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Self-propagated Lossen rearrangement induced by a catalytic amount of activating agents under mild conditions

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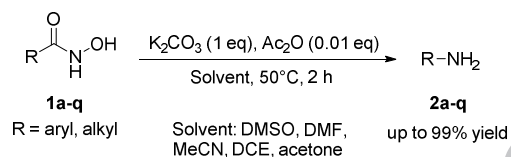## Graphical Abstract

Self-propagated Lossen rearrangement induced by a catalytic amount of activating agents under mild conditions

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Yujiro Hoshino,* Yuki Shinbo, Naoya Otsuka, Kiyoshi Honda*

1a-q

R = aryl, alkyl

K_2CO_3 (1 eq), Ac_2O (0.01 eq)

Solvent, 50°C, 2 h

Solvent: DMSO, DMF, MeCN, DCE, acetone

$R-NH_2$

2a-q

up to 99% yield

Self-propagated Lossen rearrangement induced by a catalytic amount of activating agents under mild conditions

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ABSTRACT

A mild self-propagated Lossen rearrangement induced by a catalytic amount of activating agents in medium to high polar organic solvents has been developed. The rearrangement of aromatic and aliphatic hydroxamic acids in the presence of a catalytic amount (0.01 equiv) of acetic anhydride and an equimolar amount of base such as well-dried potassium carbonate afforded the corresponding amines in high yields. This alternative to traditional Lossen rearrangement provides a simple and mild method for the synthesis of amines from free hydroxamic acids.

The Lossen rearrangement, the conversion of hydroxamates to the corresponding isocyanates, is a useful reaction for the synthesis of amine derivatives.[1,2] While the related carbon to nitrogen migration procedures such as the Curtius and Hofmann rearrangements have frequently applied in synthetic organic chemistry, the Lossen rearrangement has, however, received only little attention as a general synthetic method of amines mainly due to the need of preliminary stoichiometric *O*-activation of hydroxamic acids.[3] In addition, undesirable products such as pseudo dimers or symmetrical ureas have been reported in some cases.[4] Therefore, the development of highly selective synthesis of amines via Lossen rearrangement with in situ *O*-activation by a catalytic amount of activating agents under mild reaction conditions is warranted.

Recently, we have reported a base-mediated rearrangement of free aromatic hydroxamic acids, which highly selectively converts them to anilines in high yields under 90 °C in the presence of a catalytic or equimolar amount of bases.[5] This migration protocol represents several features as follows: a simple procedure, only exclusion of carbon dioxide as a by-product, and permission of the utilization of a catalytic amount of base. We supposed that the in situ generation of a small amount of isocyanates, derived from self-condensation and migration, induces the *O*-activation of hydroxamic acids under the basic conditions, followed by the *C*-to-*N* migration to give anilines along with carbon dioxide (Scheme 1a,c). Based on this assumption, the initial step seems to be the rate-limiting step and to limit the scope of the reaction, *i.e.*, the need to heat the reaction around 90 °C and to use high polar solvents such as DMSO and DMF. Therefore, we envisaged that the generation of a catalytic amount of isocyanates would be accelerated by

addition of a catalytic amount of activating agents (Scheme 1c), allowing the reaction to be efficiently conducted at lower reaction temperature in medium polar solvents. Herein, we report the development of a mild self-propagation-type Lossen rearrangement induced by a catalytic amount of activating agents in medium to high polar organic solvents.
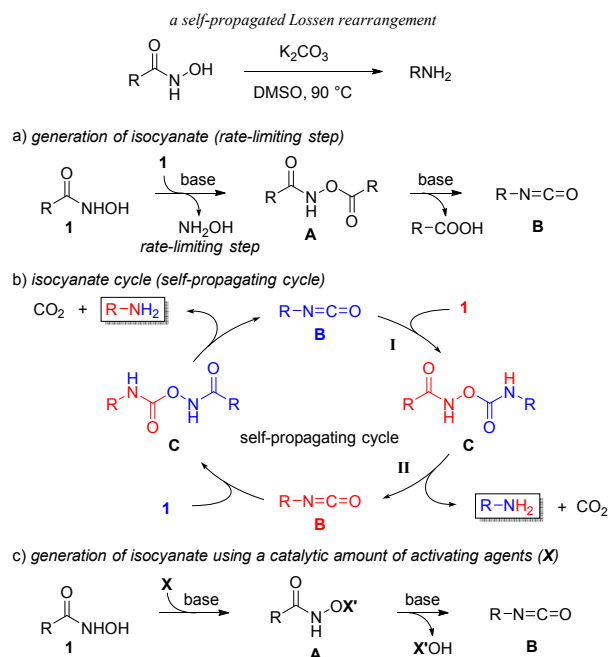

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Scheme 1. Plausible reaction mechanism for self-propagated Lossen rearrangement.

To find the optimal reaction conditions, we began to investigate the rearrangement of 2,6-dimethoxybenzohydroxamic acid as a model substrate. As shown in Table 1, hydroxamic acid **1a** readily underwent rearrangement to amine **2a** on treatment with K_2CO_3 (1 equiv) at 90 °C for only 5 min, while lowering the temperature to 50 °C resulted in significantly longer reaction time to obtain a satisfactory yield (entries 1-3). As expected above, adding a catalytic amount (0.01 equiv) of phenyl isocyanate to the reaction mixture moderately facilitated the rearrangement (entry 4). A twofold larger concentration also renders the shortening of the reaction time (entry 5). It is noteworthy that the utilization of well-dried K_2CO_3, dried under vacuum with a heating gun, distinctly shortens the time of the rearrangement (entry 6). The result seems to imply the retardation of the rearrangement by H_2O existing as impurity of K_2CO_3 probably due to the trap of isocyanate intermediate. Indeed, addition of 0.1 equivalent of H_2O in the reaction lowered the yield of aniline **2a** (entry 7). Interestingly, the reaction can be carried out even at 25 °C within a reasonable reaction time using well-dried K_2CO_3 (entry 8). K_3PO_4 is also a useful base for this reaction (25 °C, 2 h, 86% yield).

Table 1
Base-mediated rearrangement of hydroxamic acid **1a** using a catalytic amount of phenyl isocyanate[a]
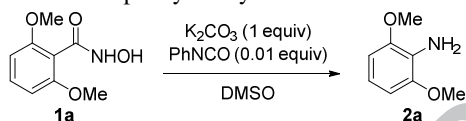
Entry	PhNCO (equiv)	Conditions	Yield (%)
1	–	90 °C, 5 min	98
2	–	70 °C, 1 h	96
3	–	50 °C, 27 h	90
4	0.01	50 °C, 10 h	96
5[b]	0.01	50 °C, 5 h	88
6[b,c]	0.01	50 °C, 10 min	92
7[b,c]	0.01	50 °C, 10min, H_2O (0.1 equiv)	66
8[b,c]	0.01	25 °C, 2 h	90

[a] Reaction conditions: hydroxamic acid (1.2 mmol), K_2CO_3 (1.2 mmol), PhNCO (12 μmol), DMSO (1 mL).

[b] The reaction was performed in DMSO (0.5 mL) under otherwise identical conditions.

[c] The reaction was performed with anhydrous K_2CO_3 that is dried under vacuum with a heating gun.

We then turned our attention to examine the scope of solvents, especially moderate to low polar solvents (Table 2). Fortunately, the rearrangement smoothly proceeded in acetonitrile, dichloroethane, and acetone at 50 °C to give aniline **2a** in good to high yields (entries 1-5). It should be noted that the relatively low polar solvent 1,2-dichloroethane also gave the desired aniline in good yields. From a practical viewpoint, it is advantageous to conduct the reaction in moderate to low polar solvents because of the water-immiscibility and the low boiling point, enabling simple extraction and evaporation processes. The low solubility of **1a** in THF may result in the low yield of **2a** (entry 6). In diethylene glycol no aniline was obtained probably due to the trap of isocyanate intermediate by hydroxyl group of diethylene glycol.

Finally several activating agents were evaluated (Table 2, entries 8-13). Using *N,N'*-dicyclohexylcarbodiimide (DCC), a kind of cumulenes such as isocyanates, gave the corresponding aniline in a low yield (entry 8). When aryl and alkyl sulfonyl chlorides, which are well known as O-activating agents of hydroxamic acids,[6] were employed, mesyl chloride gave better yields than tosyl chloride (entries 9 and 11). For tosyl chloride, the good yield was achieved if the reaction was carried out for 2 h (entry 10). After further trials, it was found that acetic anhydride gave the best result for the rearrangement (entry 13). Interestingly, the reactive trifluoroacetic anhydride gave the poor result (entry 14).

Table 2
The rearrangement of hydroxamic acid **1a** with a catalytic amount of activating agents

| Entry	Additive	Solvent	Yield (%)
1	PhNCO	DMSO	92
2	PhNCO	DMF	93
3	PhNCO	MeCN	85
4	PhNCO	DCE	86
5	PhNCO	acetone	70
6	PhNCO	THF	14
7	PhNCO	Diethylene glychol	ND
8	DCC	DMSO	15
9	TsCl	DMSO	11
10[a]	TsCl	DMSO	81
11	MsCl	DMSO	76
12	AcCl	DMSO	88
13	Ac_2O	DMSO	93
14	$(CF_3CO)_2O$	DMSO	58

[a] The reaction was performed for 2 h.
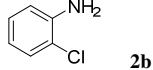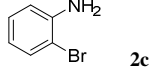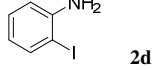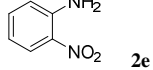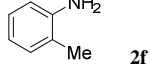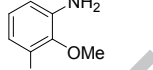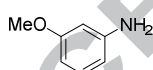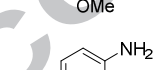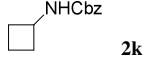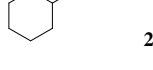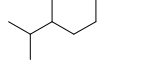
With the optimized conditions in hand, the scope of substrates was examined. As shown in Table 3, a variety of *o*-substituted aromatic hydroxamic acids gave the desired anilines in high yields (entries 1-6).[7] On the other hand, those attached electron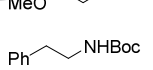-donating groups at *m*- or *p*-positions, which are usually good substrates for classical Lossen rearrangement,[8] resulted in poor yields (entries 7 and 8). The reason for these unexpected results
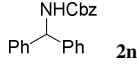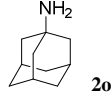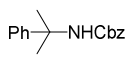
is exactly unknown at the present time, but these observation are consistent with the ortho effect of the Lossen rearrangement, in which the existence of *o*-substituent, even electron-withdrawing group, accelerate the rates of migration.[8] Aliphatic hydroxamic acids were found to require longer reaction times to obtain the desired primary amine derivatives in moderate to good yields (entries 9-17). Increasing the catalytic amount of Ac$_2$O (0.02 equiv) slightly improves the yields (entries 13 and 14) and the use of acetonitrile as solvent facilitates the separation and purification of the products. It is noteworthy that no symmetrical aliphatic urea by-products are detected under these reaction conditions.

Table 3

The rearrangement of various hydroxamic acids in the presence of a catalytic amount (0.01 equiv) of Ac$_2$O
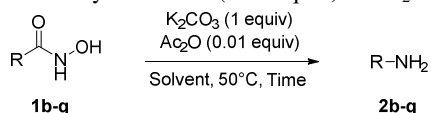
Entry	Amine 2	Solvent, Time	Yield (%)
1	2b	DMSO, 2 h	99
2	2c	DMSO, 2 h	99
3	2d	DMSO, 2 h	94
4	2e	DMSO, 2 h	68
5	2f	DMSO, 2 h	71
6[a]	2g	DMSO, 2 h	89
7	2h	DMSO, 2 h	3
8	2i	DMSO, 2 h	5
9[b]	2j	DMSO, 2 h	46
10[c,d]	2k	CH$_3$CN, 24 h	78
11[c,d]	2l	CH$_3$CN, 24 h	52
12[c,d]	2m	DMSO, 24 h	33
13[c]	2n	DMSO, 6 h	37
14[c,d]	2n	CH$_3$CN, 6 h	46
15	2o	DMSO, 2 h	67
16[c,d]	2p	DMSO, 24 h	70
17[c,d]	2q	CH$_3$CN, 24 h	28

[a] A small amount of urea (2% yield) was isolated.

[b] The protection of amino group with (Boc)$_2$O was carried out in order to easily isolate the amine product.

[c] The protection of amino group with Cbz-Cl was carried out in order to easily isolate the amine product.

[d] Ac$_2$O (0.02 equiv) was used.

In conclusion, we have demonstrated a mild self-propagation-type Lossen rearrangement of aromatic and aliphatic hydroxamic acids, which is induced by a catalytic amount of activating agents such as acetic anhydride and phenyl isocyanate in medium to high polar organic solvents, *e.g.*, 1,2-dichloroethane, acetonitrile, and DMSO. It was found that the lowering of the content of water dramatically accelerate the reaction rate. We anticipate that this alternative to traditional Lossen rearrangement will provide a simple and mild method for the synthesis of amines from various free hydroxamic acids, which can be easily prepared from carboxylic acid derivatives.

Acknowledgments

Supplementary Data

Supplementary data (experimental procedures and characterization data for **1a-k** and **2a-k**) associated with this article can be found, in the online version, at http://dx.doi.org/xxxxx.

References and notes

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7. General Procedure for the rearrangement of free hydroxamic acids to amines in the presence of a catalytic amount of acetic anhydride: To a mixture of *N*-hydroxy-2,6-dimethoxybenzamide (**1a**) (0.237 g, 1.2 mmol), K$_2$CO$_3$ (0.166 g, 1.2 mmol), and DMSO (0.5 mL) was added acetic anhydride (1.1 μL, 0.012 mmol) and heated to 50 °C. After stirring at that temperature for 10 min, the reaction mixture was cooled to 0 °C and then treated with 2 M HCl (ca. 2 mL). After the mixture became the clear solution, 2 M NaOH (ca. 2 mL) was added and extracted with Et$_2$O (15 mL x 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et$_2$O, 1:1) to yield 2,6-dimethoxyaniline (**2a**) (0.171 g, 93%) as a white crystalline solid.

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