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Bromodimethylsulfonium bromide (BDMS)-mediated Lossen rearrangement: synthesis of unsymmetrical ureas

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ABSTRACT

Bromodimethylsulfonium bromide (BDMS) was found to be a very efficient reagent for Lossen rearrangement of hydroxamic acids to the corresponding isocyanates which were subsequently trapped in situ with various amines to afford unsymmetrical ureas in good to excellent yields (64–89%). The protocol is experimentally simple, mild, and represents valuable alternative to the existing methods for in situ activation of hydroxamic acids promoting Lossen rearrangement.

Unsymmetrical urea derivatives have attracted significant interest due to their extensive applications in agriculture, petrochemicals, pharmaceuticals, and biology.[1] For example, Diuron (**A**) is a commercially accessible herbicide primarily used to eradicate weeds on hard surfaces (Fig. 1).[2] Structurally simple urea (**B**), possessing a morpholine ring, has displayed very effective role in the treatment of chronic myelogenous leukemia.[3] Similarly, substituted urea (**C**) proved to be a potent HIV-1 protease inhibitor[4] and (**D**) a receptor tyrosine kinase (RTK) inhibitor (Fig. 1).[5] Urea derivatives also impart important function in organic synthesis as intermediates and bifunctional organocatalysts.[6]

The synthesis of urea derivatives traditionally requires reagents based on either phosgene[7] and phosgene surrogates,[8] or starting directly from isocyanates.[9] These approaches are particularly competent for symmetrical urea derivatives. However, phosgene and isocyanates are noxious, unstable, and require special care for handling. In this regard, direct utilization of in situ-generated isocyanates offers a convenient entry into urea derivatives, especially

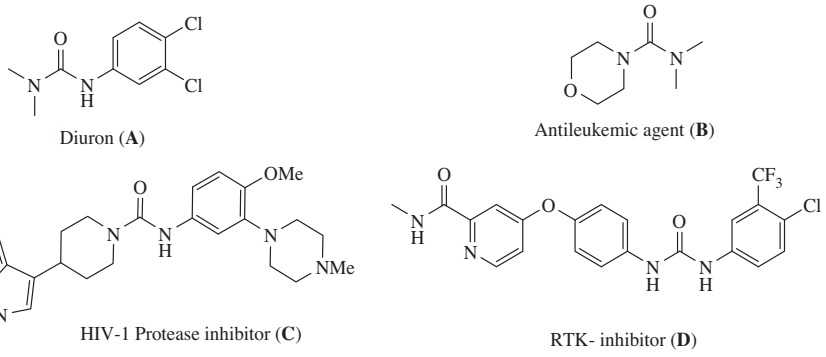

Figure 1. Biologically relevant unsymmetrical urea motifs.

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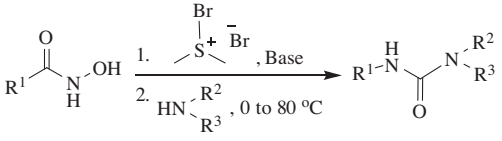
the more synthetically challenging unsymmetrically substituted ureas.[10]

The Lossen rearrangement basically involves the conversion of an O-activated hydroxamic acid into the corresponding isocyanate intermediate. Ensnaring of the isocyanate intermediate with apposite amines provides the derivatives of urea. However, the Lossen rearrangement has received comparatively little attention as a general synthetic method since its original publication.[11] The reasons for its limited use appear to be associated with complicated experimental procedure and the competing formation of self-condensation byproducts has been partially addressed by ingenious innovations.[10b,12] Thus, development of an alternative method circumventing such limitations should be welcomed among chemical communities. To overcome the dimerization[13] associated with the classical Lossen rearrangement, it would be desirable to initiate the rearrangement on the 'activated *O*-hydroxamate', after the complete consumption of the hydroxamic acid. Thus, the quest for reagents which activate hydroxamic acids via the formation of 'activated *O*-hydroxamate' under mild conditions is ongoing and there is wide scope for developing novel methods utilizing mild and efficient methodology.

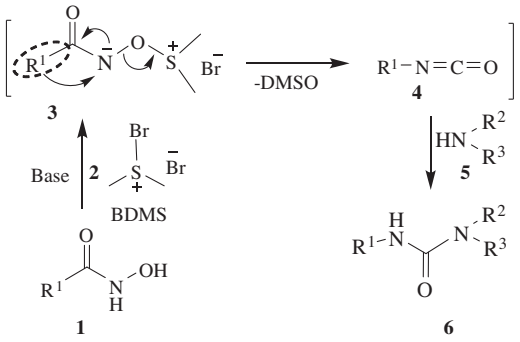
Bromodimethylsulfonium bromide (BDMS), first explored by Meerwein,[14] is a very inexpensive commercially available and easily manageable reagent with intriguing properties making its execution exceedingly attractive in organic synthesis.[15] This compound can act either as a source of molecular bromine or bromonium ions, or bromine radicals or bromide ions as well as dehydrating agent.[15a,16] Interestingly, in most of these cases the use of BDMS offered advantages compared to other classical methods in terms of cost, yield, and mildness. Thus, in the light of these results, sighting new applications for BDMS in organic synthesis are of interest. Herein, we report a simple and efficient process for the synthesis of unsymmetrical urea derivatives employing BDMS as a proficient promoter for Lossen rearrangement (Scheme 1).

Recently, our research group has illustrated the utility of BDMS in hydroxyl group activation of oximes via formation of O-activated oximates intermediate leading to the synthetic nitriles and amides.[16] These reports and our recent study[17] toward reactions involving migration to electron-deficient nitrogen atom have prompted us to investigate the possible use of BDMS as a reagent enabling the Lossen rearrangement directly from commercially available hydroxamic acids **1** via the formation of O-activated hydroxamate intermediates **3** to afford isocyanates **4**. These isocyanates could be easily captured in situ with appropriate amines **5** to give unsymmetrical ureas **6** (Scheme 2).

Initially, a pilot reaction was performed to synthesize 1-phenyl-3-*p*-tolylurea **6a** from commercially available benzhydroxamic acid **1a** and *p*-tolylamine **5a** chosen as model substrates and optimizing the general procedure with respect to solvents, bases, and reaction conditions. Thus, benzhydroxamic acid **1a** was treated with BDMS **2** in the presence of different bases in various organic solvent followed by the addition of *p*-tolylamine **5a** and the progress of the reaction was monitored by TLC. The experimental data for screening conditions are compiled in Table 1. To our amazement, we observed rapid and selective access to 1-phenyl-3-*p*-tolylurea **6a** from benzhydroxamic acid **1a** (1 mmol) and *p*-tolylamine **5a** using BDMS (1.3 mmol) and NMM (2.6 mmol) in DCE at 80 °C (Table 1, entry 9).

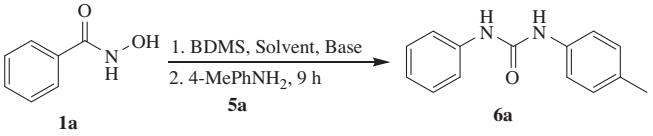


Scheme 1. Synthesis of unsymmetrical ureas utilizing BDMS.



Scheme 2. A plausible reaction pathway for Scheme 1.

Table 1
Optimization of reaction conditions for the synthesis of unsymmetrical urea via BDMS-promoted Lossen rearrangement[a]



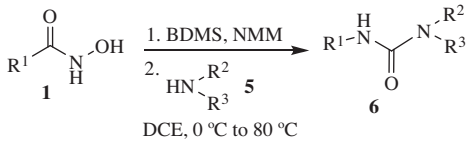
Entry	Solvent[b]	Base[c]	Temp (°C)	Yield[d] (%)
1	DCM	NMM	Reflux	<20
2	Toluene	NMM	80	45
3	THF	NMM	Reflux	72
4	EtOAc	NMM	Reflux	48
5	CH_3CN	Pyridine	80	74
6	CH_3CN	DIPA	80	71
7	CH_3CN	DIPEA	80	80
8	CH_3CN	TEA	80	70
9	**DCE**	**NMM**	80	**89**
10	CH_3CN	NMM	80	74
11	DCE	NMM	40	28
12[e]	DCE	NMM	80	64[f]
13	DCE	NMM[g]	80	36

[a] Reaction conditions: **1a** (1 mmol), BDMS **2** (1.3 mmol), base (2.6 mmol), **5a** (1.2 mmol). For experimental details, see Ref. 18.
[b] 2 mL was used.
[c] Base was added at 0 °C.
[d] Yields of the isolated pure compound.
[e] BDMS (1.0 mmol) was used.
[f] Self-condensed diphenylurea was also isolated in 27% yield.
[g] NMM (1.3 mmol) was used.

The above reaction condition was appropriate for the rearrangement and successive trapping of isocyanate intermediate **4a** with amine **5a** because when lowering the reaction temperature from 80 to 40 °C and decreasing the amount of BDMS and NMM, the yield of **6a** was noticeably reduced (Table 1, entries 11–13).

Having established the optimized reaction conditions, the generality and scope of the protocol were demonstrated across a range of hydroxamic acids **1** and amines **5** to access various unsymmetrical urea derivatives (Table 2). As evident from Table 2, both aromatic and aliphatic hydroxamic acids were equally applicable to undergo Lossen rearrangement and ensuing reaction with amines either aromatic or aliphatic in nature. Electron-rich aromatic hydroxamic acids afforded the desired products in relatively high yield in short time as compared with aromatic hydroxamic acids bearing electron-withdrawing group (Table 2, entries 14–17). This observation is in accordance with the expectation that the rate of rearrangement would be proportional to the electron density on the migrating group.[19]

Table 2
Synthesis of unsymmetrical ureas **6** via BDMS-promoted Lossen rearrangement[a]



1 **5** **6**

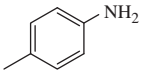
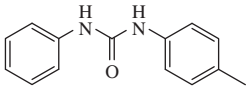
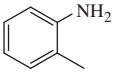
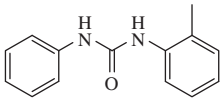
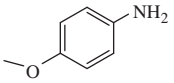
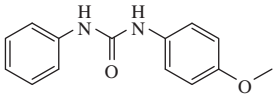
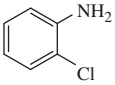
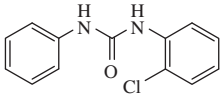
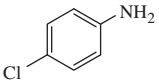
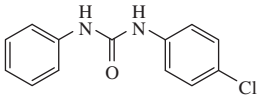
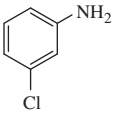
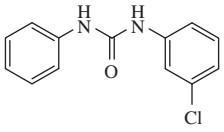
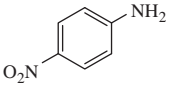
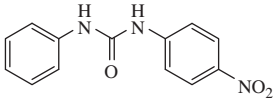
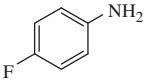
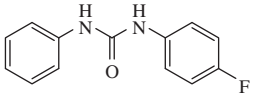
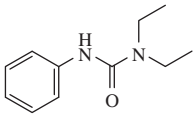
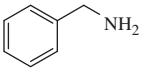
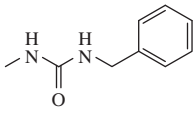
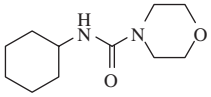
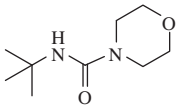
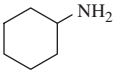
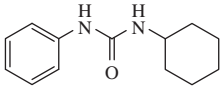
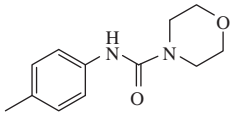
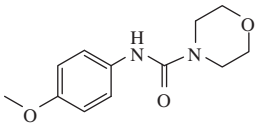
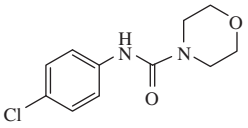
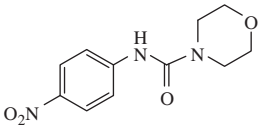
Entry	Hydroxamic acid **1** R^1	Amine **5**	Product[b] **6**	Time (h)	Yield[c] (%)
1	Ph			9.0	89
2	Ph			8.5	86
3	Ph			8.0	85
4	Ph			9.5	72
5	Ph			9.0	78
6	Ph			9.5	77
7	Ph			12	72
8	Ph			9.5	70
9	Ph			7.0	74
10	Me			8.0	83
11	Cyclohexyl			9.0	80
12	^{t}Bu			9.0	80
13	Ph			8.5	78
14	4-MeC_6H_4			7.5	84

Table 2 (*continued*)

Entry	Hydroxamic acid **1** R^1	Amine **5**	Product[b] **6**	Time (h)	Yield[c] (%)
15	4-$MeOC_6H_4$			7.0	87
16	4-ClC_6H_4			14	71
17	4-$NO_2C_6H_4$			18	64

[a] See Ref. 18 for general procedure.
[b] All the products are known compounds[10,12] and were characterized by comparison of their mp and spectral data with those of reported in the literature.
[c] Yields of pure isolated products after column chromatography.

In outline, we have exposed the efficacy and generality of bromodimethylsulfonium bromide (BDMS) as a versatile reagent promoting Lossen rearrangement at moderately low temperature. This procedure could be useful in order to avoid the safety problem of phosgene-based[7,8] approaches for the in situ preparation of isocyanates and their ensuing reaction with amines. Additionally, the prominent features of the present protocol are the simple operation, ready accessibility of the reagent, its cost effectiveness, and higher yields in relatively short reaction times. Thus, this methodology for Lossen rearrangement would be a practical alternative to the existing protocols for the synthesis of N,N′-disubstituted unsymmetrical ureas.

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References and notes

1. (a) Gallou, I. *Org. Prep. Proced. Int.* **2007**, *4*, 355; (b) Moreau, J. J. E.; Vellutini, L.; Man, M. W. C.; Bied, C. *Chem. Eur. J.* **2003**, *9*, 1559; (c) Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140; (d) Matsuda, K. *Med. Res. Rev.* **1994**, *14*, 271.
2. Cabrera, A.; Cox, L.; Velarde, P.; Koskinen, W. C.; Cornejo, J. *J. Agric. Food Chem.* **2007**, *55*, 4828.
3. Cao, P.; Huang, X.; Ding, H.; Ge, H.; Li, H.; Ruan, B.; Zhu, H. *Chem. Biodivers.* **2007**, *4*, 881.
4. Matzen, L.; van Amsterdam, C.; Rautenberg, W.; Greiner, H. E.; Harting, J.; Seyfried, C. A.; Bottcher, H. *J. Med. Chem.* **2000**, *43*, 1149.
5. Wilhelm, S. M.; Carter, C.; Tang, L.; Wilkie, D.; McNabola, A.; Rong, H.; Chen, C.; Zhang, X.; Vincent, P.; McHugh, M.; Cao, Y.; Shujath, J.; Gawlak, S.; Eveleigh, D.; Rowley, B.; Liu, L.; Adnane, L.; Lynch, M.; Auclair, D.; Taylor, I.; Gedrich, R.; Voznesensky, A.; Riedl, B.; Post, L. E.; Bollag, G.; Trail1, P. A. *Cancer Res.* **2004**, *64*, 7099.
6. (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187; (b) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367; (c) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841; (d) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008; (e) Yu, S.; Haight, A.; Kotecki, B.; Wang, L.; Lukin, K.; Hill, D. R. *J. Org. Chem.* **2009**, *74*, 9539.
7. (a) Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75; (b) Smith, M. B.; March, J., 5th ed. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley: New York, 2001; (c) Knolker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497.
8. Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, *59*, 1937.
9. (a) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457; (b) Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927; (c) Koya, S.; Yamanoi, K.; Yamasaki, R.; Azumaya, I.; Masu, H.; Saito, S. *Org. Lett.* **2009**, *11*, 5438.
10. (a) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 57170; (b) Dube, P.; Noah, F.; Nathel, F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622; (c) Peterson, S. L.; Stucka, S. M.; Dinsmore, C. J. *Org. Lett.* **2010**, *12*, 1340.
11. (a) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209; (b) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.
12. (a) Stafford, J. A.; Gonzales, S. S.; Barrett, D. G.; Suh, E. M.; Feldman, P. L. *J. Org. Chem.* **1998**, *63*, 10040; (b) Hamon, F.; Prie, G.; Lecornue, F.; Papot, S. . *Tetrahedron Lett.* **2009**, *50*, 6800; (c) Wallace, R. G.; Barker, J. M.; Wood, M. L. *Synthesis* **1990**, 1143; (d) Salomon, C. J.; Breuer, E. *J. Org. Chem.* **1997**, *62*, 3858.
13. Anilkumar, R.; Chandrasekhar, S.; Sridhar, M. *Tetrahedron Lett.* **2000**, *41*, 5291.
14. (a) Meerwein, H.; Zenner, K. F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, *67*, 688; (b) Olah, G. A.; Vankar, Y. D.; Arvanaghi, M.; Surya Prakash, G. K. *Synthesis* **1979**, 720.
15. (a) Choudhury, L. H.; Pravin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513; (b) Khan, A. T.; Parvin, T.; Choudhury, L. H. . *J. Org. Chem.* **2008**, *73*, 8398; (c) Das, B.; Ravikanth, B.; Thirupathi, P.; Rao, B. V. *Tetrahedron Lett.* **2006**, *47*, 5041; (d) Das, B.; Srinivas, Y.; Holla, H.; Laxminarayana, K.; Narender, R. *Tetrahedron Lett.* **2007**, *48*, 6681; (e) Yadav, D. K.; Patel, R.; Srivastava, V. P.; Watal, G.; Yadav, L. D. S. . *Tetrahedron Lett.* **2010**, *51*, 739.
16. (a) Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2009**, *50*, 5532; (b) Yadav, L. D. S.; Garima; Srivastava, V. P. *Tetrahedron Lett.* **2010**, *51*, 5701.
17. Srivastava, V. P.; Patel, R.; Garima; Yadav, L. D. S. *Chem. Commun.* **2010**, *46*, 5808.
18. *General procedure for the synthesis of unsymmetrical urea derivatives* **6**: To a solution of hydroxamic acid **1** (1 mmol) in DCE (2 mL) at 0 °C under nitrogen atmosphere, *N*-methylmorpholine (NMM) (2.6 mmol) then bromodimethylsulfonium bromide **2** (BDMS) (1.3 mmol) were added and the mixture was stirred at 0 °C for 2 h. The amine **5** (1.2 mmol) was then added and the temperature of reaction mixture was raised to 80 °C and stirred at the same temperature for 7–18 h (Table 2). Upon completion of the reaction as indicated by TLC, the reaction mixture was cooled to rt and acidified with 2 mL HCl (0.1 N) and the solution was extracted with DCM (2 × 10 mL) and EtOAc (1 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a gradient mixture of hexane/ethyl acetate as eluent to give the corresponding pure urea derivatives **6.** All the products are known compounds and were characterized by the comparison of their mp and spectral data with those of reported in the literature.[10,12]
19. Swenson, J. S.; Davis, A. M.; Deyo, R. A.; Graham, B. W.; Jahn, E. P.; Mattice, J. D. *J. Org. Chem.* **1973**, *38*, 3956.