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LiOH-mediated *N*-monoalkylation of α-amino acid esters and a dipeptide ester using activated alkyl bromides

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Abstract—Selective *N*-monoalkylation of α-amino esters with activated alkyl bromides was studied using various alkali or alkali earth metal bases. In the production of *N*-monoalkylated amino ester derivatives and suppression of *N*,*N*-dialkylation, lithium hydroxide was more effective than any other alkali or alkali earth bases examined. Using this protocol, a variety of *N*-alkylated α-amino esters and even dipeptide esters have been successfully prepared using various activated alkyl bromides.

N-Alkylated amino acids are often key components of peptide turn structures[1] and small cyclic peptide mimetics.[2] Most of these secondary amino acids form tertiary amide bonds in bioactive peptides and peptidomimetics. Also, recent advances in solid-phase synthesis using organic polymer supports in relation to the construction of combinatorial libraries often require highly efficient *N*-alkylation methods for connecting an amine functionality onto various supports or linkers.[3]

Recently, a new *N*-monoalkylation protocol employing cesium hydroxide as a base has been reported by Jung et al.[4] to remedy shortcomings of common preparatory methods for secondary amines from primary amines, including reductive amination and direct nucleophilic *N*-alkylation.[5] In the course of our study employing biologically active peptides and peptide mimics, we needed an efficient method for *N*-monoalkylation of α-amino esters. However, when the cesium hydroxide protocol was employed for the alkylation of various α-amino acid esters, the desired *N*-monoalkylated products were obtained only in moderate yields. Therefore, we screened a variety of alkali and alkali earth metal hydroxides and carbonates to find that lithium hydroxide performs far better than any other metal bases examined for our purposes. Herein we wish to report this LiOH-promoted, selective *N*-monoalkylation of α-amino ester derivatives.

First we examined alkylation of several α-amino esters with either allyl bromide or *p*-nitrobenzyl bromide (PNBBr) in the presence of CsOH or Cs_2CO_3 following the reported procedure[4] and the results are summarized in Table 1. In the alkylation of phenylalanine or leucine methyl ester hydrochloride, yields of *N*-monoalkylated amino esters were in the range 58–67% (entries 1–4). *N*-Monoalkylation of alanine methyl ester, which is less hindered than the phenylalanine or leucine derivative, proceeded in about 10% higher yields either with CsOH or Cs_2CO_3 (entries 5–8). The reaction of glycine methyl ester gave about 50% of mono-alkylated amino esters and 10–20% of *N*,*N*-dialkylated products (entries 9–12). The low reactivity of α-substituted amino ester deriva-

Table 1. Direct *N*-monoalkylation of α-amino esters using cesium bases

Entry	Amino ester	R	Base	Yield (%)[a]
1	PheOMe	Allyl	Cs_2CO_3	67
2	PheOMe	PNB	Cs_2CO_3	64
3	LeuOMe	Allyl	$CsOH{\cdot}H_2O$	58
4	LeuOMe	PNB	$CsOH{\cdot}H_2O$	61
5	AlaOMe	Allyl	Cs_2CO_3	78
6	AlaOMe	PNB	Cs_2CO_3	74
7	AlaOMe	Allyl	$CsOH{\cdot}H_2O$	65
8	AlaOMe	PNB	$CsOH{\cdot}H_2O$	70
9	GlyOMe	Allyl	Cs_2CO_3	48[b]
10	GlyOMe	PNB	Cs_2CO_3	52[b]
11	GlyOMe	Allyl	$CsOH{\cdot}H_2O$	54[b]
12	GlyOMe	PNB	$CsOH{\cdot}H_2O$	47[b]

[a] Isolated yields from silica gel chromatography.
[b] The *N*,*N*-dialkylated product was obtained in 10–20% yields.

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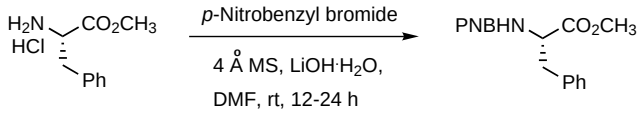
tives in the presence of cesium bases may be due to increased steric hindrance at the amine nucleophile through chelated cesium complex involving both the nitrogen and the carbonyl oxygen of the amino acid ester.

Then we decided to screen various alkali and alkali earth metal bases. For this purpose, we chose the reaction between L-phenylalanine and *p*-nitrobenzyl bromide in the presence of activated 4 Å molecular sieves in anhydrous *N*,*N*-dimethylformamide (DMF) as a control set[4] and tested various metal hydroxides and carbonates. As documented in Table 2, when alkylations employing 2.15–2.20 equiv. of each metal bases were screened, reactions employing rubidium hydroxide, cesium hydroxide, and calcium hydroxide provided reasonable yields of alkylation products (entries 7, 10, and 13, respectively). However, lithium hydroxide and lithium carbonate proved to be superior to all other metal bases in furnishing the desired *N*-monoalkylation product (entries 1 and 2). In fact the reaction involving lithium hydroxide provided the highest yield (95%) (entry 1). It is quite intriguing to note that LiOH was rather ineffective in selective *N*-monoalkylation of simple primary amines.[6] This appears to be due to the fact that, compared to other metals, lithium metal is smaller and possesses strong covalent character to bind the nitrogen and oxygen atoms of α-amino esters.[7]

With the LiOH protocol in hand, we examined alkylation of various α-amino esters with *p*-nitrobenzyl bromide as depicted in Table 3.[8] Alkylation of alanine, phenylalanine and leucine methyl esters all went through smoothly under the LiOH conditions (entries 1–6). Even with valine methyl ester, a highly hindered amino ester, the reaction involving LiOH ensured clean conversion to *N*-monoalkylated derivative in 85% yield (entry 7). Several multifunctional amino acid derivatives such as serine, aspartic acid, arginine, tyrosine and ornithine derivatives have also been examined under the same reaction conditions and in all cases respectable yields of the desired *N*-monoalkylated products were obtained (entries 8–12). Alkylation of the most unhindered amino acid, glycine methyl ester gave mono-alkylated products in 61 and 54% yields from the reaction with allyl bromide and *p*-nitrobenzyl bromide, respectively (entries 14 and 15). In these cases, *N*,*N*-dialkylated side products were obtained in 10–15% yields.

In order to investigate the stereochemical integrity at the α-carbon center of amino esters in the course of alkylation under the conditions employing LiOH, we have examined the enantiomeric purity of the L-phenylalanine methyl ester derivative upon reaction with *p*-nitrobenzyl bromide and compared it with a racemic derivative. Chiral HPLC analyses of both derivatives (Daicel Chiracel OD-H column; eluent: *n*-hexane/isopropanol 90:10; 1.0 mL/min) clearly indicated that no enantiomerization of the amino acid derivative has occurred. As for other side reactions, hydrolysis of the ester moiety followed by subsequent alkylation was not observed to a detectable extent, which was similar to the previously reported case involving cesium bases.[4]

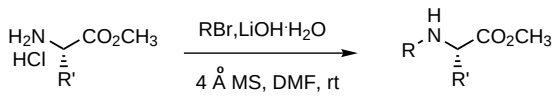
Table 2. Direct *N*-monoalkylation of phenylalanine methyl ester hydrochloride using various alkali and alkali earth metal bases



Entry	Base	Reaction time (h)	Yield (%)[a]
1	$LiOH·H_2O$	12	95
2	Li_2CO_3	12	87
3	NaOH	12	55
4	Na_2CO_3	24	50
5	KOH	12	60
6	K_2CO_3	24	31
7	$RbOH·xH_2O$	12	71
8	Rb_2CO_3	24	25
9	$CsOH·H_2O$	12	70
10	Cs_2CO_3	12	64
11	$Mg(OH)_2$	12	36
12	$MgCO_3$[b]	24	63
13	$Ca(OH)_2$	12	75
14	$CaCO_3$	24	52
15	$Sr(OH)_2$	12	68
16	$SrCO_3$	24	42
17	$Ba(OH)_2·H_2O$	12	60
18	$BaCO_3$	24	21

[a] Isolated yields after silica gel chromatography.
[b] $(MgCO_3)_4·Mg(OH)_2·5H_2O$ was employed.

Table 3. Direct *N*-monoalkylation of representative α-amino esters using LiOH



1 **2**

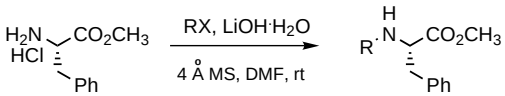
Entry	Amino ester	R	$[\alpha]_D^{25}$ [a]	Yield (%)[c]
1	AlaOMe	PNB	−52.7	86
2	AlaOMe	Allyl	−45.5	82
3	PheOMe	PNB	−25.9	95
4	PheOMe	Allyl	+23.0	90
5	LeuOMe	PNB	−19.5	88
6	LeuOMe	Allyl	−7.4	94
7	ValOMe	PNB	−64.5	85
8	Ser(O*t*Bu)OMe	PNB	−18.7	87
9	Asp(O*t*Bu)OMe	Bn	−26.0	75[d]
10	$Arg(Cbz)_2OMe$	Allyl	−2.6	80
11	Tyr(O*t*Bu)OMe	Allyl	+22.7	76
12	Orn(NHBoc)OMe	Bn	−18.8[b]	73[d]
13	AsnO*t*Bu	Bn	+18.6	74[d]
14	GlyOMe	Allyl	–	61[e]
15	GlyOMe	PNB	–	54[e]

[a] $[\alpha]_D^{25}$ (*c* 1.0, MeOH).
[b] $[\alpha]_D^{25}$ (*c* 0.5, MeOH).
[c] Isolated yields after silica gel chromatography.
[d] The dialkylated product was obtained in 4–5% yields, respectively.
[e] The dialkylated product was obtained in 10–15% yields, respectively.

However, an acid salt form (e.g. HCl salt) of the *N*-alkylated amino esters is recommended for a longer period of storage.

We then screened a variety of activated and unactivated alkyl halides under the LiOH-promoted alkylation conditions. As depicted in Table 4, when alkylation with iodomethane, propargyl bromide, benzyl bromide, 2-nitrobenzyl bromide and methyl bromoacetate were examined, all but one provided high yields of the monoalkylated products (entries 2–5). In the case of alkylation with iodomethane, a very low yield of the desired *N*-monoalkylated product was obtained, extensive dialkylation (30%) being a major side reaction (entry 1). Reactions with unactivated alkyl bromides such as 3-butenyl bromide and isopropyl bromide were examined and a modest yield of desired product was obtained in the former case (entry 6). However, no reaction proceeded with sterically hindered isopropyl bromide even for 48 h and unreacted starting material was recovered (entry 7).

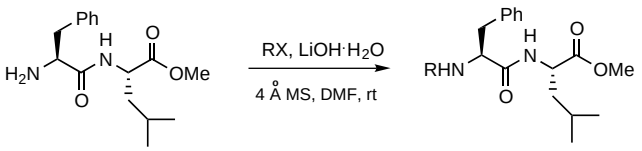
Table 4. Alkylation of phenylalanine methyl ester hydrochloride with various alkyl halides



Entry	RX	Reaction time (h)	$[\alpha]_D^{25}$ [a]	Yield (%)[c]
1	Iodomethane	36	+27.9[b]	22[d]
2	Propargyl bromide	24	+9.3	80
3	Benzyl bromide	12	−6.1	87
4	2-Nitrobenzyl bromide	12	+14.5	90
5	Methyl bromoacetate	24	+6.5	86
6	3-Butenyl bromide	24	+12.2[b]	52[e]
7	Isobutyl bromide	48	–	0

[a] $[\alpha]_D^{25}$ (*c* 1.0, MeOH).
[b] $[\alpha]_D^{25}$ (*c* 0.5, MeOH).
[c] Isolated yields after silica gel chromatography.
[d] The dimethylated product was obtained in 30% yield.
[e] The dimethylated product was obtained in 10% yield.

Table 5. Alkylation of PheLeuOMe using activated alkyl bromides



Entry	R	Reaction time (h)	Yield (%)[a]
1	2-Nitrobenzyl	24	82
2	Allyl	24	70

[a] Isolated yields after silica gel column chromatography.

With the efficient *N*-alkylating protocol for α-amino esters in hand, we investigated the possibility of extending this methodology to the alkylation of a dipeptide ester derivative. As shown in Table 5, when we examined the alkylation of PheLeuOMe using 2-nitrobenzyl bromide or allyl bromide, we were pleased to find that selective *N*-monoalkylation went smoothly to provide 82 and 70% yields, respectively, of the desired *N*-monoalkylated products (entries 1 and 2).

In summary, an efficient and economical protocol has been developed for chemoselective *N*-alkylation of α-amino esters with activated alkyl bromides except for methyl iodide employing lithium hydroxide as a base. Various α-amino esters could be selectively monoalkylated under the reaction conditions. A variety of activated alkyl groups including propargyl, benzyl, 2-nitrobenzyl and methoxycarbomethyl groups could be alkylated to the amino groups of α-amino esters in high yields. Alkylation with unactivated alkyl bromides has not been as successful. Selective *N*-monoalkylation of a representative dipeptide ester was also successful with allyl bromide and 2-nitrobenzyl bromide. Further studies on the scope of this reaction both in solution and solid phase are in progress and will be reported in due course.

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References

1. (a) Yang, J.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 9090; (b) Feng, Y.; Wang, Z.; Jin, S.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 10768; (c) Soth, M. J.; Nowick, J. S. *J. Org. Chem.* **1999**, *64*, 276.
2. (a) Sutton, P. W.; Bradley, A.; Elsegood, M. R. J.; Farrás, J.; Jackson, R. F. W.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 2629; (b) Pettit, G. R.; Srirangam, J. K.; Herald, D. L.; Erickson, K. L.; Doubek, D. L.; Schmidt, J. M.; Tackett, L. P.; Bakus, G. L. *J. Org. Chem.* **1992**, *57*, 7217; (c) Yang, L.; Morriello, G. *Tetrahedron Lett.* **1999**, *40*, 8193.
3. (a) *Combinatorial Peptide and Nonpeptide Libraries*; Jung, G., Ed.; VCH: New York, 1996; (b) *Combinatorial Chemistry*; Wilson, S. R.; Czarnik, A. W., Eds.; Wiley: Singapore, 1997; (c) *Combinatorial Chemistry and Molecular Diversity*; Gordon, E. M.; Kerwin, J. E., Jr., Eds.; Wiley-Liss: Singapore, 1998; (d) *Solid-Phase Synthesis*; Kates, S. A.; Albericio, F., Eds.; Marcel Dekker: New York, 2000.

4. Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Org. Lett.* **1999**, *1*, 1893.
5. Marson, C. M.; Hobson, A. D. In *Comprehensive Organic Functional Group Transformations*; Katrizky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds. Alkylnitrogen compounds: amines and their salts. Elsevier: New York, 1995; Vol. 2, pp. 297–332.
6. A 3:1 mixture of mono- versus dialkylated products were obtained in the alkylation of 2-phenylethylamine according to Ref. 4.
7. Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Elsevier: London, 1991; Vol. 2, p. 99.
8. General experimental procedure: To activated 4 Å molecular sieve powder (1.0 g) in DMF (10.0 mL) was added lithium hydroxide monohydrate (0.16 g, 3.79 mmol) and then the suspension was vigorously stirred for 20 min. L-Phenylalanine methyl ester hydrochloride (0.38 g, 1.76 mmol) was added and the mixture was additionally stirred for 45 min. To the white suspension was added *p*-nitrobenzyl bromide (0.46 g, 2.13 mmol) and then the mixture was allowed to stir for 12 h at room temperature. After filtration through a sintered glass filter to remove insoluble inorganic salts and washing the residue several times with EtOAc, the combined filtrate was washed with water (3×20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on silica gel column (hexane:EtOAc, from 6:1 to 4:1 v/v) to give the secondary amino ester derivative (0.52 g, 1.67 mmol, 95% yield) as a pale yellow oil. $R_f = 0.20$ (hexane:EtOAc = 4:1 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 2H, $J = 8.8$ Hz), 7.33 (d, 2H, $J = 8.8$ Hz), 7.29 (m, 3H), 7.17 (m, 2H), 3.94 (d, 1H, $J = 14.7$ Hz), 3.70 (d, 1H, $J = 14.7$ Hz), 3.69 (s, 3H), 3.46 (dd, 1H, $J = 5.8$, 7.7 Hz), 3.02 (dd, 1H, $J = 5.8$, 13.5 Hz), 2.91 (dd, 1H, $J = 7.7$, 13.5 Hz), 1.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.17, 147.92, 147.44, 137.61, 129.68, 128.93, 128.84, 127.24, 123.89, 62.48, 52.25, 51.53, 40.18; IR (KBr, neat, cm^{-1}) 3343, 3062, 3028, 2949, 2849, 1735, 1602, 1519, 1453, 1346, 1202, 1173, 853, 741, 701; HRMS (FAB) calcd for $C_{17}H_{19}N_2O_4$ ($M+H^+$) 315.1346, found 315.1349.