

Amide Hydrolysis Reaction Catalyzed by KF/Al₂O₃ under Microwave Irradiation and Solvent Free Conditions

Zhang, Xiuli^{a,c}(张袖丽) Luo, Kai^a(罗凯) Chen, Wei^b(陈巍) Wang, Lei^{*b,c}(王磊)

^a Department of Chemistry, Anhui Agricultural University, Hefei, Anhui 230036, China

^b Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, China

^c State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

A microwave-enhanced hydrolysis of amides utilizing KF/Al₂O₃ in the absence of solvents has been developed. Amines are produced in excellent yields along with the corresponding carboxylic acids.

Keywords amide, hydrolysis, KF/Al₂O₃, microwave irradiation, solvent free, amine

Introduction

Protection and de-protection of functional groups are widely used procedures in organic synthesis.¹ Amides are used to protect amines as well as carboxylic acids since they are stable to the mild hydrolysis. However, amides yet can be hydrolyzed in a variety of ways, some of them are harsh methods.² In addition, the hydrolytic procedures often proceed in moderate yields and the requisite solvents can pose waste handling problems. Recently, a solventless ester deprotection sequence utilizing potassium fluoride doped alumina and microwave irradiation was reported for use with a variety of esters.³

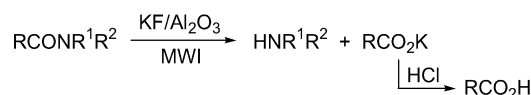
Alumina was found to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways which enhance its reactivity.⁴ In addition, potassium fluoride alumina mixture as a commercially available reagent has been widely used in organic synthesis. For example, alumina-potassium fluoride mixture added either palladium powder, or copper(II) chloride, catalyzing Suzuki, Sonogashira and Glaser coupling reactions on a wide variety of aromatic moieties without the use of solvent under microwave irradiation was reported.⁵

Microwave irradiation (MWI) of organic reactions has gained its popularity since it was found to accelerate a wide variety of transformation.⁶ We now wish to report a general, solventless, microwave-enhanced hydrolysis reaction utilizing potassium fluoride doped alumina which can be utilized on a wide variety of amides to generate the corresponding amines and carboxylic acids in excellent yields (Scheme 1).

Results and discussion

We first investigated the generation of amines from a

Scheme 1



variety of amides. The results are summarized in Table 1. The data indicate that, in the presence of potassium fluoride doped alumina under microwave irradiation (MWI) and solvent free reaction conditions, a wide variety of amides derived from aromatic amines and acetyl chloride or acetic anhydride readily undergo hydrolysis. Amides of aromatic primary and secondary amines are cleaved to generate the corresponding amines in excellent yields (Table 1, Entries 1–8). Aromatic amides derived from aromatic primary amines, whatever electron-donating or electron-withdrawing groups attached to the benzene rings, were able to undergo hydrolysis smoothly and generated the corresponding products in high yields (Table 1, Entries 1–7).

The hydrolysis reaction can be carried out in the absence of microwaves by simply heating the amides on the potassium fluoride doped alumina, but reaction times are relatively long. As an example, the hydrolysis of acetanilide requires 8 h at 80 °C whereas the reaction requires only 4 min under microwave irradiation (Table 1, Entry 1).

With respect to the KF/Al₂O₃ loading, when less than 0.6 g of KF/Al₂O₃ (40 wt% KF) for 2.0 mmol of amide was used, the reaction did not bring to completion, but that a higher loading (up to 0.6 g) of KF/Al₂O₃ gave a good result. However, with an increased loading of KF/Al₂O₃ up to 1.0 g, there was no increase in the isolated yield of the product.

* E-mail: leiwang@chnu.edu.cn; Tel.: 0086-0561-3802069; Fax: 0086-0561-3090518
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Table 1 Generation of amines from amides using KF/Al₂O₃^a

Entry	Reactant	Product	Yield ^b /%
1			92 88 ^c
2			98
3			99
4			97
5			94
6			91
7			90
8			96

^a Amide (2.0 mmol) and KF/Al₂O₃ (0.6 g, 40 wt% KF) were mixed and then subjected to microwave irradiation (4 min, 100% power). ^b Isolated yield of amine. ^c Oil bath for 8 h at 80 °C.

We then tried a wide variety of amides derived from aromatic acids with aromatic primary amines, aliphatic primary and secondary amines under microwave irradiation and solvent free reaction conditions. The results listed in Table 2 indicated that the above amides also underwent hydrolysis smoothly, and the corresponding carboxylic acids and amines were isolated in high yields (Table 2, Entries 1–7). For the low boiling point amine, gas chromatographic analyses of the reaction mixtures showed essentially quantitative yields of the amine product (Table 2, Entry 5). The ease of isolation is especially noteworthy. The product amines are obtained simply by washing off the solid matrix and then evaporating the solvent. Meanwhile, the product carboxylic acids are generated from neutralization of potassium carboxylate with aqueous HCl and then isolated by filtration.

Experimental

Physical measurements and materials

All ¹H NMR and ¹³C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometers. All chemi-

cal shifts are given as δ value with reference to tetramethylsilane (TMS) as an internal standard. Products were purified by flash chromatography on 230–400 mesh silica gel, SiO₂.

A commercially available Glanze WD900SL23-2, 900-watt microwave oven was utilized at 2450 MHz in this study at 100% power. Requisite amides were obtained from the Aldrich Chemical Company or were prepared via standard procedures. KF/Al₂O₃ was purchased from the Aldrich Chemical Co.

The representative hydrolysis of acetanilide

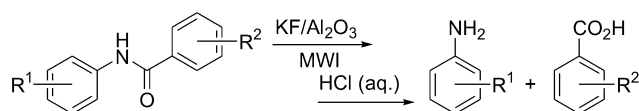
Acetanilide (0.270 g, 2.00 mmol) was added to KF/Al₂O₃ (0.6 g, 40 wt% KF) contained in a 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum, placed in the Glanze WD900SL23-2, 900-watt microwave oven at 2450 MHz and irradiated at 100% power for 4 min. (CAUTION: the reaction temperature of the solid mixture is reached up to 85 °C after the reaction, and heating volatile materials in commercial microwave ovens for extended periods is hazardous). After cooling, diethyl ether (5.0 mL) and water (5.0 mL) were added to the solid and stirred for 10 min to ensure the potassium acetate and aniline was removed from the surface and the mixture filtered. The organic layer was separated, evaporated and dried under vacuum to afford aniline (0.172 g, 92%).

The procedure for regeneration of amine and carboxylic acid from amide is also more straightforward. Benzanilide (0.394 g, 2.00 mmol) was added to KF/Al₂O₃ (0.60 g, 40 wt% by weight) contained in a 10.0 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum, placed in the microwave oven and irradiated at 100% power for 4 min. After cooling, diethyl ether (5.0 mL) and water (5.0 mL) were added to the solid and stirred for 10 min to ensure the potassium benzoate and aniline were removed from the surface and the mixture filtered. The organic layer was separated, evaporated and dried under vacuum to afford aniline (0.173 g, 93%). The water layer was neutralized by addition of aqueous HCl. The product was filtered off and dried under vacuum to afford benzoic acid (0.232 g, 95%).

Aniline Oil.⁷ ¹H NMR (CDCl₃, 400 MHz) δ : 7.17–7.13 (m, 2H), 6.77–6.75 (m, 1H), 6.68–6.66 (m, 2H), 3.57 (brs, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ : 146.26, 129.19, 118.41, 114.98.

m-Methylaniline Oil.⁷ ¹H NMR (CDCl₃, 400 MHz) δ : 7.05–7.00 (m, 1H), 6.54–6.51 (m, 1H), 6.47–6.43 (m, 2H), 3.50 (brs, 2H), 2.23 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ : 146.22, 138.83, 128.92, 119.11, 115.68, 112.01, 21.23.

o-Methylaniline Oil.⁸ ¹H NMR (CDCl₃, 400 MHz) δ : 7.31–7.27 (m, 2H), 6.99–6.96 (m, 1H), 6.84–6.81 (m, 1H), 3.73 (brs, 2H), 2.36 (s, 3H); ¹³C NMR (CDCl₃,

Table 2 Generation of carboxylic acids and amines from amides using $\text{KF}/\text{Al}_2\text{O}_3^a$


Entry	Reactant	Product		Yield/%
		carboxylic acid	amine	
1				95 ^b 93 ^c
2				98 ^b 92 ^c
3				99 ^b 90 ^c
4				97 ^b 91 ^c
5				96 ^b 97 ^d
6				98 ^b 95 ^c
7			<i>n</i> -C ₁₂ H ₂₅ NH ₂	96 ^b 93 ^c

^a Amide (2.0 mmol) and $\text{KF}/\text{Al}_2\text{O}_3$ (0.6 g, 40 wt% KF) were mixed and then subjected to microwave irradiation (4 min, 100% power).

^b Isolated yield of carboxylic acid. ^c Isolated yield of amine. ^d Gas chromatographic yield of amine.

100 MHz) δ : 145.05, 130.73, 127.27, 122.56, 118.76, 115.18, 17.63.

N-Methylaniline Oil.⁹ ¹H NMR (CDCl_3 , 400 MHz) δ : 7.21–7.17 (m, 2H), 6.73–6.70 (m, 1H), 6.61–6.58 (m, 2H), 3.62 (brs, 1H), 2.80 (s, 3H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 149.22, 129.12, 117.12, 112.30, 30.64.

Piperidine Oil.¹⁰ ¹H NMR (CDCl_3 , 400 MHz) δ : 3.32 (t, $J=6.2$ Hz, 1H), 1.83–1.81 (m, 2H), 1.71–1.55 (m, 4H), 1.30–1.25 (m, 4H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 53.18, 36.10, 23.78.

Dibenzylamine Oil.¹¹ ¹H NMR (CDCl_3 , 400 MHz) δ : 7.33–7.18 (m, 10H), 3.80 (s, 4H), 1.68 (brs, 1H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 140.53, 128.68, 128.43, 127.22, 53.39.

Dodecylamine Oil.¹² ¹H NMR (CDCl_3 , 400 MHz) δ : 2.69 (t, $J=7.0$ Hz, 2H), 1.43–1.26 (m, 22H), 0.88 (t, $J=5.6$ Hz, 3H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 42.30, 33.89, 31.94, 29.70, 29.67, 29.54, 29.39, 26.92, 22.72,

14.17.

p-Methylaniline m.p. 53–54 °C (lit.¹³ 52–53 °C). ¹H NMR (CDCl_3 , 400 MHz) δ : 6.96 (d, $J=7.6$ Hz, 2H), 6.48 (d, $J=7.6$ Hz, 2H), 3.44 (brs, 2H), 2.24 (s, 3H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 143.70, 129.67, 127.68, 115.16, 20.40.

p-Chloroaniline m.p. 71–73 °C (lit.¹⁴ 70–70.5 °C). ¹H NMR (CDCl_3 , 400 MHz) δ : 7.09 (d, $J=7.6$ Hz, 2H), 6.59 (d, $J=8.0$ Hz, 2H), 3.61 (brs, 2H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 144.86, 129.03, 122.99, 116.15.

p-Bromoaniline m.p. 59–61 °C (lit.¹⁵ 60–61 °C). ¹H NMR (CDCl_3 , 400 MHz) δ : 7.12 (d, $J=8.4$ Hz, 2H), 6.46 (d, $J=8.4$ Hz, 2H), 4.08 (brs, 2H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 143.18, 131.11, 116.65, 109.54.

p-Nitroaniline m.p. 150–152 °C (lit.¹⁶ 148–151 °C). ¹H NMR (CDCl_3 , 400 MHz) δ : 8.08 (d, $J=8.4$ Hz, 2H), 6.60 (d, $J=8.8$ Hz, 2H), 4.40 (brs, 2H); ¹³C NMR (CDCl_3 , 100 MHz) δ : 156.07, 139.12, 126.35, 113.33.

Benzoic acid m.p. 125–127 °C (lit.¹⁷ 124–126 °C). ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 8.15–8.12 (m, 2H), 7.63–7.60 (m, 1H), 7.50–7.46 (m, 2H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 172.67, 133.84, 130.19, 129.24, 128.46.

***p*-Methoxybenzoic acid** m.p. 182–184 °C (lit.¹⁸ 184–185 °C). ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 8.07 (d, *J*=8.0 Hz, 2H), 6.95 (d, *J*=8.0 Hz, 2H), 3.89 (s, 3H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 167.31, 162.69, 132.34, 123.46, 113.71, 55.48.

***p*-Bromobenzoic acid** m.p. 248–250 °C (lit.¹⁹ 250–252 °C). ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 7.87 (d, *J*=8.4 Hz, 2H), 7.62 (d, *J*=8.0 Hz, 2H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 166.77, 131.12, 130.77, 129.23, 126.92.

***p*-Nitrobenzoic acid** m.p. 122–124 °C (lit.²⁰ 120–122 °C). ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 8.31 (d, *J*=8.0 Hz, 2H), 8.15 (d, *J*=8.0 Hz, 2H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ : 165.77, 149.75, 136.54, 130.73, 123.31.

Conclusions

A reliable, rapid and practical procedure for the deprotection of amides has been developed which involves the use of a solvent-free mixture of potassium fluoride doped alumina under microwave irradiation. The reaction is environmentally friendly and results in excellent yields of desired products.

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