α-Azidonation of Amides, Carbamates, and Ureas with the Iodosylbenzene/Trimethylsilyl Azide Reagent Combination: *N*-Acyliminium Ion Precursors

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Recently, we reported that the reagent combination PhIO/$TMSN_3$ rapidly converts *N,N*-dimethylanilines into *N*-(azidomethyl)-*N*-methylanilines at 0 °C, in excellent yields, eq 1.[1] As an extension of this work, we report the oxidation of amides, carbamates, and ureas using PhIO/$TMSN_3$ or *o*-iodosylbenzoic acid/$TMSN_3$ in dichloromethane, to give α-azido derivatives, Scheme 1. The only known α-azido amides were previously reported in a study of 4-substituted azetidinones.[2]

$$ArNMe_2 + PhIO/TMSN_3 \longrightarrow Ar-N(Me)(CH_2N_3) + PhI + TMS_2O \quad \text{Eqn 1}$$

Table I, lists the results of a systematic study of pyrrolidine and piperidine derivatives, Scheme 1, X = Ph, $C_6H_4NO_2$-*p*, C_6H_4-OMe-*p*, C_6H_2(3,4,5-OMe), NPh_2, OPh, OCH_2Ph (Cbz), OBu-*t* (BOC), and Me. Two sets of conditions (A or B) were employed, and all reactions were allowed to proceed for 15 h. For example, $TMSN_3$ (4.8 equiv) was added to a suspension of PhIO (2.4 equiv) in CH_2Cl_2 at –40 °C. The amides **1** or **4** were added to the suspension, which was warmed to –25 °C, and stirred under argon overnight. Raising the temperature above –20 °C leads to rapid evolution of dinitrogen and destruction of the suspected reactive intermediate(s).[3]

The pyrrolidine derivatives **1** are considerably more reactive than the piperidine derivatives **4**, and the rate (and yield) of α-azidonation increases with respect to the electron-donating ability of X. The rate of the α-azidonation process competes with the rate of decomposition of the reactive intermediate(s) (N_2 evolution), and for the less reactive amides (X = C_6H_4-NO_2-*p*) there is a considerable amount of remaining starting material.[4] The best conversion was observed for the urea **1** (X = NPh_2) [>95% into **2** (X = NPh_2) by ^1H NMR, the structure of product was confirmed by X-ray crystallography].[5] Good conversions in the pyrrolidine series were also possible at –5 °C by using a large excess of PhIO (5 equiv)/$TMSN_3$ (10 equiv) (rapid effervescence of dinitrogen was initially observed). Isolated yields of 71% for the carbamate **2** (X = OPh) and 61% for the urea **2** (X = NPh_2) were obtained. In all cases except BOC (entry 8), small amounts (*ca.* 5%) of side products resulting from further reaction of the α-azido products were observed. The BOC derivative (entry 8) proved to be the most reactive, and the diazides **8/8a** were the major products. At lower temperatures (–40 to –25 °C) using PhIO/$TMSN_3$ the *trans* diastereomer of the 2,5-disubstituted diazido **8** [X = C_6H_2(3,4,5-OMe), X-ray] species predominated, Scheme 2.[5]

It appears that not only is the α-azidonation slower in the piperidine series (under the same reaction conditions) and lower yielding, but also the α-azido amides **5** are less stable. In entries

Scheme 1

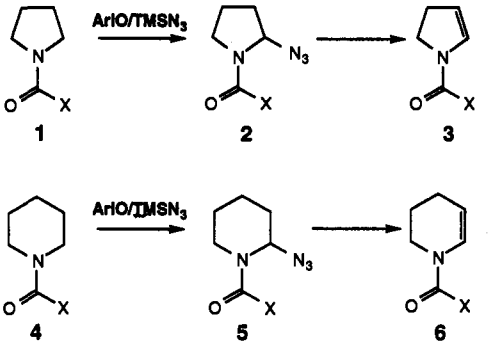
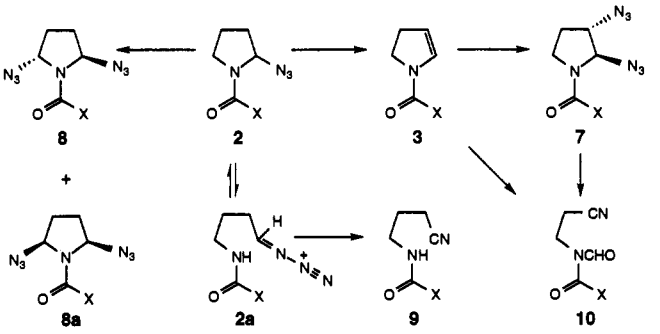


Table 1

		% yield					
		conditns A[a]			conditns B[b]		
entry	X	2	5	6	2	5	6
1	NPh_2	82	(32)[c]	14	64		54
2	OPh	78	41[c]		51	85[c]	
3	C_6H_2(3,4,5-OMe)	78	19[c]		47	19[c]	16
4	C_6H_4OMe-*p*	76	15[c]		54	15[c]	28
5	Ph	62[c]	13[c]		45	39[c]	
6	$C_6H_4NO_2$-*p*	29[c]	10[c]		49[c]	30[c]	
7	OCH_2Ph	73	40[c]	13	32	66[c]	
8	OBu-*t*	25 (48% **8**)	36[c]	21	0	48[c]	35
9	Me	60[c]	11[c]		40	47[c]	14

[a] PhIO (2.4 equiv)/$TMSN_3$ (4.8 equiv)/CH_2Cl_2, –40 °C or warm to –25 °C. [b] *o*-Iodosylbenzoic acid (2.4 equiv)/$TMSN_3$ (4.8 equiv)/CH_2Cl_2, reflux. [c] Starting material remaining; ( ) not isolated ^1H NMR.

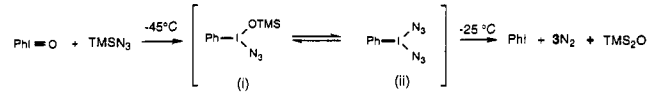
Scheme 2



(1) Magnus, P.; Lacour, J.; Weber, W. *J. Am. Chem. Soc.* **1993**, *115*, 9347. For previous synthetic uses of the PhIO/$TMSN_3$ reagent with TIPS silyl enol ethers: 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**, *34*, 2933. For the preparation of PhIO, see: Saltzman, H.; Sharefkin, J. G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 485. Porta, F.; Crotti, C.; Cenini, S.; Palmisano, G. *J. Mol. Catal.* **1989**, *50*, 333. These authors report the dehydrogenation of primary and secondary benzylamines with PhIO to give the corresponding imines. Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**, *29*, 6913. Ochiai, M.; Inenaga, M.; Nagao, Y.; Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. *Tetrahedron Lett.* **1988**, *29*, 6917. For a comprehensive survey of hypervalent iodine chemistry: Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992.

(2) Clauss, K.; Grimm, D.; Prossel G. *Justus Liebigs Ann. Chem.* **1974**, 539–560.

(3) If this solution is warmed to 0 °C, it cleanly decomposes to iodobenzene, nitrogen, and hexamethyldisiloxane. For the decomposition of $TMSN_3$/PhIO to dinitrogen, iodobenzene, and hexamethyldisiloxane, see: Zefirov, N. S.; Safronov, S. O.; Kaznacheev, A. A.; Zhdankin, V. V. *Zh. Org. Khim.* **1989**, *25*, 1807; **1990**, *25*, 1633.



We have speculated that the adducts i and ii are present, and may be responsible for the observed dehydrogenation chemistry, although this is not known.

(4) We have treated the corresponding sulfonamides with PhIO/$TMSN_3$ and isolated the α-azido derivatives in low yields. They are less reactive than the *p*-nitrobenzamides.

(5) The structures of the azides **2** (X = NPh_2), **8** [X = C_6H_2(3,4,5-OMe)] and the tricyclic urea **12** were confirmed by single-crystal X-ray crystallography.

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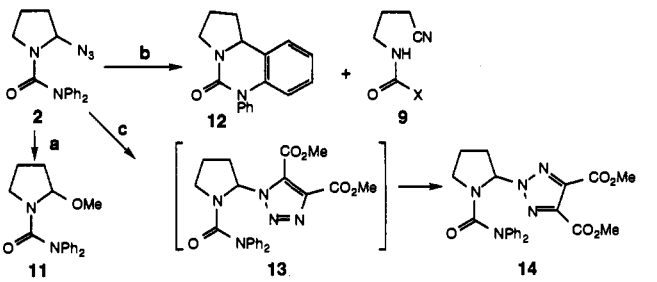
1, 3, 4, and 5 the α-azido amide **5** eliminates azide ion to give the enamide **6**, thus reducing the yields. The pyrrolidine α-azido amides **2** are stable under the reaction conditions and do not eliminate azide (hydrazoic acid) to give the enamide **3**.

To attempt to overcome the problem of preferential decomposition of the reactive intermediate(s) [PhI(OTMS)N_3] a more stable aryl iodosyl reagent was required. *o*-Iodosylbenzoic acid was substituted for PhIO (conditions B).[6] The intermediate produced on treatment with $TMSN_3$ was found to have a greatly enhanced stability. Rapid evolution of dinitrogen was observed only on performing these reactions in 1,2-dichloroethane at temperatures higher than 60 °C. In a typical procedure $TMSN_3$ (4.8 equiv) was added to a suspension of *o*-iodosylbenzoic acid (2.4 equiv) in CH_2Cl_2. The mixture was stirred at room temperature for 10 min, followed by addition of the amides **1** or **4**. The resulting suspension was heated at reflux and became homogeneous after 1–2 h. All reactions, except entry 6, showed complete disappearance of starting material; however, yields of α-azidonation were lower due to further reactions of the initially formed α-azido amide **2**. Exposure of the α-azido benzamide **2** (X = C_6H_4OMe-*p*) to the *o*-iodosylbenzoic acid/$TMSN_3$ reagent combination yielded two previously undetected products, the 2,3-diazido adduct **7** [38% (X = C_6H_4OMe-*p*)], **8** [16% (X = C_6H_4-OMe-*p*)], and the cyano formamide **10** [10% (X = C_6H_4-OMe-*p*)].[7] Treatment of the urea **1** (X = NPh_2) with *o*-iodosylbenzoic acid/$TMSN_3$ in 2-nitropropane at 50 °C gave the corresponding formamide **10** (49%) and the 2,3-diazido compound **7** (15%). Presumably formation of both the formamide and the 2,3-diazido compound results from an intermediate enamide **3**. The enamide **6** was isolated in the piperidine series, but not in the pyrrolidine series. Heating **2** (X = NPh_2) gave the enamide **3** [6% (X = NPh_2)], (*N*,*N*-diphenylcarbamoyl)pyrrole (7%), **2** [11% (X = NPh_2)], and the nitrile **9** [trace (X = NPh_2)].

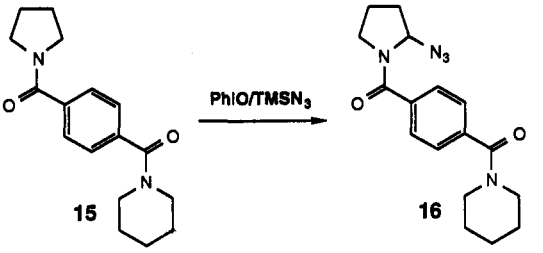
The chemistry of the α-azido amide functionality was briefly explored. First, to establish a connection with acyliminium chemistry, and secondly, to see if there are any differences.[8] Treatment of **2** (X = NPh_2) in methanol, at reflux in the presence of silica gel, gave the corresponding α-methoxy amide **11** (86%). This transformation is equivalent to that seen in the electrochemical oxidation of similar substrates by Shono.[9] Intramolecular trapping of the *N*-acyliminium ion was also possible *via* aromatic electrophilic substitution of the urea in the presence of $TiCl_4$ (3 equiv) to give **9** and **12** (30% and 49%, respectively),[5] whereas **11** under the same Lewis acid conditions as above gave only **12** (74%). 1,3-Dipolar cycloadditions of the α-azido amide **2** to dimethyl acetylenedicarboxylate proceeded with simultaneous migration of the triazole to give **14** (*via* **13**) (Scheme 3).

Scheme 3



[a] (a) MeOH, SiO_2/reflux (86%). (b) $TiCl_4$ (3 equiv)/1,2-dichloroethane, reflux (49% and 30%). (c) Dimethyl acetylenedicarboxylate/CH_2Cl_2, reflux (77%).

Scheme 4



The evident increased reactivity of the pyrrolidine derivatives compared with the piperidine derivatives was explored in the following experiments. Treatment of a 1:1 mixture of **1** (X = OPh) and **4** (X = OPh) with PhIO/$TMSN_3$ at −25 °C gave **2** [69% (X = OPh)], **5** [28% (X = OPh)], and **8** [7% (X = OPh)]. The mixed bis-amide **15** was treated under the usual azidonation conditions (A) and gave as the only isolable product the α-azido pyrrolidine derivative **16** (32%) (Scheme 4).

Currently, we are examining the reactions of the ArIO/$TMSN_3$ reagent combinations with proline derivatives and the development of different ArIO reagents.

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Supplementary Material Available: Spectral details for compounds **2**, **5–12**, **14**, and **16** and crystallographic details for **2** (X = NPh_2), **8** [X = C_6H_2(3,4,5-OMe)], and the tricyclic urea **12** are available (51 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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