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Synthesis of Aryl 1-(*tert*-Butyl)-4,4-dimethyl-2,5-dioxo-3-pyrrolidinecarboxylates

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Reaction of *tert*-butyl isocyanide with isopropylidene Meldrum's acid in the presence of phenols in dichloromethane leads to aryl 1-(*tert*-butyl)-4,4-dimethyl-2,5-dioxo-3-pyrrolidinecarboxylates in good yields.

Key words: Meldrum's acid, alkyl isocyanides, Ugi reaction, three-component reaction, pyrrolidine-2,5-dione

Pyrrolidine system is present in biologically active compounds and pharmaceuticals [1–5]. The known methods employed for preparation of pyrrolidine-2,5-diones deal with the reaction of amines with derivatives of succinic anhydride [6], Diels-Alder [7] and ene [8] reactions of maleimides, and Stobbe type condensation [9]. Furukawa and coworker's [10] were the first to prepare pyrrolidine-2,5-diones by introducing carbonyl function at 3-position.

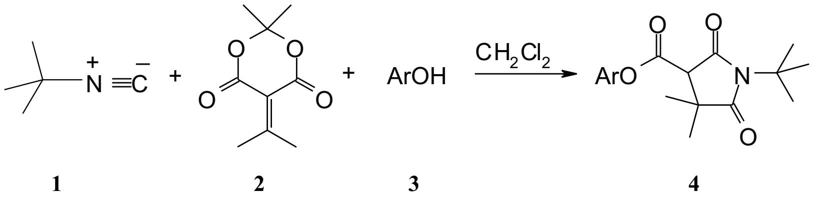
Currently, we have been interested [11,12] in the reaction between isocyanides and isopropylidene Meldrum's acid [13] (prepared from Meldrum's acid and acetone [14]), as electron-deficient alkene in the presence of phenols. Here, we report a new, one-pot synthesis of pyrrolidine-2,5-diones containing carboxylate group at 3-position.

RESULTS AND DISCUSSION

The reaction of *tert*-butyl isocyanide (**1**) with isopropylidene Meldrum's acid **2** was performed in the presence of phenols **3a**–**g**. This reaction proceeded slowly at room temperature in CH_2Cl_2 and was completed within 24 h. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of phenyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (**4**) (Scheme 1).

The ^{1}H NMR spectrum of **4a** exhibited three singlets assigned to *gem*-dimethyl (δ 1.24 and 1.38) and methine (δ 3.66) protons. The ^{13}C NMR spectrum of **4a** showed ninteen signals in agreement with the proposed pyrrolidine structure. The IR spectra of **4a** showed two absorption bands in the carbonyl region. The ^{15}N NMR spectrum of **4a** exhibited a signal at 185.69 ppm for the imide nitrogen atom. The observed ^{15}N shift for the imide moiety of **4a** is in good agreement with the previously reported values for *N*-alkylsuccinimide derivatives [15,16]. The ^{1}H and ^{13}C NMR spectra of **4b**–**4g** were similar with characteristic signals in aliphatic and aromatic region.

Scheme 1

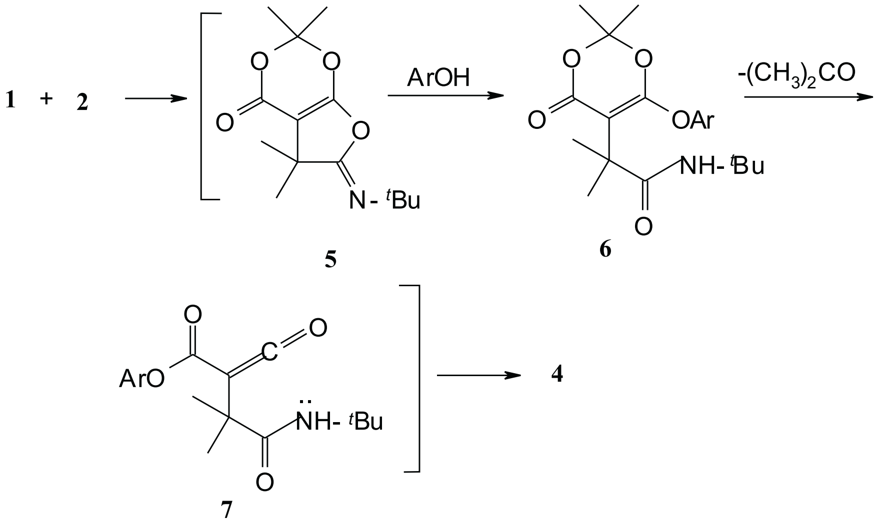


3,4	Ar
a	1-Naphthyl
b	2-Naphthyl
c	Quinolin-8-yl
d	C_6H_5
e	p-CH_3-C_6H_4
f	p-Nitro-C_6H_4
g	2,4-Cl_2-C_6H_3

The plausible way of formation of the product is proposed in Scheme 2. The reaction starts from [4+1]cycloaddition of isocyanide to the electron-deficient heterodiene moiety of isopropylidene Meldrum's acid to form intermediate iminolactone **5** [17,18]. Then conjugate addition of phenol to enone moiety of **5**, results in opening of a five-membered ring to form amide **6**, that eliminates acetone to form ketene **7** [19]. Ring closure of the ketene **7** leads to the product **4**.

The presented reaction gives a simple entry to the synthesis of pyrrolidine-2,5-dione derivatives.

Scheme 2



EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer; the results agreed favourably with the calculated values. IR spectra were measured on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded at 500.1, 125.7 and 50.7 MHz on a Bruker DRX-500 Avance instrument with $CDCl_3$ as solvent and TMS as internal standard (for ^{15}N NMR, liquid NH_3 was used as external standard). Meldrum's acid and other reagents were obtained from Fluka (Buchs, Switzerland) and used without further purification

1-Naphthyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4a), General procedure. To a magnetically stirred solution of **2** (0.368 g, 2 mmol) and **3a** (0.286 g, 2 mmol) in CH_2Cl_2 (10 cm^3), a solution of *tert*-butyl isocyanide (0.170 g, 2 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise at room temperature. The reaction mixture then was stirred for 24 h. The solvent was removed under reduced pressure, and the oily residue was dissolved in ethyl acetate. The product was precipitated by addition of *n*-hexane, collected by filtration, and recrystallized from a 3:2 mixture of *n*-hexane-ethyl acetate. Yield 0.57 g (81%). Colorless crystals; m.p.: 93–95°C; IR (KBr) $\bar{\nu}$ = 1742, and 1695 (C=O) cm^{-1}; MS: *m*/*z* (%) = 353 (33), 298 (20), 144 (100), 115 (24), 83 (44), 57 (33); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 and 1.49 (6H, 2s, CMe_2), 1.62 (9H, s, CMe_3), 3.74 (1H, s, CH), 7.23–7.96 (7H, m, 1-naphthyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.61 and 27.30 (CMe_2), 28.19 (CMe_3), 43.35 (CMe_2), 58.98 (CH), 59.11 (CMe_3), 117.72, 121.02, 125.14, 126.46, 126.60, 126.67, 126.92, 127.98, 134.66, 145.95 (1-naphthyl), 165.91, 172.40 and 182.16 (3C=O) ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = 185.69 ppm. Anal. Calcd for $C_{21}H_{23}NO_4$ (353.4): C, 71.4; H, 6.6; N, 4.0%. Found: C, 71.3; H, 6.4; N, 3.9%.

The following compounds were obtained:

2-Naphthyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4b). Yield 82%. Colorless crystals; m.p.: 84–86°C; IR (KBr) $\bar{\nu}$ = 1740, and 1694 (C=O) cm^{-1}; MS: *m*/*z* (%) = 353 (48), 144 (100), 115 (21), 83 (40), 57 (33); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 and 1.46 (6H, 2s, CMe_2), 1.62 (9H, s, CMe_3), 3.64 (1H, s, CH), 7.21–7.85 (7H, m, 2-naphthyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.60 and 27.13 (CMe_2), 28.18 (CMe_3), 43.32 (CMe_2), 58.86 (CH), 58.91 (CMe_3), 118.37, 120.44, 126.04, 126.79 , 127.68, 127.78, 129.64, 131.65, 133.59, and 147.66 (2-naphthyl), 166.08, 172.19 and 182.08 (3C=O) ppm. Anal. Calcd for $C_{21}H_{23}NO_4$ (353.4): C, 71.4; H, 6.6; N, 4.0%. Found: C, 71.2; H, 6.5; N, 3.9%.

8-Quinolyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4c). Yield 86%. Pale red crystals; m.p.: 56–58°C; IR (KBr) $\bar{\nu}$ = 1742, and 1694 (C=O) cm^{-1}; MS: *m*/*z* (%): 354 (6), 226 (17), 194 (17), 172 (44), 145 (100), 117 (21), 83 (36), 57 (48); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.55 and 1.60 (6H, s, CMe_2), 1.62 (9H, s, CMe_3), 3.9 (1H, s, CH), 7.40–8.89 (6H, m, quinoline) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.13 and 26.36 (CMe_2), 28.1 (CMe_3), 43.71 (CMe_2), 58.53 (CH), 58.73 (CMe_3), 121.53, 121.88, 126.1, 126.36, 129.47, 136.1, 140.53, 146.54, and 150.37 (quinoline), 165.99, 172.34 and 182.76 (3C=O) ppm. Anal. Calcd for $C_{20}H_{22}N_2O_4$ (354.4): C, 67.8; H, 6.3; N, 7.9%. Found: C, 67.4; H, 6.6; N, 7.6%.

Phenyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4d). Yield 65%. Colorless crystals; m.p.: 90–92°C; IR (KBr) $\bar{\nu}$ = 1743, 1634 (C=O) cm^{-1}; MS: *m*/*z* (%) = 304 (50), 248 (55), 210 (70), 183 (20), 154 (85), 127 (30), 83 (100), 57 (85); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 and 1.43 (6H, 2 s, CMe_2), 1.61 (9 H, s, CMe_3), 3.58 (1H, s, CH), 7.1–7.38 (5H, m, C_6H_5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.47 and 27.12 (CMe_2), 28.15 (CMe_3), 43.27 (CMe_2), 58.80 (CH), 58.85 (CMe_3). 121.60, 126.41, 129.57, and 150.06 (C_6H_5), 165.89, 172.16, and 182.06 (3C=O) ppm. Anal. Calcd for $C_{17}H_{21}NO_4$ (303.4): C, 67.3; H, 7.0; N, 4.6%. Found: C, 67.1; H, 6.6; N, 4.6%.

***p*-Tolyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4e).** Yield 68%. Colorless crystals; m.p.: 58–60°C; IR (KBr) $\bar{\nu}$ = 1740, and 1695 (C=O) cm^{-1}; MS: *m*/*z* (%) = 318 (8), 154 (19), 108 (100), 83 (46), 57 (38), 41 (27); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 and 1.43 (6H, 2s, CMe_2), 1.60 (9H, s, CMe_3), 2.33 (3H, s, Ar-*Me*), 3.56 (1H, s, CH), 6.97 (2H, d, *ortho*-CH, $^2J_{HH}$ = 8.5 Hz), 7.17 (2H, d, *meta*-CH, $^2J_{HH}$ = 8.5 Hz) ppm; ^{13} C NMR (125 MHz, $CDCl_3$): δ = 20.46 and 20.86 (C*Me*$_2$), 27.19 (Ar-*Me*), 28.18 (C*Me*$_3$), 43.28 (*C*Me$_2$), 58.85 (*C*Me$_3$), 120.87, 130.06, 136.18, and 147.86 (C_6H_4), 166.10, 172.28, and 182.15 (3C=O) ppm. Anal. Calcd for $C_{18}H_{23}NO_4$ (317.4): C, 68.1; H, 7.3; N, 4.4%. Found: C, 68.7; H, 7.5; N, 4.4%.

***p*-Nitrophenyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4f).** Yield 68%. Colorless crystals; m.p.: 89–9°C; IR (KBr) $\bar{\nu}$ = 1748, and 1694 (C=O) cm^{-1}; MS (*m/z*, %): 349 (15), 293 (20), 228 (31), 210 (36), 172 (15), 154 (17), 83 (100), 57 (63), 41 (33); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 and 1.47 (6H, 2s, C*Me*$_2$), 1.62 (9H, s, C*Me*$_3$), 3.65 (1H, s, CH), 7.32 and 8.29 (4H, 2d, $^3J_{HH}$ = 8.9 Hz, C_6H_4) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.74 and 26.92 (C*Me*$_2$), 28.16 (C*Me*$_3$), 43.38 (*C*Me$_2$), 58.62 (CH), 59.17 (*C*Me$_3$), 122.26, 125.38, 145.82, and 154.50 (C_6H_4), 165.12, 171.67, and 181.71 (3C=O) ppm. Anal. Calcd for $C_{17}H_{20}N_2O_6$ (348.4): C, 58.6; H, 5.8; N, 8.0%. Found: C, 59.1; H, 5.9; N, 7.8%.

2,4-Dichlorophenyl 1-*tert*-butyl-4,4-dimethyl-2,5-dioxo-pyrrolidine-3-carboxylate (4g). Yield 73%. Colorless crystals. m.p.: 99–106°C; IR (KBr) $\bar{\nu}$ = 1748, and 1695 (C=O) cm^{-1}; MS: *m/z* (%) = 374 (12), 372 (19), 210 (50), 154 (29), 83 (100), 57 (73); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 and 1.46 (6H, 2s, CMe$_2$), 1.60 (9H, s, CMe$_3$), 3.66 (1H, s, CH), 7.13–7.46 (3H, m, C_6H_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.89 and 26.69 (C*Me*$_2$), 28.15 (C*Me*$_3$), 43.37 (*C*Me$_2$), 58.51 (CH), 58.99 (*C*Me$_3$), 124.38, 127.29, 127.97, 130.28, 132.47, and 144.96 (C_6H_3), 164.80, 171.62, and 181.82 (3C=O) ppm. Anal. Calcd for $C_{17}H_{19}Cl_2NO_4$ (372.2): C, 56.9; H, 5.1; N, 3.8%. Found: C, 57.4; H, 5.0; N, 3.6%.

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