Silicon-Induced General, Mild, and Efficient One-Pot, Three-Component Synthesis of Amidoalkyl Naphthol Libraries

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Abstract: A general mild and efficient protocol for the synthesis of amidoalkyl naphthol libraries was achieved utilizing tetrachlorosilane and zinc chloride in dichloromethane at ambient temperature via a one-pot, three-component condensation of various aldehydes, nitriles (amides), and β-naphthol.

Key words: multicomponent reactions, amidoalkyl naphthols, tetrachlorosilane, Ritter reaction, combinatorial synthesis

1,3-Amino-oxygenated functionalized compounds are important in synthesis and medicinal chemistry fields. A variety of them act as potent drugs such as nucleoside antibiotics and HIV protease inhibitors.[1] Amidoalkyl naphthol derivatives are of particular value because of their use as important biological building blocks and intermediates in synthesis. They are important precursors of heterocycles[2] as well as of 1-aminomethyl-2-naphthol derivatives which are pharmacologically important compounds. For example, they exhibit depressor and bradycardia effects in humans.[3] Moreover, antibacterial and antiviral activity of a number of amidoalkyl naphthols have been reported more recently.[4]

Multicomponent coupling reactions (MCR) represent powerful time-, energy-, and material-saving synthetic protocols in modern chemistry in which molecular complexity could be generated in a single synthetic operation.[5] MCR protocols have been developed for the synthesis of amidoalkyl naphthols from aryl aldehydes, 2-naphthols, and carboxylic acid amides in the presence of a plethora of Lewis or Brønsted acid catalysis, generally under thermal conditions.[6] Although significant progress has been achieved, many of the reported methods suffer from one or more limitations such as high reaction temperature, lower product yield, tedious workup, and use of toxic reagents. They also lack general applicability to produce arrays of 1-amidoalkyl naphthols as they are restricted to only a few amides. Therefore, the development of a more general, cost-effective MCR protocol for the synthesis of 1-amido-alkyl phenols remains a challenge. Compared to amides, nitriles are more readily available substrates, thus, MCR of aldehydes, 2-naphthol, and nitriles (as substitute of amides) to give amidoalkyl naphthols in a Ritter-type reaction have also been reported.[7–12] However, most of these approaches were restricted to acetonitrile giving the corresponding 1-acetamidomethyl naphthols in the presence of $Ce(SO_4)_2$,[7] $HClO_4$–SiO_2,[8] $FeCl_3$–SiO_2,[9] $NaHSO_4 \cdot H_2O$[10a], Ph_3CCl,[10b] or CF_3SO_3H[10c] under reflux conditions in almost all of these methods. In the presence of I_2 and MeCOCl, only α-hydrogenated nitriles yielded the corresponding amidophenols, while aromatic nitriles did not yield the desired products.[11] More recently, one report has described the synthesis of 1-benzamidomethyl-2-naphthols through this protocol involving benzonitrile by using superacidic ionic liquid $[MeC(OH)_2]^+ClO^-_4$ under heating under solvent-free conditions.[12] To our knowledge, there is no general protocol employing various nitriles in such condensations so far. Therefore, the introduction of new, efficient, and general methods involving various nitriles for this multicomponent reaction under milder conditions is still required. Towards this goal, and in continuation of our investigations[13] on the development and applications of new in situ reagents derived from tetrachlorosilane (TCS)[14] in organic synthesis, we have developed an efficient, general, and convenient protocol for the one-pot synthesis of 1-amidoalkyl-2-naphthols, biologically active druglike molecules. The reaction proceeds via a three-component condensation of various aldehydes, 2-naphthol, and nitriles including alkyl, aralkyl, aryl, and α,β-unsaturated nitriles as well as cyano esters utilizing the inexpensive and readily available tetrachlorosilane–zinc chloride reagent[13f] in dichloromethane at room temperature. Under the same reaction conditions, the MCR of aldehydes, 2-naphthols, and amides have also been tested and proven to be successful exploring the synthetic versatility of the present protocol.

An equimolar mixture of benzaldehyde, 2-naphthol, and acetonitrile in dichloromethane was allowed to react in the presence of TCS (2 equiv) and $ZnCl_2$ (1 equiv) at room temperature to furnish the corresponding 1-acetamidomethyl-2-naphthol (**4a**) in good yield (Table 1, entry 1).

To optimize the reaction conditions, we examined the reaction in various solvents. Chlorinated solvents such as dichloromethane or 1,2-dichloroethane were found to be effective solvents while donor solvents such as diethyl ether completely inhibited the reaction. $SnCl_2$ as a Lewis acid was examined, and similar results were obtained but it was less effective than $ZnCl_2$. It is noteworthy that no reaction was observed in the absence of either the Lewis acid or $SiCl_4$. To determine the optimum quantity of $SiCl_4$

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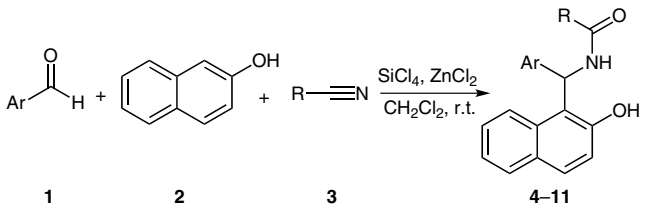
and $ZnCl_2$, the reaction was carried out in dichoromethane at room temperature using different quantities of the catalyst. The use of two equivalents of $SiCl_4$ and one equivalent of $ZnCl_2$ resulted in the highest yield. A slight excess of the acetonitrile was found to be advantageous, therefore the molar ratio of 2-naphthol, aldehyde, and nitrile was kept at 1:1:1.3, respectively.



Scheme 1

In order to create a library of compounds, we have allowed various aldehydes, 2-naphthol, and nitriles to react under the optimized conditions to afford a diverse set of 1-amido alkyl naphthols (Scheme 1, Table 1).

As seen in the results of Table 1 and Figure 1, the reaction proved to be general and tolerated a variety of aromatic aldehydes with substituents carrying either electron-donating (Table 1, entries 5–9, 13–16, 18–20, 23, and 24) or electron-withdrawing groups (Table 1, entries 2–4, 9, 12, 17, 22, 25, 26). A unique example of heteroaryl as well as α,β-unsaturated aldehyde was introduced through the MCR of 3-formylchromone with β-naphthol and acetonitrile which gave acetamidoalkyl naphthol **5** in moderate yield (Table 1, entry 10). The reaction was successful with a variety of nitriles. Thus, beside to acetonitrile, the MCR of aldehydes and β-naphthol with alkyl, aralkyl, aryl, and α,β-unsaturated nitriles as well as with cyano esters were studied. Propionitrile, phenylacetonitrile, benzonitrile, acrylonitrile, and ethyl cyanoacetate were chosen as representative examples. In all the cases studied, the reaction proceeded smoothly under the above conditions giving the corresponding amidoalkyl naphthols typically within 12 hours except for the reaction with benzonitrile where reaction times of up to 18 hours were required which might be attributed to steric factors as well as to the low nucleophilicity of benzonitrile (Table 1, entries 21–24).

As possible precursors of oxazepinone derivatives **13**, we tried the MCR of aldehydes, 2-naphthol, and α-halonitriles, expecting the formation of haloamidoalkyl naphthol **12**; however, we got instead the Friedel–Crafts alkylation product **11**[15] as the sole product without participation of the aldehyde (Scheme 2, Table 1, entry 27).

To demonstrate the merit of the present work in comparison with previously reported results, we compared the results of $Ce(SO_4)_2$,[7] $HClO_4$–SiO_2,[8] $FeCl_3$–SiO_2,[9] $NaHSO_4 \cdot H_2O$,[10a] Ph_3CCl,[10b] triflic acid,[10c] I_2/MeCOCl,[11] and $[MeC(OH)_2]^+ClO^-_4$[12] in the synthesis of 1-amidoalkyl-2-naphthols via Ritter-type reaction. As shown in Table 2, TCS/$ZnCl_2$ is superior to the previously reported catalysts in terms of ready availability, cost-effectiveness, general applicability to various nitriles, and mildness of the reaction conditions.

Table 1 $SiCl_4$-$ZnCl_2$ Induced One-Pot Three-Component Reaction of Aldehydes with β-Naphthol and Nitriles Giving the Corresponding 1-Amidoalkyl Naphthols

Entry	Ar	R	Product	Time (h)	Yield (%)[a]
1	Ph	Me	**4a**	9	77
2	4-ClC_6H_4	Me	**4b**	10	74
3	4-BrC_6H_4	Me	**4c**	10	71
4	4-$O_2NC_6H_4$	Me	**4d**	13	69
5	4-MeC_6H_4	Me	**4e**	9	82
6	4-$MeOC_6H_4$	Me	**4f**	8	76
7	3-$MeOC_6H_4$	Me	**4g**	11	73
8	3,4-$(MeO)_2C_6H_3$	Me	**4h**	10	71
9	3,4-$(OCH_2O)C_6H_3$	Me	**4i**	12	77
10	2-chromonyl	Me	**5**	10	64
11	Ph	Et	**6a**	11	85
12	4-ClC_6H_4	Et	**6b**	12	78
13	4-$MeOC_6H_4$	Et	**6c**	10	81
14	3-$MeOC_6H_4$	Et	**6d**	11	83
15	3,4-$(MeO)_2C_6H_3$	Et	**6e**	10	77
16	3,4-$(OCH_2O)C_6H_3$	Et	**6f**	12	80
17	4-ClC_6H_4	Bn	**7a**	13	76
18	4-$MeOC_6H_4$	Bn	**7b**	12	73
19	3,4-$(MeO)_2C_6H_3$	Bn	**7c**	11	77
20	3,4-$(OCH_2O)C_6H_3$	Bn	**7d**	12	80
21	Ph	Ph	**8a**	18	70
22	4-ClC_6H_4	Ph	**8b**	16	74
23	4-MeC_6H_4	Ph	**8c**	18	72
24	4-$MeOC_6H_4$	Ph	**8d**	17	75
25	4-ClC_6H_4	CH_2=CH	**9**	11	69
26	4-ClC_6H_4	CH_2COOEt	**10**	12	65
27	4-BrC_6H_4	$ClCH_2$	**11**	16	71

[a] Isolated yields after column chromatography except for products **6a**–**d**.

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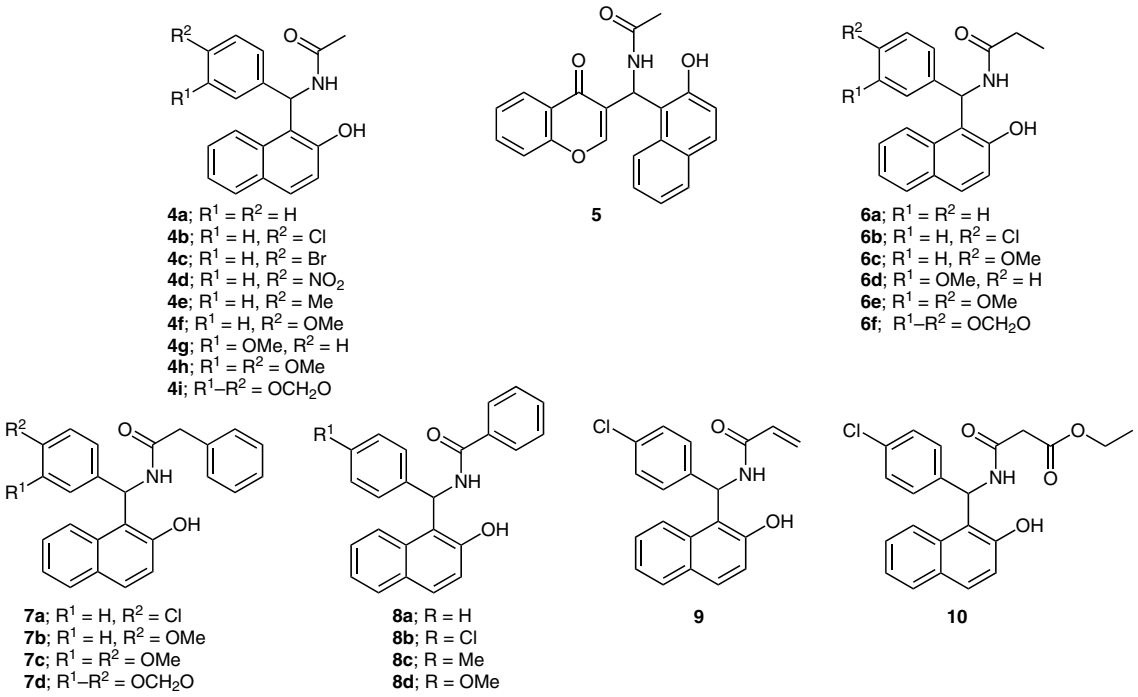
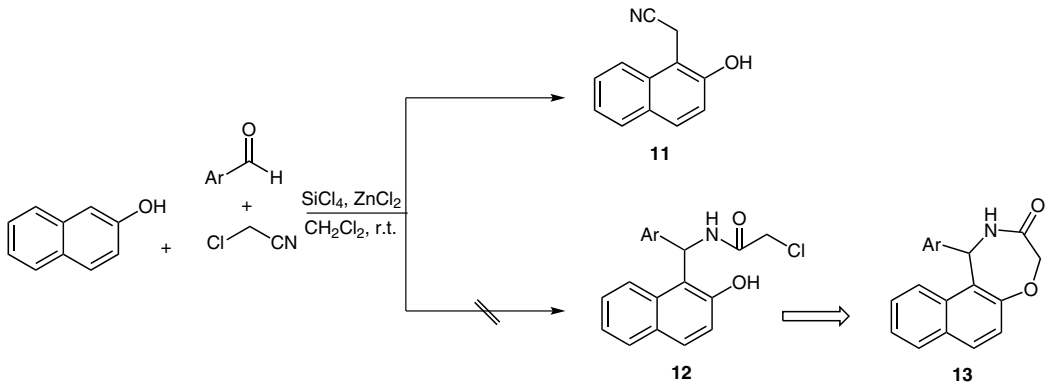


Figure 1



Scheme 2

Table 2 Comparison of TCS/$ZnCl_2$ with Reported Catalyst Systems in the Synthesis of Amidoalkyl Naphthols via MCR–Ritter-Type Reaction

Nitrile	Catalyst	Conditions	Time (h)	Yield (%)
MeCN	$Ce(SO_4)_2$	MeCN, 85 °C	24–48	42–72[7]
MeCN	$HClO_4$–SiO_2	MeCN, 85 °C	20	60–88[8]
MeCN	$FeCl_3$–SiO_2	MeCN, 85 °C	20	72–88[9]
MeCN	$NaHSO_4 \cdot H_2O$	MeCN, 85 °C	20	71–88[10a]
MeCN	Ph_3CCl	sealed tube, r.t.	0.75–4	86–94[10b]
MeCN, CH_2=CHCN	CF_3SO_3H	80–85 °C	1.5–6	60–91[10c]
alkyl nitriles	I_2/MeCOCl	DCE, r.t.	3–14	45–90[11]
aryl nitriles	$[MeC(OH)_2]^+ClO^-_4$	solvent-free, 80 °C	5.5–7	84–91[12]
alkyl, aryl, aralkyl, unsaturated nitriles, cyano esters	$SiCl_4/ZnCl_2$	DCE, r.t.	9–17	65–83[a]

[a] Present work.

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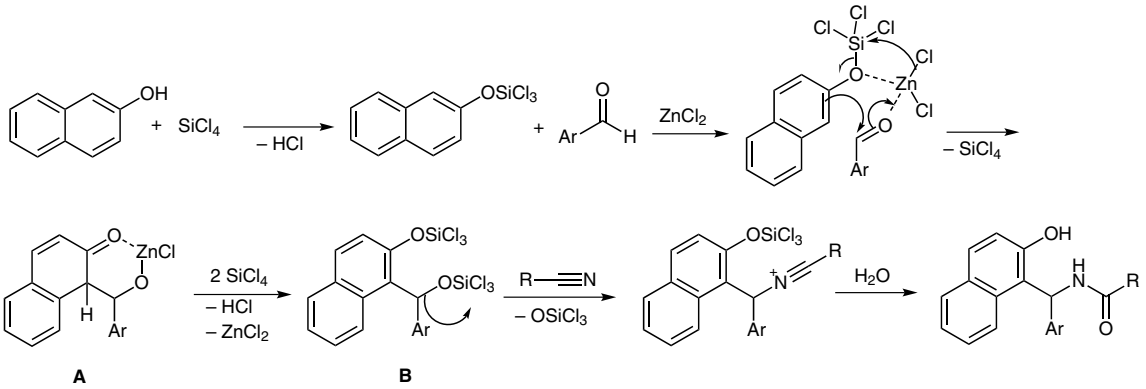


Scheme 3 A plausible mechanism for the formation of amidoalkyl napthols

A reasonable mechanism for the present reaction may proceed as depicted in Scheme 3 through nucleophilic addition of β-naphthol to the aldehyde followed by amidoalkylation.[16] Use of $ZnCl_2$ as a radical initiator as well as a chelating agent has been documented.[17] Thus, coordination of $ZnCl_2$ to the carbonyl group would enhance the electrophilicity of the aldehyde.[18] On the other hand, β-naphthol may be exist as silyl enol ether in the presence of $SiCl_4$. We presume that the mechanism is formally analogous to the Lewis acid catalyzed addition of silyl enol ethers to carbonyl compounds. Indeed, the reaction may proceed via the prior complexation of the CO with $ZnCl_2$ according to the well-established Zimmerman–Traxler chairlike transition-state model[19] to afford the intermediate **A** which is converted into **B**. Formation of **A** is analogous to the formation of the well-documented *ortho*-quinone methides (*o*-QM) under similar conditions.[6a–c,9] On the other hand, in analogy to $SnCl_4$,[20] $SiCl_4$ may coordinate with nitriles activating addition of the nitrile to **B** in a Ritter-type reaction[21] giving eventually the desired amidoalkyl naphthol after aqueous workup.

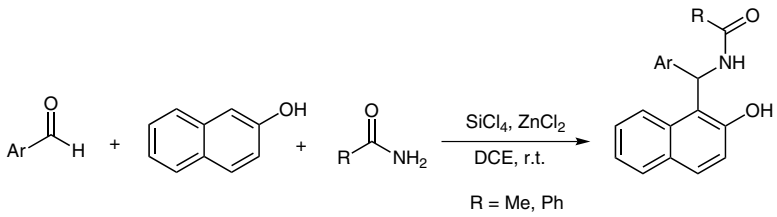
Prompted by the above results from nitriles and exploring the present procedure to other substrates increasing its versatility, we decided to test this protocol with amides envisaging the formation of corresponding amidoalkyl naphthols. Fortunately, stirring a mixture of aldehyde, 2-naphthol, and amide (ratio = 1:1:1.3) in dichloroethane as solvent in the presence of $SiCl_4$ (2 mol) and $ZnCl_2$ (1 mol) at room temperature gave the respective amidoalkyl naphthols in excellent isolated yields (Scheme 4, Table 3).

In conclusion, we have reported $SiCl_4$–$ZnCl_2$ as a readily available and inexpensive reagent for an efficient one-pot, three-component synthesis of amidoalkyl naphthol libraries, biologically active druglike molecules, under very mild conditions.[22] The present protocol is convenient and applicable to a wide variety of aldehydes, phenols, and nitriles or amides, features that would make it amenable to high-throughput synthesis of combinatorial libraries for potential drug development.

Table 3 $SiCl_4$–$ZnCl_2$-Induced One-Pot, Three-Component Reaction of Aldehydes with β-Naphthol and Amides

Entry	Ar	R	Product	Time (h)	Yield (%)[a]
1	Ph	Me	**4a**	4	91
2	4-ClC_6H_4	Me	**4b**	4	93
3	4-$MeOC_6H_4$	Me	**4f**	5	90
4	Ph	Ph	**8a**	6	88
5	4-$MeOC_6H_4$	Ph	**8d**	6	85

[a] Isolated yields.



Scheme 4

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References and Notes

(1) (a) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015. (b) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (c) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859. (d) Juaristi, E. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; John Wiley and Sons: New York, **1997**.

(2) Damodiran, M.; Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 5474.

(3) (a) Dingermann, T.; Steinhilber, D.; Folkers, G. In *Molecular Biology in Medicinal Chemistry*; Wiley-VCH: Weinheim, **2004**. (b) Shen, A. Y.; Tsai, C. T.; Chen, C. L. *Eur. J. Med. Chem.* **1999**, 877. (c) Shen, A. Y.; Chen, C. L.; Lin, C. I. *Chin. J. Physiol.* **1992**, *35*, 45. (d) Szatmari, I.; Fülop, F. *Curr. Org. Synth.* **2004**, *1*, 155.

(4) Abou-Elmagd, W. S. I.; Hashem, A. I. *Med. Chem. Res.* **2013**, *22*, 2005.

(5) (a) For a review, see: Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (b) Thomson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopala, L. *Acc. Chem. Res.* **2003**, *36*, 899. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.

(6) (a) PTSA: Khodaei, M. M.; Khosropour, A. R.; Moghanian, H. *Synlett* **2006**, 916. (b) P_2O_5: Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7220. (c) [TEBSA][HSO_4] Bronsted acidic ionic liquid: Hajipour, A. R.; Ghayeb, Y.; Sheikhan, N.; Ruoho, A. E. *Tetrahedron Lett.* **2009**, *50*, 5649. (d) Thiamine hydrochloride: Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2009**, *50*, 6393. (e) $Yb(OTf)_3$ in ionic liquid: Kumar, A.; Rao, M. S.; Ahmad, I.; Khungar, B. *Can. J. Chem.* **2009**, *87*, 714. (f) $H_3Mo_{12}O_{40}P$: Gawand, P.; Deokar, H.; Langi, B.; Yadav, A.; Chaskar, A. *Synth. Commun.* **2009**, *39*, 4171. (g) Ferrocene-labeled supported ionic liquid phase: Rashinkar, G.; Salunkhe, R. *J. Mol. Catal. A: Chem.* **2010**, *316*, 146. (h) Silica gel supported dual acidic ionic liquid: Zhang, Q.; Luo, J.; Wei, Y. *Green Chem.* **2010**, *12*, 2246. (i) [TBBDA]: Ghorbani-Vaghei, R.; Malaekehpour, S. M. *Cent. Eur. J. Chem.* **2010**, *8*, 1086. (j) PEG-based dicationic acidic ionic liquids: Lue, J.; Zhang, Q. *Monatsh. Chem.* **2011**, *142*, 923. (k) Copper *p*-toluenesulfonate: Wang, M.; Liang, Y. *Monatsh. Chem.* **2011**, *142*, 153. (l) Copper *o*-toluenesulfonate: Zhigue, S.; Shuang, Z.; Xin, W. *Chin. J. Org. Chem.* **2011**, *31*, 870. (m) 1,3-Dibromo-5,5-dimethylhydantoin: Habibzadeh, S.; Ghasemnejad-Bosra, H. *J. Chin. Chem. Soc.* **2011**, *58*, 1. (n) Silica gel supported ionic liquid: Kotadia, D. A.; Soni, S. S. *J. Mol. Catal. A: Chem.* **2011**, *353-354*, 44. (o) Nanosulfated zirconia: Zali, A.; Shokrolahi, A. *Chin. Chem. Lett.* **2012**, *23*, 269. (p) Ethylammonium nitrate ionic liquid: Mulla, S. A. R.; Salama, T. A.; Pathan, M. Y.; Inamdar, S. M.; Chavan, S. S. *Tetrahedron Lett.* **2013**, *54*, 672.

(7) Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 7481.

(8) Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Tetrahedron* **2008**, *64*, 1263.

(9) Shaterian, H. R.; Yarahmadi, H. *Tetrahedron Lett.* **2008**, *49*, 1297.

(10) (a) Shaterian, H. R.; Yarahmadi, H. *ARKIVOC* **2008**, *(ii)*, 105. (b) Khazaei, A.; Moosavi-Zare, A. R.; Zare, A.; Parhami, A.; Khalafi-Nezhad, A. K. *Appl. Catal., A* **2010**, *386*, 179. (c) Das, B.; Laxminarayana, K.; Thirupathi, P. R. *Synlett* **2007**, 3103.

(11) Silvam, N. P.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2972.

(12) Tamaddon, F.; Bistgani, J. M. *Synlett* **2011**, 2947.

(13) (a) Salama, T. A.; Ismail, M. A.; Khalil, A. M.; Elmorsy, S. S. *ARKIVOC* **2012**, *(ix)*, 242. (b) Salama, T. A.; Novak, Z. *Tetrahedron Lett.* **2011**, *52*, 40263. (c) Salama, T. A.; Elmorsy, S. S.; Khalil, A. M.; Ismail, M. A. *Chem. Lett.* **2011**, *40*, 1149. (d) Salama, T. A.; Elmorsy, S. S. *Chin. Chem. Lett.* **2011**, *22*, 1171. (e) Salama, T. A.; El-Ahl, A. S.; Elmorsy, S. S.; Khalil, A. M.; Ismail, M. A. *Tetrahedron Lett.* **2009**, *50*, 5933. (f) Salama, T. A.; Elmorsy, S. S.; Khalil, A. M.; Ismail, M. A. *Tetrahedron Lett.* **2007**, *48*, 6199. (g) Salama, T. A.; Elmorsy, S. S.; Khalil, A. M. *Tetrahedron Lett.* **2007**, *48*, 4395. (h) Salama, T. A.; Elmorsy, S. S.; Khalil, A. M.; Girges, M. M.; El-Ahl, A. S. *Synth. Commun.* **2007**, *37*, 1313. (i) Salama, T. A.; El-Ahl, A. S.; Khalil, A. M.; Girges, M. M.; Lackner, B.; Steindl, C.; Elmorsy, S. S. *Monatsh. Chem.* **2003**, *134*, 1241. (j) Elmorsy, S. S.; Khalil, A. M.; Girges, M. M.; Salama, T. A. *Tetrahedron Lett.* **1997**, *38*, 1071. (k) Elmorsy, S. S.; Khalil, A. M.; Girges, M. M.; Salama, T. A. *J. Chem. Res., Synop.* **1997**, 231.

(14) (a) Al-Hourani, B. J.; Sharma, S. K.; Suresh, M.; Wuest, F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2235. (b) Shimoda, Y.; Kotani, S.; Sugiura, M.; Nakajima, M. *Chem. Eur. J.* **2011**, *17*, 7992. (c) Rossi, S.; Benaglia, M.; Genoni, A.; Benincori, T.; Celentano, G. *Tetrahedron* **2011**, *67*, 158. (d) Kashiwagi, T.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron* **2011**, *67*, 531. (e) Khatab, T. K.; El-Bayouki, K. A. M.; Basyouni, W. M. *Tetrahedron Lett.* **2011**, *52*, 1448. (f) Azizi, N.; Bagh, R.; Ghafuri, H.; Bolourtchian, M.; Hashemi, M. *Synlett* **2010**, 379. (g) He, Y.; Bian, Z.; Kang, C.; Cheng, Y.; Gao, L. *Tetrahedron* **2010**, *66*, 3553. (h) Sato, S.; Hoshino, H.; Sugimoto, T.; Kashiwagi, K. *Chem. Lett.* **2010**, *39*, 1319. (i) El-Deeb, I. M.; Lee, S. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 1757. (j) Malkov, A. V.; Gordon, M. R.; Stonius, S.; Hussain, J.; Koovsk, P. *Org. Lett.* **2009**, *11*, 5390.

(15) Merijan, A.; Gardner, P. D. *J. Org. Chem.* **1965**, *30*, 3965.

(16) (a) Zaugg, H. E. *Synthesis* **1984**, 85. (b) Zaugg, H. E. *Synthesis* **1984**, 181. (c) Katritzky, A. R.; Fang, Y.; Silina, A. *J. Org. Chem.* **1999**, *64*, 7622.

(17) (a) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421. (b) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *Heterocycles* **1998**, *47*, 765.

(18) (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (b) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745.

(19) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Wessjohann, L.; Wilde, H. *Synlett* **1997**, 731.

(20) Lora-Tamayo, M.; Madronero, R.; Muñoz, G. G.; Leipprand, H. *Chem. Ber.* **1964**, *97*, 2234.

(21) Icrimen, L. I.; Cota, D. K. *Org. React.* **1969**, *17*, 213.

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(22) **Typical Procedure for the MCR of Compounds 1–3 with $SiCl_4/ZnCl_2$**

To a solution of anhyd $ZnCl_2$ (0.7 g, 5 mmol) in CH_2Cl_2 (20 mL) were added aldehyde (5 mmol), 2-naphthol (5 mmol), and nitrile or amide (6.5 mmol). The reaction mixture was stirred at ambient temperature for 10 min, $SiCl_4$ (1.2 mL, 10 mmol) was added, and the reaction mixture was stirred with exclusion of moisture. On completion (TLC monitoring of the progress of the reaction), the mixture was poured onto H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extract was dried over anhyd $MgSO_4$, evaporated, and the residue chromatographed on silica gel using PE–EtOAc (1:1 for **4**–**6** and 2:1 for **7**–**10**) as eluent to give pure 1-amidoalkyl naphthols. Compounds **6a**–**d** were isolated without chromatography in pure form by trituration with Et_2O. Spectral data for representative (new) examples of 1-amidoalkyl naphthols are shown in the Supporting Information.

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