One-pot synthesis of cinnamoyl hydrazides

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Abstract
An efficient one-pot conversion of cinnamic acids and heterocyclic analogs into the corresponding hydrazides in good to excellent yields under mild conditions involves hydrazinolysis of the intermediate N-acylbenzotriazoles.

Keywords: N-Acylbenzotriazole, cinnamoyl hydrazides, synthesis

Introduction
The synthesis of cinnamoyl hydrazides has attracted significant attention due to their utility as intermediates for the preparation of 1,2,4,5-tetrazines1 and their biological activity, e.g. as tuberculostats.2 Hydrazides are generally prepared by the hydrazinolysis of esters;3 however, cinnamic esters form pyrazolidones resulting from Michael addition as the main products.4a,4b Published routes to cinnamoyl hydrazides involve i) preliminary preparation of activated esters and/or amides using 1-hydroxybenzotriazole (HOBt) followed by reaction with a hydrazine,5 ii) treatment of activated esters4b or mixed anhydrides1,4a with hydrazine. As a continuation of our study on N-acylbenzotriazole chemistry, we describe herein an efficient procedure allowing for the direct conversion of cinnamic acids and heterocyclic analogs into hydrazides in excellent yields under mild conditions (Scheme 1).

Results and Discussion
In our earlier work, N-acylbenzotriazoles were used for formylation,6a trifluoroacetylation,6b and for preparation of oxamides.6c Recent work has extended the applicability of acylbenzotriazoles
as neutral acylating reagents to the preparation of primary, secondary and tertiary amides, although no \(N\)-acylbenzotriazoles derived from \(\alpha,\beta\)-unsaturated carboxylic acids were investigated in such reactions. Acylbenzotriazoles 2a-f can be prepared by the reaction of benzotriazole with acyl halides. However, our recently reported methodology provides a mild preparative method (Scheme 1), which can be applied to the synthesis of many molecules with sensitive groups. This technique was used to prepare 2a-f in excellent yields (Table 1). The structures of 2a-f were characterized on the basis of \(^1\)H and \(^{13}\)C NMR spectra and CHN analytical data.

\[
\text{Scheme 1}
\]

**Table 1. Preparation of \(N\)-acylbenzotriazoles 2a-f and hydrazides 3a-f**

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R)</th>
<th>Mp(^b) [°C ]</th>
<th>Yield(^b) [%]</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>phenyl</td>
<td>157–159</td>
<td>116–117</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(158–159)</td>
<td>(116–117)</td>
<td>(90)</td>
</tr>
<tr>
<td>b</td>
<td>4-chlorophenyl</td>
<td>183–184</td>
<td>154–155</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(191–192)</td>
<td>(154–157)</td>
<td>(88)</td>
</tr>
<tr>
<td>c</td>
<td>4-nitrophenyl</td>
<td>242–243.5</td>
<td>210–212</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(244–245)</td>
<td>(215–216)</td>
<td>(90)</td>
</tr>
<tr>
<td>d</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>136–137</td>
<td>153–154</td>
<td>98</td>
</tr>
<tr>
<td>e</td>
<td>2-furyl</td>
<td>142–144</td>
<td>93–94</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(143–144)</td>
<td>(108–109)</td>
<td>(58)</td>
</tr>
<tr>
<td>f</td>
<td>2-thienyl</td>
<td>169–170</td>
<td>108–110</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^{a}\) 2d, 2f and 3d are novel compounds. \(^{b}\) Data in parentheses are literature values. \(^{c}\) Yield by one-pot synthesis is 81%. \(^{d}\) Yield by one-pot synthesis is 84%.

Treatment of 2a-f with anhydrous hydrazine in THF gave 3a-f in more than 75% yields. One-pot synthesis, converting 1b,d into 3b,d by direct hydrazinolysis without isolation of 2b,d, also succeeded in rather good yields. Thus, hydrazinolysis in situ is a more effective strategy. Hydrazides 3a-f obtained are also summarized in Table 1. The benzotriazole byproduct formed in these reactions can be easily removed by washing with saturated aqueous \(\text{Na}_2\text{CO}_3\).

In summary, we have developed an efficient general method to convert cinnamic acids and heterocyclic analogs into their hydrazides in one pot under mild conditions.
Experimental Section

General Procedures. Melting points were determined on a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR: spectra were recorded on a Varian GEMINI NMR spectrometer in CDCl$_3$ unless stated otherwise, with TMS for $^1$H and a solvent for $^{13}$C as the internal standard. THF was distilled from sodium/ benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere. Column chromatography was conducted with silica gel (230−400 mesh). 1-(Methylsulfonyl)benzotriazole was prepared according to the literature.7

General procedure for the preparation of N-acylbenzotriazoles 2a–f. To a solution of the carboxylic acid 1 (10.0 mmol) and 1-(methylsulfonyl)benzotriazole (1.97 g, 10.0 mmol) in of THF (50 mL), triethylamine (2.0 mL, 14 mmol) was added dropwise at room temperature, and then the mixture was heated under reflux overnight. After the removal of the solvent and excess triethylamine under reduced pressure, the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with water, dried over anhydrous MgSO$_4$, and evaporated. The resulting crude product was recrystallized from an appropriate solvent to provide the desired compounds 2a–f.

(E)-1-(Benzotriazol-1-yl)-3-phenyl-2-propen-1-one (2a). Cinnamic acid (1a) (1.48 g, 10 mmol) provided colorless needles 2a (2.24 g, 90%), mp 157−159 °C (lit.8a 158−159 °C); $^1$H NMR: δ 8.41 (d, $J$ = 8.2 Hz, 1H), 8.16−8.13 (m, 3H), 7.76−7.73 (m, 2H), 7.67 (dd, $J$ = 8.0, 7.3 Hz, 1H), 7.53 (dd, $J$ = 8.0, 7.4 Hz, 1H), 7.48−7.46 (m, 3H); $^{13}$C NMR: δ 163.9, 148.7, 146.3, 134.0, 131.4, 130.2, 129.0, 128.9, 127.7, 126.2, 120.1, 115.9, 114.8.

(E)-1-(Benzotriazol-1-yl)-3-(4-chlorophenyl)-2-propen-1-one (2b). From 4-chlorocinnamic acid (1b) (1.82 g, 10 mmol) colorless needles 2b (2.72 g, 96%) were obtained, mp 183−184 °C (lit.8b 191−192 °C); $^1$H NMR: δ 8.40 (d, $J$ = 8.2 Hz, 1H), 8.14 (d, $J$ = 8.5 Hz, 1H), 8.11 (d, $J$ = 16.4 Hz, 1H), 8.05 (d, $J$ = 16.4 Hz, 1H), 7.68−7.66 (m, 3H), 7.53 (dd, $J$ = 7.9, 7.3 Hz, 1H), 7.43 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR: δ 163.6, 147.0, 146.3, 137.4, 132.5, 131.4, 130.3, 130.0, 129.4, 126.3, 120.2, 116.6, 114.7.

(E)-1-(Benzotriazol-1-yl)-3-(4-nitrophenyl)-2-propen-1-one (2c). 4-Nitrocinnamic acid (1c) (1.93 g, 10 mmol) afforded yellow microcrystals 2c (2.68 g, 90%), mp 242−243.5 °C (lit.8b 244−245 °C); $^1$H NMR: δ 8.42 (d, $J$ = 8.2 Hz, 1H), 8.33 (d, $J$ = 8.0 Hz, 2H), 8.26 (d, $J$ = 16.1 Hz, 1H), 8.17 (d, $J$ = 5.3 Hz, 1H), 8.16 (d, $J$ = 16.1 Hz, 1H), 7.91 (d, $J$ = 8.1 Hz, 2H), 7.73 (dd, $J$ = 8.1, 7.4 Hz, 1H), 7.57 (dd, $J$ = 8.0, 7.5 Hz, 1H); $^{13}$C NMR: δ 163.0, 149.0, 146.4, 145.2, 139.9, 131.3, 130.6, 129.5, 126.6, 124.3, 120.4, 120.3, 114.7.

(E)-1-(Benzotriazol-1-yl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (2d). 3,4,5-Trimethoxycinnamic acid (1d) (2.38 g, 10 mmol) gave yellow needles 2d (3.3 g 98%), mp 136−137 °C; $^1$H NMR: δ 8.29 (d, $J$ = 8.2 Hz, 1H), 8.07 (d, $J$ = 8.2 Hz, 1H), 7.95 (d, $J$ = 15.7 Hz, 1H), 7.88 (d, $J$ =
15.7 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.46 (dd, J = 7.6, 7.3 Hz, 1H), 6.87 (s, 2H), 3.93 (s, 6H), 3.92 (s, 3H); 13C NMR: δ 163.2, 153.1, 148.2, 145.9, 140.9, 131.0, 129.7, 129.0, 125.7, 119.7, 114.5, 114.4, 105.9, 60.6, 55.9. Anal. Calcd for C18H17N3O4 (339.35): C, 63.71; H, 5.05; N, 12.38. Found: C, 63.37; H, 5.37; N, 11.93.

(E)-1-(Benzotriazol-1-yl)-3-(2-furyl)-2-propen-1-one (2e). 3-(2-Furyl)acrylic acid \(1e\), (1.38 g, 10 mmol) gave dark-red needles \(2e\) (2.27 g, 95%), mp 142–144 °C (lit.8b 143–144 °C); 1H NMR: δ 8.37 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 15.5 Hz, 1H), 7.84 (d, J = 15.7 Hz, 1H), 7.67–7.60 (m, 2H), 7.49 (dd, J = 7.9, 7.3 Hz, 1H), 6.84 (d, J = 3.2 Hz, 1H), 6.55 (br s, 1H); 13C NMR: δ 163.8, 151.0, 146.2, 145.9, 133.9, 131.3, 130.0, 125.9, 120.0, 117.5, 114.6, 113.4, 112.8.

(E)-1-(Benzotriazol-1-yl)-3-(2-thienyl)-2-propen-1-one (2f). 3-(2-Thienyl)acrylic acid \(1f\) (1.54 g, 10 mmol) afforded yellow needles \(2f\) (2.50 g, 98%), mp 169–170 °C; 1H NMR: δ 8.40 (d, J = 8.2 Hz, 1H), 8.24 (d, J = 15.5 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 15.5 Hz, 1H), 7.67–7.60 (m, 2H), 7.49 (dd, J = 7.9, 7.6 Hz, 1H), 7.13 (dd, J = 4.4, 4.1 Hz, 1H); 13C NMR: δ 163.7, 146.2, 140.7, 139.6, 133.0, 131.4, 130.5, 130.2, 128.4, 126.1, 120.1, 114.7, 114.4. Anal. Calcd for C13H9N3OS (255.30): C, 61.16; H, 3.55; N, 16.46. Found: C, 61.27; H, 3.32; N, 16.47.

General procedure for the preparation of hydrazides 3a–f
To a solution of the appropriate N-acylbenzotriazoles 2 (10 mmol) in THF (50 mL), a solution of anhydrous hydrazine (0.38 mL, 12 mmol) in THF (5 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for about 4 h. After THF was removed under reduced pressure, the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with saturated aqueous Na2CO3, water, dried over anhydrous MgSO4, and evaporated to give a crude product, which was recrystallized from benzene.

(E)-3-Phenyl-2-propenohydrazide (3a). From 2a (2.49 g, 10 mmol) were obtained white plates \(3a\) (1.38 g, 85%), mp 116–117 °C (lit 1 116–117 °C); 1H NMR: δ 7.68 (d, J = 15.7 Hz, 1H), 7.48–7.51 (m, 2H), 7.40–7.43 (m, 1H), 7.34–7.39 (m, 3H), 6.40 (d, J = 15.7 Hz, 1H), 3.95–4.11 (br s, 2H); 13C NMR: δ 167.1, 141.3, 134.5, 129.7, 128.7, 127.7, 118.1.

(E)-3-(4-Chlorophenyl)-2-propenohydrazide (3b). 2b (2.84 g, 10 mmol) afforded white plates \(2b\) (1.69 g, 86%), mp 154–155 °C (lit.2 154–157 °C); 1H NMR: δ 7.64 (d, J = 15.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.26 (br s, 1H), 6.33 (d, J = 15.5 Hz, 1H), 4.08 (br s, 2H); 13C NMR: δ 166.7, 140.5, 135.8, 132.9, 129.1, 128.9, 118.2.

(E)-3-(4-Nitrophenyl)-2-propenohydrazide (3c). 2c (2.94 g, 10 mmol) provided white plates \(3c\) (1.61 g, 78%), mp 210–212 °C (lit.4a 215–216 °C); 1H NMR: (DMSO-d6) δ 9.55 (s, 1H), 8.26 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 15.9 Hz, 1H), 6.73 (d, J = 15.9 Hz, 1H), 4.56 (br s, 2H); 13C NMR: (DMSO-d6) δ 163.5, 147.5, 141.6, 135.9, 128.5, 124.6, 124.2.

(E)-3-(3,4,5-Trimethoxyphenyl)-2-propenohydrazide (3d). 2d (3.39 g, 10 mmol) gave white needles \(3d\) (2.10 g, 83%), mp 153–154 °C; 1H NMR: δ 7.60 (d, J = 15.4 Hz, 1H), 7.22 (br s, 1H), 6.73 (s, 2H), 6.33 (d, J = 15.5 Hz, 1H), 4.10 (br s, 1H), 3.87 (s, 9H); 13C NMR: δ 166.9, 153.3, 141.6, 139.7, 130.0, 117.1, 104.9, 60.9, 56.1. Anal. Calcd for C12H16N2O4 (252.27): C, 57.13; H,
6.39; N, 11.10. Found: C, 57.25; H, 6.75; N, 11.05.

(E)-3-(2-Furyl)-2-propenohydrazide (3e). From 2e (2.39 g, 10 mmol) were obtained white needles 3e (1.23 g, 81%), mp 93–94 °C (lit.9 108–110 °C); $^1$H NMR: $\delta$ 7.46 (d, $J = 15.2$ Hz, 1H), 7.43 (s, 1H), 7.36 (br s, 1H), 6.56 (d, $J = 2.9$ Hz, 1H), 6.45 (d, $J = 1.5$ Hz, 1H), 6.30 (d, $J = 15.2$ Hz, 1H), 4.06 (br s, 2H); $^{13}$C NMR: $\delta$ 167.0, 150.9, 144.1, 128.3, 115.5, 114.2, 112.1. Anal. Calcd for C$_7$H$_8$N$_2$O$_2$ (152.15): C, 55.25; H, 5.30; N, 18.41. Found: C, 55.49; H, 4.93; N, 18.25.

(E)-3-(2-Thienyl)-2-propenohydrazide (3f). 2f (2.55 g, 10 mmol) provided white needles 3f (1.30 g, 77%), mp 108–110 °C (lit.10 123 °C); $^1$H NMR: $\delta$ 7.81 (d, $J = 15.5$ Hz, 1H), 7.47 (s, 1H), 7.32 (d, $J = 5.0$ Hz, 1H), 7.21 (d, $J = 2.0$ Hz, 1H), 7.03 (d, $J = 3.5$ Hz, 1H), 6.21 (d, $J = 15.5$ Hz, 1H), 4.10 (br s, 2H); $^{13}$C NMR: $\delta$ 166.9, 139.6, 134.2, 130.6, 127.9, 127.5, 116.6. Anal. Calcd for C$_7$H$_8$N$_2$OS (168.22): C, 49.98; H, 4.79; N, 16.65. Found: C, 50.14; H, 4.65; N, 16.59.

References and Notes

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