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Zinc chloride catalyzed three-component Ugi reaction: synthesis of *N*-cyclohexyl-2-(2-hydroxyphenylamino)acetamide derivatives

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ABSTRACT

The ability of zinc chloride as a catalyst to promote the three-component Ugi reaction of 2-aminophenols, aliphatic or aromatic aldehydes, and cyclohexyl isocyanide in methanol at room temperature is described. The *N*-cyclohexyl-2-(2-hydroxyphenylamino) amide products are obtained in high yields. When *N*,*N*-dimethylformamide dimethyl acetal and triethyl orthoformate, as two new components of the three-component Ugi reaction are used instead of the aldehyde the reaction gives *N*-cyclohexyl-2-(dimethylamino)-2-(2-hydroxyphenylamino)acetamide and *N*-cyclohexyl-2-(2-hydroxyphenylamino)-2-ethoxyacetamide derivatives, respectively.

2-Aminoacetamides are an important class of compounds with pharmaceutical activity.[1] Milacemide (*n*-pentylaminoacetamide, **1**)[2] and safinamide (NW 1015, **2**)[3] were introduced as promising anti-epileptic agents (Fig. 1). Due to the importance of compounds with this scaffold many efforts have been made on the synthesis of 2-aminoacetamide[4] and its derivatives.[5] Therefore, the introduction of new routes for the synthesis of 2-aminoacetamide derivatives is important.

The reactivity of isocyanides, with a formally monovalent carbon, has been well described.[6,7] Synthetic interest in isocyanides is generally associated with their reaction with carbonyl and imine derivatives as exemplified in the Passerini and Ugi reactions, respectively. From a mechanistic point of view, a carboxylic acid as the fourth component plays a dual role in the Ugi reaction. It serves as a catalyst for the formation of iminium ion intermediates and as a donor of an acyl group. There are a few reports of Ugi reactions in which water acts as an internal nucleophile instead of a carboxylic acid.[8,9] These three-component Ugi reactions lead to the transformation of an aldehyde, a secondary amine, and an isocyanide into an α-aminoamide. Recently, Pan and List reported the first catalytic three-component Ugi reaction with primary amines.[9] They identified phenylphosphinic acid as the best catalyst for this reaction at 80 °C in toluene.[9] $Sc(OTf)_3$ as a Lewis acid also promotes this reaction but with low conversion (30%).[9]

As part of our current studies on multi-component reactions (MCRs),[10] and the chemistry of isocyanides,[11] we investigated the three-component Ugi reaction of aldehydes **1**, 2-aminophenols **2,** and cyclohexyl isocyanide (**3**) under non protic acid reaction conditions using $ZnCl_2$ as the catalyst (Scheme 1).

This reaction does not proceed in the absence of catalyst at room temperature or refluxing conditions in methanol even after 24 h. We initially investigated various Lewis acid catalysts for this reaction (Table 1). Some of the catalysts including $SnCl_4$, $AlCl_3$, and $InCl_3$ gave no conversion into the product (Table 1, entries 1, 2 and 3). The desired product was obtained in a poor yield when $Sc(OTf)_3$ was used as the catalyst (Table 1, entry 4). Remarkably, we found $ZnCl_2$ and $ZnBr_2$ to be highly active catalysts for this reaction, giving the desired product in 91% and 88% conversions, respectively (Table 1, entries 5 and 6). Decreasing the catalyst loading from 10 to 5 mol % resulted in a considerably lower yield of product.

In order to find the best solvent, the reaction between 2-aminophenol (**2**), 4-chlorobenzaldehyde (**1a**), and cyclohexyl isocyanide (**3**) in the presence of $ZnCl_2$ was investigated in water and various organic solvents. As can be seen in Table 2, MeOH was the best solvent with respect to the yield and reaction time.

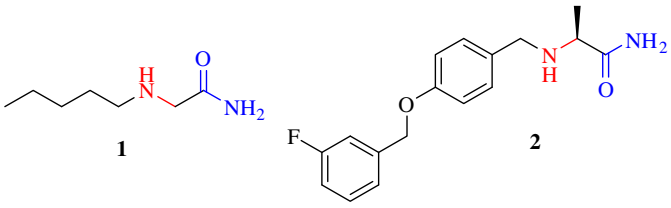

Figure 1. Examples of biologically active 2-aminoacetamide derivatives.

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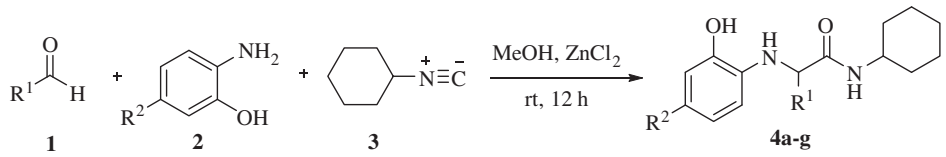


Scheme 1. Synthesis of *N*-cyclohexyl-2-(2-hydroxyphenylamino)acetamide derivatives **4a**–**g**.

Table 1
Identification of an efficient catalyst for the three-component Ugi reaction[a]

Entry	1	2	3	4	5	6
Catalyst	$SnCl_4$	$AlCl_3$	$InCl_3$	$Sc(OTf)_3$	$ZnCl_2$	$ZnBr_2$
Yield[b] (%)	0	0	0	27 (30)[9]	91	88

[a] Reaction conditions: 4-Chlorobenzaldehyde (1 mmol), 2-aminophenol (1 mmol), cyclohexyl isocyanide (1 mmol), catalyst (10 mol %), MeOH, room temperature, 12 h.
[b] Isolated yield.

Table 2
The effect of solvent on the reaction time and yield[a]

Entry	1	2	3	4	5	6
Solvent	H_2O	EtOH	MeOH	CH_3CN	CH_2Cl_2	$C_6H_5CH_3$
Yield[b] (%)	43	62	91	0	0	57

[a] Reaction conditions: 4-Chlorobenzaldehyde (1 mmol), 2-aminophenol (1 mmol), cyclohexyl isocyanide (1 mmol), $ZnCl_2$ (10 mol %), room temperature, 24 h (except in MeOH, 12 h).
[b] Isolated yield.

Using $ZnCl_2$ as the catalyst and MeOH as the solvent, we initiated a study to explore the scope of this new three-component Ugi reaction (Scheme 1). Various aldehydes **1** containing electron-donating and electron-withdrawing groups reacted with 2-aminophenol derivatives **2** and cyclohexyl isocyanide (**3**) in the presence of $ZnCl_2$ via a 1:1:1 addition reaction in MeOH at ambient temperature to produce *N*-cyclohexyl-2-(2-hydroxyphenylamino)acetamide derivatives **4a–g** in high yields (Fig. 2).

The structures of the products were deduced from their IR, ^1H NMR and in some cases, ^{13}C NMR spectra. The ^1H NMR spectrum of **4a** consisted of a multiplet due to the cyclohexyl ring protons ($\delta = 1.07–1.78$), a broad singlet for the NH–*CH* cyclohexyl proton ($\delta = 3.47$), a doublet for the NH–*CH*-Ar methine ($\delta = 5.01$, $^3J_{HH} = 7.2$ Hz), a doublet for the *NH*–CH-Ar proton ($\delta = 5.35$, $^3J_{HH} = 7.2$ Hz), a multiplet at $\delta = 6.19–6.69$ for the aromatic protons of the phenol ring, two doublets for the aromatic protons of the phenyl chloride ring ($\delta = 7.37$, $^3J_{HH} = 7.2$ Hz and $\delta = 7.45$, $^3J_{HH} = 7.2$ Hz), a broad singlet for NH ($\delta = 8.25$) and a singlet for the OH ($\delta = 9.50$). The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 18 distinct resonances, and partial assignment of these resonances is given in the experimental section.

The versatility of this MCR with respect to the *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (**7**) and triethyl orthoformate (**8**) instead of aldehydes, under the same reaction conditions, was also studied (Scheme 2). Using this approach, gave new classes of products: *N*-cyclohexyl-2-(dimethylamino)-2-(2-hydroxyphenylamino)acetamides **9a**,**b** and *N*-cyclohexyl-2-(2-hydroxyphenylamino)-2-ethoxyacetamides **10a**,**b**, respectively.

This reaction proceeded under mild conditions and afforded good yields of products.

To the best of our knowledge, this is the first report of a three-component Ugi reaction with DMF-DMA (**7**) or triethyl orthoester (**8**).

Although no detailed mechanistic studies have been carried out at this point, it is conceivable that the initial event is the formation of imine **5** from condensation between the aldehyde and 2-aminophenol. Next, the Zn(II) coordinated iminium intermediate **6** undergoes addition to the isocyanide **3** to give the nitrilium ion

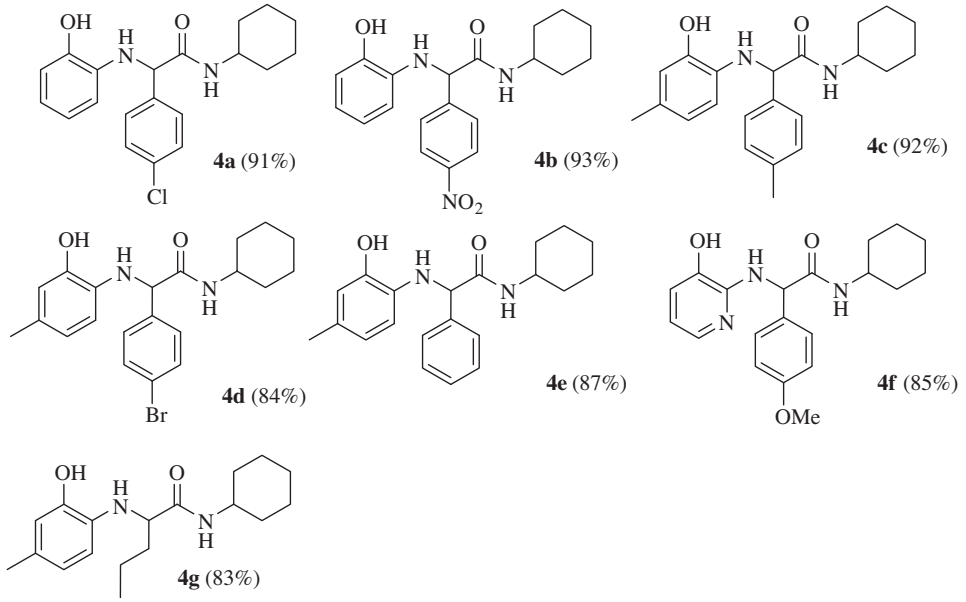
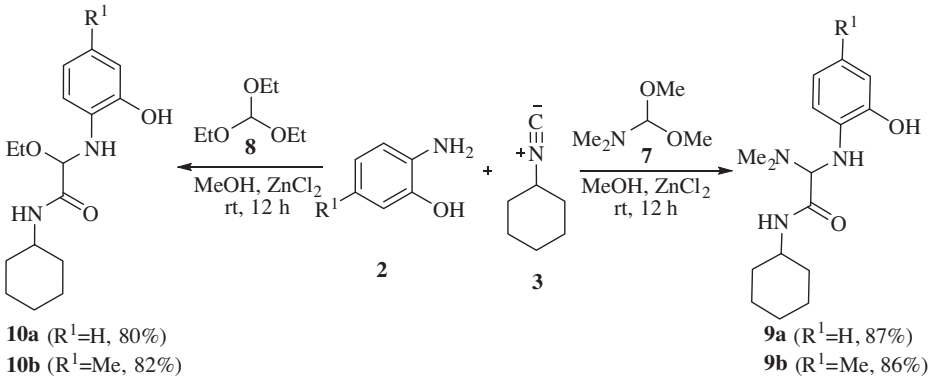
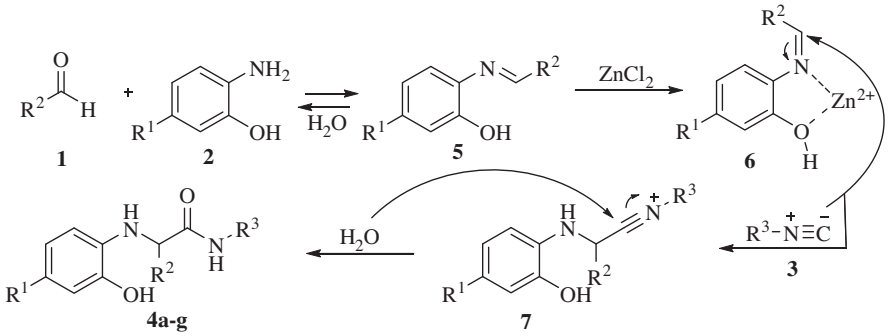


Figure 2. The structures of products **4a**–**g**.



Scheme 2. Synthesis of *N*-cyclohexyl-2-(dimethylamino)-2-(2-hydroxyphenylamino)acetamides **9a**,**b** and *N*-cyclohexyl-2-(2-hydroxyphenylamino)-2-ethoxyacetamide derivatives **10a**,**b**.



Scheme 3. Proposed mechanism for the formation of compounds **4a**–**g**.

7. Finally, H_2O which is released during imine formation reacts with intermediate **7** to generate the products **4a–g** (Scheme 3).

It is important to note that our attempts to replace the 2-aminophenols with aniline, *o*-phenylenediamine and 2-aminobenzenethiol failed.

In conclusion, we have developed an efficient and potentially useful protic acid free, Zn(II)-catalyzed, three-component Ugi reaction. *N*-Cyclohexyl-2-(2-hydroxyphenylamino)acetamide, *N*-cyclohexyl-2-(dimethylamino)-2-(2-hydroxyphenylamino)acetamide, and *N*-cyclohexyl-2-(2-hydroxyphenylamino)-2-ethoxyacetamide derivatives were formed in good yields upon Ugi reaction of readily available substrates. Moreover, the present synthesis offers additional points of structural diversity on the product skeleton for further transformation. The broad scope, operational simplicity, and mild reaction conditions should render this method an attractive approach for the generation of 2-aminoacetamides.

2-(4-Chlorophenyl)-*N*-cyclohexyl-2-(2-hydroxyphenylamino)acetamide (4a); typical procedure

To a stirred solution of $ZnCl_2$ (0.01 g, 0.10 mmol), 2-aminophenol **2** (0.11 g, 1.0 mmol), and cyclohexyl isocyanide **3** (0.11 g, 1.0 mmol) in MeOH (10 mL), 4-chlorobenzaldehyde (**1a**) (0.14 g, 1.0 mmol) was added. The mixture was stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and the residue crystallized from CH_2Cl_2/*n*-hexane (3:1) to give **4a** as a brown solid (0.33 g, 91%); mp 196–198 °C. IR (KBr) cm^{-1}: 3521, 2934, 2856, 1739, 1662, 1591, 1526, 1450. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.07–1.78 (10H, m, $5CH_2$ of cyclohexyl), 3.47 (1H, m, CH of cyclohexyl), 5.01 (1H, d, $^3J_{HH}$ = 7.2, NH–*CH*), 5.35 (1H, d, $^3J_{HH}$ = 7.2, CH–*NH*), 6.19–6.69 (4H, m, CH-Ar), 7.37 (2H, d, $^3J_{HH}$ = 7.2, CH-Ar), 7.45 (2H, d, $^3J_{HH}$ = 7.2, CH-Ar), 8.25 (1H, d, $^3J_{HH}$ = 6.8, NH), 9.50 (1H, s, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.7, 24.8, 25.6, 32.5, 32.7, 48.1, 59.4, 111.3, 114.1, 117.2, 119.9, 128.8, 128.9, 132.4, 135.3, 139.5, 144.8, 169.6. MS (EI, 70 eV), *m*/*z* (%): 358 (M^+, 15), 265 (35), 232 (100), 210 (20), 149 (40), 139 (80), 126 (40), 83 (70), 55 (60). Anal. Calcd for $C_{20}H_{23}ClN_2O_2$: C, 66.94; H, 6.46; N, 7.81. Found C, 66.93; H, 6.39; N, 7.78.

N-Cyclohexyl-2-(2-hydroxy-4-methylphenylamino)-2-*p*-tolylacetamide (4c)

Brown powder (0.32 g, 92%); mp > 290 °C. IR (KBr) cm^{-1}: 3419, 2932, 2856, 1721, 1592, 1526, 1489. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.06–1.76 (10H, m, $5CH_2$ of cyclohexyl), 2.03 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.47 (1H, m, CH of cyclohexyl), 4.95 (1H, d, $^3J_{HH}$ = 7.8, NH–*CH*), 5.21 (1H, d, $^3J_{HH}$ = 7.8, CH–*NH*), 6.11 (1H, s, CH-Ar), 6.20 (1H, d, $^3J_{HH}$ = 7.6, CH-Ar), 6.56 (1H, d, $^3J_{HH}$ = 7.6, CH-Ar), 7.11 (2H, d, $^3J_{HH}$ = 7.6, CH-Ar), 7.34 (2H, d, $^3J_{HH}$ = 7.6, CH-Ar), 8.18 (1H, d, $^3J_{HH}$ = 7.7, NH), 9.24 (1H, br s, OH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 21.1, 21.3, 24.8, 24.9, 25.6, 32.5, 32.8, 48.0, 59.9, 112.0, 113.9, 117.1, 127.0, 128.1, 129.3, 135.6, 136.9, 137.4, 142.6, 170.3. MS (EI, 70 eV), *m*/*z* (%): 354 (M^++2, 10), 353 (8), 339 (15), 313 (8), 281 (100), 265 (30), 253 (40), 225 (20), 151 (100), 115 (60), 83 (70), 57 (60). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found C, 74.78; H, 8.12; N, 7.88.

N-Cyclohexyl-2-(dimethylamino)-2-(2-hydroxyphenylamino) acetamide (9a)

Gray powder (0.25 g, 87%); mp 236–239 °C. IR (KBr) cm^{-1}: 3402, 3183, 2959, 2856, 1631, 1589, 1527, 1443. ^1H NMR

(300.13 MHz, DMSO-d_6) δ: 1.31–1.77 (10H, m, $5CH_2$ of cyclohexyl), 3.14 (3H, s, CH_3), 3.35 (3H, s, CH_3), 3.46 (1H, m, CH of cyclohexyl), 4.10 (1H, br s, NH–*CH*), 4.56 (1H, br s, CH–*NH*), 6.22–6.89 (4H, m, CH-Ar), 8.42 (1H, br s, NH), 9.42 (1H, br s, OH). MS (EI, 70 eV), *m*/*z* (%): 291 (M^+, 5), 275 (15), 247 (100), 221 (20), 198 (70), 163 (65), 126 (90), 97 (80), 55 (90). Anal. Calcd for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found C, 66.12; H, 8.71; N, 14.37.

N-Cyclohexyl-2-ethoxy-2-(2-hydroxyphenylamino)acetamide (10a)

White powder (0.23 g, 80%); mp 240–242 °C. IR (KBr) cm^{-1}: 3313, 2956, 2871, 1672, 1592, 1526, 1453. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.31–1.97 (13H, m, $5CH_2$ of cyclohexyl and CH_3), 3.15 (2H, br s, OCH_2), 3.53 (1H, m, CH of cyclohexyl), 4.06 (1H, br s, NH–*CH*), 4.55 (1H, br s, CH–*NH*), 6.25–6.89 (4H, m, CH-Ar), 8.38 (1H, br s, NH), 9.38 (1H, br s, OH). MS (EI, 70 eV), *m*/*z* (%): 292 (M^+, 15), 250 (45), 211 (70), 199 (100), 184 (80), 113 (65), 104 (45), 88 (70), 57 (60). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found C, 65.57; H, 8.11; N, 9.69.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.079.

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