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

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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.

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 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,

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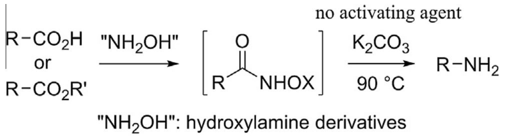
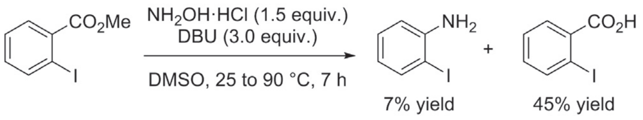


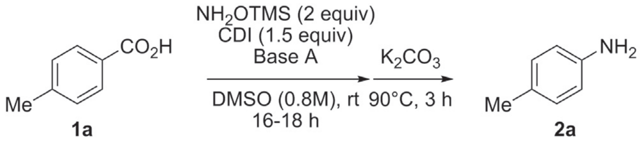
Scheme 1. A one-pot synthesis of primary amines from carboxylic acids through self-propagative Lossen rearrangement.



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

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

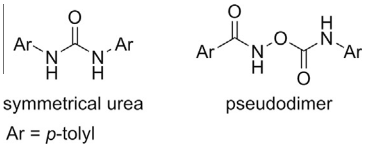
[a] The reaction was performed in DMF.

[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.



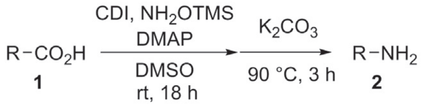
N-methylimidazole (NMI), resulted in a slight increase in the yield, several moderately or strongly basic amines improved the yields approximately two fold. Interestingly, the addition of CsF, in order to promote desilylation to generate the alkoxides or amides after exchange of the anion, smoothly induced 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).

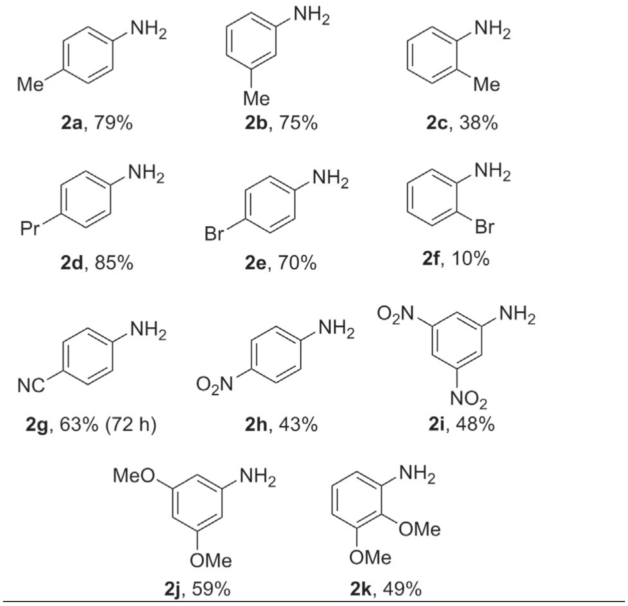
We then focused on briefly examining the scope of dehydrating agents. Although no desired product was obtained in the reaction using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and no reaction was observed in the case of diphenyl carbonate, the one-pot synthesis of *p*-toluidine was successfully conducted 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**, 63–43% 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

Table 2

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





2a, 79%

2b, 75%

2c, 38%

2d, 85%

2e, 70%

2f, 10%

2g, 63% (72 h)

2h, 43%

2i, 48%

2j, 59%

2k, 49%

[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.