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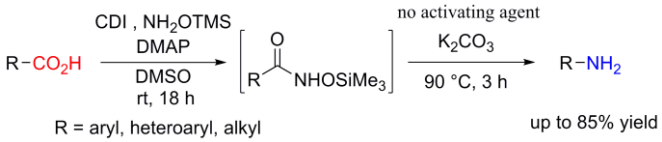

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One-pot synthesis of primary amines from carboxylic acids through rearrangement of *in situ* generated hydroxamic acid derivatives

Yujiro Hoshino,* Naoya Ohtsuka, Takuya Okada, and Kiyoshi Honda*

Graduate School of Environment and Information Sciences, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan

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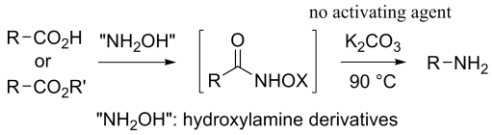
ABSTRACT

A one-pot synthesis of primary amines from carboxylic acids through a Lossen rearrangement of hydroxamic acid derivatives, which were *in situ* generated by the reaction of carboxylic acids with *O*-trimethylsilylhydroxylamine (NH_2OTMS) and carbonyl diimidazole (CDI, 1.5 equiv) in dimethyl sulfoxide at room temperature, has been achieved. This one-pot method could be applied to various carboxylic acids such as aromatic, heteroaromatic, aliphatic, and optically active substrates.

Primary amines constitute the structural basis of various pharmaceuticals, agrochemicals, and functionalized materials. Consequently, the direct synthesis of primary amines from carboxylic acids is more attractive. The Lossen rearrangement is a synthetic method for primary amines via nucleophilic migration from a carbonyl carbon of a hydroxamic acid derivative to an electron-deficient nitrogen center.[1] Although many studies have focused on the development of activation methods to promote the Lossen rearrangement using an external stoichiometric activating agent,[2] efforts for directly obtaining primary amines from carboxylic acids in one pot *via* this rearrangement are rare. Methods using nitromethane or hydroxylamine in excess polyphosphoric acid were reported in the literature, but a limited scope of aromatic carboxylic acids was described primarily because of the harsh reaction conditions required.[3,4] Moderate yields of aromatic amines were obtained *via* the Lossen rearrangement of *in situ* generated *N*-acyl-*N*,*O*-bis(ethoxycarbonyl)hydroxylamine.[5,6]

Recently, we reported a base-mediated rearrangement of free hydroxamic acids (unsubstituted hydroxamic acids, also called primary hydroxamic acids) at 90 °C in the presence of a catalytic or equimolar amount of base, leading exclusively to the desired amines in high yields.[7] We then speculated that if hydroxamic acids could be synthesized from easily available carboxylic acids under neutral or basic conditions in good yields, a one-pot synthesis of primary amines via self-propagative Lossen rearrangement would be achieved without an additional activating agent (Scheme 1). Herein, we disclose a one-pot synthesis of primary amines from carboxylic acids through rearrangement of *in situ* generated hydroxamic acid derivatives without an additional activating agent. The present direct synthesis of primary amines could also apply to various substrates including aromatic, heteroaromatic, aliphatic, and chiral carboxylic acids.

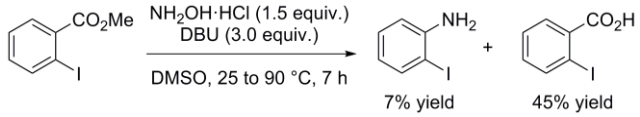


Scheme 1. A one-pot synthesis of primary amines from carboxylic acids through self-propagative Lossen rearrangement.

Our preliminary experiments were initiated by investigating the reaction of 2-iodobenzoate with hydroxylamine hydrochloride in dimethyl sulfoxide (DMSO) in the presence of various bases (Scheme 2).[8] A brief survey of bases resulted in little or no formation of the desired aniline and led to substantial decomposition of the ester to the corresponding carboxylic acid (up to 52% yield). When the reaction was quenched before warming to 90 °C in order to confirm the *in situ* generation of hydroxamic acid, the desired product was isolated in 92% yield. Thus, we postulated that the remaining proton source such as hydroxylamine hydrochloride would inhibit the rearrangement primarily owing to trapping of the isocyanate intermediate.[9] Therefore, we turned our attention to the use of *O*-trimethylsilylhydroxylamine (NH_2OTMS)[10] as a synthetic equivalent of hydroxylamine, and carbonyl diimidazole (CDI) as a dehydrating agent in DMSO. Potassium carbonate was selected

* Corresponding author. Tel.: +81-45-339-4434; fax: +81-45-339-4434; e-mail: yhoshino@ynu.ac.jp

as a base in the second step and added to the reaction mixture before the reaction temperature was increased to 90 °C. As shown in Table 1, a small amount of the desired product, toluidine (**2a**), was obtained (entry 1). Because the yield of **2a** was not dramatically increased when the reaction was conducted using double the amount of K_2CO_3, the effect of Base A in the first step was examined (entries 3–8). While the reaction using a weak base, *N*-methylimidazole (NMI), resulted in a slight increase in the yield, several moderately or strongly basic amines improved the yields approximately two fold. Interestingly, the addition of CsF, in order to promote desilylation to generate the alkoxides or amides after exchange of the anion, smoothly induced the rearrangement to give the symmetrical urea (46% yield) and pseudodimer (35% yield) (entry 9).[11] With treatment of the same base in both the first and second steps, moderate to poor yields were obtained (entries 10–11). Note that in contrast to our previous results of base-mediated rearrangement of hydroxamic acids,[7] the reaction conducted in *N*,*N*-dimethylformamide (DMF) afforded a lower yield, but the one in acetonitrile (CH_3CN) afforded a comparable yield (entries 12–14). The reduction in the amount of reagents (1 equiv of CDI and 1.5 equiv of NH_2OTMS) resulted in a slightly lower yield (entry 15).

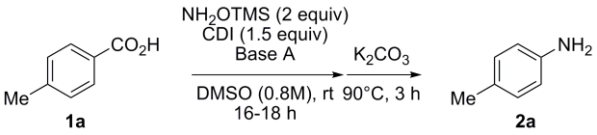


Scheme 2. The reaction of 2-iodobenzoate with hydroxylamine hydrochloride in DMSO in the presence of base.

We then focused on briefly examining the scope of dehydrating agents. Although no desired product was obtained in the reaction using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and no reaction was observed in the case of diphenyl carbonate, the one-pot synthesis of *p*-toluidine was successfully conducted using carbonate dehydrating agents, *i.e.*, *N*,*N*′-disuccinimidyl carbonate and bis(*p*-nitrophenyl) carbonate, under standard conditions to afford the desired product **2a** in 40% and 45% yields, respectively. The subtle difference in the reactivity of dehydrating agents with between *p*-toluic acid and NH_2OTMS is likely to control the first step of the reaction in the one-pot synthesis.

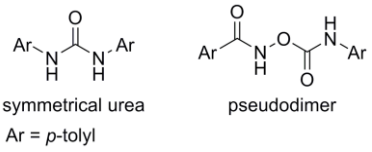
With the optimized conditions in hand, the scope of substrates was examined.[12] As shown in Table 2, various aromatic carboxylic acids afford the desired anilines in moderate to good yields, for example, carboxylic acids having electron withdrawing groups (**2g**–**i**, 63% to 43% yields). Note that the reaction of *o*-substituted benzoic acids such as *o*-toluic acid and *o*-bromobenzoic acid afforded the desired *o*-substituted anilines in low yields (**2c**: 38%, **2f**: 10%, and **2k**: 49% yields). These results seem to be inconsistent with the ortho effect of the Lossen rearrangement, in which the existence of an *o*-substituent, even an electron-withdrawing group, accelerates the rate of migration.[13] To elucidate this puzzle, the isolation of the hydroxamic acid intermediate generated in the first step was examined (Scheme 3). After stirring the reaction mixture for 18 h, 5% aq $KHSO_4$ was added and the reaction was worked up according to the literature procedure.[14] Consequently, the desired 4-methylbenzohydroxamic acid was isolated in high yield (86%). Conversely, the same reaction conditions using *o*-bromobenzoic acid as substrate afforded the desired hydroxamic acid in poor yield. It is suggested that the low yields of *o*-substituted anilines are primarily the result of the difficulty of *in situ* generation of hydroxamic acids from the parent carboxylic acids due to the steric hindrance.

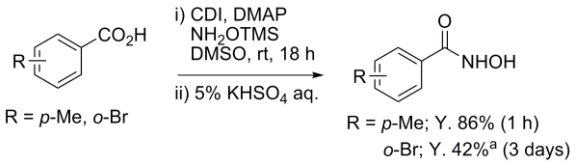
Table 1
Optimization of conditions for one-pot synthesis of amines from carboxylic acids via rearrangement of in situ generated hydroxamic acids



Entry	Base A (equiv)	K_2CO_3 (equiv)	Yield (%)
1	–	1	17
2	–	2	37
3	DABCO (0.5)	2	37
4	NMI (0.5)	2	42
5	NEt_3 (0.5)	2	70
6	iPr_2NEt (0.5)	2	75
7	DBU (0.5)	2	65
8	DMAP (0.5)	2	79
9	CsF (1)	2	–[e]
10	K_2CO_3 (2)	–	48
11	DMAP (1)	–	11
12[a]	DMAP (0.5)	2	55
13[b]	DMAP (0.5)	2	79
14[c]	DMAP (0.5)	2	42
15[d]	DMAP (0.5)	2	61

[a] The reaction was performed in DMF. [b] The reaction was performed in CH_3CN. [c] The reaction was performed in toluene. [d] Reaction conditions: CDI (1 equiv), NH_2OTMS (1.5 equiv). [e] Symmetrical urea (46% yield) and pseudodimer (35% yield) were obtained.





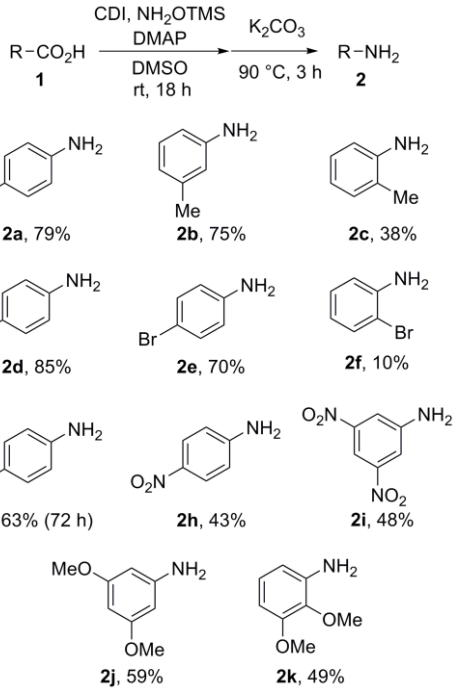
Scheme 3. Isolation of hydroxamic acids.
[a] determined by ^1H NMR.

Aliphatic carboxylic acids were also subjected to the present one-pot synthetic method, and in some cases, the amino group in the product was protected in order to simplify the purification and isolation of the product (Table 3). Primary, secondary, and tertiary aliphatic carboxylic acids afforded the desired amines in moderate yields (**3a**–**e**). For triphenylacetic acid, no reaction was observed primarily because of the difficulty of *in situ* formation of the corresponding hydroxamic acid owing to the high level of steric hindrance around the carboxylic acid functionality (*vide supra*). Heteroaromatic amines were also obtained in good to moderate yields (**3g**–**i**). In particular, *o*-carboxy pyridine and

quinoline were good substrates for this reaction, affording the *o*-amino products in good yields, which constitute an important class of compounds in synthetic organic chemistry and drug discovery.[15]

Table 2

One-pot synthesis of primary anilines from aromatic carboxylic acids[a]



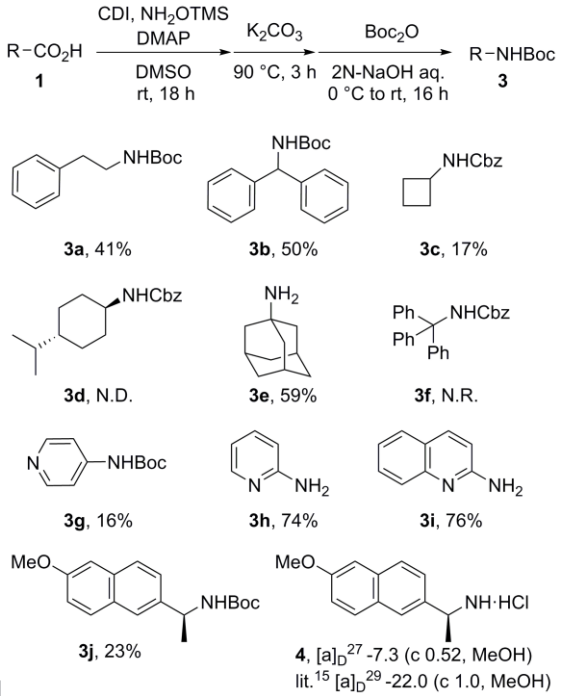
[a] Reaction Conditions: **1** (2.0 mmol), CDI (3.0 mmol), NH_2OTMS (4.0 mmol), DMAP (1.0 mmol), DMSO (2.0 mL), rt, 18 h, under argon; K_2CO_3 (4.0 mmol), 90 °C, 3 h.

We focused on the application of this one-pot synthetic method to optically active carboxylic acids as substrates. Previous studies have shown that the Lossen rearrangement proceeds in a stereospecific manner with the retention of configuration of the migrating group.[16] (*S*)-6-Methoxy-α-methyl-2-naphthaleneacetic acid was subjected to the present one-pot conditions to afford a moderate yield of the desired Cbz-protected amine,[17] which was further transformed to the amine hydrogen chloride **4** in order to confirm the optical purity. Unfortunately, a lower value of the specific rotation was observed compared with the literature one. This decrease in optical purity may be attributed to racemization in the formation of acyl imidazole from carboxylic acid.[18]

Although the mechanism of the present reaction was not studied, a plausible proposal could include the generation of intermediates *O*-trimethylsilyl hydroxamates by reaction between NH_2OTMS and *N*-acylimidazoles, which were derived from carboxylic acids and CDI, followed by production of a small amount of *O*-acyl hydroxamates by dimerization of hydroxamates in the presence of a base. *O*-Acyl hydroxamates thus formed would be subject to rearrangement under thermal conditions, affording intermediate isocyanates, which induce the self-propagative Lossen rearrangement.

Table 3

One-pot synthesis of primary amines from aliphatic and heteroaromatic carboxylic acids[a]



[a] Reaction Conditions: **1** (2.0 mmol), CDI (3.0 mmol), NH_2OTMS (4.0 mmol), DMAP (1.0 mmol), DMSO (2.0 mL), rt, 18 h, under air; K_2CO_3 (4.0 mmol), 90 °C, 3 h; 2 M HCl aq. (2 mL) then 2 M NaOH (3 mL), Boc_2O (8.0 mmol), rt, 16 h.

In conclusion, we have demonstrated a one-pot synthesis of primary amines from carboxylic acids through the Lossen rearrangement of hydroxamic acid derivatives, which were *in situ* generated by the reaction of carboxylic acids with NH_2OTMS and CDI (1.5 equiv) in DMSO at room temperature, without using an external activating agent. This one-pot method could be applied to various carboxylic acids such as aromatic, heteroaromatic, aliphatic, and optically active substrates. The present method provides a facile and promising route to primary amines from carboxylic acids in one pot.

Acknowledgments

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Supplementary Data

Supplementary data (experimental procedures and characterization data for **2a**–**k**, **3a**–**c**,**e**,**g**–**j**, and **4**) associated with this article can be found, in the online version, at http://dx.doi.org/xxxxx.

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11. See Supporting Information.
12. General Procedure for the one-pot synthesis of primary amines from carboxylic acids through rearrangement of *in situ* generated hydroxamic acid derivatives: CDI (0.486 g, 3.0 mmol) was added to a solution of *p*-toluic acid (0.272 g, 2.0 mmol) in dry DMSO (2 mL), then stirring for 1h. DMAP (0.122 g, 1.0 mmol) and NH_2OTMS (0.420 g, 4.0 mmol) were added to the reaction mixture and stirred at room temperature for 18 h. K_2CO_3 (0.552 g, 4.0 mmol) was added and the resulting mixture was heated to 90 °C. After stirring at that temperature for 3 h, the reaction mixture was cooled to 0 °C and then was treated with 2 M HCl (ca. 2 mL). After the mixture became the clear solution, 2 M NaOH (ca. 3 mL) was added and extracted with CH_2Cl_2 (15 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et_2O, 1:1) to yield *p*-toluidine (**2a**) (0.180 g, 79%) as a yellow crystalline solid. IR (KBr) ν 3418, 3337, 3222, 3010, 2914, 2859, 1622, 1514, 1280, 1268, 810, 508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.51 (s, 2H), 6.60 (d, J = 7.8 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H).
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Highlights

·A one-pot synthesis of amines from carboxylic acids *via* Lossen reaction is achieved.
·Lossen reaction was achieved by *in situ* generated hydroxamic acid derivatives.
·Hydroxamic acids were generated from acids with NH_2OTMS and CDI in DMSO.
·(Hetero)aromatic, aliphatic, and optically active acids can be used as substrates.