Base-mediated rearrangement of free aromatic hydroxamic acids (ArCO–NHOH) to anilines†

Yujiro Hoshino,*[a] Moriaki Okuno,[a] Eri Kawamura,[a] Kiyoshi Honda[b] and Seiichi Inoue[a]

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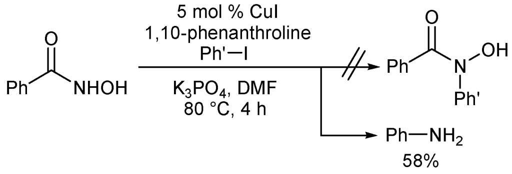
Without using activating agents, a variety of free aromatic hydroxamic acids could be rearranged to aromatic amines in the presence of base alone.

The Lossen rearrangement of hydroxamic acid derivatives, *e.g.*, *O*-acyl hydroxamic acids, is a useful method for the preparation of amines from parent carboxylic acids under mild reaction conditions.[1] It is well documented in the literature[2] and textbooks[3] that the activation of the oxygen atom of hydroxamic acids is essential for the rearrangement to take place because hydroxide is a much poorer leaving group. Thus, Lossen rearrangement is usually carried out by using prepared *O*-activated hydroxamic acid derivatives or by *in situ* activation of free hydroxamic acids with an activating agent such as polyphosphoric acid,[4] carbodiimide,[5] azodicarboxylate and triphenylphosphine (Mitsunobu condition),[6] sulfonyl chloride,[7] sulfur trioxide triethylamine complex,[8] or nitrile.[9]

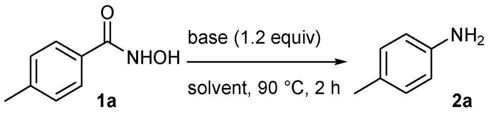
We were therefore quite surprised to observe in the course of our investigation to explore an alternative synthetic method for *N*-arylhydroxamic acids *via* copper-catalyzed *N*-arylation with aryl iodide[10] that free benzohydroxamic acid, without addition of external activating agent, could be converted to aniline in moderate yield, which means occurrence of C to N migration of the aryl group (eqn (1)). This amazing result prompted us to investigate the literature on *the rearrangement of free hydroxamic acids without activating agent*. Two groups reported the production of *N*,*N′*-diphenylurea derivatives instead of anilines.[11,12] Spontaneous Lossen rearrangement of (phosphonoformyl)hydroxamate to phosphoramidate was also reported.[13] As a notable exception, Kobayashi *et al.* reported a small production of perfluoroaniline as a by-product in the treatment of electron-deficient perfluorobenzohydroxamic acid with K_2CO_3 in boiling water.[14] As far as we know, it is the only example for the base-mediated rearrangement of free hydroxamic acid to aniline under standard solution-phase conditions[15] and, unfortunately, this reaction has not been thoroughly explored to date. Herein, we wish to report the base-mediated rearrangement of a variety of aromatic hydroxamic acids to aromatic amines without activating agents. Because of advantage associated with no use of additional reagent for activation, the direct synthesis of amines from free hydroxamic acids is more attractive.



(1)

In order to assess the influence of base and solvent, we examined the base-mediated rearrangement of *p*-methylbenzohydroxamic acid (**1a**) as a standard substrate. As shown in Table 1, several inorganic and organic bases could induce the rearrangement, and better results were obtained by using K_2CO_3, Cs_2CO_3 and K_3PO_4 (entries 3–5).‡ Increasing the basicity of metal carbonates led to increase of reaction yields (entries 1–4). Among organic bases examined, a relatively stronger base, DBU, gave a satisfactory result (entry 9). It is likely that pK_a values of conjugate acid of the bases would be required to be >9 in order to effectively promote the reaction. Although Cs_2CO_3 and K_3PO_4 gave similar yields to K_2CO_3, the latter was chosen for further study since it is much cheaper.

Table 1 The base-mediated rearrangement of *p*-methylbenzohydroxamic acid (**1a**)



Entry	Base	Solvent	Yield[a] (%)	Recovery (%)
1	Li_2CO_3	DMF	12	71
2	Na_2CO_3	DMF	81	14
3	K_2CO_3	DMF	92	—
4	Cs_2CO_3	DMF	93	—
5	K_3PO_4	DMF	96	—
6	K_2HPO_4	DMF	Trace	89
7	Imidazole	DMF	Trace	97
8	Et_3N	DMF	Trace	97
9	DBU	DMF	97	—
10	K_2CO_3	DMSO	98	—
11	K_2CO_3	NMP	90	7
12	K_2CO_3	MeCN	21	73
13	K_2CO_3	MeOH[b]	10	86
14	K_2CO_3	THF[b]	—	95
15	K_2CO_3	Toluene	12	84
16	K_2CO_3	*n*-BuOH	11	80
17[c]	K_2CO_3	DMSO	91	—
18	None	DMF	0	90

[a] Isolated yield based on **1a**. [b] The reactions were carried out at reflux. [c] The reaction was carried out at 70 °C for 6 h.

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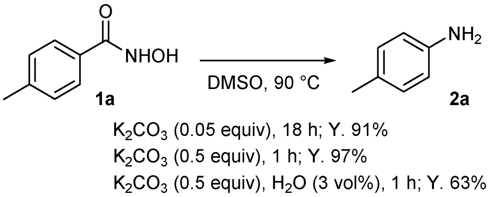
[a] *Graduate School of Environment and Information Sciences, Yokohama National University, 79-7 Tokiwadai, Hodogaya-ku, Yokohama, 240-8501, Japan. E-mail: yhoshino@ynu.ac.jp; Fax: +81-45-339-4434; Tel: +81-45-339-4434*
[b] *Graduate School of Engineering, Yokohama National University, 79-5 Tokiwadai, Hodogaya-ku, Yokohama, 240-8501, Japan*

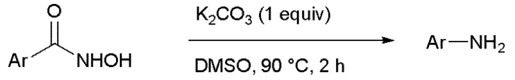
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b822806j

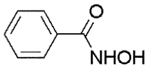
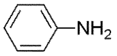
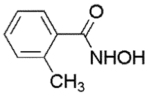
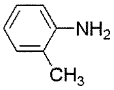
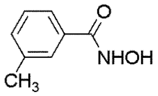
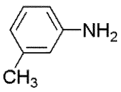
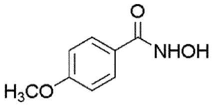
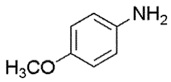
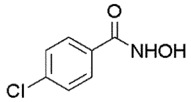
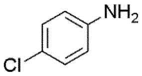
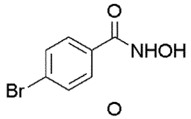
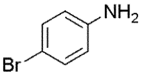
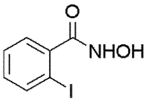
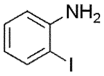
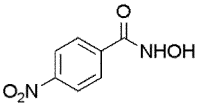
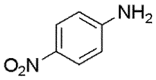
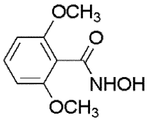
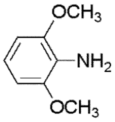
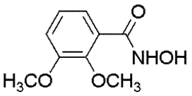
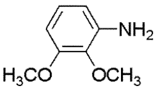
The influence of solvent was next examined (Table 1, entries 10–16). According to the solvent used, the yield of amine is dramatically varied. Polar aprotic solvents gave the best results (90–98%, entries 10 and 11), whereas medium- or non-polar aprotic or polar protic solvents afforded low yields (0–21%, entries 12–16). It is noted that increasing the polarity of solvents led to a significant improvement in yield.[16] Lowering the reaction temperature to 70 °C could also afford a good yield (91%) but the reaction needed a much longer time (6 h) to be completed (entry 17). It should be noteworthy that the rearrangement can proceed in good yields even though less than 1 equiv. of K_2CO_3 is used. For instance, with 0.05 equiv. of K_2CO_3, the corresponding aniline was obtained in 91% yield (eqn (2)).† Although it is not necessary to conduct the process under extremely anhydrous condition (the reaction was performed under air using distilled solvent), a decrease of the yield is observed when water (3 vol% in solvent, 5.6 equiv. to substrate) is added to the reaction mixture in the presence of substoichiometric base (1 h, 63% yield) (eqn (2)). Finally, we confirmed that in the absence of a base no aniline was detected (entry 18).[17]



(2)

Table 2 The base-mediated rearrangement of a variety of free aromatic hydroxamic acids **1**

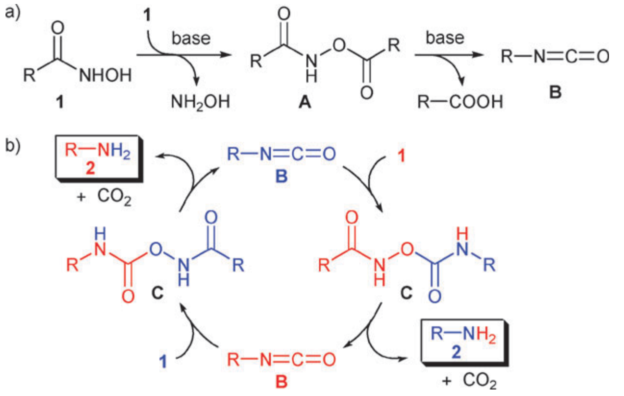


Entry	Hydroxamic acid		Product		Yield (%)
1		1b		2b	96
2		1c		2c	99
3		1d		2d	99
4		1e		2e	99
5		1f		2f	90
6		1g		2g	92
7		1h		2h	98
8[a]		1i		2i	88
9[b]		1j		2j	98
10		1k		2k	99

[a] The reaction was performed for 9 h in 4 mL of DMSO in order to dissolve the reaction mixture. [b] The reaction time is 5 min.

In order to study the scope of this reaction, a series of experiments were carried out using various aromatic hydroxamic acids (Table 2). To our delight, all substrates examined were transformed to the corresponding amines in high yields. Good yields were obtained with the parent benzohydroxamic acid **1b** (entry 1). The rearrangement of electron-rich hydroxamic acids, regardless of *o*-, *m*- and *p*-substituent pattern, proceeded smoothly (entries 2–4, 9–10, and Table 1). Similarly, electron-deficient hydroxamic acids **1f–h** were effectively converted to the synthetically important halogenated anilines, although a slight decrease of reaction rate was observed by TLC analysis. In this case, a small amount of the parent carboxylic acids was isolated as a by-product (entries 5–8). For the more electron-deficient substrate *p*-nitrobenzohydroxamic acid (**1i**), a longer reaction time was required to consume the starting material, but the good yield was maintained. This order of reactivity is consistent with the usual trend for the Lossen rearrangement of *O*-acyl hydroxamic acids,[18] but it is noted that the high yields are retained even when electron-deficient hydroxamic acids are used.[19] Interestingly, the rearrangement of sterically demanding, highly electron-rich 2,6-dimethoxybenzohydroxamic acid (**1j**) proceeded rapidly (within only 5 min) with intense generation of foam just before 90 °C. A useful synthetic intermediate 2,3-dimethoxyaniline (**2k**), used for synthesis of some alkaloids,[20] is also obtained in high yield (entry 10). It is important that in the all cases the regioisomer of the product was not detected at all. This high regiospecificity appeared to be a great merit compared to the conventional methods for preparing the amines through electrophilic aromatic substitution with nitrogen electrophiles, which frequently suffer from the lack of regioselectivity of the reaction.[21] In addition, compared to reduction of halogenated aromatic nitro compounds to haloanilines,[22] this method can give them in good to excellent yields with high chemoselectivities.

A possible reaction pathway of the base-mediated rearrangement of free hydroxamic acids to amines is shown in Scheme 1. We consider that a very small amount of isocyanate is acting in a chain reaction as a reactive intermediate, which is initially installed by self-acylation and rearrangement in the presence of base (Scheme 1(a)): *O*-acylation of hydroxamic acid by another one occurs in a small quantity to give *O*-acyl hydroxamate **A**,[23] which is rearranged to isocyanate **B** along with release of carboxylate.



Scheme 1 A possible reaction pathway of the base-mediated rearrangement of free hydroxamic acids to amines.

The isocyanate **B** is rapidly attacked by hydroxamic acid to generate *O*-carbamoyl hydroxamate **C**, the rearrangement of which gives aniline **2** and regenerates isocyanate **B**.[24] This newly generated isocyanate reacts with hydroxamic acid (**1**) in the same manner and, thus, this chain reaction cycle is completed (Scheme 1(b)). According to this scheme, it is rationalized that the reaction can be conducted using a catalytic amount of base and the addition of a small amount of water reduces the yield of aniline due to the trapping of a reactive intermediate isocyanate. Finally, in order to test the possibility of production of aniline *via* hydrolysis of urea (*vide supra*),[11,12] *N*,*N*′-bis(4-methylphenyl)urea was subjected to the identical conditions, but no reaction occurred.

In conclusion, we have demonstrated a base-mediated rearrangement of a variety of aromatic hydroxamic acids to amines without using activating agents. This reaction can be effectively performed by various inorganic and organic bases (stoichiometric or catalytic amount) in polar aprotic solvents. In addition to its simplicity and efficiency, this method produces aromatic amines in excellent yields in short reaction times. Further work is in progress in this laboratory to apply this reaction to aliphatic hydroxamic acids and to study the mechanism of this base-mediated rearrangement of free hydroxamic acids.

Notes and references

‡ General procedure for the base-mediated rearrangement of free hydroxamic acids to amines: A mixture of *p*-methylbenzohydroxamic acid **1** (0.363 g, 2.4 mmol), K_2CO_3 (0.332 g, 2.4 mmol) and DMSO (2 mL) was heated to 90 °C and stirred for 2 h. The mixture was cooled to rt, then treated with 2 M HCl (*ca.* 3 mL). After the mixture became a clear solution, 2 M NaOH (*ca.* 3 mL) was added and extracted with Et_2O (15 mL x 3). The combined 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 the pure *p*-methylaniline (0.253 g, 98%).

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