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

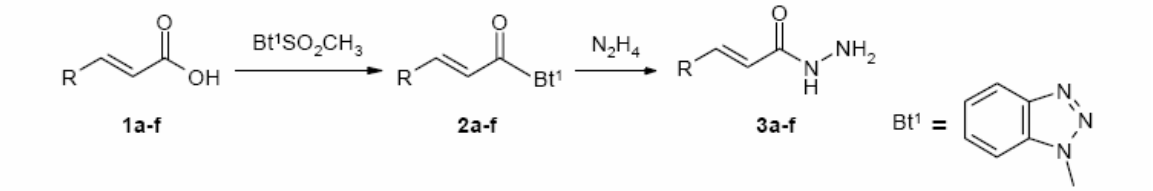
Introduction

The synthesis of cinnamoyl hydrazides has attracted significant attention due to their utility as intermediates for the preparation of 1,2,4,5-tetrazines[1] 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 esters[4b] 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,[7] although no *N*-acylbenzotriazoles derived from α,β-unsaturated carboxylic acids were investigated in such reactions. Acylbenzotriazoles **2a-f** can be prepared by the reaction of benzotriazole with acyl halides.[8a,8b] However, our recently reported methodology[7] 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.



Scheme 1

Table 1. Preparation of *N*-acylbenzotriazoles **2a-f** and hydrazides **3a-f**[a]

Entry	R	Mp[b] [°C]		Yield[b] [%]		Ref.
		2	**3**	**2**	**3**	
a	phenyl	157−159 (158−159)	116−117 (116−117)	90 (90)	85 (66)	1, 8a
b	4-chlorophenyl	183−184 (191−192)	154−155 (154−157)	96 (88)	86[c] (51)	2, 8b
c	4-nitrophenyl	242−243.5 (244-245)	210−212 (215-216)	91 (90)	78 (70)	4a, 8b
d	3,4,5-trimethoxyphenyl	136−137	153−154	98	83[d]	
e	2-furyl	142−144 (143−144)	93−94 (108−109)	95 (58)	81 (69)	8b, 9
f	2-thienyl	169−170	108−110 (123)	98	77	10

[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 Na_2CO_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-Trimethoxy cinnamic acid (**1d**) (2.38 g, 10 mmol) gave yellow needles **2d** (3.32 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); ^{13}C 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 $C_{18}H_{17}N_3O_4$ (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); ^{1}H 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); ^{13}C 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; ^{1}H 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 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.54−7.43 (m, 3H), 7.13 (dd, *J* = 4.4, 4.1 Hz, 1H); ^{13}C 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 $C_{13}H_9N_3OS$ (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 Na_2CO_3, water, dried over anhydrous $MgSO_4$, 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); ^{1}H 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); ^{13}C 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); ^{1}H 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); ^{13}C 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); ^{1}H NMR: (DMSO-d_6) 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); ^{13}C NMR: (DMSO-d_6) 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; ^{1}H 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); ^{13}C NMR: δ 166.9, 153.3, 141.6, 139.7, 130.0, 117.1, 104.9, 60.9, 56.1. Anal. Calcd for $C_{12}H_{16}N_2O_4$ (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: δ 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: δ 167.0, 150.9, 144.1, 128.3, 115.5, 114.2, 112.1. Anal. Calcd for $C_7H_8N_2O_2$ (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: δ 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: δ 166.9, 139.6, 134.2, 130.6, 127.9, 127.5, 116.6. Anal. Calcd for $C_7H_8N_2OS$ (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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