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CsOH-promoted chemoselective mono-*N*-alkylation of diamines and polyamines

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Abstract

Selective *N*-alkylation of diamines and polyamines was carried out using cesium hydroxide, 4 Å molecular sieves, and DMF. This protocol was highly chemoselective, favoring mono-*N*-alkylation over overalkylations. © 2000 Published by Elsevier Science Ltd.

Naturally occurring diamines and polyamines have attracted considerable attention in synthetic organic chemistry due to their interesting biological activities,[1] potential pharmacological applications,[2] and asymmetric catalysis.[3] However, their synthetic use is quite limited mainly due to lack of efficient methods for monofunctionalization, although this problem has been averted by employing amines in large excess, which can be rather expensive. Recently, we reported a cesium hydroxide-promoted chemoselective protocol for the mono-*N*-alkylation of a primary amine,[4] and discussed herein is the application of this methodology to diamines and polyamines, resulting in high chemoselectivity.

In our laboratories, we set out to synthesize 1,8-diamino-3-thia-6-azaoctane (NNSN) **3**, in efforts to study metal complexation effects with cobalt(III)[5] (Scheme 1). Although extensive studies for the synthesis of this compound have been reported, they lack in efficiency since the procedures are toxic[6] and low yielding.[7] In our initial synthesis, 2-thioethylamine·HCl **1** and *N*-(2-bromoethyl)phthalimide **2** were reacted using potassium carbonate in refluxing acetonitrile[8] to afford the coupled product in low yield. Upon deprotection of the phthalimide moiety, NNSN was produced in extremely low yield (9% yield over two steps), and other side products were formed concomitantly. Much to our surprise, the *N*-alkylation in the presence of cesium carbonate proved more problematic, and the desired product was not produced. As demonstrated using a model substrate such as phenethylamine **5**, 2-oxazoline **6** was isolated along with cyclic amide **7**, stemming from aminolysis followed by intramolecular alkylations.

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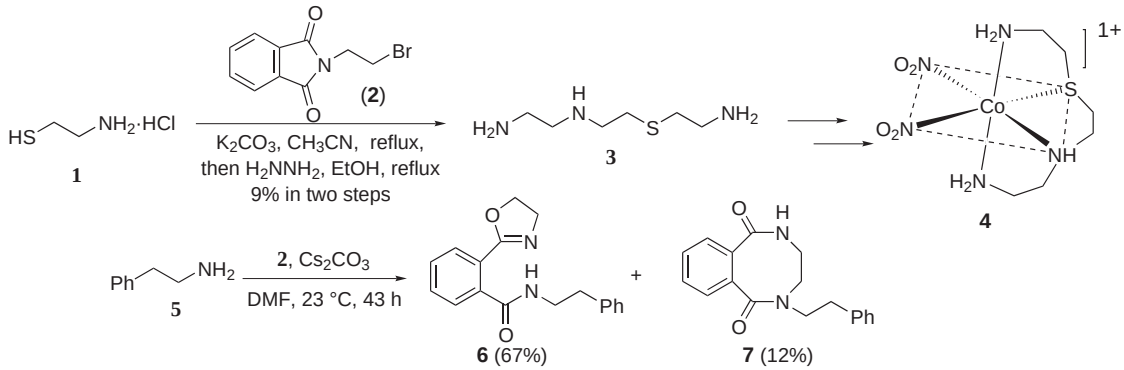
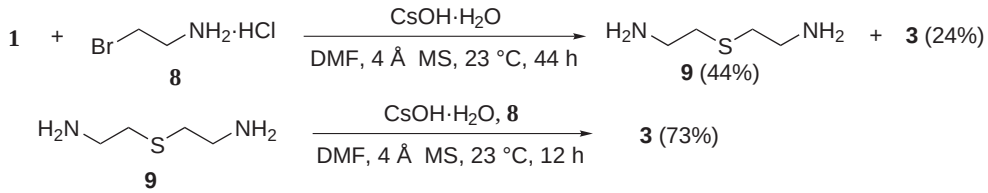


Scheme 1.

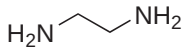
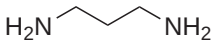
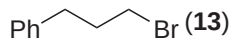
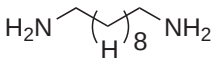
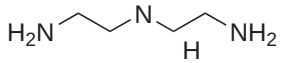
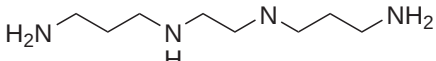
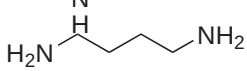
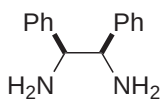
In order to avoid aminolysis, unmasked electrophiles including 2-bromoethylamine·HBr **8** were screened using a variety of bases, which met with failure. However, when CsOH was employed (Scheme 2),[4] the *S*-alkylated product **9** and the desired product **3** were acquired in 44 and 24% yields, respectively. In addition, NSN **9** was recycled for direct *N*-alkylation to deliver NNSN **3** predominantly in 73% isolated yield (56% combined yield), which is far superior to the existing methods.[9] It is noteworthy that the improved yield originated from the high chemoselectivity in the monoalkylation of diamine **9**, prompting us to further develop this technique for general applications.



Scheme 2.

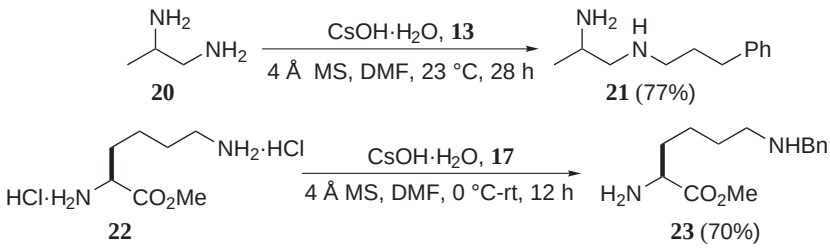
As representatively depicted in Table 1, various electrophiles as well as numerous diamines and polyamines were subjected to the *N*-alkylation conditions to evaluate the efficiency and chemoselectivity. In the presence of a catalytic amount of CsOH (0.5 equiv.), ethylene diamine was found to react with TsCl to produce the *N*-sulfonamide in high yield. Similarly, unreactive bromide **13** reacted with symmetrical diamines including **12** and **14** (entries 2 and 3), offering similar yields. Polyamines encompassing diethylenetriamine **15** still proved pragmatic, reacting at the primary amine and leaving the secondary amine untouched (entry 4). Using a reactive halide such as benzyl chloride, bis-tetramine **16** (entry 5) and putrescine **18** (entry 6) were still facile under the developed conditions, delivering the mono-*N*-alkylated polyamine and diamine, respectively. Within our detection limits, dialkylation on the same nitrogen was not detected, and bisalkylation on the different nitrogens was minimized (<10%) by performing the reaction at 0°C. Diamines containing elements of stereochemistry were also found to be compatible. (1*R*,2*R*)-(+)-1,2-Diphenyl-1,2-ethanediamine **19** underwent *N*-benzylation, breaking the symmetrical element within the molecule (entry 7) and no overalkylation was seen. Although the starting materials were not consumed, they were usually eliminated during aqueous work-up, offering the desired mono-*N*-alkylation product predominantly in the crude product.

Table 1

entry	diamine or polyamine		halide	time	yield[a]
1		(**10**)	TsCl (**11**)	2 h	75%[b]
2		(**12**)	 (**13**)	24 h	65%
3		(**14**)	**13**	14 h	61%
4		(**15**)	**13**	24 h	58%
5		(**16**)	BnCl (**17**)	12 h	52%[c]
6		(**18**)	**17**	12 h	65%
7		(**19**)	**17**	12 h	79%

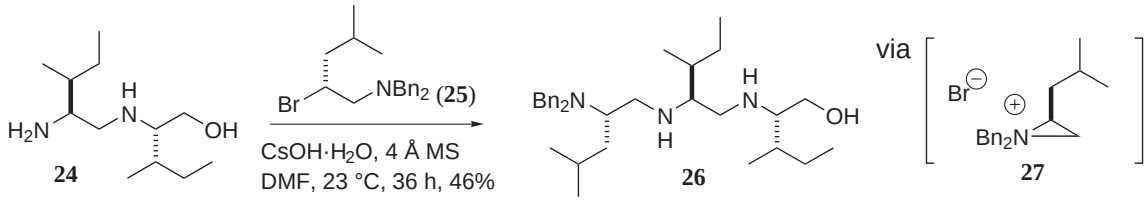
[a] Isolated yields of mono-*N*-alkylated amines. The starting amines were not consumed completely, accounting for the additional mass balance. [b] The reaction was run using a catalytic amount of CsOH at 0 °C. [c] Overalkylation was minimized by performing the reaction at 0 °C.

Unsymmetrical diamines also reacted regioselectively under the developed conditions (Scheme 3). 1,2-Diaminopropane **20** was found to alkylate exclusively at the primary amine, leaving the more sterically hindered secondary amine intact. Chiral diamine, (L)-lysine methyl ester **22**, was selectively *N*-benzylated at the primary center, and no racemization was detected.[10]



Scheme 3.

To further attest issues of chemoselectivity, *N*-alkylation of amino alcohols was performed for the preparation of higher order peptidomimetics such as trimer **26** (Scheme 4). For example, amino bromide **25** was coupled with unsymmetrical dimer **24**, where the secondary bromide was rearranged to the desired primary form via the corresponding aziridinium salt **27** during the *N*-alkylation.[11] The primary amine was found to react exclusively with the aziridinium salt, leaving the secondary amine and the alcohol functionality intact. Besides high chemoselectivity, racemizations were not detected during any alkylations of these chiral peptidomimetic substrates.[12]



Scheme 4.

In conclusion, we have developed a convenient and efficient protocol for the chemoselective mono-*N*-alkylation of diamines and polyamines using a wide variety of halides. Our protocols offered moderate to high yields, and the use of protecting groups proved to be unnecessary. Furthermore, our technology was applicable to the efficient synthesis of peptidomimetic compounds.

Acknowledgements

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9. Representative experimental procedure: To activated powdered dry 4 Å molecular sieves (5.0 g) in anhydrous *N*,*N*-dimethylformamide (45 mL), were added cesium hydroxide monohydrate (3.7 g, 22 mmol) and 1,5-diamino-3-thiopentane **9** (1.1 g, 8.8 mmol). With vigorous stirring, 2-bromoethylamine hydrobromide **8** (2.7 g, 13 mmol) was added and the mixture was stirred at room temperature for 12 h, at which time the reaction was quenched with 100 mL of 1 N NaOH. Following filtration to remove solids, the solution was concentrated by blowing air. The resulting solid was then taken up in a small amount of methanol, triturated with Et_2O, subsequently filtered, and reduced to dryness in vacuo. Trituration was repeated two more times to ensure the removal of the inorganic salts. The resulting thick yellow oil was then subjected to silica gel chromatography using 5% NH_4OH–MeOH, followed by 15% NH_4OH–MeOH, which gave **3** (1.04 g, 73% yield).
10. Product **23** was converted back to the starting diamine **22** by hydrogenolysis, followed by salt formation using dry HCl gas. The optical rotation of the resultant salt was 16.5°, whereas the reported value is 15.6° ($c=1.3$; H_2O). See: *J. Org. Chem.* **1963**, 2898.
11. Nagle, A. S.; Salvatore, R. N.; Chong, B. D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011.
12. ^1H, ^{13}C and 2-D NMR indicated the product as a single diastereomer.