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A novel approach for the synthesis of aryl amides

Ahmad Shaabani,* Ebrahim Soleimani and Ali Hossein Rezayan

Department of Chemistry, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran

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Abstract—A novel and highly efficient approach for the synthesis of aryl amides in high yields by the reaction of carboxylic acids and isocyanides in methanol at ambient temperature is reported.

1. Introduction

Amides are a very important class of organic compounds with a wide range of applications.[1,2] Some derivatives of amides exhibit biological properties such as anthelmintic, antihistamine, antifungal and antibacterial.[3–7] 6-*N*-(2-Hydroxy-3,5-dichlorophenyl)-2-hydroxy-3,5,6-trichlorobenzamide (oxyclozanide) was discovered in 1969 as an anthelmintic agent effective against *Fasciola hepatica* for the treatment of liver fluke infection.[3] 3,4-Dihydroxy-6-(*N*-ethylamino)benzamide is a natural product that has been found in green pepper (*Piper nigrum L.*) which demonstrated antibacterial activity.[5] Additionally, the benzamide derivative, BAS-118, has been found to be a novel anti-*Helicobacter pylori* agent with potent and selective antibacterial activity, which includes clarithromycin (CAM)- and metronidazole (MNDZ)-resistant isolates.[7]

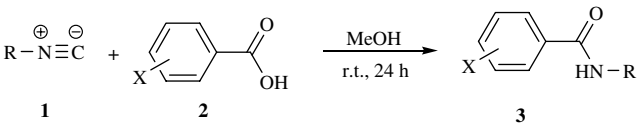
The classical method for the synthesis of amides is the reaction of carboxylic acids with amines at high temperature. Due to the low activity of carboxylic acids, various methods for their activation have been reported in the literature,[8] the most common being conversion of a carboxylic acid to a more reactive functional group, such as an acyl chloride, mixed anhydride, acyl azide, *N*-acylbenzotriazoles[9] or an active ester, or via in situ activation of the carboxylic group using peptide coupling reagents such as benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP)[10] or *N*,*N*′-dicyclohexylcarbodiimide (DCC).[11]

More recently, new systems were developed using carbon tetrabromide/triphenylphosphine, 2-chloro-1-methylpyridinium iodide (CMPI) and/or 2-bromo-1-methylpyridinium iodide (BMPI), titanium and/or divalent tin reagents,[12] or a lanthanide chloride[13] as catalyst. Drawbacks of these methods include modest yields, expensive coupling reagents and difficulty in removal of excess reagents and by-products.

Following our studies towards the development of new routes to the synthesis of organic compounds and our interest in isocyanide-based reactions,[14] we herein report a hitherto unknown reaction, which starting from simple and readily available precursors affords amide derivatives in good yields (Scheme 1).

The results on the synthesis of aryl amides are given in Table 1. The isocyanide **1** and carboxylic acid **2** in methanol undergo a smooth 1:1 addition reaction at ambient temperature to produce amide derivatives **3**.

Although the mechanism of this reaction has not yet been established experimentally, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of the reaction of isocyanides with acids,[15] it is reasonable to assume that protonation of the isocyanide by the carboxylic acid produces *O*-acylimine **4** which on quenching with methanol rearranges



1 **2** **3**

Scheme 1.

Keywords: Isocyanide; Amide; Carboxylic acid.
* Corresponding author. Fax: +98 21 22431663; e-mail: a-shaabani@cc.sbu.ac.ir

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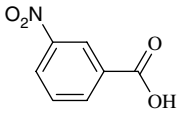
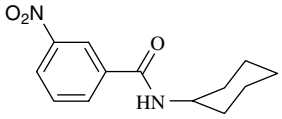
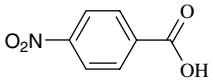
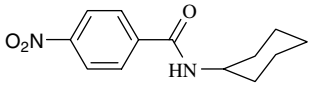
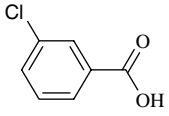
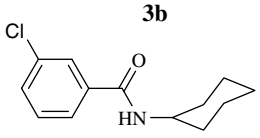
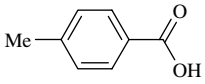
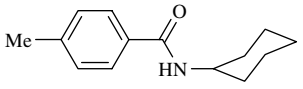
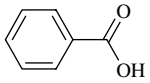
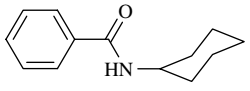
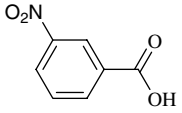
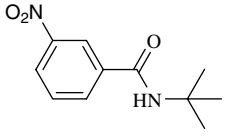
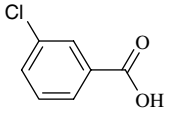
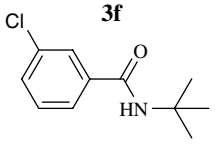
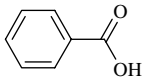
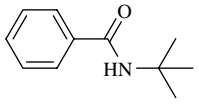
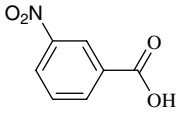
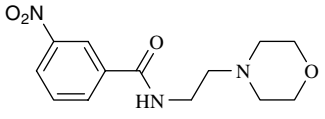
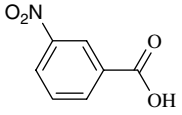
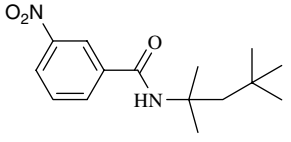
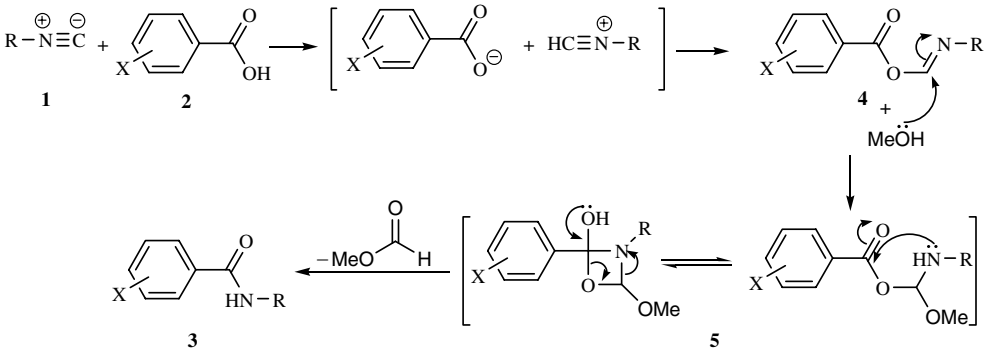
Table 1. Synthesis of aryl amides

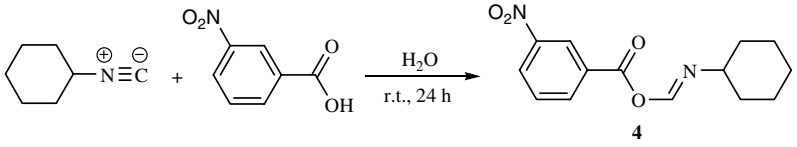
Entry	Carboxylic acid	R	Product	Yield (%)
1		Cyclohexyl	 **3a**	80
2		Cyclohexyl	 **3b**	78
3		Cyclohexyl	 **3c**	85
4		Cyclohexyl	 **3d**	83
5		Cyclohexyl	 **3e**	65
6		*tert*-Butyl	 **3f**	86
7		*tert*-Butyl	 **3g**	90
8		*tert*-Butyl	 **3h**	85
9		Ethylmorpholine	 **3i**	91
10		1,1,3,3-Tetramethyl-butyl	 **3j**	92

to generate intermediate **5**.[16] Finally elimination of methyl formate from intermediate **5** produces amide **3**. Analysis of the reaction mixture by gas chromatography–mass spectroscopy (GC–MS) identified the production of methyl formate as a by-product, which supports the proposed mechanism.

To explore the scope and limitations of this reaction, we extended the procedure to alkyl and aryl carboxylic acids. We found that the reaction proceeded efficiently with various aryl carboxylic acids to give aryl amides, however, no alkyl amides were obtained from reactions with alkyl carboxylic acids.



Scheme 2.



Scheme 3.

To illustrate the need for MeOH, the reaction of 3-nitrobenzoic acid with cyclohexyl isocyanide was studied in dry dichloromethane. Under these conditions, no product was obtained even after 24 h at room temperature. Obviously, MeOH is an important component of the reaction. When the reaction was run in EtOH, the products were isolated in lower yields. It is interesting to note that the reaction carried out in H_2O, stopped at *O*-acylimine **4** (95%), which further supports the proposed mechanism (Scheme 3).

In conclusion, we have developed a new, mild and efficient approach for the synthesis of aryl amides from carboxylic acids and isocyanides in MeOH. The advantages of the present method include good functional group tolerance, high yields of products, simple experimental procedure, no need for dry solvent, no catalyst and no prior activation.

2. Experimental

All of the products (except **3b, e**)[17] are new compounds, which were identified by IR, ^{1}H NMR and ^{13}C NMR spectral data, mass spectroscopy and elemental analyses.

2.1. Typical procedure for the preparation of *N*-cyclohexyl-3-nitrobenzamide (3a)

To a magnetically stirred mixture of 3-nitrobenzoic acid (0.17 g, 1.0 mmol) in MeOH (10 mL) was added cyclohexyl isocyanide (0.11 g, 1 mmol). The resulting mixture was stirred for 24 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 2:1), the solvent was removed under vacuum and the solid residue was washed with diethyl ether and the product **3a** was obtained as a white powder (0.20 g, yield 80%); mp 218–220 °C. IR (KBr) (ν_{max}/cm^{-1}): 3430, 2939, 2864, 1642, 1526, 1347. MS (EI, 70 eV) *m*/*z* (%): 167 ($MH_2^+-C_6H_{11}$, 20), 121 (20), 100 (15), 75 (15), 65 (70), 56 (100), 43 (35). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.10–1.95 (10H, m, $5CH_2$ of cyclohexyl), 2.97 (1H, m, CH–N of cyclohexyl), 7.60 (1H, br s, NH), 8.20–8.61 (4H, m, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 23.8, 24.65, 30.52 ($5CH_2$ of cyclohexyl), 49.03 (CH–N of cyclohexyl), 123.19, 123.74, 128.98, 135.17, 141.54, 147.38 (C-Ar), 167.10 (C=O). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.73; H, 6.62; N, 11.20.

2.2. 3-Chloro-*N*-cyclohexylbenzamide (3c)

White powder (0.20 g, yield 85%); mp 184–186 °C. IR (KBr) (ν_{max}/cm^{-1}): 3433, 2937, 2858, 1636, 1530, 1347. MS (EI, 70 eV) *m*/*z* (%): 209 (M^+-28, 5), 156 (90), 139 (95), 111 (50), 100 (25), 75 (30), 56 (100), 43 (35). ^{1}H NMR (300 MHz, D_2O, NH exchanged): δ_H (ppm) 1.02–1.82 (10H, m, $5CH_2$ of cyclohexyl), 2.98 (1H, m, CH–N of cyclohexyl), 7.28 (1H, t, $^3J_{HH} = 7.7$ Hz, H-Ar), 7.39 (1H, d, $^3J_{HH} = 7.1$ Hz, H-Ar), 7.62 (1H, d, $^3J_{HH} = 7.0$ Hz, H-Ar), 7.70 (1H, s, H-Ar). ^{13}C NMR (75 MHz, D_2O): δ_C (ppm) 23.71, 24.19, 30.23 ($5CH_2$ of cyclohexyl), 50.26 (CH–N of cyclohexyl), 126.97, 128.60, 129.68, 130.90, 133.47, 137.96 (C-Ar), 174.00 (C=O). Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.42; H, 6.85; N, 5.73.

2.3. *N*-Cyclohexyl-4-methylbenzamide (3d)

White powder (0.18 g, yield 83%); mp 162–164 °C. IR (KBr) (ν_{max}/cm^{-1}): 3439, 2942, 2860, 1628, 1523, 1381. MS (EI, 70 eV) *m*/*z* (%): 190 (M^+-28, 2), 136 (70), 119 (95), 100 (55), 91 (100), 56 (80), 43 (20). ^{1}H NMR (300 MHz, D_2O, NH exchanged): δ_H (ppm) 1.00–1.76 (10H, m, $5CH_2$ of cyclohexyl), 2.19 (3H, s, CH_3), 2.91 (1H, m, CH–N of cyclohexyl), 7.11 (2H, d,

$^3J_{HH} = 7.2$ Hz, H-Ar), 7.60 (2H, d, $^3J_{HH} = 7.2$ Hz, H-Ar). ^{13}C NMR (75 MHz, D_2O): δ_C (ppm) 20.38 (CH_3), 23.68, 24.16, 30.21 ($5CH_2$ of cyclohexyl), 50.22 (CH–N of cyclohexyl), 128.76, 128.90, 133.03, 142.04 (C-Ar), 175.53 (C=O). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.20; H, 8.75; N, 6.50.

2.4. *N-tert*-Butyl-3-nitrobenzamide (3f)

White powder (0.19 g, yield 86%); mp 228–230 °C. IR (KBr) (ν_{max}/cm^{-1}): 3340, 2917, 2820, 1639, 1527, 1346. MS (EI, 70 eV) *m*/*z* (%): 167 ($MH_2^+-C_4H_9$, 35), 150 (10), 121 (25), 74 (15), 65 (65), 58 (100), 43 (20). ^{1}H NMR (300 MHz, D_2O, NH exchanged): δ_H (ppm) 1.21 (9H, s, $C(CH_3)_3$), 7.49–8.44 (4H, m, H-Ar). ^{13}C NMR (75 MHz, D_2O): δ_C (ppm) 27.39 ($C(CH_3)_3$), 53.85 ($C(CH_3)_3$), 125.11, 128.23, 129.92, 131.06, 135.84, 148.26 (C-Ar), 169.16 (C=O). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.20; H, 6.41; N, 12.67.

2.5. *N-tert*-Butyl-3-chlorobenzamide (3g)

White powder (0.19 g, yield 90%); mp 223–225 °C. IR (KBr) (ν_{max}/cm^{-1}): 3445, 2924, 1644, 1546, 1367. MS (EI, 70 eV) *m*/*z* (%): 156 ($MH_2^+-C_4H_9$, 55), 139 (65), 111 (30), 75 (25), 58 (100), 41 (20). ^{1}H NMR (300 MHz, D_2O, NH exchanged): δ_H (ppm) 1.19 (9H, s, $C(CH_3)_3$), 7.27 (1H, t, $^3J_{HH} = 7.7$ Hz, H-Ar), 7.37 (1H, d, $^3J_{HH} = 7.7$ Hz, H-Ar), 7.60 (1H, d, $^3J_{HH} = 7.5$ Hz, H-Ar), 7.67 (1H, s, H-Ar). ^{13}C NMR (75 MHz, D_2O): δ_C (ppm) 26.48 ($C(CH_3)_3$), 51.78 ($C(CH_3)_3$), 126.95, 128.58, 129.66, 130.84, 133.45, 138.10 (C-Ar), 174.10 (C=O). Anal. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.30; H, 6.72; N, 6.53.

2.6. *N-tert*-Butylbenzamide (3h)

White powder (0.15 g, yield 85%); mp 223–224 °C. IR (KBr) (ν_{max}/cm^{-1}): 3445, 2924, 1638, 1521, 1384. MS (EI, 70 eV) *m*/*z* (%): 122 ($MH_2^+-C_4H_9$, 50), 105 (65), 77 (60), 58 (100), 43 (20). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.26 (9H, s, $C(CH_3)_3$), 7.30–7.88 (5H, m, H-Ar), 8.50 (1H, br s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.45 ($C(CH_3)_3$), 53.26 ($C(CH_3)_3$), 128.52, 129.18, 130.21, 133.89 (C-Ar), 171.68 (C=O). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.49; H, 8.61; N, 7.82.

2.7. *N*-(2-Morpholinoethyl)-3-nitrobenzamide (3i)

White powder (0.25 g, yield 91%); mp 203–205 °C. IR (KBr) (ν_{max}/cm^{-1}): 3430, 2939, 2864, 1642, 1526, 1347. MS (EI, 70 eV) *m*/*z* (%): 167 ($MH_2^+-C_6H_{12}NO$, 25), 150 (5), 121 (15), 65 (40), 58 (100), 41 (10). ^{1}H NMR (300 MHz, D_2O, NH exchanged): δ_H (ppm) 2.39 (4H, t, $^3J_{HH} = 4.1$ Hz, CH_2–N–CH_2), 2.52 (2H, t, $^3J_{HH} = 6.9$ Hz, N–CH_2–CH_2–NH), 2.98 (2H, t, $^3J_{HH} = 6.9$ Hz, N–CH_2–CH_2–NH), 3.56 (4H, t, $^3J_{HH} = 4.1$ Hz, CH_2–O–CH_2), 7.45 (1H, t, $^3J_{HH} = 7.9$ Hz, H-Ar), 8.00 (1H, d, $^3J_{HH} = 7.6$ Hz, H-Ar), 8.11 (1H, d, $^3J_{HH} = 7.8$ Hz, H-Ar), 8.39 (1H, s, H-Ar). ^{13}C NMR (75 MHz, D_2O): δ_C (ppm) 35.57 (N–CH_2–CH_2–NH), 52.36 (CH_2–N–CH_2), 54.11 (N–CH_2–CH_2–NH), 66.05 (CH_2–O–CH_2), 123.45, 125.49, 129.38, 135.01, 137.86, 147.54 (C-Ar), 172.62 (C=O). Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 55.79; H, 6.27; N, 14.93.

2.8. *N*-(2,4,4-Trimethylpentan-2-yl)-3-nitrobenzamide (3j)

White powder (0.26 g, yield 92%); mp 205–207 °C. IR (KBr) (ν_{max}/cm^{-1}): 3435, 2914, 1643, 1543, 1377. MS (EI, 70 eV) *m*/*z* (%): 167 ($MH_2^+-C_8H_{17}$, 20), 150 (2), 121 (20), 100 (100), 65 (55), 56 (40), 42 (25). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.94 (9H, s, $C(CH_3)_3$), 1.73 (6H, s, $C(CH_3)_2$), 1.64 (2H, s, CH_2), 7.61 (1H, t, $^3J_{HH} = 7.5$ Hz, H-Ar), 8.20 (1H, d, $^3J_{HH} = 7.7$ Hz, H-Ar), 8.29 (1H, d, $^3J_{HH} = 7.1$ Hz, H-Ar), 8.47 (1H, br s, NH), 8.64 (1H, s, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 27.22 ($C(CH_3)_2$), 31.29 (CH_2), 31.51 ($C(CH_3)_3$), 52.57 ($C(CH_3)_3$), 54.94 ($C(CH_3)_2$), 123.72, 124.31, 129.51, 135.68, 141.96, 147.88 (C-Ar), 167.58 (C=O). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.65; H, 7.82; N, 9.98.

2.9. (*E*)-(Cyclohexylimino)methyl 3-nitrobenzoate 4

White powder (0.26 g, yield 95%); mp 70–72 °C. IR (KBr) (ν_{max}/cm^{-1}): 3341, 2941, 2859, 1687, 1598, 1535. MS (EI, 70 eV) *m*/*z* (%): 276 (M^+, 20), 167 (35), 150 (13), 121 (15), 74 (25), 65 (60), 58 (100), 43 (25). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.12–1.72 (10H, m, $5CH_2$ of cyclohexyl), 3.58 (1H, m, CH–N of cyclohexyl), 7.80 (1H, t, $^3J_{HH} = 7.8$ Hz, H-Ar), 7.91 (1H, s, CH=N), 8.33 (1H, d, $^3J_{HH} = 7.4$ Hz, H-Ar), 8.45 (1H, d, $^3J_{HH} = 7.9$ Hz, H-Ar), 8.60 (1H, s, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 24.79, 25.58, 32.75 ($5CH_2$ of cyclohexyl), 46.48 (CH–N of cyclohexyl), 124.26, 127.72, 130.95, 133.02, 135.82, 148.30 (C-Ar), 160.38 (CH=N), 166.00 (C=O). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.76; H, 5.73; N, 10.23.

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