Short communication

Zirconyl(IV) Chloride – Catalyzed Multicomponent Reaction of β-Naphthols: An Expeditious Synthesis of Amidoalkyl Naphthols

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Abstract

Zirconyl(IV) chloride is found to be an efficient catalyst for the multicomponent condensation reaction of β-naphthol, aromatic aldehydes and urea or amide to afford the corresponding amidoalkyl naphthols in good yields. The remarkable features of this new procedure are high conversions, shorter reaction times, cleaner reaction profiles and simple experimental and work-up procedures.

Keywords: Zirconyl(IV) chloride, multicomponent reaction, condensation, β-naphthol, aryl aldehyde, urea.

1. Introduction

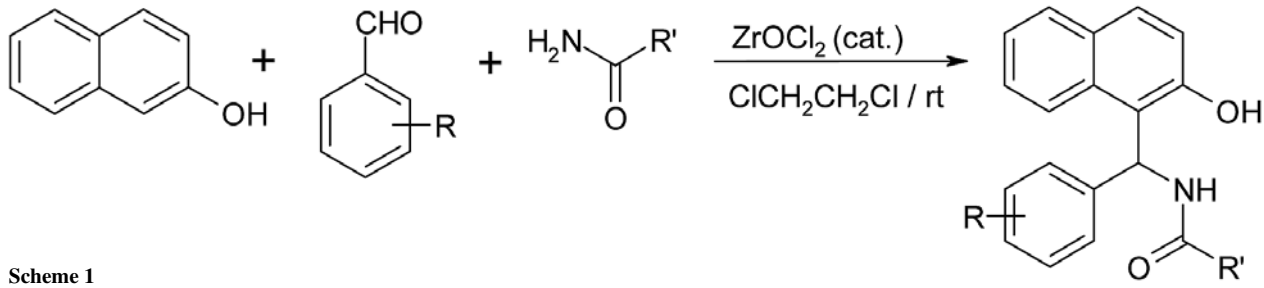
Multicomponent reactions (MCRs) have attracted considerable attention since they are performed without need to isolate the any intermediate during their processes; this reduces time and saves both energy and raw materials.[1] They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules. Biginelli,[2] Ugi,[3] Passerini[4] and Mannich[5] are some examples of MCRs. Neverthless, development and discovery of new MCRs is still in demand.

In this context, ortho-quinone methides (O-QMs) have been used in many tandem processes,[6] but only limited work on their reaction with nucleophiles has appeared in the literature.[7] Very recently, a simple and convinient method for the synthesis of dibenzoxanthenes by the condensation of aldehydes with β-naphthol in the presence of p-toluene sulfonic acid (p-TSA) as a catalyst has been reported.[8] To expand this type of tandem process that would permit the condensation of the in situ generated ortho-quninone methide with nucleophiles other than phenols, we utilized ureas and amides to produce novel amidoalkyl naphthol compounds using zirconyl(IV) chloride as a catalyst.

Zirconyl(IV) chloride is moisture stable, readily available and inexpensive oxy- salt of zirconium, and until now has not been explored in synthetic organic chemistry as a mild and versatile Lewis acid catalyst. Compared to conventional Lewis acids, particularly zirconyl(IV) chloride has advantages of low catalyst loading, moisture stability and catalyst recycling. In our attempt to explore the role of zirconyl(IV) chloride as an mild and efficient Lewis acid catalyst, we demonstrated the use of zirconyl-(IV) chloride as a catalyst for the synthesis of 1,5-benzodiazepines,[9] benzimidazoles[10] and bis(indolyl)methanes.[11] In continuation of our work on zirconyl(IV) chloride, in this paper we have demonstrated the use of zirconyl(IV) chloride as a mild and efficient catalyst for the synthesis of amidoalkyl naphthols by multicomponent reaction of β-naphthol, aromatic aldehydes and urea or amide.

2. Results and Discussion

Herein, we wish to disclose a novel protocol for the rapid synthesis of a variety of biologically important amidoalkyl naphthols using a catalytic amount of zirconyl-(IV) chloride under extremely mild conditions (**Scheme 1**). Firstly, 4-chlorobenzaldehyde and urea was chosen as a model for the reaction with β-naphthol. 4-Chlorobenzaldehyde was treated with equimolar amount of β-naphthol and urea in the presence of 10 mol % $ZrOCl_2 \cdot 8H_2O$ at room temperature in various solvents to afford amidoalkyl naphthols (**Table 1**, entries 1–8). We found that 1,2-dichloroethane was the best choice.



Scheme 1

Table 1: Solvent effect on the reaction of 4-chlorobenzaldehyde, β-naphthol and urea, catalyzed by $ZrOC_{12}$.

Entry	Solvent	Time (hr.)	Yield (%)[a]
1	$ClCH_2CH_2Cl$	11	86
2	CH_3CN	14	47
3	MeOH	14	71
4	EtOH	15	62
5	$CHCl_3$	13	77
6	CH_2Cl_2	13	81
7	DMF	14	20
8	1,4-Dioxane	15	73

[a] isolated yields

Having established the reaction conditions, various amidoalkyl naphthols were synthesized in excellent yields by the reaction of different aromatic aldehydes with β-naphthol and urea and several representative examples are summarized in **Table 2**. In all cases, amidoalkyl naphthols were the sole products and no by-product was observed. Similar results were obtained under the same conditions when N-methyl urea was used in place of urea (**Table 2**, entry 7). The reaction of aromatic aldehydes with β-naphthol and different amides including acetamide and benzamide in 1,2-dichloroethane under similar reaction conditions also provided the corresponding amidoalkyl naphthols in high yields (**Table 2**, entry 8 and 9).

In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. It was shown that the aromatic aldehydes with electron-withdrawing groups reacted faster than the aromatic aldehydes with electron-donating groups as would be expected. To demonstrate the scope and limitations of the procedure, the reaction of ortho-substituted aromatic aldehydes such as 2-chlorobenzaldehyde, and the heteroaromatic aldehyde furfural were studied and the results are summarized in **Table 2**. Aliphatic aldehyde like propionaldehyde was also examined, but the yields were low as compared to aromatic aldehyde (**Table 2**, entry 11). On the other hand, the reactions with thiourea were considered, but no corresponding products were produced. Also, amines such as ethylamine and aniline were utilized and no aminoalkyl naphthol was obtained.

3. Conclusions

A novel and highly efficient methodology for the synthesis of amidoalkyl naphthols by multicomponent condensation reaction of aromatic aldehyde, β-naphthol, and ureas or amides, catalyzed by zirconyl(IV) chloride is reported. This method offers several significant advantages: such as, high conversions, easy handling, cleaner reaction profile and shorter reaction times, which makes it a useful and attractive process for the rapid synthesis of substituted amidoalkyl naphthols.

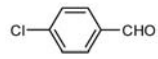
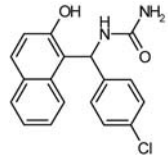
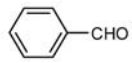
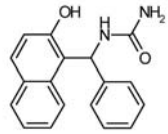
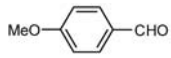
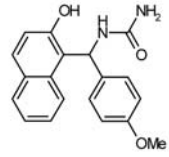
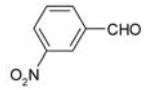
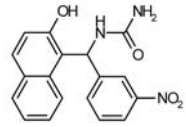
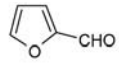
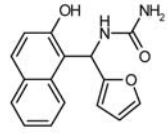
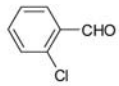
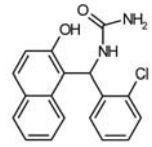
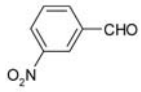
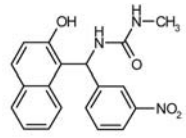
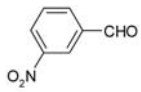
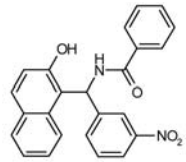
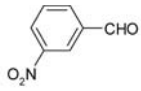
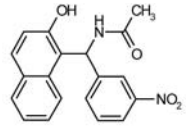
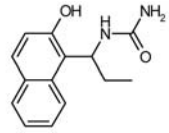
4. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Electron spray ionization mass spectra (ES-MS) were recorded on a Water-Micromass Quattro-II spectrometer. IR spectra were recorded on a Varian spectrometer. All reagents used were of AR grade and were used without further purification. Column chromatography employed silica gel of 60–120 mesh.

4. 1. General Procedure

A mixture of aromatic aldehyde (1 mmol), β-naphthol (1 mmol), urea or amide (1.1 mmol) and $ZrOCl_2 \cdot 8H_2O$ (0.1 mmol) in 1,2-dichloroethane (2 mL) was stirred at room temperature for the appropriate time (**Table 2**). The progress of the reaction was monitored by TLC (solvent system: MeOH: $CHCl_3$, 1 : 9). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and the precipitate washed well with diethyl ether and then with water. The crude compounds were purified by silica gel column chromatography (60–120 mesh size silica gel) eluting with chloroform, followed by 2% methanol in chloroform to afford the desired compound in pure form. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry (ES-MS) and elemental analysis.

Table 2: $ZrOCl_2$ – Promoted synthesis of amidoalkyl naphthol derivatives.

Entry	Aldehyde	Urea or amide	Product	Time (h)	Yield (%)
1		H_2NCONH_2		11	86
2		H_2NCONH_2		14	83
3		H_2NCONH_2		15	80
4		H_2NCONH_2		10	87
5		H_2NCONH_2		17	57
6		H_2NCONH_2		25	63
7		$H_2NCONHCH_3$		09	88
8		H_2NCOPh		11	79
9		H_2NCOCH_3		09	84
10		H_2NCONH_2		25	25

[(4-Chlorophenyl)-(2-hydroxy naphthelene-1-yl)-methyl]-urea (Table 2, entry 1): IR (neat): 3456, 3360, 3200, 2240, 1632, 1580, 1513, 1430, 1370, 1238, 816 cm^{-1}, ^1H NMR (200 MHz, DMSO-d_6): δ 10.32 (s, 1H), 7.95–7.75 (m, 3H, Ar–H), 7.50–7.10 (m, 7H, Ar–H), 6.80 (s, 2H), 5.80 (s, 2H), ^{13}C NMR (50 MHz, DMSO-d_6): δ 159.3, 153.6, 144.3, 132.8, 131.1, 130.0, 129.4, 129.1, 128.9, 128.6, 128.4, 127.4, 123.3, 120.4, 119.2, 48.4, Mass (ES/MS): m/z 325 (M–H, 100%); Anal. calcd. for $C_{18}H_{15}ClN_2O_2$: C 66.16, H 4.63, N 8.57; found: C 66.32, H 4.59, N 8.62.

[(2-Hydroxy naphthalen-1-yl)-phenyl-methyl]-urea (Table 2, entry 2): ^1H NMR (200 MHz, DMSO-d_6): δ 10.28 (s, 1H), 7.85–7.15 (m, 12H), 6.90 (s, 2H), 5.70 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 159.3, 153.6, 144.3, 132.8, 131.1, 130.0, 129.4, 129.1, 128.9, 128.6, 128.4, 127.4, 123.3, 120.4, 119.2, 48.4; Mass (ES/MS): m/z 291 (M–H, 100%); Anal. calcd. for $C_{18}H_{16}N_2O_2$: C 73.96, H 5.52, N 9.58; found: C 74.51, H 5.57, N 9.62.

[(4-Methoxyphenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-urea (Table 2, entry 3): ^1H NMR (200 MHz, DMSO-d_6): δ 10.30 (s, 1H), 7.60–7.05 (m, 8H), 6.80 (d, 2H), 6.70 (bs, 2H), 5.70 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.7, 153.5, 142.8, 135.1, 133.5, 129.3, 128.8, 128.3, 126.3, 123.2, 122.3, 118.9, 115.4, 114.8, 51; Mass (ES/MS): m/z 321 (M–H, 100%); Analysis calcd. for $C_{19}H_{18}N_2O_3$: C 70.79, H 5.63, N 8.69; found C 70.43, H 5.61, N 8.75.

[(3-Nitrophenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-urea (Table 2, entry 4): ^1H NMR (200 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.05–7.95 (m, 2H), 7.55–6.85 (m, 8H), 6.75 (bs, 2H), 5.80 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.5, 153.3, 148.7, 143.5, 133.3, 132.4, 130.2, 128.7, 128.2, 126.2, 124.4, 123.6, 123.1, 119.1, 118.6, 115.7, 50.2; Mass (ES/MS): m/z 336 (M–H, 100%); Analysis calcd. for $C_{18}H_{15}N_3O_4$: C 64.09, H 4.48, N 12.46; found C 64.37, H 4.53, N 12.52.

[(Furan-2-yl)-(2-hydroxy naphthalen-1-yl)-methyl]-urea (Table 2, entry 5): ^1H NMR (200 MHz, DMSO-d_6): δ 10.27 (s, 1H), 7.70–7.05 (m, 7H), 6.75 (s, 2H), 6.40 (bs, 1H), 6.25 (m, 1H), 6.10 (m, 1H), 5.75 (bs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.9, 153.7, 152.7, 142.3, 133.6, 129.1, 128.6, 126.5, 123.4, 122.6, 118.7, 115.6, 110.8, 106.9, 46.1; Mass (ES/MS): m/z 281 (M–H, 100%); Analysis calcd. for $C_{16}H_{14}N_2O_3$: C 68.08, H 5.00, N 9.92; found C 67.89, H 5.06, N 9.85.

[(2-Chlorophenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-urea (Table 2, entry 6): ^1H NMR (200 MHz, DMSO-d_6): δ 10.35 (s, 1H), 7.60–7.45 (m, 2H), 7.30–6.95 (m, 8H), 6.75 (s, 2H), 5.85 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.2, 154,143.9, 134.3, 134.1, 130.1, 129.9, 129.2, 128.8, 127.9, 126.8, 123.2, 119.4, 115.8, 42.3; Mass (ES/MS): m/z 325 (M–H, 100%); Analysis calcd. for $C_{18}H_{15}ClN_2O_2$: C 66.16, H 4.63, N 8.57; found C 66.02, H 4.69, N 8.51.

[(3-Nitrophenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-3-methyl-urea (Table 2, entry 7): ^1H NMR (200 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.10–7.98 (m, 2H), 7.60–6.90 (m, 8H), 6.55 (m, 1H), 5.75 (bs, 2H), 2.90 (d, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 157.8, 153.5, 148.9, 143.9, 133.8, 132.9, 130.7, 129.2, 128.7, 126.8, 124.9, 124.1, 123.6, 119.5, 119.1, 116.2, 50.8, 28.9; Mass (ES/MS): m/z 350 (M–H, 100%); Analysis calcd. for $C_{19}H_{17}N_3O_4$: C 64.95, H 4.88, N 11.96; found C 65.20, H 4.92, N 12.01.

N-[(2-Hydroxy-naphthalen-1-yl)-(3-nitro-phenyl)-methyl]-benzamide (Table 2, entry 8): ^1H NMR (200 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.10–7.85 (m, 4H), 7.65–6.95 (m, 11H), 6.55 (bs, 1H), 6.15 (bs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 167.9, 153.5, 148.9, 143.7, 134.4, 134.2, 133.5, 132.2, 130.2, 128.9, 128.8, 128.3, 127.5, 126.3, 123.5, 123.2, 122.5, 118.9, 118.6, 115.4, 48.7; Mass (ES/MS): m/z 397 (M–H, 100%); Analysis Calcd. for $C_{24}H_{18}N_2O_4$: C 72.35, H 4.55, N 7.03; found C 72.65, H 4.61, N 7.08.

N-[(3-Nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 9): ^1H NMR (200 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.10–7.85 (m, 2H), 7.65–6.95 (m, 8H), 6.60 (bs, 1H), 5.95 (bs, 1H), 2.10 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 171.1, 152.5, 147.8, 142.7, 133.4, 132.5, 129.2, 127.8, 127.3, 125.3, 122.5, 122.2, 121.5, 117.9, 117.5, 114.4, 46.9, 22.6; Mass (ES/MS): m/z 335 (M–H, 100%), Analysis calcd. for $C_{19}H_{16}N_2O_4$: C 67.85, H 4.79, N 8.33; found C 67.42, H 4.84, N 8.41.

[1-(2-Hydroxy-naphthalen-1-yl)-propyl]-urea (Table 2, entry 10): ^1H NMR (200 MHz, DMSO-d_6): δ 10.35 (s, 1H), 7.65–6.95 (m, 6H), 6.45 (bs, 1H), 5.65 (bs, 2H), 4.85 (m, 1H), 1.75 (m, 2H), 1.05 (t, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 160.5, 151.5, 131.3, 126.8, 126.1, 124.5, 121.8, 120.7, 116.4, 113.2, 43.6, 28.10, 16.2; Mass (ES/MS): m/z 243 (M–H, 100%); Analysis calcd. for $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found C 69.11, H 6.64, N 11.53.

5. Acknowledgements

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6. References

1. (a) I. Devi, P. J. Bhuyan, *Tetrahedron Lett*. **2004**, *45*, 8625–8627. (b) S. H. Mashraqui, M. B. Patil, H. D. Mistry, S. Ghadigaonkar, A. Meetsma, *Chemistry Lett*. **2004,** *33*, 1058–1059. (c) A. Chetia, C. J. Saikia, K. C. Lekhok, R. C. Boruah, *Tetrahedron Lett*. **2004**, *45*, 2649–2651.
2. (a) A. K. Bose, S. Pednekar, S. N. Ganguly, G. Chakraborty, M. S. Manhas, *Tetrahedron Lett*. **2004**, *45*, 8351–8353. (b) D. Prajapati, J. S. Sandhu, *Synlett* **2004**, 235–238.
3. (a) G. F. Ross, E. Herdtweck, I. Ugi, *Tetrahedron* **2002**, *58*, 6127–6133. (b) T. A. Keating, R. W. Armstrong, *J. Am. Chem. Soc*. **1995**, *117*, 7842–7843. (c) H. Groger, M. Hatam, J. Martens, *Tetrahedron* **1995**, *51*, 7173–7180.
4. (a) K. Kobayashi, T. Matoba, I. Susumu, M. Takashi, O. Morikawa, H. Konishi, *Chemistry Lett*. **1998**, *27*, 551–557. (b) R. Bossio, C. F. Marcos, S. Marcaccini, R. Pepino, *Tetrahedron Lett*. **1997**, *38*, 2519–2520. (c) R. Bossio, S. Marcaccini, R. Pepino, T. Torroba, *J. Chem. Soc*., *Perkin Trans. 1* **1996**, 229–230.
5. (a) T. Akiyama, K. Matsuda, K. Fuchibe, *Synlett* **2005**, 322–324. (b) G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang, D. Sun, *Green Chem*. **2004**, *6*, 75–77. (c) N. S. Chowdhari, D. B. Ramachary, C. F. Barbas III, *Synlett* **2003**, 1906–1909. (d) T. Akiyama, J. Takaya, H. Kagoshima, *Tetrahedron Lett*. **1999**, *40*, 7831–7834. (e) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed*. **1998**, *37*, 1045–1070.
6. (a) R. W. Van De Water, T. R. R. Petuss, *Tetrahedron* **2002**, *58*, 5367–5405. (b) P. Wan, B. Backer, L. Diao, M. Fischer, Y. Shi, C. Yang, *Can. J. Chem*. **1996**, *74*, 465–475. (c) G. Desimoni, G. Tacconi, *Chem. Rev*. **1975**, *75*, 651–692.
7. (a) S. R. Angle, J. D. Rainer, C. Woytowicz, *J. Org. Chem*. **1997**, *62*, 5884–5892. (b) A. Merijan, P. D. Gardner, *J. Org. Chem*. **1965**, *30*, 3965–3967. (c) W. S. Haynes, P. D. Gardner, *J. Am. Chem. Soc*. **1959**, *51*, 3065–3067.
8. A. R. Khosropour, M. M. Khodaei, H. Moghannian, *Synlett* **2005**, 955–958.
9. R. R. Nagawade, D. B. Shinde, *Mendeleev Commun*. **2006**, *16*, 113–115.
10. R. R. Nagawade, D. B. Shinde, *Russian J. Org. Chem*. **2006**, *42*, 453–454.
11. R. R. Nagawade, D. B. Shinde, *Acta. Chim. Slov*. **2006**, *53*, 210–213.

Povzetek

Cirkonijev(IV) oksidklorid je uporabljen kot učinkovit katalizator za večkomponentno reakcijo kondenzacije β-naftola, aromatskih aldehidov in uree/amida pri pripravi ustreznih amidoalkilnaftolov z visokimi izkoristki. Pomembne prednosti novega postopka so: visoka stopnja pretvorbe, kratki reakcijski časi, čiste reakcijske poti, nezahtevni eksperimentalni pogoji in enostavna izolacija produktov.