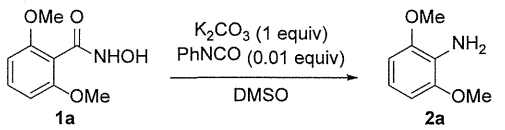
To find the optimal reaction conditions, we began to investigate the rearrangement of 2,6-dimethoxybenzohydroxamic acid as a model substrate. As shown in Table 1, hydroxamic acid 1a readily underwent rearrangement to amine 2a on treatment with K2CO3 (1 equiv) at 90 °C for only 5 min, while lowering the 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 K2CO3, 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 H2O existing as impurity of K2CO3 probably due to the trap of isocyanate intermediate. Indeed, addition of 0.1 equivalent of H2O 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 K2CO3 (entry 8). K3PO4 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 isocyanatea




| 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), K2CO3 (1.2 mmol), PhNCO (12 □mol), DMSO (1 mL).

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

c The reaction was performed with anhydrous K2CO3 that is dried under vacuum with a heating gun.

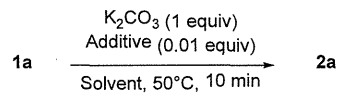
We then turned our attention to examine the scope of solvents, especially moderate to low polar solvents (Table 2). Fortunately, the rearrangement smoothly proceeded in acetonitrile, dichloroethane, and acetone at 50 °C to give aniline 2a in good to high yields (entries 1-5). It should be noted that 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 |

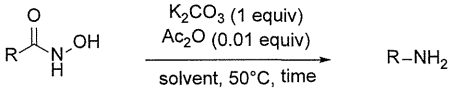
| | | | |
|---|---|---|---|
| 14 | $(CF_3CO)_2O$ | DMSO | 58 |

a The reaction was performed for 2 h.

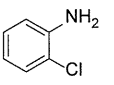
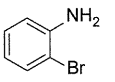
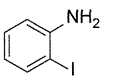
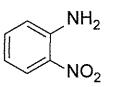
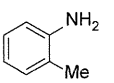
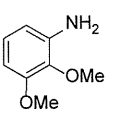
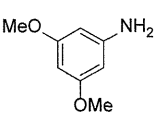
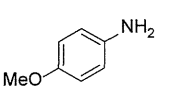
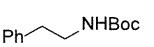
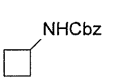
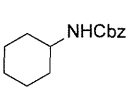
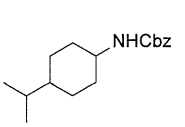
With the optimized conditions in hand, the scope of substrates was examined. As shown in Table 3, a variety of o-substituted aromatic hydroxamic acids gave the desired anilines in high yields (entries 1-6).7 On the other hand, those attached electron-donating groups at m- or p-positions, which are usually 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 Ac2O (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.

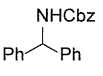
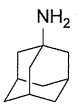
Table 3

The rearrangement of various hydroxamic acids in the presence of a catalytic amount (0.01 equiv) of Ac2O




**1b-q** **2b-q**

| 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** | $CH_3CN$, 24 h | 78 |
| 11[c,d] |  **2l** | $CH_3CN$, 24 h | 52 |
| 12[c,d] |  **2m** | DMSO, 24 h | 33 |

| | | | |
|---|---|---|---|
| 13[c] |  **2n** | DMSO, 6 h | 37 |
| 14[c,d] | **2n** | $CH_3CN$, 6 h | 46 |
| 15 |  **2o** | DMSO, 2 h | 67 |
| 16[c,d] | $PhMe_2C$–NHCbz **2p** | DMSO, 24 h | 70 |
| 17[c,d] | $Ph_3C$–NHCbz **2q** | $CH_3CN$, 24 h | 28 |

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

b The protection of amino group with (Boc)2O 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 Ac2O (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

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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), K2CO3 (0.166 g, 1.2 mmol), and DMSO (0.5 mL) was added acetic anhydride (1.1 L, 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 Et2O (15 mL x 3). The combined organic layers were dried over anhydrous Na2SO4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et2O, 1:1) to yield 2,6-dimethoxyaniline (2a) (0.171 g, 93%) as a white crystalline solid.

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**Supplementary Material**

**A mild self-propagated Lossen rearrangement induced by a catalytic amount of activating agents**

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

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

## EXPERIMENTAL DETAILS

**General.** Melting points were determined on a Buchi 535 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR PARAGON 1000 spectrometer or a JASCO FT/IR-4100. $^1$H NMR spectra were recorded on a JEOL JNM AL-400 (400 MHz) spectrometer, a Bruker DRX-300 (300 MHz) spectrometer, or a Bruker DRX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, integration, and assignment. $^{13}$C NMR spectra were recorded on a JEOL JNM AL-400 (100 MHz) spectrometer, or a Bruker DRX-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: 77.0). Column chromatography was carried out with Cica-reagent silica gel 60N (spherical, particle size 63-210 m). Thin-Layer chromatography (TLC) was carried out with Merck TLC plates with silica gel 60 $F_{254}$. Unless otherwise noted, reagents

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

were commercially available and were used without purification.

**Synthesis of Hydroxamic Acids 1a-q.**[1]

**Representative procedure:** Separate solutions of hydroxylamine hydrochloride (4.17 g, 0.060 mol) in 30 mL of MeOH, and of potassium hydroxide (6.72 g, 0.12 mol) in 30 mL of MeOH, were prepared. Both were cooled in ice bath, and the one containing alkali was added with shaking to the hydroxylamine solution. After all the alkali was added, the mixture was allowed to stand in an ice bath for five minutes to ensure complete precipitation of potassium chloride. The mixture was filtered with suction and the filtrate was added to ethyl 4-methylbenzoate (4.77 mL, 0.030 mol) in 100 mL flask. Additional potassium hydroxide was added to become a basic solution (pH 10). After 12 hr with stirring at room temperature MeOH was evaporated in vacuo and to the residue was added 20 mL of water to become a clear solution, which was acidified with 2 M HCl to be pH <4. The solid appeared was collected by filtration to give the title compound. Additionally, the filtrate was extracted with ethyl acetate and the organic phase was evaporated and purified by recrystallization from ethyl acetate/hexane to give the additional desired product.

***N*-hydroxy-2,6-dimethoxybenzamide (1a):** Yield 50%. White crystalline solid. Mp 201.2-201.5 (AcOEt) (lit.[2] 200-201 °C). IR (KBr) 3254, 2885, 2834, 1616, 1598, 1473, 1254, 1115, 897, 789 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 3.72 (s, 6H), 6.66 (d, $J$= 9.5 Hz, 2H), 7.30 (t, $J$= 9.5 Hz, 1H), 8.93 (s, 1H), 10.50 (s, 1H).

***N*-hydroxy-2-chlorobenzamide (1b):**[3] Yield 80%. White solid. IR (KBr) 3224, 2871, 1629, 1541, 1474, 1172, 1032, 907, 750, 724, 618 $cm^{-1}$; $^1H$ NMR (300 MHz,

DMSO-$d_6$) 7.35-7.44 (m, 2H), 7.46-7.52 (m, 2H), 9.24 (s, 1H), 10.97 (s, 1H).

***N*-hydroxy-2-bromobenzamide (1c)**:[4] Yield 89%. White solid. IR (KBr) 3222, 2865, 1938, 1624, 1540, 1320, 1170, 1051, 903, 746, 701, 555 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 7.34-7.43 (m, 3H), 7.66 (d, $J$ = 7.91 Hz, 1H), 9.24(s, 1H), 10.95 (s, 1H).

***N*-hydroxy-2-iodobenzamide (1d)**: Yield 71%. White solid. IR (KBr) 3237, 3039, 2876, 1622, 1542, 1467, 1170, 904, 744 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) 7.18 (dt, $J$= 8.0, 1.6 Hz, 1H), 7.29 (dd, $J$= 8.0, 1.6 Hz, 1H), 7.43 (dt, $J$= 8.0, 0.8 Hz, 1H), 7.88 (dd, $J$= 8.0, 0.8 Hz, 1H), 9.20 (s, 1H), 10.91 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) 94.4, 127.9, 128.6, 131.1, 139.2, 140.6, 165.7; Anal. Calcd for $C_7H_6INO_2$: C, 31.96; H, 2.30; N, 5.33. Found: C, 31.98; H, 2.39; N, 5.30.

***N*-hydroxy-2-nitrobenzamide (1e)**:[5] Yield 25%. Yellow solid. IR (KBr) 3216, 2882, 1625, 1518, 1354, 1173, 907, 789, 700, 611, 566 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$) 7.57 (d, $J$= 7.6 Hz, 1H), 7.72 (t, $J$= 7.6 Hz, 1H), 7.79 (t, $J$= 7.6 Hz, 1H), 8.06 (d, $J$= 8.2 Hz, 1H), 9.33 (s, 1H), 11.19 (s, 1H).

***N*-hydroxy-2-methylbenzamide (1f)**:[6] Yield 55%. White crystalline solid. IR (KBr) 3303, 3212, 1625, 1595, 1527, 1482, 1316, 1165, 1022, 901 $cm^{-1}$; $^1H$ NMR (270 MHz, DMSO-$d_6$) 2.33 (s, 3H), 7.18-7.35 (m, 4H), 9.04 (s, 1H), 10.80 (s, 1H).

***N*-hydroxy-2,3-dimethoxybenzamide (1g)**: Yield 70%. White solid. IR (KBr) 3345, 3321, 3089, 2838, 1644, 1577, 1267, 988, 812, 757 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) 3.75 (s, 3H), 3.82 (s, 3H), 6.94 (dd, $J$= 7.2, 1.2 Hz, 1H), 7.07-7.14 (m, 2H), 9.08 (s, 1H), 10.68 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) 55.9, 61.0, 114.4,

120.2, 124.0, 129.3, 146.1, 152.5, 163.5; Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.97; H, 5.59; N, 6.95.

***N*-hydroxy-3,5-dimethoxybenzamide (1h):**[7] Yield 80%. White solid. IR (KBr) 3253, 2944, 2842, 1635, 1598, 1428, 1206, 1161, 854, 794 $cm^{-1}$; $^1H$ NMR (270 MHz, DMSO-$d_6$) 3.77 (s, 6H), 6.63 (s, 1H), 6.9 (s, 2H), 9.0 (s, 1H), 11.2 (s, 1H).

***N*-hydroxy-4-methoxybenzamide (1i):**[8] Yield 81%. White crystalline solid. IR (KBr) 3285, 2971, 2755, 1644, 1610, 1568, 1507, 1443, 1305, 1254, 1024 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) 3.80 (s, 3H), 6.98 (d, $J$ = 8.4 Hz, 2H), 7.73 (d, $J$ = 8.4 Hz, 2H), 8.91 (s, 1H), 11.06 (s, 1H).

***N*-hydroxy-3-phenylpropionamide (1j):**[8] Yield 89%. White solid. IR (KBr) 3297, 3030, 2797, 1665, 1629, 1562, 1454, 1371, 718, 697, 483 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) 2.41 (t, $J$ = 7.3 Hz, 2H), 2.93 (t, $J$ = 7.8 Hz, 2H), 7.15-7.31 (m, 5H).

***N*-hydroxycyclobutanecarboxyamide (1k):** Yield 44%. Yellow solid. IR (KBr) 3198, 2945, 1701, 1627, 1536, 1253, 1071, 1005, 666 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 1.70-2.00 (m, 4H), 2.07-2.23 (m, 2H), 2.81-2.92 (m, 1H), 8.68 (br s, 1H), 10.29 (s, 1H).

***N*-hydroxycyclohexanecarboxyamide (1l):** Yield 61%. White solid. IR (KBr) 2932, 2855, 1703, 1451, 1257, 960 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 1.06-1.40 (m, 5H), 1.59-1.81 (m, 5H), 1.91-2.09 (m, 1H), 8.62 (s, 1H), 10.33 (s, 1H).

***trans*-*N*-hydroxy-4-isopropylcyclohexanecarboxamide (1m):** Yield 99%. White solid. IR (KBr) 3192, 2949, 1624, 1542, 1063, 970, 667 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 0.82 (s, 3H), 0.84 (s, 3H), 0.86-1.07 (m, 3H), 1,27-1.40 (m, 3H),

1.65-1.71 (m, 4H) 1.88 (dt, $J$ = 3.4, 12.0 Hz, 1H), 8.36 (s, 1H), 10.32 (s, 1H).

***N*-hydroxy-2,2-diphenylacetamide (1n):** Yield 81%. White solid. IR (KBr) 3266, 2914, 1626, 1494, 1051, 742, 692 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 4.71(s, 1H), 7.20-7.34(m, 10H), 8.97(s, 1H), 10.93(s, 1H).

***N*-hydroxy-adamantane-1-carboxamide (1o):**[9] Yield 91%. White solid. IR (KBr) 3448, 3275, 3153, 2906, 2849, 1694, 1604, 1477, 1451, 1287, 1124, 1022, 928, 812, 628 $cm^{-1}$; $^1H$ NMR (270 MHz, DMSO-$d_6$) 1.60-1.80 (m, 12H), 1.94 (s, 3H), 8.50 (s, 1H), 10.22 (s, 1H).

***N*-hydroxy-2-methyl-2-phenylpropanamide (1p):** Yield 81%. White solid. IR (KBr) 3248, 2906, 1692, 1624, 1495, 1030, 694 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 1.44 (s, 6H), 7.18-7.34 (m, 5H), 8.65 (br s, 1H), 10.34 (s, 1H).

***N*-hydroxy-2,2,2-triphenylacetamide (1q):** Yield 98%. White solid. IR (KBr) 3334, 3053, 1632, 1467, 1021, 744, 695, 638 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) 7.17-7.32 (m, 15H), 8.97 (s, 1H), 10.08 (s, 1H).

**General Procedure for the rearrangement of free aromatic hydroxamic acids to anilines 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), $K_2CO_3$ (0.166 g, 1.2 mmol), and DMSO (0.5 mL) was added acetic anhydride (1.1 L, 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 $Et_2O$ (15 mL x 3). The

combined organic layers were 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 2,6-dimethoxyaniline (**2a**) (0.171 g, 93%) as a white crystalline solid.

**2,6-dimethoxyaniline (2a)**:[10] Yield 93%. White solid. IR (KBr) 3464, 3373, 2962, 1603, 1505, 1478, 1144, 766, 597 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) 3.82 (s, 2H), 3.85 (s, 6H), 6.53 (d, $J$= 8.1 Hz, 2H), 6.69 (t, $J$= 8.1 Hz, 1H).

**2-chloroaniline (2b)**:[11] Yield 99%. Yellow oil. IR (KBr) 3469, 3379, 1614, 1484, 1305, 1022, 740, 676 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 5.28 (s, 2H), 6.52 (dt, $J$= 1.5, 7.9 Hz, 1H), 6.78 (dd, $J$= 1.5, 8.3 Hz, 1H), 7.00 (dt, $J$ = 1.5, 7.9 Hz, 1H), 7.16 (dd, $J$= 1.5, 7.9 Hz, 1H).

**2-bromoaniline (2c)**:[11] Yield 99%. Yellow oil. IR (KBr) 3463, 3373, 3067, 1613, 1481, 1306, 1051, 739, 654 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 5]26 (s, 2H), 6.45 (dt, $J$= 1.9, 7.2 Hz, 1H), 6.78 (dd, $J$= 1.9, 8.3 Hz, 1H), 7.04 (dt, $J$ = 1.5, 8.3 Hz, 1H), 7.31 (dd, $J$= 1.5, 7.9 Hz, 1H).

**2-iodoaniline (2d)**:[12] Yield 94%. White solid. IR (KBr) 3394, 3290, 3187, 1623, 1474, 1300, 1251, 1146, 1006, 749 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 4.08 (s, 2H), 6.47 (t, $J$= 7.2 Hz, 1H), 6.74 (d, $J$= 8.0 Hz, 1H), 7.13 (t, $J$= 7.2 Hz, 1H), 7.63 (d, $J$= 8.0 Hz, 1H).

**2-nitoroaniline (2e)**:[11] Yield 68%. Orange solid. IR (KBr) 3476, 3343, 2919, 1623, 1497, 1341, 1236, 1098, 739, 557 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 6.61 (dt, $J$= 1.5, 7.2 Hz, 1H), 7.01 (dd, $J$= 1.5, 8.3 Hz, 1H), 7.36-7.87 (m, 3H), 7.95 (dd, $J$= 1.5, 8.5 Hz, 1H).

**2-methylaniline (2f)**:[13] Yield 71%. Pale brownish liquid. IR (KBr) 3452, 3361, 3021, 2931, 1623, 1498, 1669, 1304, 1272, 753 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 2.17 (s, 3H), 3.59 (s, 2H), 6.67 (d, $J$ = 7.7 Hz, 1H), 6.71 (dd, $J$ = 1.2, 7.7 Hz, 1H), 7.03 (t, $J$ = 7.7 Hz, 2H).

**2,3-dimethoxyaniline (2g)**:[14] Yield 89%. White solid. IR (KBr) 3466, 3369, 2938, 1615, 1322, 1265, 1133, 1089, 733 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) 3.40-4.10 (br s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 6.34 (d, $J$ = 8.1 Hz, 1H), 6.38 (d, $J$ = 8.1 Hz, 1H), 6.84 (t, $J$ = 7.8 Hz, 1H).

**3,5-dimethoxyaniline (2h)**:[15] Yield 3%. Brown solid. IR (KBr) 3447, 3359, 3232, 3000, 1599, 1488, 1463, 1204, 1151, 820, 686 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 3.68 (br s, 2H), 3.78 (s, 6H), 5.87 (s, 2H), 5.93 (s, 1H).

**4-methoxyaniline (2i)**:[13] Yield 5%. White crystalline solid. IR (KBr) 3422, 3347, 2964, 2839, 1509, 1235, 1032, 826, 514 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 3.42 (s, 2H), 3.74 (s, 3H), 6.65 (d, $J$ = 9.4 Hz, 2H) 6.70 (d, $J$ = 9.4 Hz, 2H).

**General Procedure for the rearrangement of free aliphatic hydroxamic acids to amines in the presence of a catalytic amount of acetic anhydride:** To a mixture of *N*-hydroxy-3-phenylpropanamide (**1j**) (0.198 g, 1.2 mmol), $K_2CO_3$ (0.166 g, 1.2 mmol), and DMSO (0.5 mL) was added acetic anhydride (1.1 L, 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. 1 mL). After the mixture became the clear solution, 2 M NaOH (ca. 2 mL) and di-*t*-butyl dicarbonate (0.55 mL, 2.4 mmol) was added successively. After stirring for 12 h, the mixture was extracted with $Et_2O$ (15

mL x 3). The combined organic layers were 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 *t*-butyl 3-phenylpropylcarbamate (**2j**) (0.122 g, 46%) as a colorless liquid.

**benzyl cyclohexylcarbamate (2l)**:[18] Yield 52%. White solid. IR (ATR) 3317, 2932, 1774, 1685, 1536, 1228, 1044, 755, 694 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.09-1.22 (m, 3H), 1.24-1.41 (m, 2H), 1.58-1.62 (m, 1H), 1.68-1.73 (m, 2H), 1.92-1.96 (br, 2H), 3.49-3.52 (m, 1H), 4.64 (s, 1H), 5.08 (s, 1H), 7.28-7.45 (m, 5H).

***t*-butyl 3-phenylpropylcarbamate (2j)**:[16] Yield 46%. Colorless liquid. IR (ATR) 3353, 2976, 1692, 1497, 1248, 1165, 699 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.43 (s, 9H), 2.80 (t, $J$= 7.0 Hz, 2H), 3.30-3.40 (m, 2H), 7.18-7.34 (m, 5H).

**benzyl cyclobutylcarbamate (2k)**:[17] Yield 78%. White solid. IR (ATR) 3316, 2944, 1684, 1532, 1257, 1038, 908, 728 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 1.61-1.69 (m, 2H) 1.80-1.89 (m, 2H), 2.29-2.31 (m, 2H), 4.13-4.21 (m, 1H), 5.06 (s, 2H), 7.29-7.35 (m, 5H).

**benzyl *trans*-(4-isopropylcyclohexyl)carbamates (2m)**: Yield 33%. White solid. IR (ATR) 3325, 2941, 2864, 1780, 1685, 1534, 1220, 1043, 741, 695 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 0.88 (d, $J$ = 10.0 Hz, 6H), 1.00-1.14 (m, 5H), 1.40-1.48 (m, 1H), 1.75-1.77 (m, 2H), 2.05-2.07 (m, 2H), 3.44 (br, 1H), 4.59 (br s, 1H), 5.11 (s, 2H), 7.32-7.41 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 19.9, 28.4, 32.5, 33.7, 43.2, 50.6, 66.5, 128.0, 128.5, 136.7, 155.6; MS (ES) Calcd for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.2; found: 276.3. $C_{17}H_{25}NNaO_2$ $[M+Na]^+$: 298.2; found: 298.3.

**benzyl benzhydrylcabamate (2n):**[19] Yield 46%. White solid. IR (ATR) 3319, 1688, 1527, 1235, 1041, 695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 5.12 (s, 2H), 5.40 (br s, 1H), 5.98-6.02 (m, 1H), 7.26-7.36 (m, 15H).

**1-adamantylaniline (2o):**[20] Yield 67%. White solid. IR (KBr) 2909, 2851, 1640, 1551, 1457, 1341, 1317, 1291 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) 1.46-1.76 (m, 14H), 1.96 (s, 3H).

**benzyl (2-phenylpropan-2-yl)carbamates (2p):** Yield 70%. Pale yellow oil. IR (ATR) 3339, 2977, 1704, 1496, 1258, 1071, 764, 696 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 1.71 (s, 6H), 5.06 (s, 2H), 5.27 (br s, 1H), 7.26-7.45 (m, 10H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 29.3, 55.3, 66.3, 124.8, 126.7, 128.2, 128.4, 128.5, 136.7, 146.9, 154.5; MS (ES) Calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1; found: 270.2. $C_{17}H_{19}NNaO_2$ $[M+Na]^+$: 292.1; found: 292.2.

**benzyl tritylcarbamate (2q):** Yield 28%. White solid. IR (ATR) 3320, 3056, 1698, 1495, 1443, 1242, 766, 695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 5.02 (s, 2H), 6.05 (br s, 1H), 7.20-7.33 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 66.7, 70.0, 127.1, 127.9, 128.7, 144.8, 154.8; MS (ES) Calcd for $C_{27}H_{23}NNaO_2$ $[M+Na]^+$: 416.2; found: 416.2.

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G．研究発表

2. 学会発表

2.1. 星野雄二郎、大塚尚哉、奥野盛朗、新保雄基、本田 清、連鎖型Lossen転位によるアミンのワンポット合成、第3回JACI/GSCシンポジウム、東京、2014.5.22-23.

One-Pot Synthesis of Amines via Lossen Rearrangement by Self-Propagating Cycle

星野雄二郎、大塚尚哉、奥野盛朗、新保雄基、本田 清

HOSHINO, Yujiro; OHTSUKA, Naoya; OKUNO, Moriaki; SINBO, Yuki; HONDA, Kiyoshi;

〒240-8501 神奈川県横浜市保土ヶ谷区常盤台79-7 横浜国立大学大学院環境情報学府

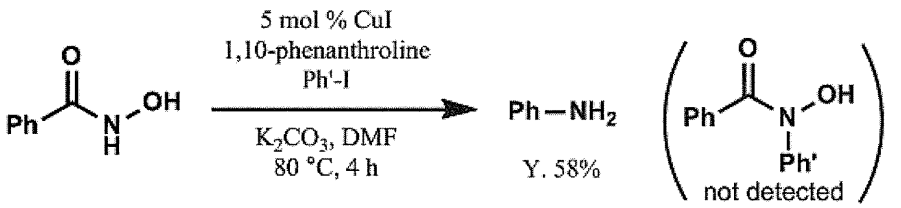
Tel & Fax +81-45-339-4434, E-mail: yhoshino@ynu.ac.jp

In previous studies, we have demonstrated that free aromatic hydroxamic acids undergo rearrangement in the presence of either a stoichiometric or catalytic amount of base at 90 °C within a relatively short reaction time (2 h) under polar aprotic solvents to give the corresponding anilines in high yields. The efficiency of this protocol in terms of atom-economy and environmentally benign process has encouraged us to apply the extension of this method to more versatile systems which would expand the scope and utility of Lossen rearrangement by self-propagating cycle. Here, we would like to report Lossen rearrangement promoted by a catalytic amount of acylating agents and one-pot synthesis of amines from carboxylic acids via Lossen rearrangement.

アミンは染料、界面活性剤、医農薬品、機能性材料など幅広く利用される重要な化合物である。アミン合成法は様々なものが報告されているが、中でもカルボン酸誘導体の転位反応によるアミン合成法は、原料が入手容易なことから優れた反応である。し

かし、爆発の危険性や、強塩基性条件下、反応段階数が多いなどの欠点があり、工業的スケールでの使用に制限がある。従って、入手容易なカルボン酸から簡潔に第一級アミンを大量合成できるプロセスは工業的にも学術的にも魅力的である。

最近、当研究室では、N-アリールヒドロキサム酸の新規合成法の探索研究において、無置換のヒドロキサム酸から特に活性化剤を添加しなくても転位反応が進行し、一炭素減炭した第一級アミンが高収率で得られる事を予期せず見出した1（Scheme 1）。




**Scheme 1**

種々検討した結果、アプロティックな極性溶媒（DMFやDMSOなど）で、等量以下の無機塩基あるいは有機塩基存在下、９０℃に加熱することで短時間（通常２時間以内）に反応が完結することを見出した。副生成物は二酸化炭素のみであり、低環境負荷型のアミン合成法として有望である。本発表では、基質適応範囲と反応機構についての検討結果を述べた後、それらの考察に基づいて、より穏和な条件での転位反応検討と、アミンのワンポット合成検討について報告する。

ヒドロキサム酸の転位反応は、９０℃では速やかに進行するが、５０℃では非常に遅くなることが分かっていた。そこで、触媒量の活性化剤を添加することにより、極少量のイソシアナート中間体が生成し、連鎖型 Lossen 転位が進行しないか種々検討した結果、無水酢酸を 1 mol %添加することにより転位反応が進行し、対応するアミンを高収率で与えることを見出した。また、より入手容易な原料であるカルボン酸誘導体から系中でヒドロキサム酸を発生させ、転位反応する検討を種々行った。その結果、カルボン酸に縮合剤を反応させてヒドロキサム酸とし、転位反応条件に付すことによ