scheme IV). The formation of **28** (in $CDCl_3$ or CH_2Cl_2) does not take place in THF; only the mono azidomethylene adduct **9** was observed. Treatment of **28** (in CH_2Cl_2) with allyl tri-*n*-butyltin/Me_2AlCl gave bis-*N*,*N*-butenylnaphthylamine (**29**) in modest overall yield.

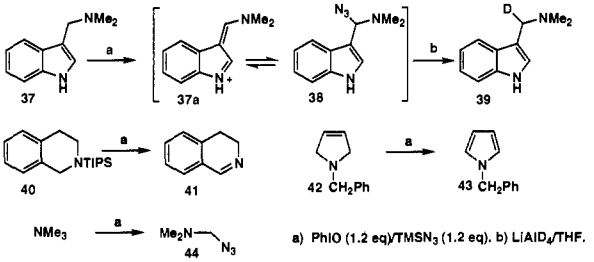
The azidonation reaction shows a preference for primary functionalization. Treatment of **23** with PhIO/$TMSN_3$ gave

Scheme IV

Scheme V



Scheme VI



preferential (2:1) primary azide **33** versus **31** (Scheme V). The benzylic amine **22** gave **30** and **32** (1.8:1). Treatment of the unsymmetrical deuterated amine **34** with PhIO/$TMSN_3$ in both chloroform and THF gave a primary kinetic isotope effect of $k_H/k_D = 4.1$ and 3.6, respectively.[10] Therefore, hydride abstraction or proton loss is the rate-determining step.

We have briefly examined the reaction of some aliphatic amines with the PhIO/$TMSN_3$ reagent and found that gramine (**37**) is rapidly converted into the azide **38**, presumably *via* **37a** (Scheme VI). Reduction of **38** with $LiAlD_4$ gave the deuterated gramine **39**. Hydrolysis of **38** gave indole-3-carboxaldehyde. The tetrahydroquinoline derivative **40** is dehydrogenated to give **41** (58%, isolated), and likewise **42** is converted into the pyrrole **43** (92%). Even trimethylamine can be converted in high yield (>95%) into the azidomethylene derivative **44**.

Currently we are examining the reactions of PhIO/$TMSN_3$, and in a more general sense ArIO/TMSX, with amine derivatives (amides, carbamates, ureas, etc.) and other functional groups.

Acknowledgment. The National Institutes of Health (GM 32718), National Science Foundation, and the Welch Foundation are thanked for their support of this research. Rhône Poulenc are thanked for a graduate fellowship to J.L.

Supplementary Material Available: Experimental procedures and spectral details for compounds **3**, **5**, **7**, **9**, **11**, **13**, **15**, **19–24**, and **27–29** (12 pages). Ordering information is given on any current masthead page.

(6) For methodology using aminomethylbenzotriazoles, see: Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683. Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1993**, *58*, 812. Katritzky, A. R.; Rachwal, S.; Rachwal, B.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 4932.

(7) For a recent and exhaustive review on Mannich bases, see: Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791. Heaney, H. The Bimolecular Aromatic Mannich Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, **1991**; Vol. 2, p 953. Grieco, P. A.; Bashas, A. *J. Org. Chem.* **1987**, *52*, 1378.

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(10) The primary kinetic isotope effect (PKIE) is modest and similar to that observed for the classical Hoffmann β-elimination: Saunders, W. H.; Cockerill, A. F. *Elimination Reactions*; Wiley: New York, 1973. We have deferred any discussion of whether the dehydrogenation involves proton loss, hydride abstraction, or hydrogen atom loss, since we presently cannot distinquish among these alternatives.