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Efficient synthesis of β-amino bromides

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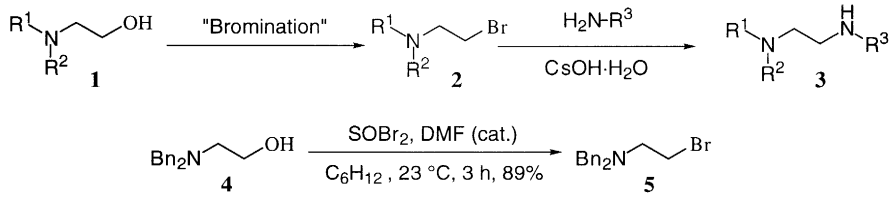
Abstract

β-Aminoalcohols were smoothly converted to β-amino bromides using thionyl bromide and DMF, which were easily isolated without any further purification. Participation by the β-amino group in brominations not only enhanced reaction rates but also promoted stereo- and regioselectivities. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: thionyl bromide; DMF; β-amino bromide; bromination; aziridinium salt.

β-Aminoalcohols and their derivatives have played seminal roles in peptidomimetic synthesis,[1] while serving as important precursors for a variety of uses.[2] During our synthesis of peptidomimetic analogs,[3] *N*,*N*-dibenzylamino bromides **2** emerged as key intermediates, which could be prepared from the corresponding β-aminoalcohols **1** (Scheme 1). Surprisingly, an extensive literature search revealed that few methods have been reported for the preparation of amino bromides. Reaction conditions were typically harsh,[4] and milder conditions gave low to moderate yields or rather unexpected products.[5] Thus, these methods lack in generality for the synthesis of amino bromides, prompting us to embark on a new bromination protocol particularly suited for β-aminoalcohols.



Scheme 1.

N,*N*-Dibenzylamino ethanol **4** was smoothly converted to the desired bromide **5** in high yield by reacting with thionyl bromide and DMF. The product was spectroscopically pure and no further purification was needed.[6] The addition of *N*,*N*-dimethylformamide as a catalyst was found to accelerate the reaction

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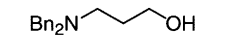
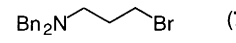
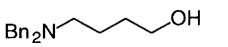
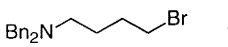
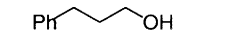
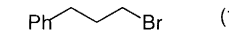
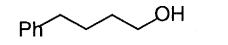
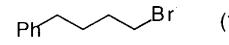
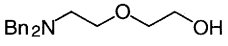
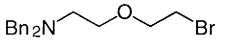
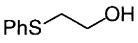
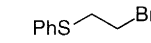
significantly through a Vilsmeier–Haack type $SOBr_2$–DMF complex. Cyclohexane was the solvent of choice, and other nonpolar solvents (hexanes and petroleum ether) also worked well. Polar solvents such as dichloromethane were avoided because undesired side reactions, including rearrangements, occasionally took place and further purifications were required.

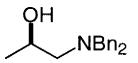
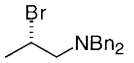
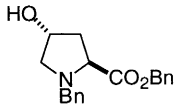
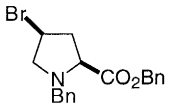
To attest our conjecture if the amino group plays a neighboring group participation role, comparative studies were performed under the developed conditions (Table 1). Similarly to 2-aminoethanol, γ- and δ-aminoalcohols underwent bromination efficiently (entries 1 and 2), whereas the reactions with higher homologues or aliphatic alcohols (entries 3 and 4) proceeded at slower paces, often affording complicated product mixtures. Other heteroatoms also facilitated brominations as shown in entries 5 and 6. These results strongly indicate that the presence of the amino group enhances the rate of bromination.

Table 1

Entry	Alcohol		Bromide		Time	Yield
1		(**6**)		(**7**)	3 h	92%
2		(**8**)		(**9**)	3 h	90%
3		(**10**)		(**11**)	5 h	87%
4		(**12**)		(**13**)	6 h	85%
5		(**14**)		(**15**)	3 h	89%
6		(**16**)		(**17**)	3 h	98%

As delineated in Table 2, stereochemical elements were examined with regards to the influence of the β-amino group. Bromination of (*R*)-1-dibenzylamino-2-propanol led to the formation of the corresponding secondary bromide **19** with inversion at the C(2) center (entry 1).[7] Likewise, complete inversion was observed with nitrogen heterocycles such as **20** although the conversion was sluggish. In the case of 1-dibenzylamino-2-cyclohexanol (entries 3 and 4),[8] both diastereomers interestingly

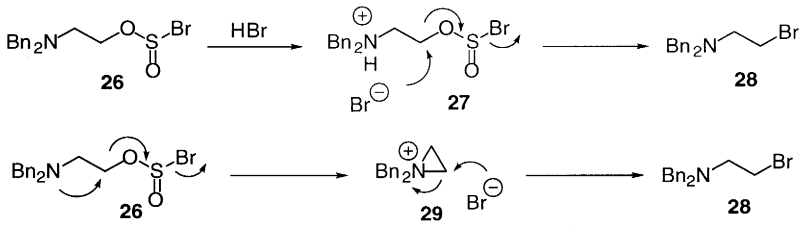
Table 2

Entry	Alcohol		Bromide *		Time	Yield
1		(**18**)		(**19**)[a]	3 h	91%
2		(**20**)		(**21**)[b]	10 h	50%
3	*trans*-1-dibenzylamino-2-cyclohexanol	(**22**)	*trans*-1-dibenzylamino-2-bromocyclohexane	(**23**)[c]	7 h	85%
4	*cis*-1-dibenzylamino-2-cyclohexanol	(**24**)	*trans*-1-dibenzylamino-2-bromocyclohexane	(**23**)[c]	27 h	65%
5	*cis*-2-dibenzylamino-1-indanol	(**25**)	No Reaction		24 h	

Stereochemistry was assigned on the basis of : a) (*S*)-MTPA ester. [7] b) ^{1}H NMR analysis. c) ^{1}H NMR analysis (J =11 Hz, 3.1 Hz; *Br*-CH) and (J =9.2 Hz, 3.1 Hz; *N*-CH). *Other isomers were not observed .

gave the *trans* isomer **23** while the reaction rate was noticeably slow with the *cis* isomer **24**.[7] As envisioned, aminoindanol **25** was also resistant to bromination, presumably due to lack of the amino group participation.

This unusual set of results, coupled with the results in Table 1, lend further credence to the fact that the neighboring amino group facilitates the reaction rates (Scheme 2). It is postulated that bromosulfite ester **26** can be protonated by in situ generated HBr to form hydrobromide salt **27**, which allows internal delivery of the bromide nucleophile, accounting for rate enhancement as well as stereochemical inversion. Conversely, when the dibenzylamino group is located at the secondary center, **26** would form the aziridinium salt **29** perhaps to relieve the steric strain, resulting in the double inversion as observed with the *trans*-aminocyclohexanol **22**. With *cis* isomers in rigid systems (**24** and **25**), neither of these internal assistance can be anticipated, where the intermolecular delivery of the bromide nucleophile is expected to be sluggish and dependent on steric demand.



Scheme 2.

Next, our attention was directed towards bromination of aminoalcohols with the amino group at the secondary center, which would allow translocation through aforementioned aziridinium salts (Table 3).[7] Diprotected aminoalcohols including **30** and **32** led to the exclusive formation of the rearranged amino bromides with complete stereochemical inversion at the secondary centers.[9] Similar results were observed for differently substituted aminoalcohols, even in the presence of ester functionality (entry 3) and the prolinol derivative **36** underwent ring expansion to afford piperidine derivative **37** (entry 4). As illustrated in entry 5, monoprotected aminoalcohol **38** also provided a rearranged product **39** exclusively.

On the contrary, in the absence of nitrogen protecting groups, a variety of aminoalcohols gave rise to the exclusive formation of hydrobromide salts (entry 6), which were easily isolated from the reaction media by simple filtration. Neither rearrangement nor aziridine ring formation was observed, implying that rapid protonation would secure internal delivery of bromide prior to cyclization. Due to mild reaction conditions, ester functionality was left intact to offer the desired bromide in high yield (entry 7).

In conclusion, we have developed a convenient and efficient protocol for the conversion of aminoalcohols to the corresponding bromides. Both primary and secondary alcohols were smoothly converted to bromides in high yields, and purification processes were not necessary. Furthermore, the amino group was found to facilitate the bromination of alcohols in their vicinity, thus offering high regio- and stereoselectivities. In our laboratories, a variety of amino bromides have been synthesized, and their applications will be reported in due course.

Acknowledgements

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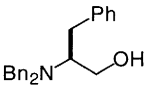
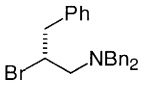
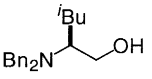
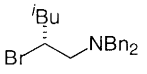
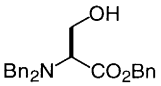
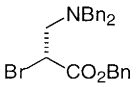
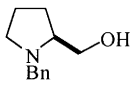
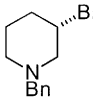
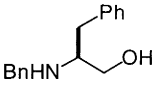
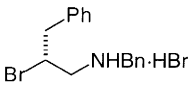
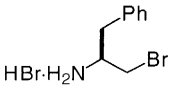
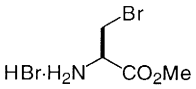
Table 3

Entry	Alcohol		Bromide		Time	Yield
1		(**30**)		(**31**)	3 h	90%
2		(**32**)		(**33**)	3 h	93%
3		(**34**)		(**35**)	4 h	92%
4		(**36**)		(**37**)	8 h	80%
5		(**38**)		(**39**)	5 h	82%
6	L-Phenylalaninol	(**40**)		(**41**)	4 h	85%
7	L-Serine methyl ester hydrochloride	(**42**)		(**43**)	4 h	86%

Compounds **31** and **33** were used as substrates for *N*-alkylation and carbamation reactions using chiral amines. In each case, the product was obtained as a single diastereomer.

References

1. For various examples, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835 and references cited therein.
2. For comprehensive reviews on aminoalcohols and related compounds, see: (a) see Ref. 1. (b) Reetz, M. T. *Chem. Rev*. **1999**, *99*, 1121. (c) Sardina, F. J.; Rapoport, H. *Chem. Rev*. **1996**, *96*, 1825.
3. For our *N*-alkylation, see: Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Org. Lett*. **1999**, *1*, 1893.
4. Cortese, F. *Organic Syntheses*; John Wiley: New York, 1943; Vol. II, pp. 91–93.
5. Chandrasekhar, S.; Mohanty, P. K.; Harikishan, M. K.; Sasmal, P. K. *Org. Lett.* **1999**, *1*, 877.
6. Representative experimental procedure: Into the opalescent solution of *N*,*N*-dibenzylaminoalcohol (1 mmol) in cyclohexane (5 mL), *N*,*N*-dimethylformamide (0.5–0.6 mmol), and thionyl bromide (1.2 mmol), were added successively under a nitrogen atmosphere. The yellow reaction mixture, separated into two layers, was then stirred for 3 h at ambient temperature. The reaction suspension was diluted with dichloromethane until it became homogeneous, then the pale yellow solution was neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with water (3×5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the desired *N*,*N*-dibenzylamino bromide as a yellow oil.
7. The stereochemistry of the bromides was elucidated by either proton NMR analysis or comparison with authentic samples. Enantioselectivities and diastereoselectivities were confirmed through Mosher's esters, which were prepared with (*S*)-MTPA acid using our cesium base promoted *O*-alkylation techniques. For our *O*-alkylations, see: (a) Parrish, J. P.; Sundaresan, B.; Jung, K. W. *Synth. Commun*. **1999**, *29*, 4423. (b) Dueno, E. E.; Chu, F.; Kim, S.-I.; Jung, K. W. *Tetrahedron Lett*. **1999**, *40*, 1843. (c) Chu, F.; Dueno, E. E.; Jung, K. W. *Tetrahedron Lett*. **1999**, *40*, 1847. (d) Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W. *J. Org. Chem*. **1999**, *64*, 4578.
8. *cis*-2-Aminocyclohexanol was prepared from the *trans* isomer. (a) Leffler, M. T.; Adams, R. *J. Am. Chem Soc*. **1937**, *59*, 2252. (b) McCasland, G. E.; Clark Jr., R. K.; Carter, H. E. *J. Am. Chem. Soc*. **1949**, *71*, 637.
9. Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766.