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ABSTRACT

One-pot, multi-component condensation reaction of phenols, aromatic aldehydes, and amides in the presence of catalytic amount of trityl chloride (TrCl) as a homogeneous organocatalyst under solvent-free condition to prepare amido-alkyl-phenols has been reported. It is interesting that TrCl by in situ generation of trityl carbocation with inherent instability catalyzes the reaction.

Keywords: amido-alkyl-phenol, multi-component reaction, trityl chloride, neutral, phenol.

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Graphical Abstract

Solvent-free preparation of amido-alkyl-phenols catalyzed by trityl chloride under neutral media

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Introduction

Multi-component reactions (MCRs) achieve important role in combinatorial chemistry due to the ability to preparation of target compounds with more atomic economy and efficiency by the reaction of several compounds together in a single step. Additionally, MCRs increase simplicity and synthetic efficiency on the conventional organic synthesis.¹⁻⁷

Development of organocatalytic transformations in which the reactions are catalyzed by organic molecules has become an area of tremendous importance in current organic synthesis specially from the green chemistry point of view.⁸ Unlike the conventional catalysis, these organocatalysts are advantageous in some ways like high stability, availability of the catalyst, metal reduced toxicity, free nature, and simple reaction conditions and can promote a chemical reaction through various activation modes.^{5,9}

1-Amidoalkyl-2-naphthols are of importance as they can be easily converted to 1-aminoalkyl-2-naphthol derivatives by hydrolysis, which are biologically interesting compounds (Figure 1).

«Figure 1»

1-Aminoalkyl-2-naphthols have been applied as bradycardiac and hypotensive agents.^{10,11} Also, 1-amidoalkyl-2-naphthols can be converted to 1,3-oxazine derivatives (Figure 1.).¹²

Some pharmaceutical properties have been reported for 1,3-oxazines, such as antibiotic,¹³ antitumor,¹⁴ and analgesic activities.¹⁵

Herein, in continuous the previous reports on the synthesis of amido-alkyl-phenols,¹⁶⁻¹⁸ we have introduced a new protocol for the preparation of amido-alkyl-phenols by the one-pot, multi-component condensation reaction of various phenols, aromatic aldehydes, and amides using of trityl chloride (TrCl) as a homogeneous organocatalyst under solvent-free and neutral condition (Scheme 1).

«Scheme 1»**Results and discussion**

At first, the condensation of 4-benzylphenol (1 mmol) with benzaldehyde (1 mmol) and acetamide (1.2 mmol) was selected as model reaction to optimize the reaction conditions. Then, different conditions such as kind of catalyst, amount of catalyst and temperature, were investigated on the model reaction.

In the next step, to optimize amount of the catalyst and temperature, the model reaction was examined using different amounts of TrCl at range of 90-130 °C under solvent-free conditions (Table 1). As Table 1, indicates that, the reaction was efficiently performed in the presence of 15 mol% of TrCl at 110 °C, and afforded the desired product in high yield (Table 1, entry 4).

«Table 1»

In a proposed mechanism that is supported by the literature,² (Scheme 2), aldehyde was activated by the trityl carbocation. Two resonance forms of activated aldehyde (**I** and **II**) could be produced and converted together in a reversible reaction.^{4,5,19,20,21} **I** and **II** were introduced by Oikawa et al as cationic intermediates for the first time.²² Therefore, **I** and **II** act as an activated complex and then react with phenolic compound to give **III**, which converts to **IV** by proton transferring. Then, **IV** could be converted to **V** by removing one molecule of triarylmethanol. Afterward, **V** or **IV** reacts with amide to obtain **VI**. Intermediate **VI** reacts with triarylmethanol to give amido-alkyl-phenols and TrCl.

«Scheme 2»

To study the efficacy of TrCl in the synthesis of amido-alkyl-phenols, various aromatic aldehydes containing electron-releasing substituents, electron-withdrawing substituents and halogens were reacted with various phenolic compounds (phenol, 4-benzylphenol and

4-bromophenol) and amides (acetamide and benzamide) to produce the desired products in moderate to high yields. The results are displayed in Table 2.

«Table 2»

As it is shown in the Scheme 1, acetamido-alkyl-phenols were prepared by the one-pot multi-component condensation reaction between phenolic compounds, aldehydes and acetamide using TrCl as catalyst. The mixture was stirred for 180-270 min at 110 °C which afforded the desired products in 64–92%. The structures of these mentioned products were confirmed by the IR, ^1H and ^{13}C NMR and mass analysis (Experimental section). In the IR spectra, the absorbance of carbonyl group ($\text{C}=\text{O}$) between 1634-1656 cm^{-1} , two strong peaks at about ca. 3179 cm^{-1} and 3410 cm^{-1} related to $\nu_{\text{O-H}}$ and $\nu_{\text{N-H}}$ stretching vibrations are useful to identify of these compounds. In the ^1H NMR spectra of them (for samples in DMSO-d_6 solution), the chemical shift of OH (phenolic hydrogen), NH (amidic hydrogen) and CH_3 (the hydrogens of methyl group) were displayed at about 9.35, 8.5 and 1.82. Also, in ^{13}C NMR spectra (for samples in DMSO-d_6 solution), the chemical shift of carbonyl group ($\text{C}=\text{O}$), aliphatic CH and CH_3 were depicted at about 168.4, 56.4 and 22.2, respectively. These important observations helped us to identify the structures of acetamido-alkyl-phenols (Experimental section, 1-9).

In another study, to confirm that *in situ* generated HCl or another H^+ in the reaction condition could not be catalyzed the reaction, the reaction was tested using DABCO (1,4-Diazabicyclo[2.2.2]octane) as a base in which no progress in the reaction was observed. Then, the model reaction was examined in the presence of TrCl together with DABCO where in the reaction was successfully carried out and the product was obtained in 75% within 210 minutes. In these conditions, DABCO as an acid scavenger, absorbs H^+ and produces $[\text{DABCO-H}_2]\text{Cl}_2$.

These experiments clearly confirm that *in situ* prepared HCl or another source of H⁺ in the reaction conditions; could not be catalyzed the reaction.

In conclusion, we have introduced the one-pot multi-component synthesis of amido-alkyl-phenols by the reaction of various aromatic aldehydes, phenolic compounds (4-benzylphenol, 4-bromophenol and phenol) and amides (acetamide and benzamide) using trityl chloride (TrCl) as catalyst at 110 °C under solvent-free conditions.

Experimental

Materials

All chemicals were purchased from Fluka or Merck Chemical Companies. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ¹HNMR (400 MHz) and ¹³CNMR (100 MHz) were recorded on a Bruker AVANCE- DRX. FT-NMR spectrometer (δ in ppm). Melting points were run on a Büchi B-545 apparatus in open capillary tubes. IR spectra were recorded on a Perkin Elmer PE-1600-FTIR. Mass spectra were run on Agilent Technology (HP) Network Mass Selective Detector 5973 (70eV) apparatus.

2.2. General procedure for the synthesis of amido-alkyl-phenols using TrCl:

To a well-ground mixture of phenolic compound (1 mmol), aldehyde (1 mmol) and amide derivative (1.2 mmol) in a 10 mL round-bottomed flask connected to a reflux condenser, was added the catalyst (15 mol%), and the resulting mixture was stirred in an oil-bath at 110 °C. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature and then petroleum ether (5 mL) was added to the crude reaction mixture and filtered to separate the catalyst which will be recycled for other reactions. Subsequently, the solid residue (crude product) was purified by plate chromatography on silica gel with n-hexan/ethylacetate (6/4) as an eluent to give the desired amido-alkyl-phenols.

2.3. Spectral data of compounds:

N-((5-benzyl-2-hydroxyphenyl)(phenyl)methyl)acetamide (**1**): mp: 174-176 °C; IR (KBr, cm^{-1}): 3410, 3179, 3024, 1644, 1611; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.96 (s, 3H), 3.85 (s, 2H), 6.48 (d, $J = 8.4$ Hz, 1H), 6.77 (d, $J = 8$ Hz, 1H), 6.99 (d, $J = 8$ Hz, 1H), 7.15-7.28 (m, 6H), 7.37-7.72 (m, 2H), 8.09 (d, $J = 8$ Hz, 2H), 8.76 (d, $J = 8$ Hz, 1H), 9.56 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 23.09, 40.98, 50.61, 115.89, 121.83, 122.14, 126.28, 127.82, 128.79, 129.26, 130.17, 132.10, 134.41, 142.21, 145.25, 148.17, 153.08, 169.28; MS: $m/z = 331$ (M^+).

N-((5-benzyl-2-hydroxyphenyl)(p-tolyl)methyl)acetamide (**2**): mp: 183-184 °C; IR (KBr, cm^{-1}): 3412, 3246, 3025, 1648, 1610; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.90 (s, 3H), 2.25 (s, 3H), 3.81 (s, 2H), 6.31 (d, $J = 5.96$ Hz, 1H), 6.71 (d, $J = 5.48$ Hz, 1H), 6.87 (dd, $J = 4.04, 1.40$ Hz, 1H), 7.07-7.28 (m, 10H), 8.47 (d, $J = 5.96$ Hz, 1H), 9.56 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO-d_6) δ (ppm) 21.04, 23.10, 41.03, 50.47, 115.63, 126.23, 127.44, 128.45, 128.53, 128.76, 128.93, 129.01, 129.19, 131.66, 135.96, 140.29, 142.30, 153.04, 168.84; MS: $m/z = 345$ (M^+).

N-((5-benzyl-2-hydroxyphenyl)(3-nitrophenyl)methyl)acetamide (**3**): mp: 210-215 °C; IR (KBr, cm^{-1}): 3381, 3025, 2733, 1635, 1606; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.88 (s, 3H), 3.79 (s, 2H), 6.44 (d, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 8$ Hz, 1H), 6.81 (s, 1H), 6.92 (d, $J = 8$ Hz, 1H), 7.13-7.58 (m, 8H), 7.59 (d, $J = 4.8$ Hz, 1H), 8.41 (1H, s), 9.39 (1H, s) ppm; ^{13}C NMR (100 MHz; DMSO-d_6) δ (ppm) 22.89, 40.97, 51.48, 115.58, 124.14, 126.26, 127.38, 127.83, 128.76, 128.82, 128.93, 128.98, 129.25, 129.58, 131.25, 133.13, 141.85, 142.15, 153.72, 168.78; MS: $m/z = 376$ (M^+).

N-((5-benzyl-2-hydroxyphenyl)(2-nitrophenyl)methyl)acetamide (**4**): mp: 226-228 °C; IR (KBr, cm^{-1}): 3403, 3271, 3027, 1656, 1614; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.79 (s, 3H),

3.68(s, 2H), 6.60-6.70 (m, 3H), 6.82 (dd, $J = 6.24, 1.96$ Hz, 1H), 7.01-7.18 (m, 3H), 7.32-7.34 (m, 2H), 7.34-7.41 (m, 1H), 7.75 (s, 1H), 7.77 (s, 1H), 7.78 (d, $J = 7.36$ Hz, 1H), 8.43 (d, $J = 7.96$ Hz, 1H), 9.36 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO- d_6) δ (ppm) 22.28, 46.91, 56.00, 115.01, 124.06, 125.73, 126.80, 127.65, 128.10, 128.43, 128.48, 128.63, 129.54, 130.89, 132.63, 135.98, 141.53, 148.81, 153.00, 168.41; MS: $m/z = 376$ (M^+).

N-((5-benzyl-2-hydroxyphenyl)(phenyl)methyl)benzamide (**5**): mp: 204-206 °C; IR (KBr, cm^{-1}): 3403, 3062, 3028, 1630, 1603; ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 3.78 (s, 2H), 6.46 (d, $J = 8.4$ Hz, 1H), 6.67-6.92 (m, 11H), 7.13-7.27 (m, 7H), 8.23 (d, $J = 8.4$ Hz, 1H), 9.25 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO- d_6) δ (ppm) 41.04, 56.45, 111.91, 112.47, 115.41, 115.55, 126.21, 128.44, 128.56, 128.74, 128.87, 128.93, 131.14, 132.07, 142.39, 151.31, 153.50, 153.58, 168.59; MS: $m/z = 393$ (M^+).

N-((5-bromo-2-hydroxyphenyl)(4-chlorophenyl)methyl)acetamide (**6**): mp: 220-225 °C; IR (KBr, cm^{-1}): 3309, 3074, 2980, 2739, 1649, 1631; ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 1.85 (s, 3H), 5.95 (d, $J = 8.4$ Hz, 1H), 6.68 (s, 2H), 6.99 (d, $J = 8$ Hz, 2H), 7.23-7.35 (m, 3H), 8.66 (s, 1H), 9.35 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO- d_6) δ (ppm) 24.19, 56.36, 116.70, 129.78, 130.14, 130.50, 132.84, 133.97, 143.90, 158.02, 169.99; MS: $m/z = 354$ (M^+).

N-((2,4-dichlorophenyl)(2-hydroxyphenyl)methyl)acetamide (**7**): mp: 228-230 °C; IR (KBr, cm^{-1}): 3300.7, 3065, 2808, 1634, 1613; ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 1.85 (s, 3H), 6.33 (d, $J = 8$ Hz, 1H), 6.47 (d, $J = 8$ Hz, 1H), 6.71 (d, $J = 8$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 7.14-7.81 (m, $J = 8$ Hz, 4H), 7.96 (s, 1H), 8.69 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO- d_6) δ (ppm) 24.08, 58.14, 117.91, 124.91, 125.23, 127.41, 129.90, 130.08, 130.48, 133.03, 133.9, 134.12, 143.26, 154.17, 170.50; MS: $m/z = 310$ (M^+).

N-((5-bromo-2-hydroxyphenyl)(2-bromophenyl)methyl)acetamide (**8**): mp: 197-200 °C; IR (KBr, cm^{-1}): 3300, 3064, 2808, 1634, 1613; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.21 (s, 3H), 6.45 (s, 1H), 6.61 (s, 1H), 6.98 (s, 1H), 7.06-7.32 (m, 5H), 7.55 (d, $J = 6.8$ Hz, 1H), 8.69 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO-d_6) δ (ppm) 22.82, 51.72, 126.26, 127.17, 127.86, 128.09, 128.67, 128.86, 129.10, 129.34, 133.25, 141.20, 141.42, 169.66; MS: $m/z = 399$ (M^+).

N-((5-bromo-2-hydroxyphenyl)(2,5-dimethoxyphenyl)methyl)acetamide (**9**): mp: 215-217 °C; IR (KBr, cm^{-1}): 3372, 3267, 2854, 1652; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.82 (s, 3H), 3.31 (s, 3H), 3.76 (s, 3H), 6.30 (d, $J = 6$ Hz, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 6.87 (d, $J = 6.4$ Hz, 1H), 7.09-7.28 (m, 4H), 8.50 (d, $J = 9.2$ Hz, 1H), 9.35 (s, 1H) ppm; ^{13}C NMR (100 MHz; DMSO-d_6) δ (ppm) 23.12, 41.05, 50.46, 115.68, 126.26, 127.32, 128.33, 128.48, 128.79, 128.96, 129.05, 131.78, 141.55, 142.32, 152.94, 168.75; MS: $m/z = 380$ (M^+).

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Figure 1. The general structures of 1-aminoalkyl-2-naphthols (a) and 1,3-oxazines (b).

Scheme 1. The Synthesis and general structure of amido-alkyl-phenols.

Scheme 2. The proposed mechanism for the synthesis of amido-alkyl-phenols.

Table 1. Effect of different amounts of the catalyst and temperature on the condensation of 4-benzylphenol (1 mmol) with benzaldehyde (1 mmol) and acetamide (1.2 mmol) under solvent-free conditions.

Entry	Mol% of Catalyst	Temp. (°C)	Time (min)	Yield ^a (%)
1	-	110	240	-
2	5	110	300	55
3	10	110	270	60
4	15	110	210	75
5	15	90	270	69
6	15	130	210	75
7	20	110	210	75

^aIsolated yield.

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Table 2. The synthesis of amido-alkyl-phenols using TrCl at 110 °C under solvent-free conditions.

1	2	3
[Time: 210 min / Yield: 75 %] Mp: 174-175 °C (174-176 °C) ⁷	[Time: 180 min / Yield: 64 %] Mp: 182-185 °C (183-184 °C) ⁷	[Time: 180 min / Yield: 71 %] Mp: 210-212 °C (210-215 °C) ⁷
4	5	6
[Time: 180 min / Yield: 87 %] Mp: 226-228 °C (226-228 °C) ⁷	[Time: 240 min / Yield: 79 %] Mp: 202-204 °C (204-206 °C) ⁷	[Time: 210 min / Yield: 87 %] Mp: 222-225 °C (220-225 °C) ⁷
7	8	9
[Time: 270 min / Yield: 92 %] Mp: 227-230 °C (228-230 °C) ⁷	[Time: 210 min / Yield: 78 %] Mp: 197-199 °C (197-200 °C) ⁷	[Time: 280 min / Yield: 75 %] Mp: 214-217 °C (215-217 °C) ⁷

^a Isolated yield.