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A New Powerful Method for the Transformation of Lactams into ω-Amino-carboxamides under High Pressure Conditions[1]

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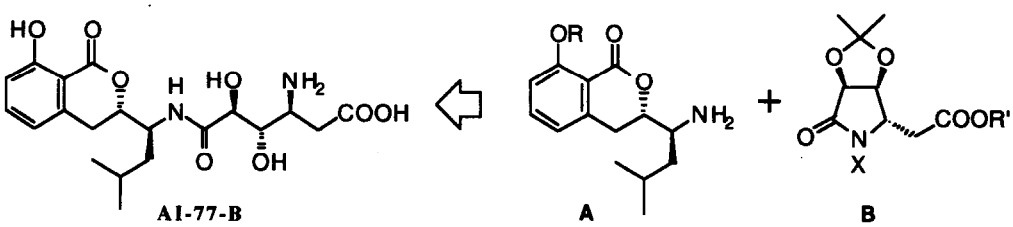
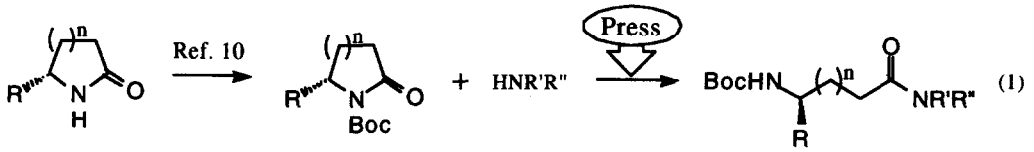
Abstract: High-pressure reaction of *N*-Boc-lactams with amines provides an efficient entry to ω-*N*-Boc-amino-carboxamide derivatives.

Organic compounds containing an amide function are widespread in Nature and are responsible for many kinds of significant biological activities.[2] Moreover, these are also important synthetic intermediates in organic chemistry and there are several methods for their preparation.[3] Among of them, the most commonly used method is based on the condensation reaction of carboxylic acid derivatives with amines. In connection with our synthetic efforts toward AI-77-B,[4] a gastroprotective substance isolated from *Bacillus pumilus* AI-77,[5] we required an efficient method for constructing an amide bond between the aminodihydroisocoumarin part **A** and the lactam part **B** (X= protective group).



In order to realize this type of transformation, usually, two kinds of procedures are employed as follows: hydrolysis of lactams into the corresponding ω-amino-carboxylic acids followed by condensation with an appropriate amine under certain dehydrating conditions[6] or direct aminolysis of lactams with amines by the assistance of organoaluminum reagents such as trimethylaluminum.[7] The former method is quite general when both of the starting materials are readily accessible and no acid- or base-sensitive functional groups are present in the molecules. On the contrary, the latter one developed by Weinreb exhibits a potential synthetic utility because of its simplicity to reach the final goals. Recently, alternative procedures using some other kinds of catalyst have also been reported,[8] but the generality is not well-established.

From these aspects, it can be recognized that there is still the lack of efficient means for converting lactams into ω-amino-carboxamides, in particular, for the stoichiometric condensation of lactam **B** with amine **A**. Although the non-protected lactams are relatively sluggish to react with amines under the conventional conditions, recently, it has been shown that *N-tert*-butoxycarbonylation (*N*-Boc) of lactams can appreciably increase the reactivity of an amide linkage.[9] Thus, selective cleavage of lactams with oxygen- or nitrogen-nucleophiles has been achieved smoothly. Since such a process for *N*-Boc-protection can be carried out easily,[10] the whole sequence would provide a new elegant approach to advance our original synthetic program. Based on these considerations, we have investigated the condensation reaction of *N*-Boc-protected lactams with amines (Eq. 1). Herein we wish to describe our successful results on this useful chemical transformation.



(1)

1: R=H, n=1; **3**: R=COOMe, n=1
2: R=H, n=2; **4**: R=COOBu^t, n=1

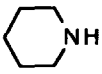
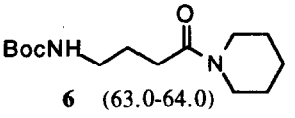
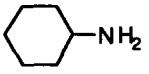
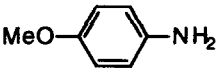
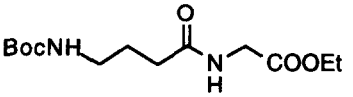
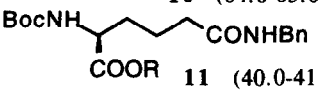
Initial attempts to realize the reaction of *N*-Boc-lactam **1** with one equivalent of benzylamine in refluxing acetonitrile resulted in a completely recovery. It can be expected, however, that the difficulty should be overcome by applying high pressure, since this type of condensation reaction is highly favorable under these conditions.[11] In fact, at 10 kbar pressure the same reaction proceeded cleanly and the desired product of *N*-benzyl-3-(*N*-Boc)aminobutanamide (**5**) was obtained in 97% yield.[12] The general scope of this synthetic technology is apparent from the results summarized in Table 1.[13]

From these results we could demonstrate again the superiority of high pressure technique to promote the important functional group transformation which we have designed. In some cases the reactions using sterically hindered or less reactive amines gave no products (Runs 3, 6, and 7). In view of the convenience for the synthesis of peptides, Runs 8, 11, and 12 show the efficiency of this procedure. Furthermore, it should be noted that the functional group selectivity is excellent: amines only attack the amide group even in the presence of ester one (Runs 11 and 12).

In summary, lactams bearing a Boc-group at nitrogen can react with a stoichiometric amount of amines at high pressure to produce ω-*N*-Boc-amino-carboxamides in high yields. Since these reactions can be conducted under fairly mild conditions without using any catalysts, the present method offers a great advantage to derive carboxamide compounds including peptides. Along this line current work is actively in progress to complete our synthetic work on AI-77-B.

Typical procedure for the preparation of 5: A mixture of *N*-Boc-lactam **1** (200 mg, 1.1 mmol) and benzylamine (116 mg, 1.1 mmol) in dry acetonitrile (1.5 mL) was placed in a Teflon reaction vessel and allowed to react at 10 kbar and 80 °C for 21 h. After evaporation of the solvent, the residue was purified by recrystallization from CH_2Cl_2-hexane to give **5** (306 mg, 97%) as colorless plates: IR (KBr) 3342, 3310, 1699. 1657, 1547 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, δ) 1.42 (9H, s), 1.81 (2H, m), 2.25 (2H, t, J=6.8 Hz), 3.15 (2H, q, J=6.4 Hz), 4.42 (2H, d, J=5.7 Hz), 4.75 (1H, br), 6.35 (1H, br), 7.29 (5H, s).

Table 1. High-Pressure Reaction of *N*-Boc-Lactams with Amines[a]

Run	*N*-Boc-Lactam	Amine	Reaction Conditions	Product (Mp, °C)	Yield, %[b]
1	**1**	$PhCH_2NH_2$	reflux, 77 h[c]	BocNH⌒⌒CONHBn	0
2	**1**	$PhCH_2NH_2$	80 °C, 21 h	**5** (119.0-120.0)	97
3	**1**	i-Pr_2NH	80 °C, 20 h		no reaction
4	**1**		75 °C, 23 h	 **6** (63.0-64.0)	84
5	**1**		85 °C, 22 h	BocNH⌒⌒$CONHC_6H_{11}$ **7** (146.5-148.0)	78
6	**1**	t-$BuNH_2$	110 °C, 48 h		no reaction
7	**1**		110 °C, 20 h		no reaction
8	**1**	H_2NCH_2COOEt[d]	90 °C, 24 h	 **8** (oil)	87
9	**2**	$PhCH_2NH_2$	reflux, 36 h[c]	BocNH⌒⌒CONHBn	90
10	**2**	$PhCH_2NH_2$	25 °C, 12 h	**9** (118.5-119.5)	88
11	**3**	$PhCH_2NH_2$	90 °C, 20 h	**10** (64.0-65.0)	89
12	**4**	$PhCH_2NH_2$	90 °C, 24 h	 **11** (40.0-41.0)	90

[a]All reactions were conducted in CH_3CN at 10 kbar using 1 equiv of *N*-Boc-lactam and 1 equiv of amine unless otherwise noted. [b]Isolated yields. [c]At atmospheric pressure. [d]Generated in situ from glycine ethyl ester hydrochloride by treatment with Et_3N and 3 equiv of amine was used due to the concomitant formation of glycine anhydride.

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12. In many cases the reaction proceeded cleanly and all of the starting materials were consumed. The rather reduced yields are due to some leaking during the reaction.
13. Satisfactory spectral and analytical data were obtained for all new compounds.

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