Reaction between 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione and *tert*-butyl isocyanide in the presence of ethane-1,2-diol or catechol

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tert-Butyl isocyanide undergoes a smooth reaction with 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (benzylidene Meldrum's acids) in the presence of ethane-1,2-diol or catechol to produce functionalised *N-tert*-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-aryl-ethanamides or bis-(2-hydroxyphenyl) 2-[2-(*tert*-butylamino)-1-aryl-2-oxoethyl]-malonates in good yields.

Keywords: benzylidene Meldrum's acid, ethane-1,2-diol, catechol, three-component reaction

As versatile reagents and important intermediates, Meldrum's acid (isopropylidene malonate) and its derivatives have been widely used in organic synthesis.[1,2] In the context of our recent studies[3-8] on the reactivity of isopropylidene Meldrum's acid, we studied the reaction between 5-benzylidene-2,2-dimetyl-1,3-dioxane-4,6-dione (**1**, benzylidene Meldrum's acid) and *tert*-butyl isocyanide (**2**) in the presence of bidentate proton sources, such as ethane-1,2-diol (**3**) or catechol (**4**). This reaction led to highly functionalised *N-tert*-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-arylethanamides **5** and bis-(2-hydroxyphenyl) 2-[2-(*tert*-butylamino)-1-aryl-2-oxoethyl]malonates **6** in good yields (Scheme 1).

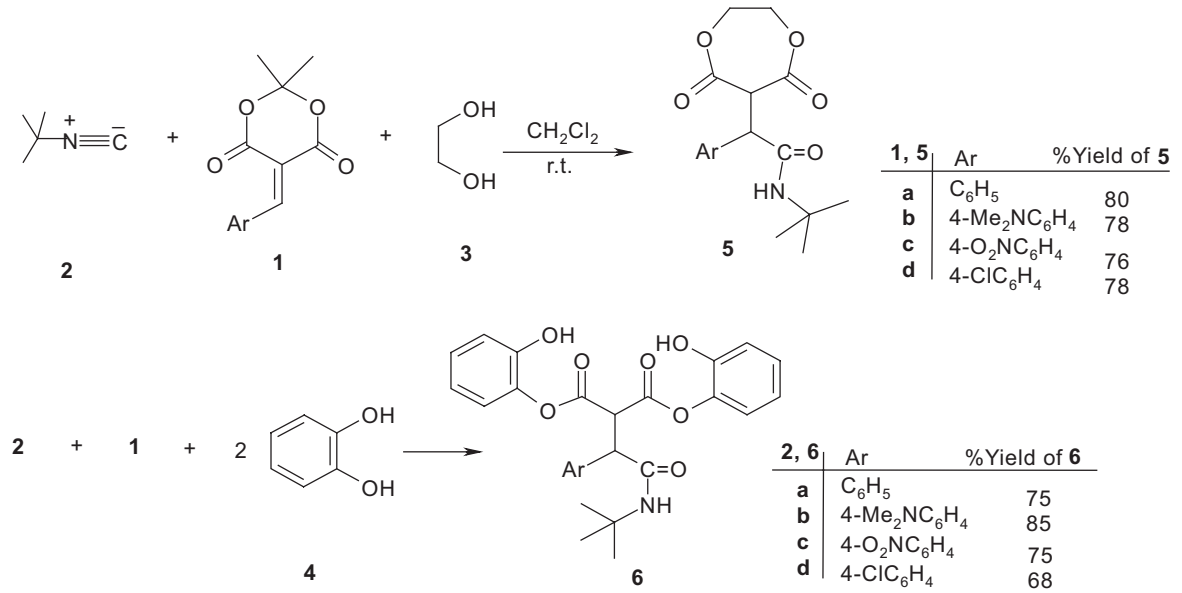
The reaction of *tert*-butyl isocyanide with **1** in the presence of **3** or **4** proceeded at room temperature in CH_2Cl_2 and was complete within 24 h. The ^{1}H NMR spectra of the crude products clearly showed the formation of **5** or **6**[9] (Scheme 1).

The structures of compounds **5** and **6** were deduced from their elemental analyses and IR, ^{1}H NMR and ^{13}C NMR data. The IR spectrum of **5a** clearly showed N–H stretching band at 3270 cm^{-1}. The ^{1}H NMR spectrum of **5a** exhibited a sharp singlet for the *tert*-butyl (δ = 1.28 ppm) along with two doublets (δ = 3.83 and 4.42 ppm; $^3J_{HH}$ = 4.5 Hz) for the methine protons. The CH_2–CH_2 moiety exhibited a complex multiplete at δ = 4.15–4.19 ppm. The N–H and aromatic protons appear at δ = 5.36 and 7.20–7.40 ppm, respectively. The ^{13}C NMR spectrum of **5a** showed 15 distinct resonances in agreement with proposed structure. Partial assignment of these resonances is given in the Experimental section. The ^{1}H NMR and ^{13}C NMR spectra of **5b–5d** are similar to those of **5a** except for the aryl residues which exhibited characteristic signals with appropriate chemical shifts (see Experimental section).

The IR spectrum of **6a** showed O–H and N–H bands at 3500, 3270 cm^{-1}. The ^{1}H NMR spectrum of **6a** exhibited sharp resonances in the aliphatic region arising from *tert*-butyl (δ = 1.29 ppm) and methine (δ = 3.80 and 5.76 ppm) protons.

On the basis of well established chemistry of isocyanides[10-13] it is reasonable to assume that compound **5** result from an initial [4 + 1] cycloaddition reaction of the electron deficient hetrodiene moiety of **1** with *tert*-butyl isocyanide, producing an iminolactone intermediate **7**, which losses acetone to produce ketene **8**. The ketene **8** can be trapped by ethane-1,2-diol to give **5**. Reaction of **1** with **2** in the presence of catechol at room temperature led to **6** (Scheme 2).

In conclusion, the reaction of *tert*-butyl isocyanide with 5-benzylidene-2,2-dimetyl-1,3-dioxane-4,6-dione in the presence of ethane-1,2-diol or catechol produce functionalised *N-tert*-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-arylethanamides or bis-(2-hydroxyphenyl) 2-[2-(*tert*-butylamino)-1-aryl-2-oxoethyl]malonates of potential synthetic interest. The one-



1, 5	Ar	%Yield of 5
a	C_6H_5	80
b	4-$Me_2NC_6H_4$	78
c	4-$O_2NC_6H_4$	76
d	4-ClC_6H_4	78

2, 6	Ar	%Yield of 6
a	C_6H_5	75
b	4-$Me_2NC_6H_4$	85
c	4-$O_2NC_6H_4$	75
d	4-ClC_6H_4	68

Scheme 1

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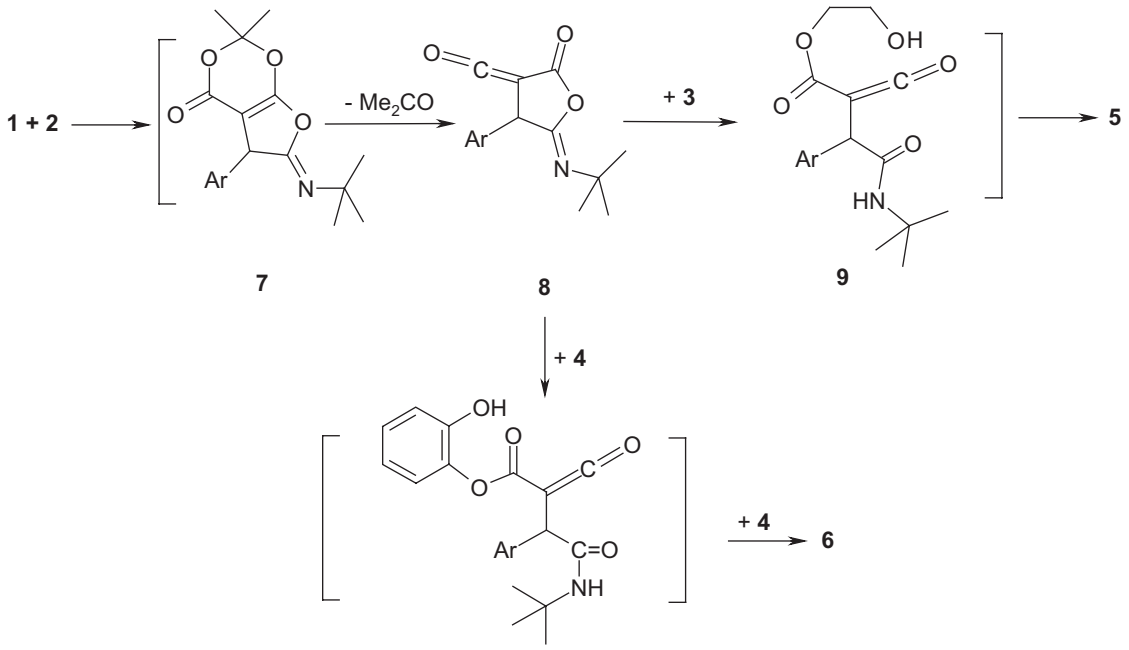

Scheme 2

pot nature of the present procedure makes it an acceptable method for preparation of target molecules with variable functionalities.

Experimental

General

Compounds **2**–**4** were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; δ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m*/*z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

General procedure for the preparation of **5**

To a stirred solution of **1** (2 mmol) and **3** (2 mmol) in 10 ml of CH_2Cl_2 was added dropwise a mixture of **2** (2 mmol) in 2 ml of CH_2Cl_2 at 0°C over 5 min. The reaction was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/AcOEt 4:1) to afford the pure title compounds.

N-tert-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-phenyl-ethanamide (**5a**): Pale yellow powder, yield: 0.51 g (80%). M.p. 57–59°C. IR (KBr): 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.28 (9 H, *s*, C*Me*$_3$), 3.83 (1 H, *d*, ^3J = 4.5, CH), 4.15–4.19 (4 H, *m*,OCH_2CH_2O), 4.42 (1 H, *d*, ^3J = 4.5, CH), 5.36 (1 H, *s*, N–H), 7.30–7.35 (5 H, *m*, C_6H_5). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 44.7, 52.7 (2 CH), 56.8 (*C*Me$_3$), 66.6, 67.6 (2OCH_2), 128.0, 128.3, 128.5, 129.0, 129.2 (5 CH), 136.9 (C), 165.9, 168.2, 169.3 (3 C=O). EI-MS: 319 (M^+, 7), 275 (18), 261 (78), 260 (46), 245 (84), 228 (82), 129 (80), 101 (47), 91 (100), 74 (47), 59 (31), 58 (26), 44 (34). Anal. Calcd for $C_{17}H_{21}NO_5$ (319.35): C, 63.93; H, 6.63; N, 4.39%; found: C, 63.62; H, 6.59; N, 4.36%.

N-tert-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-(4-dimethylaminophenyl)-ethanamide (**5b**): Yellow powder, yield: 0.56 g (78%). M.p. 79–81°C. IR (KBr): 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.28 (9 H, *s*, C*Me*$_3$), 2.97 (6 H, *s*, 2 NMe), 3.83 (1 H, *d*, ^3J = 4.7, CH), 4.14–4.18 (4 H, *m*,°CH_2CH_2O), 4.42 (1 H, *d*, ^3J = 4.7, CH), 5.37 (1 H, *s*, N–H), 6.62–6.69 (4 H, *m*, C_6H_4). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 40.8 (2 NMe), 44.7, 52.7 (2 CH), 55.6 (*C*Me$_3$), 66.6, 67.6 (2 CH_2O), 112.4, 113.2, 123.9, 126.5 (4 CH), 128.9, 129.2 (2 C), 167.4, 168.2, 171.2 (3 C=O). EI-MS: 362 (M^+, 9), 275 (18), 261 (78), 260 (46), 245 (84), 228 (82), 129 (80), 101 (47), 91 (100), 74 (47), 59 (31), 58 (26), 44 (34). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.42): C, 62.96; H, 7.23; N, 7.73%; found: C, 62.88; H, 7.31; N, 7.79%.

N-tert-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-(4-nitrophenyl)-ethanamide (**5c**): Yellow powder, yield: 0.55 g (76%). M.p. 93–95°C. IR (KBr): 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.28 (9 H, *s*, C*Me*$_3$), 3.83 (1 H, *d*, ^3J = 4.6, CH), 4.12–4.17 (4 H, *m*, CH_2CH_2O), 4.42 (1 H, *d*, ^3J = 4.6, CH), 5.52 (1 H, *s*, N–H), 8.06–8.30 (4 H, *m*, C_6H_4). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 50.9, 52.5 (2 CH), 56.2 (*C*Me$_3$), 67.51, 67.92 (2 CH_2O), 124.3, 129.0, 129.6, 130.2 (4 CH), 146.9, 147.7 (2 C), 167.2, 168.3, 169.5 (3 C=O). EI-MS: 364 (M^+, 6), 318 (23), 303 (45), 302 (32), 288 (51), 228 (49), 134 (100), 74 (50), 59 (42), 58 (33), 44 (18). Anal. Calcd for $C_{17}H_{20}N_2O_7$ (364.35): C, 56.04; H, 5.53; N, 7.69%; found: C, 56.12; H, 5.59; N, 7.75%.

N-tert-butyl-2-(5,7-dioxo-1,4-dioxepane-6-yl)-2-(4–Chlorophenyl)-ethanamide (**5d**): Yellow powder, yield: 0.55 g (78%). M.p. 76–78°C. IR (KBr): 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.28 (9 H, *s*, C*Me*$_3$), 3.83 (1 H, *d*, ^3J = 4.5, CH), 4.14–4.18 (4 H, *m*, CH_2CH_2O), 4.42 (1 H, *d*, ^3J = 4.5, CH), 5.45 (1 H, *s*, N–H), 7.29–7.33 (4 H, *m*, C_6H_4). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 51.8, 53.2 (2 CH), 55.2 (*C*Me$_3$), 61.2, 62.8 (2 CH_2O), 128.5, 128.6, 128.9, 129.2 (4 CH), 131.4, 136.7 (2 C), 168.2, 168.8, 170.4 (3 C=O). EI-MS: 354 (M^+, 7), 320 (45), 305 (48), 304 (27), 290 (62), 228 (53), 136 (100), 101 (78), 74 (39), 59 (33), 58 (29), 46 (26), 44 (22). Anal. Calcd for $C_{17}H_{20}NO_5Cl$ (353.80): C, 57.71; H, 5.70; N, 3.96%; found: C, 57.82; H, 5.66; N, 4.03%.

General procedure for the preparation of **6**

To a stirred solution of **1** (2 mmol) and **4** (4 mmol) in 10 ml of CH_2Cl_2 was added dropwise a mixture of **2** (2 mmol) in 2 ml of CH_2Cl_2 at 0°C over 5 min. The reaction was allowed to warm to room temperature and stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/AcOEt 4:1) to afford the pure title compounds.

Bis-(2-hydroxyphenyl) 2-[2-(tert-butylamino)-1-phenyl-2-oxoethyl]-malonate (**6a**): Yellow powder, yield: 0.68 g (75%). M.p. 47–49°C. IR (KBr): 3500, 3350 (O–H) 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.29 (9 H, *s*, C*Me*$_3$), 3.80 (1 H, *d*, ^3J = 4.8, CH), 4.33 (1 H, *d*, ^3J = 4.8, CH), 5.76 (1 H, *s*, N–H), 6.73–7.39 (13 H, *m*, 2 C_6H_4, C_6H_5), 8.70 (2 H, *s*, 2 O–H). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 44.5, 52.7 (2 CH), 55.8 (*C*Me$_3$), 116.2, 117.5, 118.1, 120.2, 120.5, 121.0, 122.8, 123.1, 127.8, 128.0, 128.2, 128.4, 128.7, 129.8, 138.2, 138.4, 144.7, 149.1 (3 C_6H_4), 167.6, 168.7, 173.8 (3 C=O). EI-MS: 477 (M^+, 6), 433 (23), 419 (17), 418 (31), 386 (45), 369 (35), 108 (100), 91 (39), 74 (48), 59 (24), 58 (30), 44 (18). Anal. Calcd for $C_{27}H_{27}NO_7$ (477.50): C, 67.91; H, 5.70; N, 2.93%; found: C, 67.82; H, 5.77; N, 2.97%.

Bis-(2-hydroxyphenyl) 2-[2-(tert-butylamino)-1-(4-dimethylamino-phenyl)-2-oxoethyl]-malonate (**6b**): Yellow powder, yield: 0.86 g (85%). M.p. 84–86°C. IR (KBr): 3500, 3350 (O–H) 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.28 (9 H, *s*, C*Me*$_3$), 3.17 (6 H, *s*, 2 Me) 3.83 (1 H, *d*, ^3J = 4.7, CH), 4.34 (1 H, *d*, ^3J = 4.7, CH), 5.52 (1 H, *s*, N–H), 6.66–7.50 (12 H, *m*, 3 C_6H_4), 8.81 (2 H, *s*, 2 O–H). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 40.7, 40.7 (2 Me), 45.4, 52.6 (2 CH), 55.9 (*C*Me$_3$), 113.4, 113.6, 118.1, 118.3, 120.2, 121.2, 122.6,

122.8, 130.1, 138.0, 149.0 (3 C_6H_4) 165.9, 168.8, 169.3 (3 C=O). EI-MS: 520 (M^+, 4), 476 (61), 462 (53), 461 (32), 381 (49), 134 (43), 108 (100), 101 (17), 74 (37), 59 (28), 58 (23), 44 (17). Anal. Calcd for $C_{29}H_{32}N_2O_7$ (520.57): C, 66.91; H, 6.20; N, 5.38%; found: C, 67.11; H, 6.29; N, 5.26%.

Bis-(2-hydroxyphenyl) 2-[2-(tert-butylamino)-1-(4-nitrophenyl)-2-oxoethyl]-malonate (**6c**): Yellow powder, yield: 0.74 g (75%). M.p. 71–73°C. IR (KBr): 3500, 3350 (O–H) 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.27 (9 H, *s*, C*Me*$_3$), 3.83 (1 H, *d*, ^3J = 4.9, CH),), 4.35 (1 H, *d*, ^3J = 4.9, CH), 5.52 (1 H, *s*, N–H), 6.73–7.52 (12 H, *m*, 3 C_6H_4), 8.81 (2 H, *s*, 2 O–H). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 46.9, 52.2 (2 CH), 55.3 (*C*Me$_3$), 116.1, 118.2, 122.7, 124.1, 124.7, 124.8, 125.1, 127.9, 128.8, 129.3, 130.1, 138.0, 144.2, 146.0, 148.8 (3 C_6H_4), 170.1, 170.5, 171.6 (3 C=O). EI-MS: 522 (M^+, 5), 478 (27), 464 (34), 463 (48), 388 (52), 342 (45), 252 (19), 136 (78), 108 (100), 74 (26), 59 (19), 58 (32), 46 (14), 44 (17). Anal. Calcd for $C_{27}H_{26}N_2O_9$ (522.50): C, 62.06; H, 5.02; N, 5.36%; found: C, 62.22; H, 5.08; N, 5.42%.

Bis-(2-hydroxyphenyl) 2-[2-(tert-butylamino)-1-(4–chlorophenyl)-2-oxoethyl]-malonate (**6d**): Yellow powder, yield: 0.70 g (68%). M.p. 63–65°C. IR (KBr): 3500, 3350 (O–H) 3270 (N–H), 1727, 1714, 1650, 1615 (C=O). ^{1}H NMR: δ = 1.27 (9 H, s, C*Me*$_3$), 3.83 (1 H, *d*, ^3J = 4.6, CH), 4.32 (1 H, *d*, ^3J = 4.6, CH), 5.52 (1 H, *s*, N–H), 6.56–7.44 (12 H, *m*, 3 C_6H_4), 8.83 (2 H, *s*, 2 O–H). ^{13}C NMR: δ = 28.8 (C*Me*$_3$), 47.4, 52.1 (2 CH), 55.2 (*C*Me$_3$), 119.7, 120.1, 121.6, 127.4, 130.1, 130.5, 131.2, 133.2, 137.4, 138.6, 146.1, 149.7 (3 C_6H_4) 170.2, 170.3, 171.4 (3 C=O). EI-MS: 512 (M^+, 4), 468 (35), 454 (44), 453 (52), 387 (38), 279 (43), 125 (51), 108 (100), 74 (35), 59 (41), 58 (21), 44 (27). Anal. Calcd for $C_{27}H_{26}NO_7Cl$ (511.95): C, 63.34; H, 5.12; N, 2.74%; found: C, 63.56; H, 5.19; N, 2.83%.

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