Tetrahedron Letters 52 (2011) 2579–2582

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalyst and solvent-free amidation of inactive esters of N-protected amino acids

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ARTICLE INFO

Article history:
Received 9 February 2011
Revised 4 March 2011
Accepted 8 March 2011
Available online 12 March 2011

Keywords:
Aminolysis
Inactive esters
Amino acid
Amidation

ABSTRACT

A catalyst free procedure for the preparation of amides from inactive esters of N-protected amino acids and various amines is demonstrated under mild reaction conditions. Our effort to recover excess amine and generated alcohol is an approach towards environment friendly and cost effective synthesis under easy operational conditions.

Amides are one of the versatile functional groups in many organic and biomolecules.[1] Amides derived from the reaction of amino acids and amines are important as they constitute a significant part of the chemical space of biologically active compounds. For example, *N*-(benzyloxycarbonyl)-glycine esters and amides exhibit anticonvulsant property.[2] Kohn and co-workers reported synthesis and anticonvulsant properties of some functionalized DL-amino acid derivatives as well as some *N*-benzylacetamido derivatives.[3]

There exist many protocols in literature which describe their preparation either directly from acid or by derivatization of the acid into more reactive ester, anhydride or acid halide to form amide. Usually phenolic esters are considered as active esters as they react readily with amines at room temperature. On the other hand, alkyl esters are considered as inactive and widely used as protecting groups for carboxylic acid function especially in peptide chemistry. However, amidation from inactive alkyl esters is also reported under arduous conditions using various reagents. To name a few, ammonium chloride,[4] sodium methoxide,[5] sodium amide,[6] sodium hydride,[7] sodium cyanide,[8] Grignard reagents,[9] butyllithium,[10] 2-hydroxy pyridine,[11] sodium 2- or 4-pyridinolate.[12] Han et al. introduced use of group IV metal alkoxides in combination with additives like HOBt, HOAt etc. for amidation.[13] In the same year Movassaghi and Schmidt reported the amidation of inactivated esters with amino alcohols using *N*-heterocyclic carbene as the catalyst.[14] Mioskowski achieved aminolysis of methyl esters using TBD (1,5,7-triazabicyclo [4.4.0] dec-5-ene) as catalyst.[15] Recently, catalytic activity of DBU (1,8-diazabicyclo [5.4.0] undec-7-ene)[16] and an equimolar mixture of DBU and 1,2,4-triazole[17] for such ester to amide exchange reactions has been demonstrated. Ammonolysis of inactive esters are also reported using $Mg(OCH_3)_2/NH_3$, $CaCl_2/NH_3$ and $Mg(OCH_3)_2/NH_4Cl$.[18]

Protease, Alcalase-CLEA and Lipases from different sources are also used for regioselective transformation of such esters to amide in milder conditions.[19] Due to high nucleophilicity of aluminium amides, lithium aluminium hydride-amine complexes and dimethyl aluminium amides are proved to be useful reagents for alkyl ester aminolysis.[20] Aminolysis of ethyl cyano acetate with lithium amide[21] and allyl esters with bis-lithium aryl amide is also reported later.[22] Varma and Naicker have shown preparation of amides from inactive esters using potassium tertiary butoxide[23] as the catalyst under microwave irradiation under solvent free condition.

Syntheses of inactive esters are easier and cost effective than activated aromatic esters. Therefore, methods for amidation from inactive esters are always desired. Almost all the examples cited in the above mentioned publications deal with nonpeptidic substrates and harsh reaction conditions such as, highly basic or acidic media, high temperature and/or long reaction time. To the best of our knowledge, there are only two reports of catalyst and solvent free amidation procedures available at ambient temperature. However, in one case purely nonpeptidic substrates (pyridone analogs) were explored[24] while in another amidation was achieved from the ester situated at the side chain carboxylic acid group of a homopolymer of aspartic acid.[25] Herein we report preparation of amides from alkyl esters of N-protected amino acids at 40 °C temperature without the use of any catalyst under a solvent free condition and

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doi:10.1016/j.tetlet.2011.03.039

explored the reactivity of different amino acids by varying N-terminus protection.

For our ongoing research, we needed benzyl amides of various amino acid derivatives. Among many protocols available in literature we chose the one reported by Perreux et al.[26] as they avoided the use of –COOH activating reagent, catalyst or extra solvent. We first tried to reproduce the original work using benzyl amine and phenyl acetic acid in a domestic microwave oven at 160 °C (convection heating mode) instead of a dedicated microwave reactor (Synthwave® 402 from Prolabo was used in the original article) and found the amide was produced in good yield. However, replacing phenyl acetic acid with benzoyl glycine produced only a trace amount of amide.

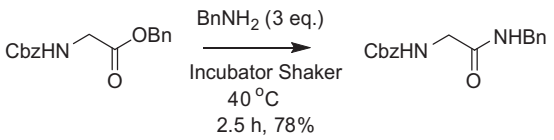
The relative inertness of carboxylic acid group of amino acids towards amidation prompted us to follow mild activation strategy by forming benzyl ester. Benzyl group is commonly used for C-protection of amino acids similar to methyl and ethyl esters. When benzyl ester of *N*-benzoyl glycine was reacted with 10 equiv of benzyl amine for 30 min at 160 °C under a microwave heating it gave corresponding amide in good yield. Thus the use of benzyl ester is more efficient and convenient compared to the methods using unprotected amino acids. This result inspired us to explore the possibility of preparation of amides from inactive esters of amino acids. At first, various parameters were optimized to find out the best condition for such reactions. There was no decrement in the yield of the product with decrease in the temperature of the microwave oven (reactions were performed at 160, 120, 100 and 40 °C). Later we repeated the reaction in a shaking incubator at 40 °C (Scheme 1). Since incubator provides uniform heating we considered it as a better option. If desired, an oil bath or a microwave oven also can be used. Subsequently, from several trials we found that the use of 3 equiv of amine was found to be equally effective in giving corresponding amide.

After completion of the reaction (monitored by TLC), the reaction mixture was directly loaded on to a silica gel column. Our desired amide along with benzyl alcohol, which was produced during the course of the reaction and unreacted amine, was separated and collected back easily.

Other common N-protecting groups such as Boc and Cbz were found to be compatible under the present experimental condition[27] as shown in Table 1.

Next, we investigated the reactivity of esters of neutral amino acids such as, Ala, Leu, Val and Phe as shown in Table 2. It was observed that the time required for complete conversion is very much dependent on the side chain present. With the increase in the bulkiness of the group at the side chain time required for complete conversion is more. Also it was noticed that in the case of Boc valine benzyl ester (entry 4, Table 2) the reaction mixture was solidified after 36 h and TLC analysis indicated the partial conversion with only 40% yield. Addition of more amine and increase in temperature did not improve further yield. However, phenylalanine derivatives gave excellent yield (85%) within 25 h for the complete conversion (entry 5, Table 2). This method was also equally successful for Leu derivative (entry 3, Table 2) and no precipitation was observed as in the case of Val derivative in spite of similar bulkiness in their side chain.

We were interested to study the reactivity of benzyl esters with different types of amines. Therefore, we applied the optimized



Scheme 1. Synthesis of benzyl amide from benzyl ester of Cbz-glycine.

Table 1
Time required for completion is independent of N-protection

Entry	Benzyl ester	Amine	Time (h)
1	Bz-Gly-OBn	$BnNH_2$	2.5
2	Boc-Gly-OBn	$BnNH_2$	2.5
3	Cbz-Gly-OBn	$BnNH_2$	2.5

amidation condition to several amino acid benzyl esters with various aliphatic primary and secondary amines as well as aromatic primary amines (Table 3). Various aliphatic primary amines such as, *n*-butylamine, benzylamine, cyclohexylamine and 2-picolylamine react efficiently giving corresponding amides as shown in Table 3. In the case of ethanolamine, a bis-nucleophile, regioselective amidation occurs over transesterification. (entry 1, Table 3) In case of alanine derivatives the time required for complete amidation for ethanolamine was about 1 h (entry 11) which probably was because of the presence of a more bulky methyl group. Primary aromatic amines such as aniline did not react with benzyl ester of benzyl amine in the current condition. However, when heated at 120 °C for 4 h conversion completed was achieved (entry 8) as judged from the TLC.

Further we were interested to explore the feasibility of the current methodology for secondary amines as well. When a cyclic secondary amine, for example, piperidine, was used under the optimized condition complete conversion was observed within 6 h (entry 10). However, bulky diisopropyl amine did not react up to 24 h under the present condition (entry 18) when reacted with uncongested glycine benzyl ester. The same reaction mixture was heated at 80 °C for further 12 h and no progress was noted and unreacted starting material was recovered quantitatively. This could be due to the steric congestion of the isopropyl groups on the nucleophilic nitrogen atom.

All the final products in the above table were characterized using NMR, IR and HRMS. Moreover, the structure of the products of entry 7 and 13 of Table 3 were further confirmed from the X-ray crystallography. The ORTEP diagrams along with atomic numbering of the compounds are furnished below (Fig. 1 and Fig. 2). (Crystallographic data in detail are provided in the Supplementary data.)

We investigated the scope of this methodology with other inactive esters of amino acids that are commonly employed as protecting agents under the same reaction conditions and results are given in the following table.

We investigated the scope of this methodology under the same reaction condition with other inactive esters of amino acid that are commonly employed as protecting groups and results are summarized in Table 4.

It is clear from the data presented in Table 4, that present methodology is applicable to various other inactive esters as well. Reactions with both benzyl and allyl are faster than ethyl and methyl esters as the first two are better leaving group.

It is noteworthy that, if in any molecule any of these moieties are employed as protecting group(s) presence of free or bound amine (as discussed above) in the reaction mixture could generate amides, if the reaction condition is maintained at or above 40 °C. This information is particularly important for peptide chemists as these esters are frequently used as protecting groups for the carboxylic acid terminus of an amino acid. Moreover, medicinal chemists may need a library of esters as well as amide derivatives of amino acids as reported by Geurts et al.[2] In such a situation, one can generate different amides from the same pool of esters, which will save time and cost of synthesis.

We have described a method of preparation of amides of N-protected amino acids with amines at 40 °C without any catalyst and solvent achieving good yield. We could recover excess amine and

Table 2
Yields and conditions for the synthesis of benzyl amides from Boc protected amino acids

Entry	Benzyl ester	Amine	Time (h)	Isolated yield (%)	Benzyl alcohol rec/exp (mg)	Benzyl amine rec/exp (mg)
1	BocGly OBn	$BnNH_2$	2.5	78	31/40	48/118
2	BocAla OBn	$BnNH_2$	10	84	30/38	41/76
3	BocLeu OBn	$BnNH_2$	44	70[a]	––	32/66
4	BocVal OBn	$BnNH_2$	36	40	12/35	41/68
5	BocPhe OBn	$BnNH_2$	25	85	20/30	42/89

Where, rec = recovered, exp = expected, Boc = *tert* butoxycarbonyl.
[a] R_f of the product and benzyl alcohol was found to be same (0.2, EtOAc/hexane, 1:9) and therefore could not be separated from column chromatography. The sample was analyzed as a mixture itself.

Table 3
Yields and conditions for the synthesis of amides from benzyl ester of N-protected amino acids (100 mg scale)

Entry	Benzyl ester	Amine (3 equiv)	Time required	Isolated yield (%)	Benzyl alcohol rec/exp (mg)	Amine rec/exp (mg)
1.	Bz-Gly-OBn	$NH_2CH_2CH_2OH$	20 min	73	35/40	40/67
2.	Bz-Gly-OBn	*n*-$BuNH_2$	20 min	82	30.6/40	36/54
3.	Bz-Gly-OBn	$BnNH_2$	2.5 h	70	28/40	50/108
4.	Bz-Gly-OBn	2-Picolylamine	2.5 h	76	32/35	54/108
5.	Bz-Gly-OBn	Cyclohexylamine	5 h	85	33.3/40	42/73
6.	Cbz-Gly-OBn	2-Picolylamine	1.5 h	80	29/35	40/107
7.	Cbz-Gly-OBn	$BnNH_2$	2.5 h	78	32/35	54/108
8.	Cbz-Gly-OBn	NH_2Ph	4 h[a]	72	20/35	38/62
9.	Cbz-Gly-OBn	Cyclohexylamine	5 h	80	30/35	60/98
10.	Cbz-Gly-OBn	Piperidine	6 h	70	24/35	38/57
11.	Bz-Ala-OBn	$NH_2CH_2CH_2OH$	1 h	83	22/38	36/65
12.	Bz-Ala-OBn	$BnNH_2$	10 h	77	26/38	28/68
13.	Bz-Ala-OBn	2-Picolylamine	10 h	74	36/38	42/114
14.	Cbz-Val-OBn	*n*-$BuNH_2$	24 h	51	14/30	25/63
15.	Cbz-Val-OBn	$BnNH_2$	36 h	40	10/31	42/93
16.	Boc-Phe-OBn	*n*-$BuNH_2$	10 h	72	25/30	20/40
17.	Boc-Phe-OBn	2-Picolylamine	23 h	85	22/30	32/60
18.	Bz-Gly-OBn	*i*Pr_2NH_2	36 h[b]	NA	NA	62/112

Shown amount of benzyl alcohol and amine recovered versus expected. Bz = benzoyl, Cbz = *N*-benzyloxycarbonyl, Boc = *tert* butoxycarbonyl.
[a] Reaction performed in oil bath maintaining temperature at 120 °C.
[b] After 24 h reaction mixture was shifted under reflux conditions at 80 °C for more than 12 h starting materials were recovered back.

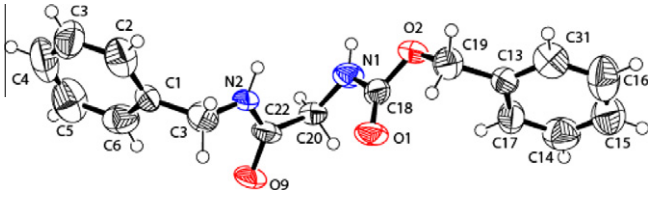


Figure 1. ORTEP diagram of Cbz glycine benzylamide with 50% ellipsoid.

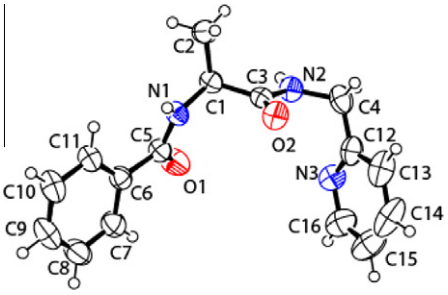


Figure 2. ORTEP diagram of benzoyl alanine pyridine methyl amine with 50% ellipsoid.

produced benzyl alcohol which can be reused. This is a cost effective and environment friendly method for the synthesis of amide derivatives of protected amino acids.

Table 4
Aminolysis with different inactive esters

Entry	Inactive ester	Amine	Time (h)	Isolated yield (%)
1	BzGlyOBn	$BnNH_2$	2.5 h	70
2	BzGlyOAll[a]	$BnNH_2$	2.5 h	80
3	BzGlyOMe	$BnNH_2$	4 h	80
4	BzGlyOEt	$BnNH_2$	5 h	82

[a] All = allyl.

Acknowledgements

We are thankful to DST for XRD facility; CIF, IITG for NMR and HR-MS facility; Chemical Engineering Department, for specific rotation, IITG and DST SERC (NO. SR/FT/CS-011/2008) for research grant. NKC, TK and PNB thank IITG for fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.039.

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27. General procedure for the preparation of amides from benzyl ester of N-protected amino acids.
    Benzyl ester of N-protected amino acid (0.5 mmol) was taken in a glass vial (5 mL). To the same vial amine (1.5 mmol) was added and covered with a plastic cap, reaction mixture was vortexed for a minute for thorough mixing. The reaction mixture was then kept in an incubator shaker which was maintained at 40 °C. Progress of the reaction was monitored by TLC. After complete conversion, reaction mixture was directly loaded on to the silica gel (60–120 mesh) column for purification and eluted with a mixture of ethyl acetate and hexane.
    Benzylcarbamoyl-methyl carbamic acid benzyl ester. R_f product 0.2 (EtOAc/Hexane, 2:3). Yield 78%, white solid, mp 120 °C (Lit.[2]) IR (KBr, ν/cm^{-1}) 1663, 1715, 3322; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 10H, Ph), 5.09 (s, 2H, OCH_2Ph), 4.44–4.42 (d, J = 5.6 Hz, 2H, NHCH_2Ph), 3.89–3.87 (d, J = 5.2 Hz, 2H, NHCH_2CO), ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 156.8, 137.9, 136.2, 128.7, 128.6, 128.3, 128.1, 127.7, 127.6, 67.2, 44.6, 43.5 LRMS m/z 299 $[M+H]^+$, 321 $[M+Na]^+$, 337 $[M+K]^+$ HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1396 found: 299.1406.