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Carbonyldiimidazole-Mediated Lossen Rearrangement

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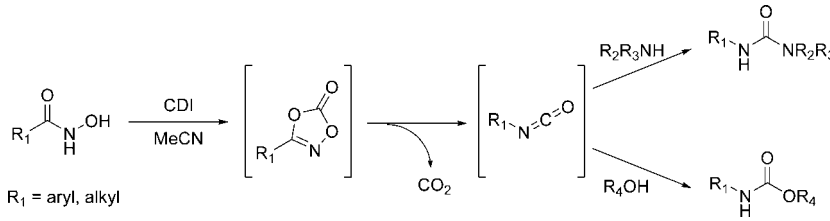
ABSTRACT



Carbonyldiimidazole (CDI) was found to mediate the Lossen rearrangement of various hydroxamic acids to isocyanates. This process is experimentally simple and mild, with imidazole and CO_2 being the sole stoichiometric byproduct. Significant for large-scale application, the method avoids the use of hazardous reagents and thus represents a green alternative to standard processing conditions for the Curtius and Hofmann rearrangements.

The oxidative degradation of carboxylic functions is now viewed as a standard chemical transformation.[1] Both the Hofmann[2] and Curtius[3] rearrangements have been developed to a point where reaction understanding and process engineering have enabled their utilization on a kilogram scale.[4] Examples of large-scale applications of the Hofmann rearrangement feature controlled addition of the oxidant along with flow processes.[5] Moreover, procedures involving reverse addition of sensitive reagents and flow engineering have rendered the Curtius reaction accessible to the process groups of the pharmaceutical industry.[6] However, these methods are inherently limited by the safety hazards associated with the handling of azides and transient high-energy intermediates along with impractical dilution requirements.[7] The development of an alternative method avoiding such limitations is thus still of interest.

The Lossen rearrangement, which describes the transformation of an activated hydroxamic acid into the corresponding isocyanate, has received comparatively little attention since its original publication.[8] Although many studies have focused on the development of activation methods to promote the Lossen rearrangement,[9] the inherent problems associated with competitive dimerization have been partially addressed by creative solutions.[10] Nonetheless, the complexity of existing procedures and the presence of many stoichiometric byproduct have limited the application of the Lossen rearrangement on a kilogram scale.[11]

(1) Shioiri, T. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 800.
(2) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.
(3) (a) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Smith, P. A. S. *Org. React.* **1946**, *3*, 337.
(4) For a review, see: Caron, S.; Dugger, R. W.; Gut Ruggeri, S.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943.
(5) For selected examples, see: (a) Amato, J. S.; Bagner, C.; Cvetovich, R. J.; Gomolka, S.; Hartner, F. W., Jr.; Reamer, R. *J. Org. Chem.* **1998**, *63*, 9533. (b) Zhang, L.-H.; Chung, J. C.; Costello, T. D.; Valvis, I.; Ma, P.; Kauffman, S.; Ward, R. *J. Org. Chem.* **1997**, *62*, 2466. (c) Kaufhold, M.; Kleemiss, W.; Feld, M. European Patent EP970943, 2000. (d) Jones, S. A.; Jersak, U. German Patent DE3909142 , 1990.
(6) (a) Am Ende, D. J.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Process Res. Dev.* **1998**, *2*, 382. (b) Nettekoven, M.; Jenny, C. *Org. Proc. Res. Dev.* **2003**, *7*, 38. (c) Govindan, C. K. *Org. Process Res. Dev.* **2002**, *6*, 74. (d) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1587.
(7) (a) Landgrebe, J. A. *Chem. Eng. News* **1981**, *59*, 47. (b) Middleton, W. J. *J. Org. Chem.* **1984**, *49*, 4541.
(8) (a) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209. (b) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.

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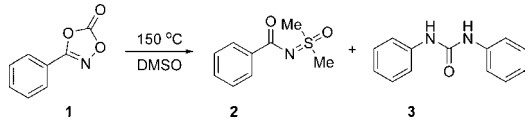
We came across a report by Sauer and Mayer where the thermolysis of 3-phenyl-1,4,2-dioxazol-5-one **1** produced sulfoximine **2** along with symmetrical urea **3** (Scheme 1).[12]

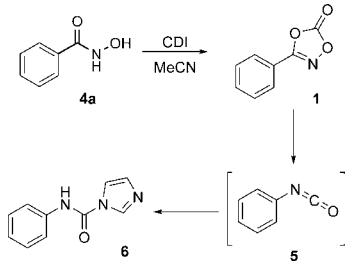
Scheme 1. Thermolysis of 3-Phenyl-1,4,2-dioxazol-5-one **1**[12]



The latter was proposed to form through the addition of aniline, from the partial decomposition of phenylisocyanate with residual water, onto isocyanate **5**. Inspired by their results, we hoped to optimize the oxidative rearrangement pathway via the screening of various additives.

Although dioxazolone **1** can be prepared by treatment of benzohydroxamic acid **4a** with phosgene,[13] we sought a less hazardous phosgene equivalent. Initial experiments using carbonyldiimidazole (CDI) in acetonitrile led to the formation of dioxazolone **1** within 10 min at ambient temperature. Surprisingly, partial conversion to *N*-phenyl-1*H*-imidazole-1-carboxamide **6** by way of addition of imidazole to phenylisocyanate **5** was also observed under these conditions (Scheme 2).[14] Complete conversion of dioxazolone **1** to urea

Scheme 2. CDI-Mediated Formation of **1** and Subsequent Rearrangement

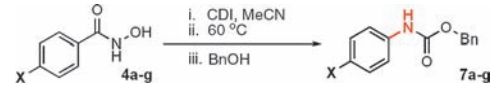


6 could be achieved within 15 min by heating the reaction mixture to 60 °C.

The fact that rearrangement occurred under such mild conditions sharply contrasted with the reported high temperature required for the thermolysis (Scheme 1). Our screen of various solvents revealed that conversion and purity was optimal in acetonitrile[15] and that **1** could be secured by performing the CDI reaction in toluene at 0 °C. Moreover, control experiments established that imidazole was essential for the conversion of dioxazolone **1** into phenylisocyanate **5**.

As this CDI-mediated Lossen rearrangement compared favorably with established conditions, we evaluated the electronic requirements of the reaction. The conversion of various *para*-substituted phenyl hydroxamic acids into the corresponding Cbz carbamates was thus investigated (Table 1). Accordingly, treatment of hydroxamic acid **4a** with CDI

Table 1. Lossen Rearrangement of *para*-Substituted Phenyl Hydroxamic Acids[a]



entry	X	cmpd	time of rearrangement	yield (%)[b]
1	H	a	15 min	93
2	NMe_2	b	<5 min	99
3	OMe	c	<5 min	93
4	Me	d	10 min	82
5	Cl	e	40 min	85
6	F	f	40 min	81
7	NO_2	g	24 h	5[c]

[a] Conditions: hydroxamic acid (1.0 equiv), CDI (1.2 equiv), BnOH (3 equiv). [b] Isolated yield. [c] Conversion by HPLC.

and heating the reaction mixture to 60 °C led to the smooth formation of the desired isocyanate over the course of a few minutes, with the Cbz-protected aniline **7a** being isolated in high yield after a simple aqueous workup.[16] Whereas the rearrangement of electron-rich arenes was complete upon reaching 60 °C (entries 1−4), the conversion was significantly affected by the presence of electron-withdrawing substituents (entries 5−7). As expected, the rate of rearrangement proved to be proportional to the electron density of the migrating group.[17,18]

Having confirmed the electronic nature of the rearrangement, a broader study of the scope revealed the generality of the method (Table 2). The capture of isocyanates with morpholine typically provides ureas in quantitative yield.[19] We thus opted for a consistent use of this nucleophile to evaluate the efficiency of the oxidative rearrangement itself.

(9) For selected examples, see: (a) Wallace, R. G.; Barker, J. M.; Wood, M. L. *Synthesis* **1990**, 1143. (b) Bachman, G. B.; Goldmacher, J. E. *J. Org. Chem.* **1964**, *29*, 2576. (c) Hoare, D. G.; Olson, A.; Koshland, D. E., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1638. (d) Bittner, S.; Grinberg, S.; Kartoon, I. *Tetrahedron Lett.* **1974**, *23*, 1965. (e) King, F. D.; Pike, S.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 3521. (f) Salomon, C. J.; Breuer, E. *J. Org. Chem.* **1997**, *62*, 3858. (g) Pihuleac, J.; Bauer, L. *Synthesis* **1989**, 61. (h) Burungule, A. S.; Bondge, S. P.; Munde, S. B.; Bhingolikar, V. E.; Mane, R. A. *Synth. Commun.* **2003**, *33*, 1923.

(10) (a) Stafford, J. A.; Gonzales, S. S.; Barrett, D. G.; Suh, E. M.; Feldman, P. L. *J. Org. Chem.* **1998**, *63*, 10040. (b) Anilkumar, R.; Chandrasekhar, S.; Sridhar, M. *Tetrahedron Lett.* **2000**, *41*, 5291. (c) Miller, M. J.; Loudon, G. M. *J. Am. Chem. Soc.* **1975**, *97*, 5295.

(11) Marzoni, G.; Varney, M. D. *Org. Process Res. Dev.* **1997**, *1*, 81.

(12) Sauer, J.; Mayer, K. K. *Tetrahedron Lett.* **1968**, *3*, 319.

(13) Beck, G. *Chem Ber.* **1951**, *84*, 688.

(14) Such a rearrangement was proposed to explain the decomposition of α-hydroxy hydroxamic acids. Geffken, D. *Liebigs Ann. Chem.* **1982**, 211.

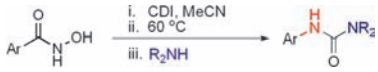
(15) Other solvents led to lower conversion of **4a** after 2 h: toluene (50%), THF (90%), EtOAc (60%), dichloroethane (55%).

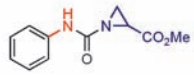
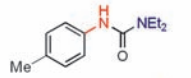
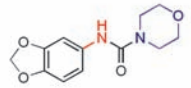
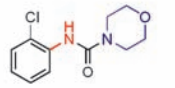
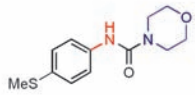
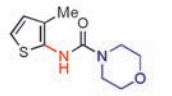
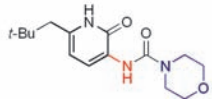
(16) See Supporting Information.

(17) For a comparative rate study of Hofmann rearrangements, see: Hauser, C. R.; Renfrow, W. B., Jr. *J. Am. Chem. Soc.* **1937**, *59*, 121.

(18) For rate studies of the Lossen rearrangement, see: (a) Swenson, J. S.; Davis, A. M.; Deyo, R. A.; Graham, B. W.; Jahn, E. P.; Mattice, J. D. *J. Org. Chem.* **1973**, *38*, 3956. (b) Bright, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1939**, *61*, 618. (c) Renfrow, W. B., Jr.; Hauser, C. R. *J. Am. Chem. Soc.* **1937**, *59*, 2308.

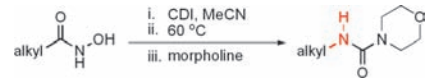
Table 2. Rearrangement of Aryl and Hetero Aryl Hydroxamic Acids[a]

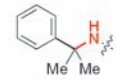
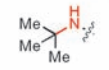
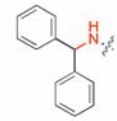
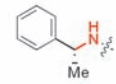
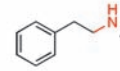
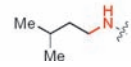


entry	urea		yield (%)[b]
1		8	95%
2		9	78%
3		10	73%
4		11	81%
5		12	95%
6		13	81%
7		14	68%

[a] Conditions: hydroxamic acid (1.0 equiv), CDI (1.2 equiv), R_2NH (3 equiv). [b] Isolated yield.

Table 3. Rearrangement of Aliphatic Hydroxamic Acids[a]



entry	morpholine urea		yield (%)[b]
1		15	72%
2		16	94%
3		17	91%
4		18	95%
5		19	84% >99:1 er[c]
6		20	75%
7		21	88%
8		22	89%

[a] Conditions: hydroxamic acid (1.0 equiv), CDI (1.2 equiv), R_2NH (3 equiv). [b] Isolated yield. [c] Determined by chiral SFC analysis. See Supporting Information for details.

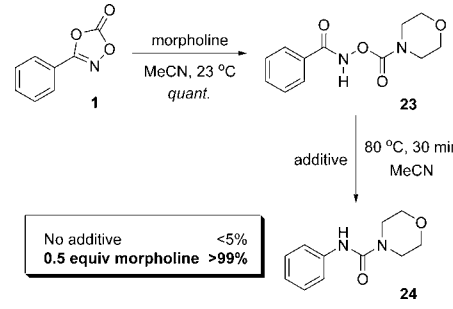
Accordingly, a variety of ureas could be obtained in good yields without a need for purification on silica gel. The mildness of these conditions was highlighted by the isolation of thioanisole urea **12** in 95% yield and aminothiophene **13** in 81%. Moreover, aminopyridone **14** was obtained in 68% yield via the CDI-promoted Lossen rearrangement. It is worth mentioning that conversion of these substrates into the corresponding isocyanates would have been a challenging task under Hofmann-like conditions.

Further exploration of the scope showed that a wide range of aliphatic hydroxamic acids undergo the rearrangement in high yield (Table 3). Aryl- and alkyl-substituted tertiary hydroxamic acids were effectively converted to the corresponding amines in high yields by treatment with CDI (entries 1−3). As secondary substrates performed equally well, enantio-enriched α-methylphenyl carboxamide **19** was obtained with complete retention of stereochemistry through our mild conditions.[20] Finally, the rearrangement of unsubstituted alkyl hydroxamic acid cleanly provided primary amines in high yields (entries 7 and 8).

(19) The reaction of isocyanates with various nucleophiles has been extensively reported in the literature. For selected examples, see: (a) Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927. (b) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457. (c) Spino, C.; Joly, M.-A.; Godbout, C.; Arbour, M. *J. Org. Chem.* **2005**, *70*, 6118, and reference therein. (d) Han, C.; Porco, J. A. *Org. Lett.* **2007**, *9*, 1517.

Having established the generality of the CDI-mediated Lossen rearrangement, we sought to gain mechanistic insights into the reaction. Treatment of dioxazolone **1** with morpholine at ambient temperature led to the smooth formation of *O*-hydroxamic carbamate **23** in quantitative yield (Scheme 3).

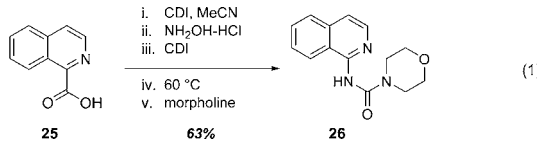
Scheme 3. Isolation and Lossen Rearrangement of Carbamate **23**



When **23** was heated to 80 °C for 30 min, only traces of the corresponding urea could be observed. However, complete conversion was obtained when 0.5 equiv of morpholine was

added to the reaction mixture. This result suggests that the conversion of **1** into phenylisocyanate **5** proceeds through an acyclic precursor with the assistance of a second amine in the rate-limiting step, in agreement with mechanistic studies on the Lossen rearrangement supporting an initial N−H deprotonation of the activated hydroxamic acid followed by migration.[18,21]

A current limitation to the method is the availability of hydroxamic acids. A more practical method would promote the direct conversion of a carboxylic acid moiety into the desired amine functionality. Preliminary results indicate the feasibility of such a transformation using CDI as activating agent twice (eq 1). Following a stepwise addition procedure, isoquinoline-1-carboxylic acid **25** was converted into carboxamide **26** in 63% yield through a one-pot operation.



(1)

Our studies support the generality and versatility of the CDI-mediated Lossen rearrangement. The nature of the byproducts enables the direct oxidative rearrangement of carboxylic acids, thus providing a rapid access to in situ generated isocyanates. The simplicity and mildness of this method should make it a versatile and useful transformation with potential for large scale application. Preliminary data supports a second order in amine and detailed kinetic studies will be reported in due course.

Acknowledgment. The authors would like to thank Professor Justin Du Bois of Stanford University for discussions.

Supporting Information Available: Experimental procedures and compound characterization data with corresponding ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org

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(20) (a) Hirrlinger, B.; Stolz, A. *App. Environ. Microbiol.* **1997**, *63*, 3390. (b) Bauer, L.; Miarka, S. V. *J. Org. Chem.* **1959**, *24*, 1293. (c) Chandrasekhar, S.; Sridhar, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3467.
(21) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed.* **1974**, *13*, 376.