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Oxidation of L-Proline Methyl Ester Derivatives with the Iodosylbenzene/Trimethylsilylazide Reagent Combination

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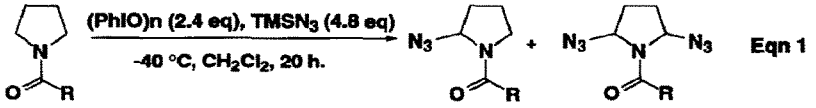
Abstract: Oxidation of a series of L-Proline derivatives with the $(PhIO)_n/TMSN_3$ reagent combination is reported. Subsequent utilization of the 5-azido N-acyl functionality as a N-acyl iminium ion precursor is described.

Recently we have reported the oxidation of amides, carbamates and ureas using $(PhIO)_n/TMSN_3$ or *o*-iodosybenzoic acid/$TMSN_3$ in dichloromethane to give α-azidoamides, **Eqn 1**.[1] This unexplored functionality was shown to act as an N-acyliminium ion precusor.[2]



Eqn 1

To further illustrate the use of this new methodology, the oxidation of suitably N-protected L-proline methyl esters was explored. In recent years many proline analogs have been synthesized to study a variety of problems in peptide chemistry and drug design.[3] The following letter reports an alternative to Shono's electrochemical oxidative procedure for amides.[4] **Table 1** lists the results of a study of urethane derivatives of L-proline methyl ester. At 25 °C all four substrates were seen to exist as two major conformers by ^1H NMR.[5] In a typical reaction, $TMSN_3$ (4.8 eq.) was added to a suspension of $(PhIO)_n$ (2.4 eq.) in CH_2Cl_2 at -40 °C. The proline derivatives **1** were added to the suspension which was stirred under argon for 15 hours. Raising the temperature above -20 °C leads to rapid evolution of dinitrogen, and decompostion of the suspected azidonation reagent.[6] The proline substrates were found to be considerably less reactive than the corresponding pyrrolidine derivatives. The rate and yield of α-azidonation increases with respect to the electron donating ability of R.[1] The Boc derivative proved to be the most reactive substrate with 70% conversion into **2** using 2.4 eq. and 4.8 eq. of $(PhIO)_n$ and $TMSN_3$ respectively. Trapping of the suspected N-acyliminium ion intermediate by chloride (CH_2Cl_2 has been reported to be a good source of chloride nucleophile)[7] and water (produced in the reaction)[6] gave **3** and **4** , **Scheme 1**. Over oxidation to the imide **5** was also observed. In related studies Moriarty *et al.* has shown that oxidation of pyrrolidine to lactams is possible with $(PhIO)_n$ in water.[8] The structures of the imides **3** were confirmed by $RuO_2/NaIO_4$ oxidations of substrates **1**.[9]

Scheme 1

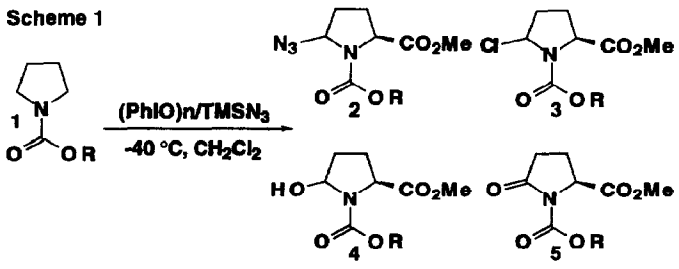
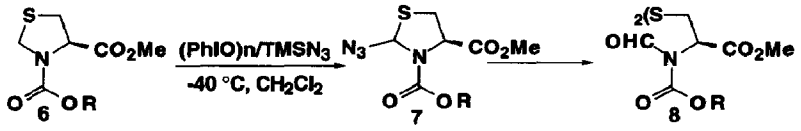


TABLE 1. Oxidation of 1 using $(PhIO)_n/TMSN_3$

ENTRY	R	2.4 and 4.8 eq.	5 and 10 eq.	10 and 20 eq.	OVERALL
1	Bu^t	70% 2	65% 2	57% 2, 5% 3, 12% 4, 22% 5,	74%
2	Ph	27% 2		56% 2, 8% 3, 6% 4, 10% 5, 12% 1.	74%
3	Me	24% 2		56% 2, 4% 3, 14% 4, 19% 5, 3% 1.	74%
4	$PhCH_2$	30% 2	50% 2	55% 2, 11% 3, 6% 4, 6% 5, 4% 1.	72%

The Boc thiaproline substrate **6** was also investigated. Quantitiative conversion (^1H NMR) to the 5-azido product **7** was observed. This high conversion is presumably due to the extra stability of the suspected N-acyl iminium ion conferred by the adjacent sulfur atom, **Scheme 2**. The α-azidoamide **7** was readily hydrolyzed to the N-formyldisulfide **8**.

Scheme 2



Oxidation of amide derivatives **9** showed lower overall conversion to 5-substituted proline derivatives **10**, an indication that the N-acyl iminium ion is greater stabilized by the urethane derivative and therefore more readily formed. The lack of any 5-chloro products further emphasizes this point. As with the urethanes imide formation **11** was also observed. Unlike the urethanes the 5-azido product **10** derived from the amide substrates shows slow decomposition to the aldehyde, **Scheme 3**. The α-azido derivatives **2** and **10** are isolated as a mixture of *cis*- and *trans*-isomers (1:2-5, *cis*- is more polar).

Scheme 3

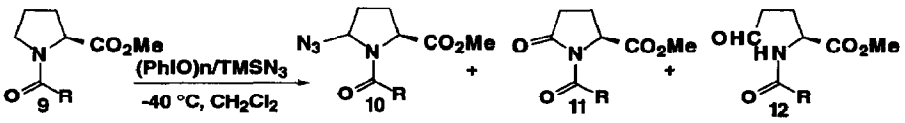
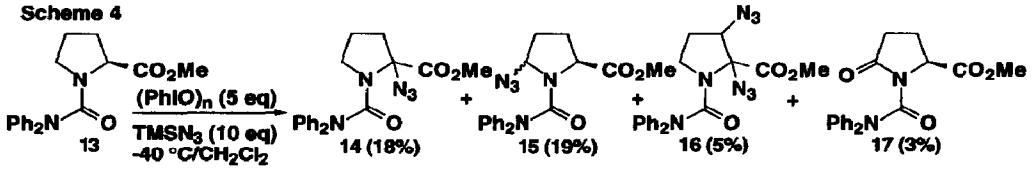


TABLE 2. Oxidation of 9 using $(PhIO)_n/TMSN_3$

ENTRY (R)	2.4 and 4.8 eq.	10 and 20 eq.	OVERALL
Ph	9% 10	52% 10, 15% 11, 20% 9	52%
3,4,5-OMe Ph	31% 10	57% 10, 8% 11, 20% 9	57%
Me	24% 10	62% 10, 12% 11, 5% 9	62%

High conversions of ureas to 5-azido products was expected based on results seen in the pyrrolidine series.[1] Surprisingly, on treatment of the N,N-diphenylcarbamoyl L-proline methyl ester **13** with the reagent combination relatively low conversions to **14**, **15**, **16** and **17** were observed by ^1H NMR.

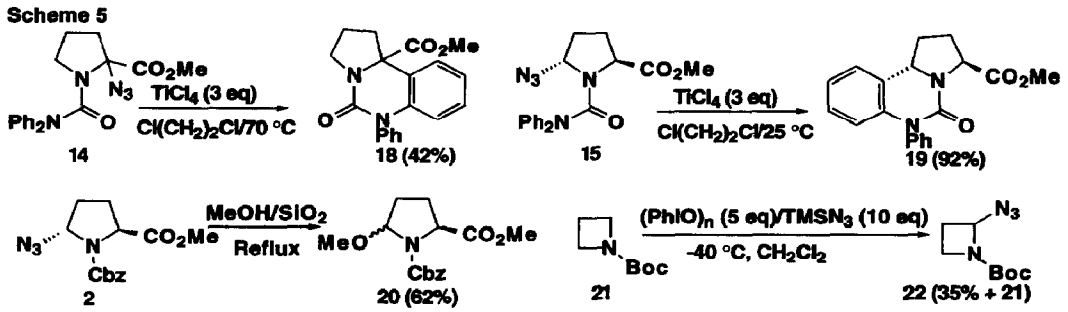
Scheme 4



Interestingly the ^1H NMR of **13** showed it to exist as one conformer in solution, presumably due to a large steric interaction between the $-NPh_2$ and the $-CO_2Me$ functionality. A 1:1 ratio of 2- and 5-azido products (**14** and **15**) was observed. The compound **15** was seen to occur as a 3:1 ratio of *trans:cis* diastereomers. The structures of the *cis*-**15** and the 2-azido **14** were shown by X-ray, **Scheme 4**.

Use of the 2- and 5-azido substituted proline urea derivatives **14** and **15** as N-acyliminium ion precursors was shown by intramolecular trapping upon ionisation by $TiCl_4$ (3 eq.) to give **18** (42%) and **19** (92%, 15:1, *trans:cis*) respectively.[10]

Scheme 5



Treatment of **2** with methanol in the presence of SiO_2 gave the α-methoxyamide **20** as a 1:1 mixture of epimers. The overall conversion is equivalent to that seen in the electrochemical

oxidation of similar substrates by Shono, **Scheme 5**.[4] Finally, the azetidine **21** was converted into the α-azido adduct **22** (35%), and as expected is less reactive than the pyrrolidine substrates.

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