Lanthanum(III) chloride/chloroacetic acid as an efficient and reusable catalytic system for the synthesis of new 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl) semicarbazides/thiosemicarbazides

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KEYWORDS
2-Naphthol; Multi-component reaction; La(III) chloride; Solvent free

Abstract A one-pot, multi-component coupling reaction of aromatic aldehydes, 2-naphthol and semicarbazide (hydrochloride)/thiosemicarbazide using LaCl₃/ClCH₂COOH as an efficient catalyst system under solvent free condition at elevated temperature was investigated. High yields, short reaction time, easy work-up, green environment which requires no toxic organic solvents and reusability of the catalyst are the advantages of this procedure.

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1. Introduction
Semicarbazide derivatives are an important class of compounds because they have been found to possess useful biological activities (Bonaluto et al., 2010; Takahashi et al., 2007; Olivieri et al., 2010). Their tendency to be potent inhibitors of metallo-enzymes has been approved. Thus, the synthesis of semicarbazide derivatives is an important and useful task in organic chemistry.

Multi-component reactions (MCRs) are powerful and useful synthetic tool to produce complex organic molecules due to the formation of carbon–carbon and carbon–heteroatom bonds in a one-pot pathway (Lu et al., 2000; Domling and Ugi, 2000; Zhu and Bienaymé, 2005).

Therefore, the design of novel MCRs has attracted a great attention of the research groups working in medicinal chemistry and drug discovery.

One example of the MCRs is the synthesis of 1-amidoalkyl 2-naphthols which can be carried out by condensation of aryl aldehydes, 2-naphthol and acetonitrile or amide in the presence of different catalysts such as montmorillonite K10 clay (Nagarapu et al., 2007), HClO₄·SiO₂ (Shaterian et al., 2008), Iodine (Das et al., 2007), p-toluene sulfonic acid (p-TSA) (Khodaei et al., 2010), sulfamic acid/ultrasound (Patil et al., 2007a,b), cation-exchange resins (Patil et al., 2007a,b), heteropoly acid (Dorehgiaree et al., 2009; Nagarapu et al., 2007), wet cyanuric chloride (Mahdavinia and Bigdeli, 2009), triytl chloride (Khazaei et al., 2010), P₂O₅ (Nandi et al., 2009),...
Lanthanum(III) chloride/chloroacetic acid as an efficient and reusable catalytic system

Scheme 1 Synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)semicarbazides/thiosemicarbazides catalyzed by LaCl₃/ClCH₂COOH under solvent free conditions.

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>Condition</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>Reflux</td>
<td>6 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>Reflux</td>
<td>5 h</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>Reflux</td>
<td>5 h</td>
<td>15%</td>
</tr>
<tr>
<td>4</td>
<td>ET₃N·N[HSO₄]</td>
<td>125 °C</td>
<td>3 h</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>CH₃COOH</td>
<td>125 °C</td>
<td>55–95 min</td>
<td>95%</td>
</tr>
</tbody>
</table>

4-(1-imidazolium)butane sulfonate (Kundu et al., 2010), N-(4-sulfonic acid)butyl triethylammonium hydrogensulfate (Hajipour et al., 2009), 1-butyl-3-methylimidazolium hydrogen sulfide (Sapkal et al., 2009), 1-butyl-3-methylimidazolium bromide ([Bmim] Br) (Zare et al., 2011), and 1-Hexanesulfonic acid sodium salt (Niralwad et al., 2011).

Nevertheless, development and discovery of new MCRs are still in demand. Recently a one-pot, multi-component reaction for the preparation of 4-semicarbazonoalkyl-2-naphthols by reacting aldehydes, 2-naphthol and semicarbazide (hydrochloride) or thiosemicarbazide in stoichiometric ratio of 2:1:1 in the presence of PTSA/NaOAC as a catalyst was reported (Foroughifar et al., 2008).

Herein we wish to report the synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)semicarbazides/thiosemicarbazides, from condensation reaction of aldehyde, 2-naphthol and semicarbazide (hydrochloride) in stoichiometric ratio of 1:1:1 in the presence of LaCl₃/ClCH₂COOH as a catalyst (Scheme 1).

2. Experimental section

2.1. Reagents and analysis

Starting materials, solvents, and reagents were either prepared in our laboratories or purchased from Merck, Fluka chemical companies, and used without purification. LaCl₃ was prepared by unhydrating LaCl₃·7H₂O at 140 °C for 24 h. IR spectra were recorded by using a BRUKER FT-IR spectrophotometer with KBr plates, ¹H and ¹³C NMR spectra were recorded on a BRUKER FT-NMR spectrometer and were recorded on an electrothermal apparatus and were fully characterized by IR, Mass, ¹H NMR, ¹³C NMR spectral data and also micro elemental analyses.

Note: ¹H NMR spectra of some compounds clearly exhibit hydrogen bonding between phenolic OH and neighboring N which causes an extensive signal overlap in the aromatic region, therefore complete ¹H NMR characterization was not possible.

2.3. 1-((2-Hydroxynaphthalen-1-yl)(phenyl)methyl) semicarbazide (3a)

Mp 183–185 °C; IR (KBr): 3492, 3234, 3063, 1674, 1591, 1247, 815 cm⁻¹; ¹H NMR (400 MHz; ((CD₃)₂CO): δ = 6.74(s, 1H, CH), 7.14(brd, 1H, NH), 7.16–7.30(m, 5H, ArH, NH), 7.53(d, J = 7.8 Hz, 2H, ArH), 7.62(t, J = 8.7 Hz, 2H, ArH), 7.67(d, J = 7.5 Hz, 2H, ArH), 7.8(br, 1H, NH), 7.91(d, J = 8 Hz, 2H, ArH), 8.68(s, 1H, OH); ¹³C NMR (100 MHz, CDCl₃): δ 35.40 (CH), 117.62, 117.74, 123.74, 124.25, 124.50, 125.18, 126.05, 126.29, 126.8, 128.24, 128.33, 128.50, 128.68, 129.01, 131.22, 131.48, 145.69 (C, CH, Ar), 148.54(CO); MS (ESI): m/z (%): 307 [M⁺; 3]; Anal. Caled for C₁₈H₁₆N₃O₂Cl: C, 70.53; H, 5.41; N, 13.68%. Found: C, 70.53; H, 5.41; N, 13.54%.

2.4. 1-((2-Hydroxynaphthalen-1-yl)(2-chlorophenyl)methyl) semicarbazide (3b)

Mp 197–199 °C; IR (KBr): 3450, 3359, 3031, 1590, 1564, 1187, 854 cm⁻¹; ¹H NMR (400 MHz; CDCl₃): δ = 6.84(s, 1H, CH), 6.94(brd, 2H, NH₂), 7.43–7.51(m, 4H, ArH, NH), 7.53(d, J = 8.7 Hz, 2H, ArH), 7.64(d, J = 7.5 Hz, 2H, ArH), 7.76(brd, 1H, NH), 7.84(t, J = 7.5 Hz, 3H, ArH), 8.78(s, 1H, OH); ¹³C NMR (100 MHz, CDCl₃): δ 34.65(CH), 118.04, 118.11, 123.45, 124.44, 126.93, 127.55, 127.87, 127.95, 128.65, 129.07, 129.61, 130.91, 131.77, 131.80(C, CH, Ar), 148.99(CO); MS (ESI): m/z (%): 342 [M⁺; 4]; Anal. Caled for C₁₈H₁₆N₃O₂Cl: C, 63.25; H, 4.68; N,12.30%. Found: C, 63.97; H, 4.92; N, 12.63%.

2.5. 1-((2-Hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl) semicarbazide (3c)

Mp 325–327 °C; IR (KBr): 3471, 3163, 3064, 1687, 1514, 1249, 750 cm⁻¹; ¹H NMR (400 MHz; CDCl₃): δ 6.64(s, 1H, CH), 7.46–7.62(m, 4H, ArH, NH₂), 7.65(t, J = 7.8 Hz, 2H, ArH), 7.71(d, J = 7.7, 2H, ArH), 7.81(brd, 1H, NH), 7.89 (t, J = 8 Hz, 2H, ArH), 8.04 (d, J = 8.7 Hz, 2H, ArH),
Table 2 Synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)semicarbazides/thiosemicarbazides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Time (min)</th>
<th>Yield (^a) (%)</th>
<th>X</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>PhCHO</td>
<td>70</td>
<td>94</td>
<td>O</td>
<td>183–185</td>
</tr>
<tr>
<td>2b</td>
<td>2-ClC₆H₄CHO</td>
<td>50</td>
<td>97</td>
<td>O</td>
<td>292–294</td>
</tr>
<tr>
<td>2c</td>
<td>4-O₂NC₆H₄CHO</td>
<td>55</td>
<td>94</td>
<td>O</td>
<td>325–327</td>
</tr>
<tr>
<td>2d</td>
<td>4-OMeC₆H₄CHO</td>
<td>75</td>
<td>87</td>
<td>O</td>
<td>146–148</td>
</tr>
<tr>
<td>2e</td>
<td>4-MeC₆H₄CHO</td>
<td>60</td>
<td>92</td>
<td>S</td>
<td>210–212</td>
</tr>
<tr>
<td>2f</td>
<td>PhCHO</td>
<td>60</td>
<td>94</td>
<td>S</td>
<td>252–253</td>
</tr>
<tr>
<td>2g</td>
<td>4-ClC₆H₄CHO</td>
<td>65</td>
<td>93</td>
<td>S</td>
<td>245–247</td>
</tr>
<tr>
<td>2h</td>
<td>4-OHC₆H₄CHO</td>
<td>95</td>
<td>94</td>
<td>S</td>
<td>166–168</td>
</tr>
<tr>
<td>2i</td>
<td>3-O₂NC₆H₄CHO</td>
<td>65</td>
<td>92</td>
<td>S</td>
<td>201–203</td>
</tr>
</tbody>
</table>

\(^a\) Yields refer to the pure isolated products.

Table 3 Recyclability of the catalyst in the reaction of benzaldehyde and 2-naphthol in the presence of semicarbazide in the presence of LaCl₃/CICH₂COOH under solvent free condition at 125 °C.

<table>
<thead>
<tr>
<th>Run no.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>

2.6. 1-((2-Hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)semicarbazide (3d)

Mp 146–148 °C; IR (KBrs): 3381, 3060, 1627, 1595, 1515, 1247, 745 cm\(^{-1}\); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 3.78(s, 3H, OMe); 6.46(s, 1H, CH); 7.08 (d, \(J = 7.5\) Hz, 1H, ArH), 7.17(brd, 1H, NH), 7.36–7.57(m, 5H, ArH, NH), 7.61(t, \(J = 7.5\) Hz, 2H, ArH), 7.63(d, \(J = 7.7\) Hz, 2H, ArH), 7.76(brd, 1H, NH), 7.83(d, \(J = 7.8\) Hz, 2H, ArH), 8.32(s, 1H, OH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 48.79(CH), 53.40(CH), 106.45, 109.93, 118.15, 124.06, 126.50, 126.79, 128.19, 128.39, 130.28, 130.38, 131.07(C, CH, Ar), 155.79(CO); Anal. Calcd for C\(_{19}\)H\(_{18}\)N\(_3\)O\(_3\): C, 67.65; H, 5.46; N, 12.46%. Found: C, 68.02; H, 5.78; N, 12.94%.

2.7. 1-((2-Hydroxynaphthalen-1-yl)(4-Methylphenyl)methyl)semicarbazide (3e)

Mp 210–212 °C; IR (KBrs): 3463, 3333, 1690, 1572, 1476, 1294, 725 cm\(^{-1}\); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 2.15(s, 3H, Me), 6.49(s, 1H, CH); 6.89(d, \(J = 8\) Hz, 2H, ArH), 7.15(br, 2H, NH\(_2\)), 7.40–7.58(m, 4H, ArH, NH), 7.60(t, \(J = 7.5\) Hz, 2H, ArH), 7.7–7.8(brd, 1H, NH), 7.82(m, 3H, ArH), 8.43(s, 1H, OH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 20.89(Me), 37.62(CH), 117.45, 118.00, 122.70, 124.21, 124.76, 126.87, 128.09, 128.75, 128.79, 129.17, 129.50, 131.08, 131.45, 135.89, 142.00, 142.11(C, CH, Ar), 148.68(CO); MS (ESI): \(m/z\) (%) = 277, 235, 167, base peak: 143(100%); Anal. Calcd for C\(_{19}\)H\(_{19}\)N\(_3\)O\(_2\): C, 71.03; H, 5.92; N, 13.08%. Found: C, 71.54; H, 5.31; N, 13.73%.

2.8. 1-((2-Hydroxynaphthalen-1-yl)(phenyl)methyl)thiosemicarbazide (3f)

Figure 1 Effect of LaCl\(_3\) on the reaction of 2-chlorobenzaldehyde, 2-naphthol and semicarbazide (as hydrochloride) (reactions carried out at 125 °C for 50 min).

Table 3 Recyclability of the catalyst in the reaction of benzaldehyde and 2-naphthol in the presence of semicarbazide in the presence of LaCl\(_3\)/CICH\(_2\)COOH under solvent free condition at 125 °C.

<table>
<thead>
<tr>
<th>Run no.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>
2.10. 1-((2-Hydroxynaphthalen-1-yl)(4-hydroxyphenyl) methyl)thiosemicarbazide (3h)

Mp 201–203 °C; IR (KBr): 3381, 3102, 3138, 1614, 1550, 1520, 1254, 746 cm⁻¹; ¹H NMR (400 MHz; CDCl₃): δ 6.65(s, 1H, CH), 7.25–7.50(m, 3H, ArH, NH₂), 7.49 (t, J = 7.7 Hz, 2H, ArH), 7.54 (d, J = 8.5 Hz, 2H, ArH), 7.65(t, J = 7.5 Hz, 2H, ArH), 7.81(s, 1H, NH), 7.89–7.91(m, 4H, ArH), 8.41(s, 1H, OH), 8.45(s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ 37.87(CH), 117.19, 120.05, 122.80, 124.79, 127.34, 129.32, 129.52, 130.27, 131.48, 131.67, 131.99(C, CH, Ar), 149.13(CO); Anal. Calcd for C₁₈H₁₇N₃O₂S: C, 63.72; H, 5.015; N, 12.39%. Found: C, 63.98; H, 5.58; N, 12.24%.

2.11. 1-((2-Hydroxynaphthalen-1-yl) (4-chlorophenyl)methyl)thiosemicarbazide (3i)

Mp 201–203 °C; IR (KBr): 3288, 3113, 2734, 1620, 1510, 1263, 776 cm⁻¹; ¹H NMR (400 MHz; CDCl₃): δ 6.47(s, 1H, CH), 7.08(d, J = 7.8 Hz, 2H, ArH), 7.17(s, 1H, NH), 7.30–7.51(m, 5H, ArH, NH), 7.60(t, J = 7.5 Hz, 2H, ArH), 7.78(brd, 1H, NH), 7.82(m, 2H, ArH), 8.33(s, 1H, OH/NH); ¹³C NMR (100 MHz, CDCl₃): δ 37.87(CH), 117.19, 120.05, 122.80, 124.79, 127.34, 129.32, 129.52, 130.27, 131.48, 131.67, 131.99(C, CH, Ar), 149.13(CO); Anal. Calcd for C₁₈H₁₇N₃OS: C, 63.72; H, 5.58; N, 12.24%. Found: C, 63.98; H, 5.58; N, 12.24%.

3. Results and discussion

In order to clarify the roll of LaCl₃ as a catalyst, the three-component reaction was carried out in the presence of CH₂COOH and in the absence of the catalyst. In this case the reaction needed a longer time to be completed and lower yield was obtained and also increasing reaction temperature does not have any significant affect on the yield of the reaction.

Proper catalyst conditions were obtained by using LaCl₃ at different various organic solvents, and the results are shown in Table 1, thus the best results were obtained when the reactions were carried out in the presence of chloroacetic acid.

The amount of LaCl₃ was optimized on the reaction of 2-chlorobenzaldehyde, 2-naphthol and semicarbazide (hydrochloride). The results were shown that a proper amount was 0.03 g (0.12 mmol) LaCl₃ (Fig. 1).

Encouraged by this result, a wide variety of aromatic aldehydes (2a–2i) were treated under optimized conditions and afforded the corresponding products (Table 2) in good to excellent yields.

The separated catalyst can be reused after washing with CHCl₃ and drying at 100 °C. The reusability of the catalyst was checked by the reaction of benzaldehyde and 2-naphthol in the presence of semicarbazide (hydrochloride) using 0.122 mmol of LaCl₃/CH₂COOH under solvent free condition at 125 °C. The results indicate that the catalyst can be used three times without any loss of its activity (Table 3).
A plausible mechanism for the synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)semicarbazide/thiosemicarbazide has been shown in Scheme 2.

We believe that LaCl$_3$ is coordinated to the carbonyl group of the aromatic aldehyde followed by the attack of the NH$_2$ group of semicarbazide to the activated carbonyl group, by removing the O that was coordinated to La$^{+3}$, then the imine group was formed, chloroacetic acid activates imine which will be attacked by 2-naphtol and the final product will be formed.

In order to obtain more information regarding the nature of the reaction, the reaction was run with a different pathway, which was done by a two-step procedure as it has been shown in Scheme 3. The product of two-step reaction and one-pot reaction was identical in both cases.

4. Conclusion

In conclusion, the synthesis of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)semicarbazides/thiosemicarbazides is reported, which is achieved by condensation of semicarbazide (hydrochloride)/thiosemicarbazide, 2-naphthol and aromatic aldehydes in the presence of a catalytic amount of lanthanum(III) chloride/chloroacetic acid as an efficient, green, readily available and environmentally benign catalyst. This new approach provides good yields of the corresponding final products with short reaction times and also simple experimental procedure. In addition it is consistent with the green chemistry approach, since no organic solvent is needed.

Acknowledgement

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References


