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Cesium Hydroxide Promoted Chemoselective *N*-Alkylation for the Generally Efficient Synthesis of Secondary Amines

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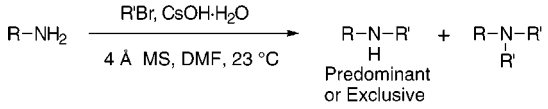
ABSTRACT



Selective *N*-alkylation of primary amines was developed using cesium hydroxide to prepare various secondary amines efficiently. A cesium base not only promoted monoalkylations of primary amines but also suppressed overalkylations. Various amines and alkyl bromides were examined, and the preliminary results demonstrated this methodology was highly chemoselective, favoring mono-*N*-alkylation over dialkylation. In particular, use of amino acid derivatives afforded the desired secondary amines exclusively.

Secondary amines, which are widely utilized in various fields, are important in many organic syntheses.[1] The synthetic approaches to secondary amines from primary amines include reductive alkylation,[2] the use of protecting groups,[3] and direct *N*-alkylation.[4] However, these methods are limited in application because of concomitant overalkylations to tertiary amines and quartenary ammonium salts. While reductive alkylation is known to be a reliable method, it is often accompanied by overalkylation.[2a] Traditional methods typically use protecting groups during amine alkylations by routes which require lengthy sequences.

Direct *N*-alkylation techniques are also inefficient due to overalkylations, and the most practical method is to use a large excess of an amine, which is often expensive. Overalkylations are still observed to a considerable extent under these conditions. In an effort to circumvent this chronic problem, we embarked on a cesium hydroxide mediated *N*-alkylation procedure, which exhibited enhanced chemoselectivities in amine alkylations compared to the previously reported protocols.

In our laboratories, Williamson-type ether synthesis was investigated in the presence of cesium hydroxide and tetrabutylammonium iodide to prepare various aliphatic ethers efficiently.[5] As delineated in Scheme 1, the represen-

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(2) (a) Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720 and references therein. (b) Pillai, R. B. C. *J. Mol. Catal.* **1993**, *84*, 125. (c) Gribble, G. W.; Nutaitis, C. F. *Synthesis* **1987**, 709. (d) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766. (e) Marchini, P.; Liso, G.; Reho, A. *J. Org. Chem.* **1975**, *40*, 3453. (f) Rische, T.; Kitsos-Rzychon, B.; Eilbracht, P. *Tetrahedron* **1998**, *54*, 2723.

(3) (a) Phanstiel, IV, O.; Wang, Q. X.; Powell, D. H.; Ospina, M. P.; Leeson, B. A. *J. Org. Chem.* **1999**, *64*, 803. (b) Croce, P. D.; La Rosa, C.; Ritieni, A. *J. Chem. Research (S)* **1988**, 346.

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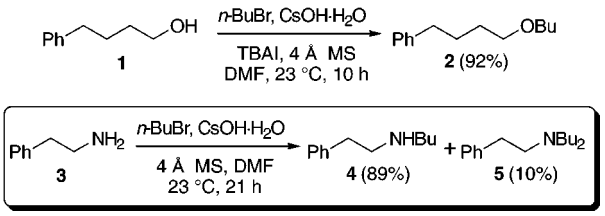
Scheme 1



tative example demonstrates the mild conditions for the preparation of ether **2**. Subsequently, we applied this technology to *N*-alkylation, anticipating high chemoselectivity. With the use of the amine as a limiting reagent, *N*-alkylation of phenethylamine (**3**) with 1-bromobutane was conducted to probe the optimal reaction conditions, under which secondary amine **4** was produced in high yield. Observed selectivity between mono- and dialkylations (9:1, respectively) was superior to existing methods.[1] It was also found that dry powdered 4 Å molecular sieves accelerated the alkylation by removal of water from the reaction media.[6] Overall, the reaction was remarkably facile and selective compared to the known conditions.

Among the cesium bases examined, cesium hydroxide monohydrate, in general, gave the highest yields and selectivities although cesium carbonate also worked well, depending on substrates.[6] To confirm the possible cesium effect, defined by the enhanced reactivities in the presence of cesium salts,[7] comparative studies between cesium bases and other bases were performed, demonstrating that cesium hydroxide was superior to other alkali bases tried with the regard to the observed chemoselectivities. As depicted in Table 1, other alkali hydroxides produced moderate yields

Table 1. *N*-Alkylation Utilizing Different Bases

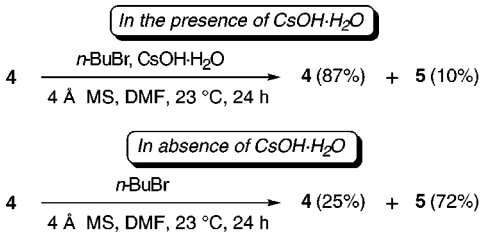
3 —(*n*-BuBr, MOH, 4 Å MS; DMF, 23 °C, 18 h)→ **4** + **5**

entry	base	yield (**4**)	yield (**5**)	ratio (4/5)
1	LiOH	62%	21%	3/1
2	NaOH	51%	26%	2/1
3	KOH	55%	29%	2/1
4	RbOH	65%	24%	3/1
5	$CsOH·H_2O$	89%	10%	9/1

of the desired product along with a considerable amount of the tertiary amine **5**, whereas cesium hydroxide allowed for a greater selectivity of 9/1 in preference for the monoalkylation product **4**. It was apparent that an unprecedented "cesium effect" in *N*-alkylation was observed as seen in *O*-alkylation.[7]

Interestingly, the next comparative study implied that the cesium base not only promoted *N*-alkylation of primary amines, but also inhibited the formation of tertiary amines. As illustrated in Scheme 2, the intended alkylation of

Scheme 2



secondary amine **4** was very sluggish under our conditions, affording the tertiary amine **5** in only 10% yield, whereas 72% of **5** was obtained along with the recovery of 25% of **4** in absence of cesium hydroxide after the same duration. Under our cesium base promoted *N*-alkylation conditions, primary and secondary amines exhibited opposing reactivities, suggesting that the improvement of chemoselectivity would stem mainly from the retarded overalkylation or reversal of normally observed alkylation rates.[8]

When various solvents were examined, *N*,*N*-dimethylformamide was found to be the solvent of choice as represented in Table 2. Several solvents such as dimethyl

Table 2. Use of Various Solvents in Cesium Base Promoted *N*-Alkylation of **3**

entry	solvent	yield (**4**)	yield (**5**)	ratio (4/5)
1	DMF	89%	10%	9/1
2	DMSO	70%	11%	7/1
3	NMP	82%	10%	8/1
4	DMAC	75%	13%	6/1

* In other solvents such as CH_3NO_2, CH_3CN, EtOH, Et_2O, acetone, $PhCH_3$, and CH_2Cl_2, the reactions were sluggish and the starting material **3** was recovered predominantly.

sulfoxide, 1-methyl-2-pyrrolidinone, and *N*,*N*-dimethylacetamide were comparable to DMF in terms of the yields of **4** and the selectivities of **4** over **5**. It is worthy to mention that high chemoselectivity was observed regardless of solvent choice. On the contrary, the reactions were sluggish in most other solvents including acetonitrile and dichloromethane. Next, various bromides and amines were subjected to *N*-alkylations under the standard conditions to evaluate the efficiency and the chemoselectivity in general.

(5) For our *O*-alkylations, see: (a) Dueno, E. E.; Chu, F.; Kim, S.-I.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1843. (b) Chu, F.; Dueno, E. E.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1847. (c) Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W. *J. Org. Chem.* **1999**, *64*, 4578. (d) Parrish, J. P.; Sundaresan, B.; Jung, K. W. *Synth. Commun.* **1999**, *29*, 4423.

(6) When molecular sieves were not activated, yields and selectivities diminished. Further studies on optimization of reaction conditions will be subject to future publication in the format of a full paper.

(7) Galli, C. *Org. Prep. Proced. Int.* **1992**, *24*, 287 and references therein.

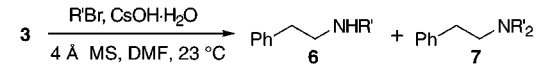
As demonstrated in Table 3, the newly developed techniques were compatible with various bromides, both active and unreactive. Unreactive bromide such as **8** and active bromides including benzyl and allyl bromides gave similar results[9] to the standard reaction shown in Scheme 1 while *N*-alkylation with active halides proceeded efficiently with use of a catalytic amount of cesium hydroxide. Introduction of a small degree of sterics such as an isobutyl moiety gave rise to the exclusive synthesis of the monoalkylation product in good yield (entry 4). Secondary bromides also led to the exclusive formation of secondary amines as expected (entries 5 and 6). Keeping the theme of peptidomimetics and chiral auxiliaries in mind, amino bromides[10] such as **9** and **10** were subjected to our conditions, successfully affording the desired *N*-alkylation products without concomitant production of the overalkylated products.[9]

Primary and secondary bromides were generally applicable to this methodology. As predicted, tertiary bromides were resistant to alkylations under our conditions. One crucial feature embedded in this protocol is the excellent chemoselectivity, where most added bromides delivered only the mono-*N*-alkylated product **6**. Unhindered primary bromides still bestowed high chemoselectivities compared to the previously reported methods.

Similar trends were noted in varying amines as shown in Table 4. Primary and secondary alkyl groups offered secondary amines **11** as major products (entries 1−4), whereas sterically demanding aliphatics furnished the desired products exclusively (entries 5−8). CsOH promoted *N*-alkylations of sterically hindered amines were facile and pragmatic, whereas the known methodologies were inefficient to complete conversions or required extremely prolonged reaction times.[3,4] To our surprise, synthesis of lipophilic secondary amines was completely selective (entry 9), which was presumably due to the produced hydrocarbons residing on the cesium surface.

Next, our attention was directed toward *N*-alkylation of amino acid derivatives due to demand in numerous syntheses (Table 5).[11] *N*-Alkylation of *β*-amino ether **13** gave rise to the mixture of secondary and tertiary amines in 84% and

Table 3. *N*-Alkylation using Various Bromides



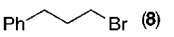
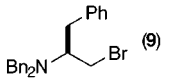
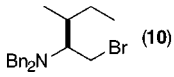
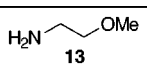
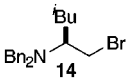
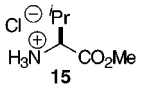
entry	bromide (R'Br)	CsOH	time	6	7
1	 (**8**)	1 eq	24 h	85%	10%
2	BnBr	0.1 eq	4 h	85%	15%
3	allyl bromide	0.1 eq	4.5 h	85%	15%
4	isobutyl bromide	3 eq	24 h	74%	none
5	isopropyl bromide	3 eq	24 h	70%	none
6	2-bromobutane	3 eq	48 h	80%	none
7	 (**9**)	1 eq	28 h	45%	none
8	 (**10**)	1 eq	36 h	54%	none

Table 4. *N*-Alkylation using Various Amines

entry	amine (RNH_2)	bromide (R'Br)	**11**	**12**
1	$PhCH_2NH_2$	1-bromooctane	75%	13%
2	$C_6H_{11}CH_2NH_2$	**8**	90%	10%
3	cyclopropylamine	**8**	83%	12%
4	cyclooctylamine	**8**	75%	10%
5	1-admantanamine	**8**	82%	none
6	1-admantanamine	(*E*)-cinnamyl bromide	66%	none
7	*tert*-butylamine	**8**	90%	none
8	*tert*-octylamine	BnBr*	87%	none
9	octylamine	1-bromobutane	93%	none

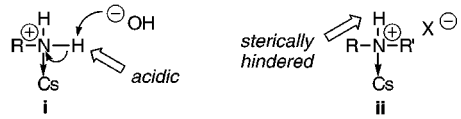
* The *N*-alkylation with benzyl bromide was run for 12 hours.

Table 5. Chemoselective *N*-Alkylation of Amino Acid Derivatives in the Presence of $CsOH·H_2O$

entry	amine (RNH_2)	bromide (R'Br)	conditions[a]	yield[b]
1[c]	 **13**	**8**	1 eq, 22 h	84%
2	Valinol	BnBr	0.1 eq, 12 h	74%
3	Leucinol	 **14**	1 eq, 14 h	60%
4	 **15**	5-bromo-1-pentene	1.1 eq, 5 h	65%
5		allyl bromide	1.1 eq, 10 h	67%
6		BnBr	2 eq, 4.5 h	68%

[a] Representing the equivalent of CsOH and reaction time.
[b] Isolated yield of the mono *N*-alkylation product.
[c] Less than15% of dialkylation product was also obtained.

(8) Rationale for reversal of normally observed alkylation rates is proposed to orginate from the amine−cesium ion complexes. Amine protons in complex **i** should be sufficiently acidic to be abstracted by bases. On the other hand, owing to the increased sterics in quatenary salt **ii** compared to **i**, access of bases to available protons would be minimized, inhibiting the alkylation of secondary amines.



(a) Constable, E. C. In *Metals and Ligand Reactivity*; VCH Publishers: New York, 1996; p 102. (b) Dehmlow, E. V.; Thieser, R.; Zahalka, H. A.; Sasson, Y. *Tetrahedron Lett.* **1985**, *26*, 297. (c) Santhanalakshmi, J.; Raja, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2829. (d) Ando, T.; Yamawaki, J. *Chem. Lett.* **1979**, 45. (e) Onaka, M.; Ishikawa, K.; Izumi, Y. *Chem. Lett.* **1982**, 1783. (f) Blum, Z. *Acta Chem. Scand.* **1989**, *43*, 248. (g) Soong, L.-L.; Leroi, G. E.; Popov, A. I. *J. Solut. Chem.* **1989**, *18*, 561.

15%, respectively, presumably mimicking the aforementioned unhindered amines. However, when amino alcohols[12] encompassing valinol and leucinol were reacted with active or unreactive bromides (entries 2 and 3), chemoselectivities were excellent and the secondary amines were obtained in satisfactory yields. As discussed above, only a catalytic amount of cesium hydroxide was necessary with the employment of benzyl bromide to afford the dialkylamine in good yield. Remarkablly, no *O*-alkylation was observed, and as a result, the hydroxyl group was left intact.

Amino esters such as valine ester **15** were also smoothly converted to the corresponding monoalkylated products with various bromides (entries 4−6). To investigate possible side pathways, reactions were performed intentionally under relatively harsh conditions, for longer duration (entry 5) and excess cesium hydroxide (entry 6). Racemizations were not detected in alkylations of chiral substrates,[13] and complications stemming from hydrolysis and subsequent esterification were not experienced to a detectable extent. Thus, our developed protocols are mild, efficient, and chemoselective, averting common side reactions under basic conditions. Another noteworthy feature is the ability to carry out this C−N bond formation without the use of protecting groups as demonstrated in entries 3−6, allowing for efficient peptidomimetic syntheses.

In summary, cesium hydroxide promoted *N*-alkylation of primary amines gives rise to the predominant or exclusive synthesis of secondary amines, which are otherwise difficult to prepare. This account illustrates a powerful potential since the selective alkylation of various amines and amino acid derivatives is carried out in a single step without the use of unnecessary protecting groups. Furthermore, the reaction conditions are mild and general, and the chemoselectivities are greatly enhanced over the existing methods. Procedures are also simple, convenient, and inexpensive, offering alternatives in both laboratory- and industrial-scale preparations.[14] It is strongly believed that this technology will be of great significance as a solution to the existing problems in numerous *N*-alkylations, providing a general synthetic methodology. Further studies into the mechanism[8] and applications of these techniques will be reported in due course.

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(9) Side reactions including elimination were not observed within our detection limits.

(10) Bromination of the corresponding dibenzylamino alcohols was developed in our laboratories, which will be published elsewhere. We found that DMF catalyzed bromination using thionyl bromide in cyclohexane, and the desired product was easily isolated on an even larger scale by either precipitation as the hydrobromide salt or separation of the DMF layer containing only the desired bromide.

(11) (a) Gray, B. D.; Jeffs, P. W. *J. Chem. Soc., Chem. Commun*. **1987**, 1329. (b) Bhatt, U.; Mohamed, N.; Just, G. *Tetrahedron Lett.* **1997**, *38*, 3679. (c) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095. (d) Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787.

(12) (a) Andrés, J. M.; Barrio, R.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem*. **1996**, *61*, 4210. (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 1141.

(13) Optical rotations of the synthetic samples were matched with the known values; see ref 11d. Observed values for pentenyl and benzyl derivatives were −49.5° and −10.0°, respectively, whereas the reported values were −50.2° and −9.9° for the same compounds.

(14) **Representative Experimental Procedure:** To activated powdered 4 Å molecular sieves (500 mg) in anhydrous *N*,*N*-dimethylformamide (8.3 mL), was added cesium hydroxide monohydrate (280 mg, 1.7 mmol), and then the white suspension was vigorously stirred for 10 min. After phenethylamine **3** (0.21 mL, 1.7 mmol) was added and followed by additional 30 min of stirring, 1-bromobutane (0.21 mL, 2.0 mmol) was added into the white suspension. The reaction was stirred for 20 h, filtered to remove the molecular sieves and undissolved inorganic salts, and rinsed several times with EtOAc. After the filtrate was concentrated to a nominal volume by blowing air, the residue was taken up in 1 N NaOH, and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (EtOAc−EtOH, 9:1 v/v) afforded the secondary amine **4** (260 mg, 1.5 mmol; 89%) as a colorless oil as well as tertiary amine **5** (40 mg, 0.17 mmol; 10%) as a pale yellow oil.