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Generation of Glycinyl Radicals *via* a 1,5-Hydrogen Atom Transfer Reaction. Applications to γ-lactam Formation.

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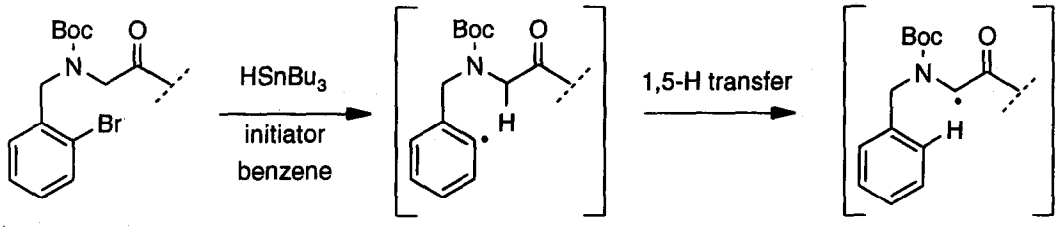
Abstract

Glycinyl radicals can be generated using a simple protecting/radical translocating group and used in the preferential formation of *trans*-3,4-disubstituted γ-lactams *via* a radical cyclisation reaction.

Keywords: cyclisation; lactams; peptide analogues/mimics; radical reactions.

Glycinyl radicals are important intermediates in the preparation of unnatural α-amino acid derivatives [1,2] and peptidomimetics [3,4]. Their preparation and use have been recently reviewed [1]. They are generally generated *via* the corresponding halogen [5], thioether [6] or xanthate [7] precursors. These radical intermediates have also been produced using both inter- and intramolecular hydrogen atom transfer reactions. Examples of intermolecular processes generating glycinyl radicals include photoalkylation of peptides [8], and radical bromination [9], benzoylation [10] and carboxylation [11] of glycine derivatives. Most intramolecular approaches involve photocyclisation reactions of amino acid or peptide derivatives [1,3,4].

In this paper we describe an intramolecular access to glycinyl radicals based on the use of a protecting/radical translocating group (PRT) [12] (**Scheme 1**) and its application to the formation of γ-lactams.



Scheme 1

This PRT approach offers the advantage of avoiding chemically unstable radical precursors such as, for example, α-halo amino acid derivatives. The PRT group used can survive a variety of different reaction conditions, thus allowing for more synthetic flexibility. As a first illustration of our methodology, unsaturated amide **1a** was prepared from ethyl glycine

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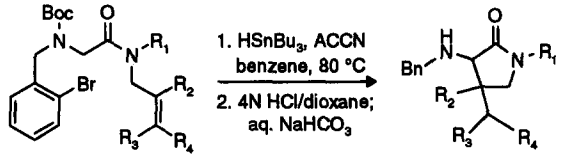
hydrochloride salt in four steps[1]. When **1a** (0.01 M in benzene) was treated with tri-*n*-butyltin hydride (2.0 eq.) and a catalytic amount of 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) [13] (0.15 eq.) at 80 °C, γ-lactams **2a** (*trans/cis*= 7/1) were obtained in 60% yield (**Table 1**, entry a) after Boc removal (4N HCl/dioxane) and neutralization[2]. In order to evaluate the scope and limitations of this tandem 1,5-hydrogen atom transfer-cyclisation reaction, we prepared a series of unsaturated glycine amides. The results obtained for the lactam formation are collected in **Table 1**.

Table 1
Tandem 1,5-Hydrogen Atom Transfer-Cyclisation Reaction of Unsaturated Glycine Amides[3]



1 2

Entry	R_1	R_2	R_3	R_4	*trans/cis*[a]	yield (%)[b]
a	allyl	H	H	H	7/1	60
b	PMB	H	H	H	8/1	58
c	PMB	H	H	CO_2Et	10/1[d]	72[c]
d	PMB	H	CH_3	CH_3	10/1	75
e	CH_2CO_2Bn	H	H	H	8/1	59
f	PMB	CH_3	H	H	—	59
g	C_2H_5	CH_3	H	H	—	61

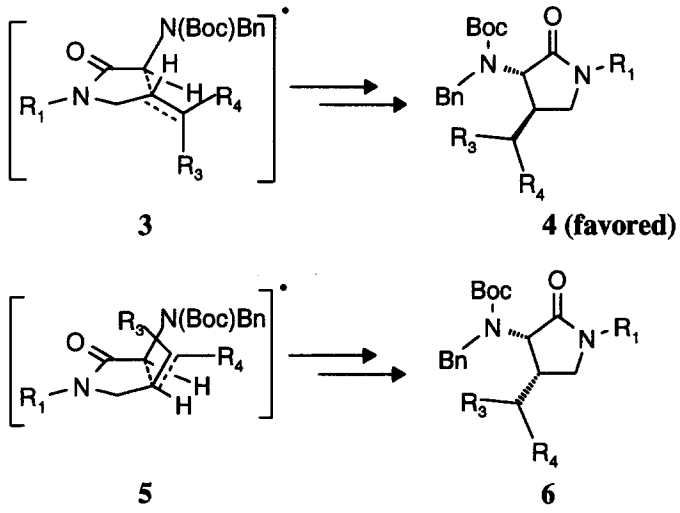
[a] Determined by ^1H NMR, except when otherwise indicated.
[b] Combined, isolated yield of pure *trans* and pure *cis* compounds (when applicable).
[c] In this particular case the Boc group was not removed.
[d] Ratio obtained by weight of isolated *trans* and *cis* compounds.

[1] The starting materials presented in **Table 1** were prepared by coupling an unsaturated amine with *N*-2-bromobenzyl *N*-*tert*-butoxycarbonyl glycine using TBTU and *N*-methylmorpholine in CH_2Cl_2. In turn, the requisite *N*-protected glycine residue was prepared in 3 steps (66 % overall yield) from ethyl glycine hydrochloride by 1) introduction of the 2-bromobenzyl group with 2-bromobenzylbromide and K_2CO_3 in EtOH, 2) protection of the nitrogen atom using $(Boc)_2O$ and DMAP in CH_3CN and 3) saponification of the ethyl ester with LiOH in a mixture of MeOH, THF and water.

[2] The *cis* and *trans* lactams were easily separated by flash chromatography on silica gel. The relative configurations at C3 and C4 were established by comparing the results of nOe experiments carried out on each isomer separately.

[3] Consistent spectral data (^{13}C NMR and/or ^1H NMR, IR) and correct EA and/or HRMS were obtained for all new compounds.

When one of the allyl substituents present on **1a** was replaced by a *p*-methoxybenzyl (PMB) group (R_1), a similar yield of cyclic material was also obtained (entry b), indicating that the reaction is not limited to di-unsaturated symmetrical amides. Keeping R_1 constant (PMB), we looked at the effect of varying the nature of the substituent on the allyl group. As illustrated in **Table 1**, electron deficient (entry c) or electron rich (entry d) olefins can be used as radical acceptors with similar efficiency, suggesting that the glycinyl radical intermediate is ambiphilic. In all cases, the *trans*-3,4-disubstituted γ-lactam was formed as the major product of the reaction. A possible rationalization for this preference is presented in **Scheme 2**.



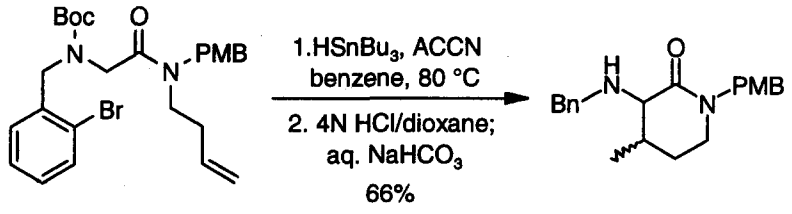
Scheme 2

We believe that the *trans* selectivity observed can be attributed to the fact that in the transition state **5** leading to the *cis* lactam **6** there is an unfavored steric interaction between the C-N(Boc)Bn and the C-CR_3R_4 bonds. This interaction is less severe in the case of the formation of the major *trans* -γ-lactam (**3** to **4**) as depicted above.

When a more functionalized R_1 substituent was used (entry e), we were able to prepare a rigidified, racemic, dipeptide fragment that contains a benzyl glycinate unit. This example increases the scope of this transformation and offers an alternative approach to various peptidomimetics [14, 15].

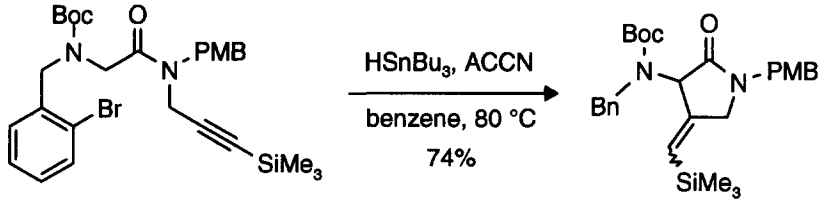
Interestingly, quaternary centers can also be produced in reasonable yield using this methodology (entries f and g). Thus, the 5-exo-trig pathway is still favored even when an alkyl group, such as methyl, is present at R_2 . The 4,4-disubstituted γ-lactams **2f** and **2g** were isolated.

Six-membered ring δ-lactams are also accessible using the above reaction (**eq. 1**). Contrary to the formation of γ-lactams, no *trans/cis* selectivity was observed in this case (*trans/cis*= 1.2/1).



eq. 1

The cyclisation reaction is not limited to olefins. We found that a 1-trimethylsilyl alkyne group can also be used to intercept the intermediate glycinyl radical, as illustrated below (**eq. 2**).



eq. 2

In conclusion, we have shown that glycinyl radicals can be formed using a *N*-2-bromobenzyl group and that these intermediates can be used to produce a variety of *trans*-3,4-disubstituted γ-lactams in fair to good yields.

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