JOC*Note*

Application of Peptidyl Radicals into a New Radical Cascade Leading to Unsaturated γ-Lactams

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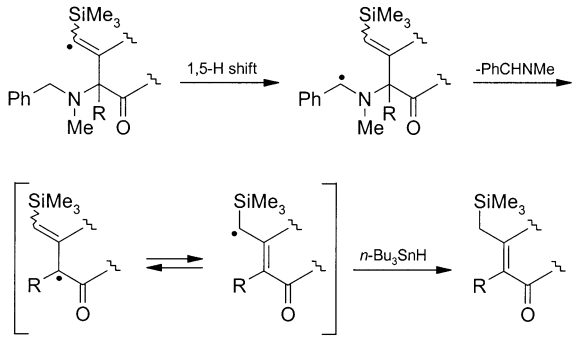
Received September 16, 2002

Abstract: Radical cyclization of dipeptides **1a**−**h** proceeds smoothly to give five- and seven-membered rings in good to moderate total yields using Stork's catalytic tin hydride method. A radical is generated on a protecting group and translocated to the peptide moiety. Following a cyclization reaction, the vinyl radical can abstract hydrogen from a benzyl group on an amine, which results in elimination of the protected amine group. Encouraging results have notably been obtained with amino acids other than glycine.

In recent years, many examples of hydrogen-atom transfer reactions affording amidocarboxy-substituted radicals have been reported.[1] Such radicals, classified as captodative, mero, or push−pull systems are stabilized by the combined action of an electron-releasing amido substituent and an electron-withdrawing carboxy substituent.[2] Among them, glycinyl ones appeared to be important intermediates in the preparation of unnatural α-amino acid derivatives[3] and peptidomimetics.[4] Derivatives of many other amino acids also form α carbon-centered radicals in a similar manner, and these react in an way identical to that of the corresponding glycinyl radicals. Recent rapid synthetic advances in the formation of such radicals established protecting/radical translocating groups (PRT) as an alternative way for their generation.[5] In general, a radical is initially generated in a "protecting group" and then translocated by 1,5-hydrogen transfer to the desired site before any further radical event.[6] A number of PRT groups are available now.[7] They differ from each other from the standpoint of protecting and functional groups. However, in most of the cases they do not undergo elimination during radical processes and consequently such groups require, if necessary, an additional synthetic step to be removed.[8]

In this context, we envisioned that it would be useful to test a group that once used to activate the peptidyl position could be eliminated after radical transformations. In this Note we would like to disclose a promising protocol for such transformation as generally described in Scheme 1. Vinyl radicals necessary for this process can be generated via addition of peptidyl radicals to alkynes. Following a cyclization reaction, the vinyl radical could abstract hydrogen from a benzyl group on an amine, which might result in elimination of the protected amine group. A driving force for such a process should be isomerization of the exocyclic double bond to form α,β-unsaturated γ-lactams. Recently Rancourt reported that glycinyl radicals were formed using a *N*-Boc,*N*-2-bromobenzyl group and a 1-trimethylsilyl alkyne group could be used to intercept the intermediate radical to form a vinyl radical and finally functionalized five-membered heterocycles.[9] However, any further elimination process was not observed. We supposed that alkyl substituents on a nitrogen atom were necessary for the overall process. We decided to examine a slightly modified system (*N*-2-bromobenzyl,*N*-methyl group) and for that purpose *N*,*N*-substituted dipeptides **1a**−**h** having a triple bond on a side chain were chosen as radical precursors.

SCHEME 1. General Strategy



The dipeptides were prepared by coupling methyl *N*-3-(trimethylsilyl)propargyl glycinate with *N*-2-bromo-benzyl,*N*-methyl amino acids using TBTU and *N*-methylmorpholine in CH_2Cl_2. In turn, the *N*-protected amino acids were prepared in three steps (40−80% overall yields) from the corresponding methyl ester hydrochloride by (1) introduction of the 2-bromobenzyl group with 2-bromobenzaldehyde and anhydrous $MgSO_4$ in CH_2Cl_2 followed by reduction of the imines with $NaBH_4$, (2)

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(1) Easton, Ch. J. *Chem. Rev.* **1997**, *97*, 53−82.

(2) (a) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, R. *Acc. Chem. Res.* **1985**, *18*, 148−154. (b) Balaban, A. T. *Rev. Roum. Chim.* **1971**, *16*, 724. (c) Katritzky, A. R.; Soti, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1427.

(3) Renaud, P.; Giraud L. *Synthesis* **1996**, 913−926.

(4) (a) Wyss, C.; Batra, R.; Lehmann, C.; Sauer, S.; Giese, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2529−2531. (b) Sauer, S.; Staehelin, C.; Wyss, C.; Giese, B. *Chimia* **1997**, *51*, 23−24.

(5) Curran, D. P.; Xu, J. *J. Am. Chem. Soc.* **1988**, *110*, 5900−5902.

(6) Generally, other 1,*n*-H transfers are known, for example. 1,3-H transfer: Damour, D.; Barreau, M.; Dhaleine, F.; Doerfingler, G.; Vuilhorgne, M.; Mignani, S. *Synlett* **1996**, 890−892. 1,4-H transfers: (a) Wallace, T. J.; Gritter, R. J. *J. Org. Chem.* **1961**, *26*, 5256. (b) Johnson, R. A.; Greene, F. D. *J. Org. Chem.* **1975**, *40*, 2186−2192. (c) Gilbert, B. C.; Parry, D. J.; Grossi, L. *J. Chem. Soc., Faraday Trans. 1* **1987**, 77−83. (d) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893−1896. 1,6-H transfers: (a) Gross, A.; Fensterbank, L.; Bogen, S.; Thouvenot, R.; Malacria, M. *Tetrahedron Lett.* **1997**, *53*, 13797−13810. (b) Nedelec, J. Y.; Lefort, D. *Tetrahedron* **1975**, *31*, 411−417. (c) Curran, D. P.; Yu, H. S.; Liu, H. T. *Tetrahedron* **1994**, *50*, 7343−7366. 1,7-H transfers: (a) Curran, D. P.; Somayajula, K. S.; Yu, H. *Tetrahedron Lett.* **1992**, *33*, 2295−2298. (b) Denenmark, D.; Winkler, T.; Waldner, A.; De Mesmaeker, A. *Tetrahedron Lett.* **1992**, *33*, 3613−3616. (c) Curran, D. P.; Xu, J.; Lazzarini, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3049−3059.

(7) Curran, D. P.; Xu, J. *J. Am. Chem. Soc.* **1996**, *118*, 3142−3147 and references therein.

(8) Curran, D. P.; Yu, H. *Synthesis* **1992**, 123.

(9) Rancourt, J.; Gorys, V.; Jolicoeur, E. *Tetrahedron Lett.* **1998**, *39*, 5339−5342.

10.1021/jo020602w CCC: $25.00
Published on Web 01/28/2003

SCHEME 2. Radical Cyclizations of Dipeptides 1a−h

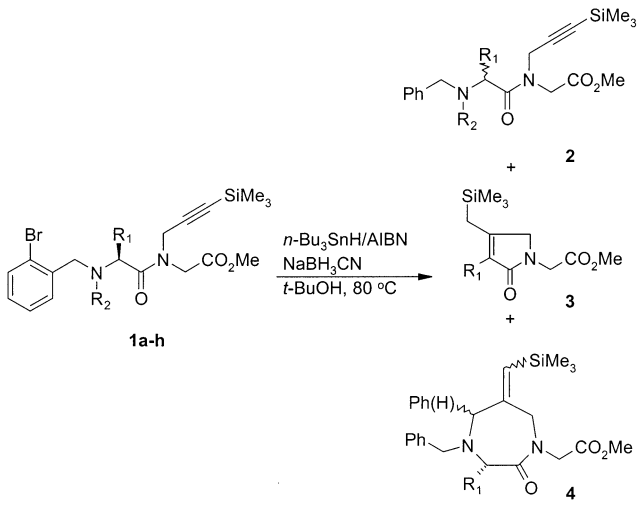


TABLE 1. Yields of Isolated Products[a]

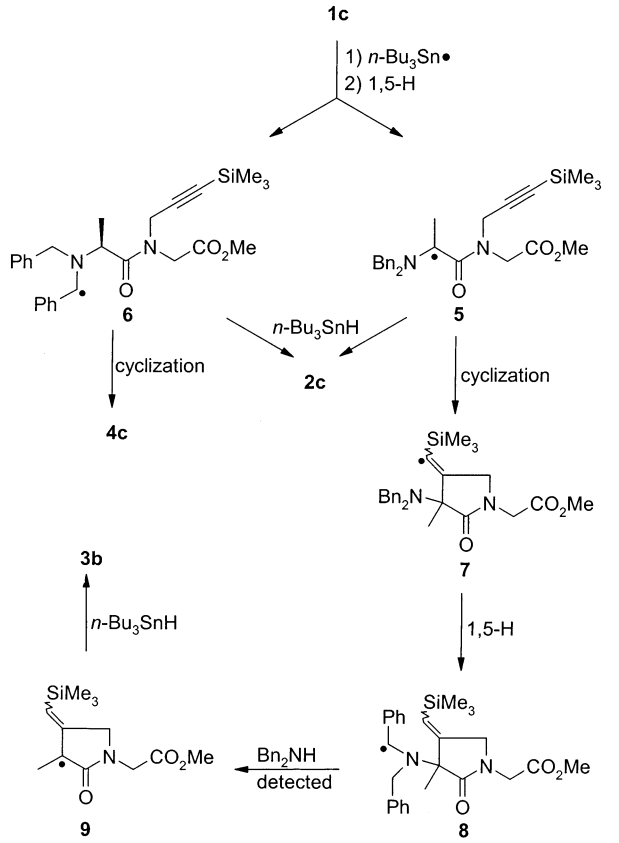
	R^1	R^2	**2** (%)	**3** (%)	**4** (%)
1a	H	Me	4	90	
1b	Me	Me	17	68	9
1c	Me	Bn	8	39	49
1d	Et	Me	14	45	11
1e	CH_2Ph	Me	17	37	10
1f	*i*-Pr	Me	22	32	13
1g	*i*-Bu	Me	36	32	11
1h	$CH_2CH_2CH_2$		23	39	

[a] Consistent spectral data (IR, MS, ^1H, and ^{13}C NMR) and correct HRMS were obtained for all compounds.

reductive methylation of the nitrogen atom using formaldehyde, and (3) acidic hydrolysis of the *N*,*N*-protected methyl esters with HCl_{aq}. The cyclization reactions were initially conducted under different concentration conditions with *n*-tributyltin hydride (0.01−0.05 M). After some experimentation, it was found that Stork's catalytic procedure[10] gave better results. Isolated yields were determined in these reactions (Scheme 2, Table 1). Noncatalytic procedures lowered yields slightly and did not significantly improve reaction time. Reaction time varied from one to several days. In the case of **1a**, the reaction proceeded very cleanly in high yield (90%). In contrast, the attempted cyclization reactions with **1b**−**h** gave products **3b**−**h** in lower yields. At ∼80 °C, the yields were in the vicinity of 35% (except 3**b**, 68%) under either set of the conditions. Two types of side products were observed. One of them reflected direct reduction of radicals before any further cyclization (**2a**−**h**). At this point it is not clear if it comes from direct reduction of the aryl radical prior to 1,5-hydrogen shift or takes place after it. Labeling experiments are currently underway. The second type of products resulted from another possible 1,5-hydrogen transfer from the *N*-methyl group followed by 7-*exo* cyclization (**4b**−**h**). Generally, amidocarboxy-substituted radicals are considerable more stable and they should be formed preferentially, but hydrogen-transfer processes may afford less stable products if a radical character in the reaction transition state is important. For example, Easton reported regioselective

(10) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

SCHEME 3. Mechanistic Pathway



radical chlorination of derivatives of valine and sarcosine where reaction occurred at other than amidocarboxy-positions.[11]

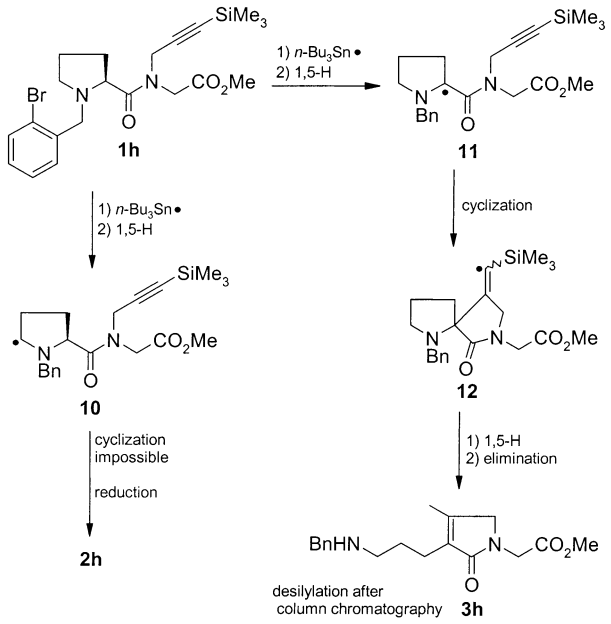
A reasonable mechanism for the reaction of **1c** is illustrative of all of the substrates, and this is depicted in Scheme 3. Bromine abstraction to generate the aryl radical is followed by a competition among direct reduction (leading to **2c**), and 1,5-hydrogen transfer (leading to **3b** or **4c**). Fortunately, the hydrogen transfer reactions of aryl radicals are sufficiently rapid to allow the following cyclizations.[12] From two possible modes of cyclization 5-*exo* one is largely favored over a 7-*exo* ring-closure (**6**). However, they are independent from each other. Once formed, radical **5** can smoothly undergo 5-*exo* cyclization to afford vinyl radical **7**. This, in turn can be reduced; however, in practice another 1,5-hydrogen transfer takes place, which is at the heart of the whole system (**8**). Similar intramolecular 1,5-hydrogen transfers producing α-amino radicals have been reported.[13] The next step presumably involves *β*-fragmentation to form radical **9**. This in turn could follow a two-step process: reduction and subsequent isomerization of the exocyclic double bond or more preferentially allylic isomerization to a more stable conjugated system and finally its reduction with the tin hydride to **3b**.

(11) (a) Bowman, N. J.; Hay, M. P.; Love, S. G.; Easton, Ch. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 259−264. (b) Hay, M. P.; Love, S. G.; Easton, Ch. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 265−268.

(12) Aryl radical/solvent reactions are quite fast; therefore rates of the cyclization should be at least $\sim 10^6$.

(13) (a) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 794−795. (b) Undheim, K.; Williams, L. *J. Chem. Soc., Chem. Commun.* **1994**, 883−884.

SCHEME 4. Radical Cascade of Dipeptide 1h



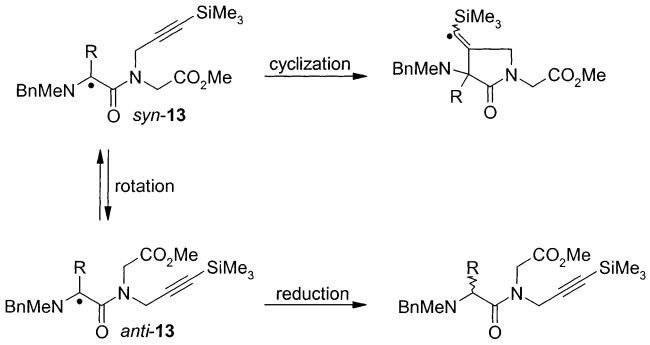
The proposed mechanism raised a question about a source of hydrogen atom in the final 1,5-hydrogen transfer. One approach should involve hydrogen atom transfer from the benzylic position; the second one indicated the *N*-methyl group as a possible explanation. The main problem in answering this question was how to prove it experimentally. Compound **1c** (Table 1) served also as a probe for the existence of a radical in the benzylic position just before splitting off amine. Indeed, when dipeptide **1c** was heated in *t*-BuOH under Stork's conditions, product **3b** was produced along with **4c** as a mixture of two isomers (~1:1). Moreover, dibenzylamine was isolated (21%), which provided other evidence concerning the proposed mechanism. The experiment with **1c** did not constitute an unambiguous proof, because the *N*-methyl group was not present in the substrate. However, this explanation seems to be reasonable.

A similar conversion was also applicable to proline derivative **1h**. A plausible mechanism for the cyclization is shown in Scheme 4. A radical is generated on the protecting group and translocated to the peptide moiety. Hydrogen transfer from a methylene group competes with hydrogen transfer from the α position (**10** and **11**). It has been reported that radicals of type **10** were formed preferentially to those of type **11** as a result of the severe nonbonding interactions associated with planar conformations of the radical **11**.[14] However, in an intramolecular process like this is it does not seem to be so obvious; **10** for steric reasons is reduced to **2h**. The peptidyl radical **11** closes to **3h** via spiro intermediate **12**.

A possible explanation for the lower yields in the case of amino acid derivatives other than glycine may be also derived from consideration of rotamers of the dipeptides.

(14) Burgess, V. A.; Easton, C. J.; Hay, M. P. *J. Am. Chem. Soc.* **1989**, *111*, 1047−1052.

SCHEME 5. Rotamers of α-Amidocarboxy Radicals



It has been suggested that the geometry of an initial rotamer of amidocarboxy-substituted radicals played a crucial role in deciding the course of radical reactions.[15] The radical generated from *syn*-**13** can cyclize, whereas the radical from *anti*-**13** is topologically prohibited from cyclizing. It is not clear whether at 80 °C the conformational barrier can be efficiently traversed within the lifetime of the radical, providing a cyclization option for it (Scheme 5). Thus, in the tin hydride reaction direct reduction of *anti*-rotamer **13** is observed.

The idea of the self-deprotecting group is already useful, but further improvements are desirable. This is perhaps due to relatively slow 1,5-hydrogen transfer in the case of amino acids other than glycine and another competing 1,5-H transfer leading to seven-membered rings. Further work is clearly needed to improve efficiency of the overall process. This problem constitutes a potentially serious limitation that, depending on substituents, may be difficult to overcome in some cases. However, there is a hope that an alternative would be to use the "double-barreled"[16] *o*,*o*-dibromobenzyl group. If the directly reduced product is formed after abstraction of the first bromine atom and subsequent reduction, then this molecule gets a second chance at cyclization when the second bromine exists. The results of these investigations will be reported in due course.

In conclusion, although the results here reported are largely preliminary, the radical cascade provides an accessible route starting from amino acids to a range of nitrogen-containing heterocycles in good to moderate yields when other methods fail.

Acknowledgment. This work was supported by Institute of Organic Chemistry, Polish Academy of Sciences.

Supporting Information Available: Experimental procedures and spectral data for compounds **1**−**4** (**a**−**h**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO020602W

(15) (a) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723−727. (b) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746−2750. (c) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012−11013. (d) Musa, M. O.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022−1025.

(16) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102−3104.