$[MeC(OH)_2]^+ClO_4^-$: A New Efficient Organocatalyst for the Preparation of 1-Amido- and 1-Carbamato-alkyl Naphthols

Fatemeh Tamaddon,* Javad Moazeni Bistgani

Department of Chemistry, Yazd University, P. O. Box 89195-741, Yazd, Iran
Fax +98(351)8210644; E-mail: ftamaddon@yazduni.ac.ir

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Abstract: $[MeC(OH)_2]^+ClO_4^-$ as a super acidic ionic liquid is found to be a new and highly efficient catalyst in the synthesis of amidoalkyl naphthols via three-component condensation of β-naphthol and aldehydes with nitriles, amides, or carbamates.

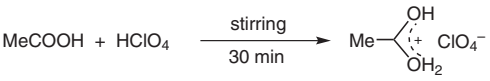
Key words: multicomponent reactions, amidoalkyl naphthols, ionic liquids, super acids

Multicomponent reactions (MCR) are of great interest to generate products by forming multiple new bonds in a single pot. Efficiency, atom economy, and simplicity are features that make MCR useful for the one-pot synthesis of complex molecules.[1] Amidoalkyl naphthols are used as precursors in the synthesis of aminoalkyl phenols[2] and oxazines.[3] These compounds exhibit a broad spectrum of medicinal activities such as antibiotic, antitumor, antimalarial, antianginal, antihypertensive, antipsychotic, and antirheumatic properties.[4–8]

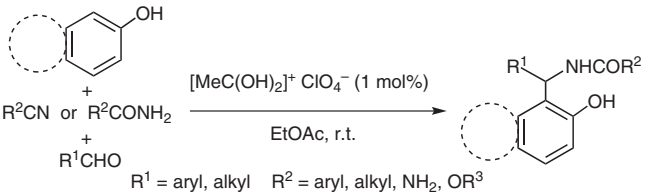
Amidoalkyl naphthols are mainly prepared via the one-pot, three-component condensation of phenol derivatives and aldehydes with nitriles, amides, or carbamates.[9–11] Although this reaction has been promoted by a variety of homogeneous and heterogeneous Lewis or Brønsted acid catalysts,[12–16] some of these procedures suffer from limited scope, low yields, use of expensive catalysts, and long reaction times. In addition, few catalyzed syntheses of amidoalkyl phenols take place at room temperature, and some investigations have pointed to the generation of dibenzoxanthene as a side product at high temperature.

One-pot catalytic organic transformations using organocatalysts have attracted significant interest in recent years.[17–19] The readily prepared nonaqueous mixture of acetic acid and percholoric acid which is able to protonate very weak organic bases was proposed as a super acid (pH = –4.4) by Conant and Hall in 1927.[20–22] This mixture, with the composition $[MeC(OH)_2]^+ClO_4^-$, can be considered as an acidic room-temperature ionic liquid and should be a good catalyst in organic transformations (Scheme 1). To our knowledge, this super acid has not been previously evaluated.

In a continuation of our investigations into catalytic organic transformations,[23–26] we have recently reported Ritter and Ritter-type reactions using silzic (silica-supported zinc chloride, $ZnCl_2/SiO_2$) as catalyst.[27] In continuation of our work, we have studied the catalytic behavior of $[MeC(OH)_2]^+ClO_4^-$ as a super acid in the synthesis of amidoalkyl naphthols. Herein we report an improved method for the synthesis of various types of amidoalkyl phenols via three-component condensation of phenols and aldehydes with nitriles, amides, or carbamates (Scheme 2).



Scheme 1



Scheme 2

Initially, to find the optimal conditions, reaction of benzaldehyde, 2-naphthol, and benzamide as a model system was performed under various conditions and loading of catalyst. As Table 1 shows, the best results were obtained in the presence of 1 mol% of $[MeC(OH)_2]^+ClO_4^-$ either at 80 °C under solvent-free conditions or in ethyl acetate at room temperature (Table 1, entries 5 and 6). In both cases, as the reaction progressed, the reaction product precipitated. Comparative studies of the model reaction using the same amounts of AcOH or $HClO_4$ on their own under solvent-free conditions showed that the desired amidoalkyl naphthol was formed in 50% yield together with the corresponding dibenzoxanthene as side product in 50% yield.

With these results in hand, we carried out further reactions in EtOAc at room temperature. A control experiment without catalyst did not afford the product even after heating. Various 1-amidoalkyl phenols were isolated in excellent yields by the reaction of 2-naphthol, aromatic or aliphatic aldehydes and amides using 1 mol% of $[MeC(OH)_2]^+ClO_4^-$ at room temperature. As illustrated in Table 2, various substrates were well tolerated. Aromatic aldehydes bearing electron-withdrawing groups reacted faster than those with electron-donating groups while the

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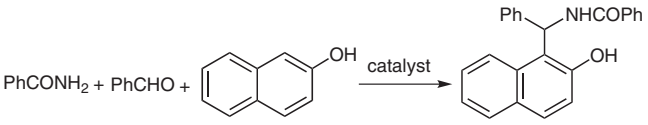
position of substitution did not have a significant effect on the reaction.

Table 1 Optimization of the Reaction of Benzaldehyde, 2-Naphthol, and Benzamide

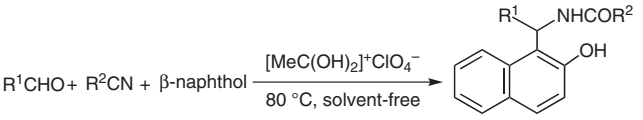


Entry	Catalyst (mol%), solvent	Temp (°C)	Time (min)	Yield (%)[a]
1	AcOH (50), –	80	80	50[b]
2	$HClO_4$ (20), –	80	80	50[b]
3	$[MeC(OH)_2]^+ClO_4^-$(0.5), EtOAc	r.t.	23	85
4	$[MeC(OH)_2]^+ClO_4^-$ (0.5), –	80	19	85
5	$[MeC(OH)_2]^+ClO_4^-$ (1), EtOAc	r.t.	12	94
6	$[MeC(OH)_2]^+ClO_4^-$ (1), –	80	9	95
7	$[MeC(OH)_2]^+ClO_4^-$ (2), EtOAc	r.t	8	91
8	$[MeC(OH)_2]^+ClO_4^-$ (2), –	80	8	92
9	$[MeC(OH)_2]^+ClO_4^-$ (5), EtOAc	r.t.	6	90
10	$[MeC(OH)_2]^+ClO_4^-$ (5), –	80	5	90

[a] Isolated yield.
[b] Dibenzoxanthene was formed as a side product.

Furthermore, this protocol was not limited to amides. Thus three-component reaction of 2-naphthol and aldehydes with methyl carbamat or urea led to the formation of the corresponding adducts in high yield (Table 2, entries 12 and 13).

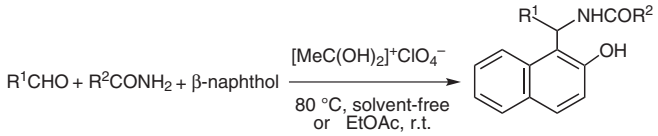
Table 3 Synthesis of Amidoalkyl Naphthols via Ritter-Type Reaction Using $[MeC(OH)_2]^+ClO_4^-$



Entry	R^1	R^2	Time (h)	Yield (%)[a]	Obs. mp (°C)	Lit. mp (°C)
1	Ph	Ph	5.5	88	237–239	239–240[8]
2	Ph	4-$O_2NC_6H_4$	5	91	246–248	247–249[8]
3	Ph	4-MeC_6H_4	7	84	222–224	223–225[8]
4	Ph	*n*-Pr	6.5	85	239–242	240–242[10]
5	4-BrC_6H_4	Ph	6	87	239–242	
6	4-BrC_6H_4	4-$O_2NC_6H_4$	5.5	90	237–240	
7	4-BrC_6H_4	2-furyl	5	90	241–244	
8	4-ClC_6H_4	Ph	5.5	85	236–239	

[a] Isolated yield.

Table 2 Synthesis[33,34] of 1-Amidoalkyl and 1-Carbamato-alkyl Naphthols Using $[MeC(OH)_2]^+ClO_4^-$



Entry	R^1	R^2	Time (min)	Yield (%)[a]	Obs. mp (°C)	Lit. mp (°C)
1	Ph	Ph	9	95	237–239	239–240[9]
2	4-$O_2NC_6H_4$	Ph	8	94	246–248	247–249[9]
3	4-MeC_6H_4	Ph	23	88	222–224	223–225[9]
4	2-furyl	Ph	11	90	235–238	234–236[11]
5	2-pyrrole	Ph	13	91	228–231	–
6	*n*-Pr	Ph	16	90	239–242	240–242[11]
7	Ph	Me	12	91	232–234	232–233[12]
8	2-pyrrole	Me	17	89	222–225	–
9	*n*-Pr	Me	20	88	232–235	–
10	Ph	4-BrC_6H_4	13	91	239–242	–
11	4-$O_2NC_6H_4$	4-BrC_6H_4	12	91	237–240	–
12	Ph	MeO	27	85	216–218	217–218[31]
13	Ph	NH_2	33	87	174–176	176–178[32]

[a] Isolated yield.

Ritter-type reaction of acetonitrile, β-naphthol, and aldehydes has been also reported as an alternative for the preparation of amidoalkyl naphthols.[31] Therefore, we studied reaction of β-naphthol and aldehydes with nitriles in the presence of $[MeC(OH)_2]^+ClO_4^-$ under solvent-free conditions. A series of amidoalkyl naphthols was prepared in good to excellent yields (Table 3).

In conclusion, we have developed an efficient catalytic process for the synthesis of amidoalkyl naphthols from both amides or nitriles in the presence of 1 mol% of $[MeC(OH)_2]^+ClO_4^-$ as a super acidic ionic liquid. Short reaction times, high yield, purity of the products, and simple workup and isolation are the features of this procedure.

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(33) **General Procedure for the $[MeC(OH)_2]^+ClO_4^-$-Catalyzed Synthesis of Amidoalkyl Naphthols**
A mixture of an aldehyde (1 mmol), β-naphthol (1 mmol) with amide, nitrile, urea, or carbamate (1 mmol) in the presence of $[MeC(OH)_2]^+ClO_4^-$ (1 mol%) was stirred in EtOAc (1 mL) at r.t. (or at 80 °C under solvent-free conditions) for the given times. After completion of the reaction (TLC monitoring), H_2O was added, and the precipitate was filtered off to give the corresponding amidoalkyl naphthols. Most of the products were known and characterized by comparison of their melting points and spectral data with those reported in the literature without further purification. In some cases the products were recrystallized from EtOH–H_2O (60:40).
(34) **Selected Characterization Data**
***N*-[(2-Hydroxynaphthalen-1-yl)(phenyl)methyl]-benzamide (Table 2, Entry 1)[9,18]**
White solid; mp 235–237 °C. IR (KBr): ν_{max} = 1625, 3065, 3418 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.20–7.90 (m, 16 H), 8.10–8.13 (d, 1 H, *J* = 8.4 Hz), 9.02 (d, 1 H, *J* = 8.4 Hz), 10.33 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 50.0, 119.1, 119.4, 123.4, 127.1, 127.2, 127.5, 127.8, 128.9, 129.1, 129.2, 129.3, 130.1, 132.1, 133.0, 135.0, 142.7, 147.0, 153.9, 166.4 ppm.
***N*-[(2-Hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl]-benzamide (Table 2, Entry 2)[29,8]**
Yellow solid; mp 247–249 °C. IR (KBr): ν_{max} = 1641, 3234, 3410 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.22–7.56 (m, 9 H), 7.82–7.91 (m, 4 H), 8.06 (d, 1 H, *J* = 8.4 Hz), 8.14 (d, 2 H, *J* = 8.4 Hz), 9.04 (d, 1 H, *J* = 8.1 Hz), 10.35 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 49.1, 117.4, 118.6, 122.6, 122.8, 123.4, 127.0, 127.4, 127.5, 128.4, 128.7, 130.0, 131.6, 132.2, 134.0, 146.2, 150.2, 153.4, 166.3 ppm.
***N*-[(2-Hydroxynaphthalen-1-yl)(*p*-tolyl)methyl]-benzamide (Table 2, Entry 3)[8,9]**
White solid; mp 223–225 °C. IR (KBr): ν_{max} = 1627, 3043, 3413 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.97 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 7.05–7.38 (m, 8 H), 7.74–7.81 (m, 2 H), 7.85 (d, 1 H, *J* = 8.4 Hz), 8.38 (d, 1 H, *J* = 8.4 Hz), 9.94 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.5, 22.6, 47.6, 118.4, 119.0, 122.3, 126.0, 126.2, 128.5, 129.0, 132.3, 135.0, 139.5, 153.0, 169.0 ppm.
***N*-[1-(2-Hydroxynaphthalen-1-yl)butyl]benzamide (Table 2, Entry 6)[30]**
White solid; mp 240–242 °C. IR (KBr): ν_{max} = 3415, 3222, 3204, 1633, 1575, 1528, 1342, 1074, 815, 747, 716 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 10.09 (s, 1 H), 8.60 (d, 1

H, *J* = 6.3 Hz), 8.23 (d, 1 H, *J* = 7.6 Hz), 7.81 (t, 3 H, *J* = 7.2 Hz), 7.71 (d, 1 H, *J* = 8.8 Hz), 7.53–7.44 (m, 4 H), 7.31 (t, 1 H, *J* = 7.3 Hz), 7.20 (d, 1 H, *J* = 8.8 Hz), 6.04 (q, 1 H, *J* = 7.1 Hz), 2.15–2.10 (m, 1 H), 1.90–1.80 (m, 1 H), 1.51–1.42 (m, 1 H), 1.30–1.20 (m, 1 H), 0.95 (t, 3 H, *J* = 7.3 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.2, 152.8, 134.7, 132.1, 131.1, 128.5, 128.4, 128.3, 128.2, 126.9, 126.3, 122.3, 119.8, 118.6, 118.5, 46.6, 36.0, 19.6, 13.8 ppm.

***N*-[Phenyl-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, Entry 7)[11,28]**

White solid; mp 232–233 °C. IR (KBr): ν_{max} = 3390, 3246, 3062, 1640, 1582, 1514, 1372, 1337, 1060, 808, 742, 696, 623 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (s, 3 H), 7.10 (m, 1 H), 7.12 (m, 1 H), 7.15 (m, 1 H), 7.17 (m, 1 H), 7.20 (m, 2 H), 7.21 (m, 1 H), 7.25 (m, 1 H), 7.35 (t, 1 H, *J* = 7.5 Hz), 7.70 (d, 1 H, *J* = 9.1 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.2, 40.3, 119.2, 122.9, 123.8, 126.6, 126.8, 128.5, 128.8, 128.9, 129.1, 129.8, 132.8, 143.1, 153.7, 169.0 ppm.

4-Bromo-*N*-[(2-hydroxynaphthalen-1-yl)(phenyl)-methyl]benzamide (Table 2, Entry 10)

Yellow solid; mp 239–242 °C. IR (KBr): ν_{max} = 3408, 3246, 3146, 1626 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.22 (m, 7 H), 7.41 (t, 2 H, *J* = 8.0 Hz), 7.66 (t, 2 H, *J* = 4.4 Hz), 7.78 (m, 4 H), 8.02 (d, 1 H, *J* = 8.0 Hz), 7.20 (m, 2 H), 9.08 (d, *J* = 4.0 Hz, 1 H), 10.26 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.7, 115.5, 118.2, 122.6, 126.8, 128.3, 128.8, 128.9, 133.1, 142.8, 153.6, 167.8 ppm. Anal. Calcd for $C_{24}H_{18}BrNO_2$: C, 66.68; H, 4.20; Br, 18.48; N, 3.24; O, 7.40. Found: C, 66.75; H, 4.11; N, 3.15.