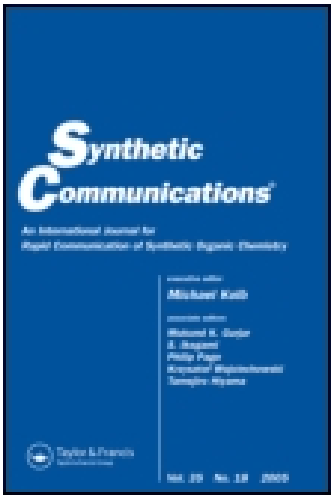

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Synthesis of 1-(2,6-Dimethylphenyl)-N-hydroxy-4,4-dialkyl-2,5 from Reaction of 2,6-Dimethylphenyl Isocyanide, Alkylidene Meldrum's Acids, and Arylhydroxylamines

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Synthesis of 1-(2,6-Dimethylphenyl)-*N*-hydroxy-4,4-dialkyl-2,5-dioxo-*N*-aryl-3-pyrrolidine-carboxamides from Reaction of 2,6-Dimethylphenyl Isocyanide, Alkylidene Meldrum's Acids, and Arylhydroxylamines

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Abstract: Alkylidene Meldrum's acids and 2,6-dimethylphenyl isocyanide react smoothly in the presence of arylhydroxylamines at room temperature to produce 2,5-dioxo-pyrrolidines in fairly high yield.

Keywords: alkylidene Meldrum's acid, 2,5-dioxopyrrolidine, heterocyclic synthesis, isocyanide, three-component reaction

Multicomponent reactions (MCRs) are special types of useful organic reactions in which three or more starting materials react to give a product.[1] MCRs, by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention. Of pivotal importance in this area are the isocyanide-based MCRs such as the versatile Ugi and Passerini reactions.[2] The discovery of novel MCRs has become an increasingly active area of research, yielding novel

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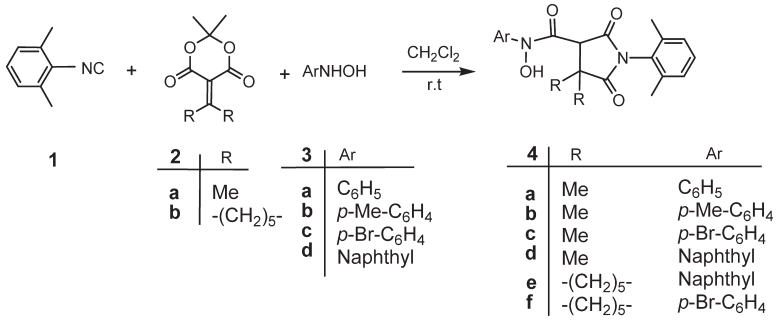
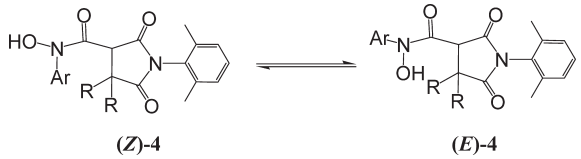


Scheme 1.

chemical scaffolds for drug discovery efforts. As part of our current studies on the development of new routes to heterocyclic systems,[3,4] we now report the reaction between 2,6-dimethylphenyl isocyanide (1) and alkylidene Meldrum's acids **2** in the presence of arylhydroxylamines **3**, which led to 1-(2,6-dimethylphenyl)-*N*-hydroxy-4,4-dialkyl-2,5-dioxo-*N*-aryl-3-pyrrolidine-carboxamides **4** in excellent yield (Scheme 1).

The reaction proceeded smoothly and was complete within 8 h. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **4**. The structures of compounds **4a**–**f** were deduced from their elemental analyses and their IR and ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. Any initial fragmentation involved the loss of the ester and amide moieties.

The ^{1}H NMR spectrum of **4a** exhibited four single sharp lines readily recognized as arising from *tert*-butyl (δ 1.38 ppm), methyl (δ 2.92 and 3.05 ppm) and methoxy (δ 3.71 ppm) protons. Observation of $^{3}J = 1.7$ Hz for the vicinal methine protons in **4a** indicates the presence of the *trans* isomer (*anti* arrangement).[5] The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 11 distinct resonances in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **4b**–**f** are similar to those of **4a** except for the aryl and alkyl moieties, which exhibited characteristic signals with appropriate chemical shifts. In three cases, namely **4a**–**4c**, both *cis* and *trans* isomers (Scheme 2) were observed. The observation of two geometrical



Scheme 2.

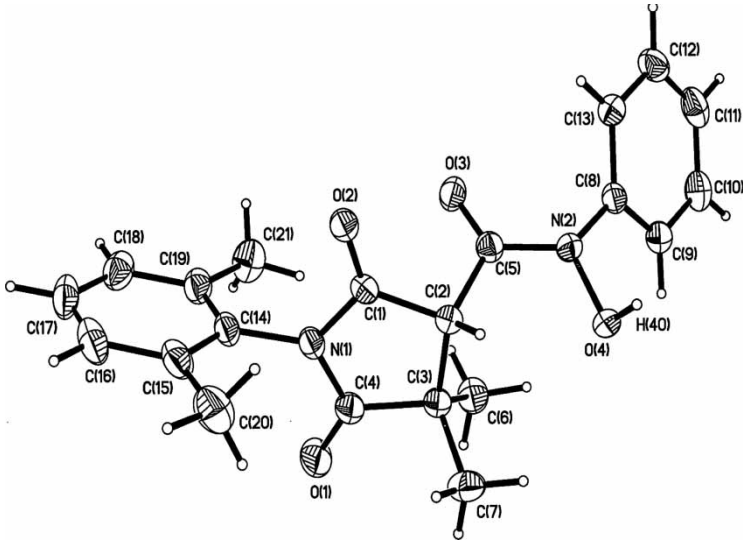


Figure 1. X-ray crystal structure of **4a** (ORTEP-III plot; arbitrary numbering of atoms).

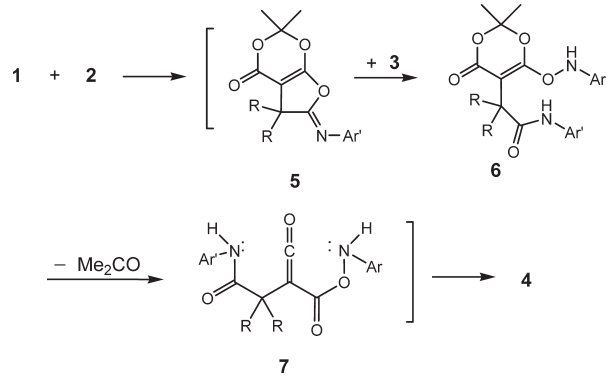
isomers for these compounds is attributed to restricted rotation about the partial double bond of the *N*-hydroxyamide moiety.[6]

Unambiguous evidence for the structure of **4a** was obtained from a single-crystal X-ray analysis. An ORTEP[7] diagram of **4a** is shown in the Fig. 1. There are four molecules of **4a** in the unit cell.

The ^{1}H and ^{3}C NMR spectra of **4b** and **4c** show similar resonances that arise from the presence of two rotamers, namely, (*Z*)-**4** and (*E*)-**4** (Scheme 2).

Although the mechanism of reaction between alkylidene Meldrum's acid and 2,6-dimethylphenyl isocyanide in the presence of arylhydroxylamines was not established in an experimental manner, a plausible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[8] the reaction starts from [4 + 1]-cycloaddition of **2** and **1**, producing an iminolactone intermediate **5**. Conjugate addition by the hydroxylamine on the enone moiety of **5** followed by cleavage of the five-membered ring gives **6** and hence the ketene **7** by electrocyclic ring opening of the *O*-alkylated Meldrum's acid (Scheme 3). The ketene **7** can then undergo intermolecular reaction between the nitrogen of the hydroxylamine and ketene moietiy to give product **4**.

In conclusion, a convenient route to 1-(2,6-dimethylphenyl)-*N*-hydroxy-4,4-diethyl-2,5-dioxo-*N*-aryl-3-pyrrolidine-carboxamides from a one-pot reaction of alkylidene Meldrum's acids with 2,6-dimethylphenyl isocyanide in the presence of arylhydroxylamines is described. These products may be considered as potentially useful synthesis intermediates because they possess atoms with different oxidation states. The advantage of the present



Scheme 3.

procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

EXPERIMENTAL

Compounds **1** and **3** were obtained from Fluka and were used without further purification. Compound **2** were prepared according to a known procedure.[2] Melting points were determined with an Electrothermal 9100 apparatus, IR spectra, Shimadzu IR-460 spectrometer; ^{1}H and ^{13}CNMR spectra, Bruker DRX-300 Avance instrument in $CDCl_3$ at 300 and 75 MHz, respectively, with δ in parts per million and J in hertz, EI-MS (70 eV), Finnigan-MAT-8430 mass spectrometer in m/z; elemental analyses (C, H, N), Heraeus CHN-O-Rapid analyzer.

General Procedure for the Preparation of Compounds 4

To a stirred solution of **2** (0.36 g, 2 mmol) and **3** (2 mmol) in anh. CH_2Cl_2 (10 ml), a mixture of **1** (2 mmol) in CH_2Cl_2 (5 ml) was added dropwise at -5°C, over 10 min. The mixture was then allowed to warm to rt and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (SiO_2; hexane/AcOEt 3:2) to afford the pure title compounds.

Compound **4a**

Colorless crystals, mp 157–159°C; IR (KBr), $\bar{\nu}$= 3190 (OH), 1711, 1719 and 1793 (3 C = O) cm^{-1}. MS: m/z (%): 366 (M^+, 4), 119 (26), 108 (40), 91 (59),

83 (100), 78 (82), 56 (78). Anal. calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C, 68.78; H, 6.0; N, 7.64%. Found: C, 67.92; H, 5.82; N, 7.52%. NMR data for the major isomer (70%); ^{1}H NMR: $\delta = 1.24$ and 1.43 (6H, 2 s, C*Me*$_2$), 1.93 and 2.28 (6H, 2 s, *Me*$_2$Ar), 3.76 (1H, s, CH), 7.10–7.34 (8 CH, m, 2 Ar), 8.86 (1H, s, OH) ppm. ^{13}C NMR: $\delta = 17.4$ and 19.8 (C*Me*$_2$), 27.6 and 27.8 (*Me*$_2$Ph), 44.6 (*C*Me$_2$), 55.4 (CH), 121.1, 126.6, 128.3, 129.6, 130.0 (CH, Ph), 130.3, (C_{ipso}-N, phenyl), 135.3, (C_{ipso}-N, *Me*$_2$Ar), 162.5, 171.3, 182.4 (3 C═O) ppm. NMR data for the minor isomer (30%); ^{1}H NMR: $\delta = 1.31$ and 1.59 (6H, 2 s, C*Me*$_2$), 2.05 and 2.22 (6H, 2 s, *Me*$_2$Ar), 4.51 (1H, 1s, CH), 7.10–7.34 (8 CH, m, 2 Ph), 8.86 (1H, s, OH) ppm. ^{13}C NMR: $\delta = 17.7$ and 20.0 (C*Me*$_2$), 27.6 and 31.2 (*Me*$_2$Ph), 44.6 (*C*Me$_2$), 57.2 (CH), 121.5, 126. 6, 128.3, 129.6, 130.0 (5 CH, Ph) 130.3, (C_{ipso}-N, Ph) 135.3, (C_{ipso}-N, Me$_2$Ph), 165.2, 174.7, 183.0 (3 C═O) ppm.

X-ray Crystal Structure of the Major Isomer of **4a**

Structure determination and refinement of data: formula ($C_{21}H_{22}N_2O_4$), $F_w = 364.41$, monoclinic, $Z = 4$, $a = 7.4991$ (6) Å, $b = 13.3360$ (11) Å, $c = 19.3906$ Å, $\alpha = 90^\circ$, $\beta = 99.716^\circ$, $\gamma = 90^\circ$, $V = 3725.7$ (4) Å^3, $D_{\text{calcd}} = 1.266$ g cm^{-3}, $R = 0.0548$, $R_w = 0.1089$, $-9 \leq h \leq 9$; $-17 \leq k \leq 14$; $-25 \leq l \leq 25^\circ$; Mo ($\lambda = 0.71073$ Å), $T = 120$ (2) K. The crystallographic data of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC615090. Copies of the data can be obtained, free of charge, via the Internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44-1223-336033).

Compound **4b**

White powder, mp 150–152°C. IR (KBr), $\bar{\nu} = 3163$ (OH), 1711, 1719 and 1793 (3 C═O) cm^{-1}. MS: m/z (%) = 381 (M$^+$, 4), 380 (M$^+ - 1$, 30), 258 (38), 123 (72), 58 (71), 44 (76), 83 (100). Anal. calcd. for $C_{22}H_{24}N_2O_4$ (380.44): C, 69.39; H, 6.31; N, 7.36; Found: C, 68.57; H, 6.15; N, 7.15%. NMR data for the major isomer (65%); ^{1}H NMR: $\delta = 1.31$ and 1.59 (6H, 2 s, C*Me*$_2$), 2.05 and 2.22 (6H, 2 s, *Me*$_2$Ar), 4.51 (1H, 1 s, CH), 7.10–7.34 (8 CH, m, 2 Ph), 8.86 (1H, s, OH) ppm. ^{13}C NMR: $\delta = 17.7$ and 20.0 (C*Me*$_2$), 27.6 and 31.2 (*Me*$_2$Ph), 44.6 (*C*Me$_2$), 57.2 (CH), 121.5, 126.6, 128.3, 129.6, 130.0 (5 CH, Ph), 130.3 (C_{ipso}-N, Ph), 135.3 (C_{ipso}-N, Me$_2$Ph), 165.2, 174.7, 183.0 (3 C═O) ppm. NMR data for the minor isomer (35%); ^{1}H NMR: $\delta = 1.26$ and 1.47 (6H, 2 s, C*Me*$_2$), 1.96 and 2.2 (6H, 2 s, *Me*$_2$Ph), 2.39 (3H, 2 s, Ph*Me*), 3.76 (1H, s, CH), 7.1–7.43 (8 CH, m, Ph), 8.6 (1H, s, OH) ppm; ^{13}C NMR: $\delta = 17.4$ and 19.8 (C*Me*$_2$), 21.0, and 27.6 (*Me*$_2$Ph), 31.2 (*p-Me*Ph), 44.0 (*C*Me$_2$), 55.3 (CH), 121.8, 127.6, 128.2, 128.8, 129.2, 129.5 and 130.6 (7 CH, 2 ph), 134.3 (C_{ipso}, *Me*$_2$Ph), 135.3 (C_{ipso}, *p-Me*Ph),

136.6 (C_{ipso}-N, Ph), 136.9 (C_{ipso}-N, $PhMe_2$), 161.8, 172.8, and 182.1 (3 C═O) ppm.

Compound **4c**

White powder, mp 185°C; IR (KBr), $\bar{\nu} = 3299$ (OH), 1759, 1792 (3 C═O) cm^{-1}. Anal. calcd. for $C_{21}H_{21}BrN_2O_4$ (445.31): C, 54.59; H, 4.72; N, 6.29. Found: C, 54.25; H, 4.55; N, 6.10%. NMR data for the major isomer (60%): ^{1}H NMR: $\delta = 1.21$ and 1.54 (6H, 2 s, CMe_2), 1.92 and 2.21 (6H, 2 s, Me_2Ph), 3.76 (1H, 1s, CH), 7.1–7.51 (7H, m, 2 Ph) 9.08 (1H, s, OH) ppm; ^{13}C NMR: $\delta = 17.4$ and 19.8 (CMe_2), 27.4 (Me_2-Ph), 44.0 (CMe$_2$), 55.6 (CH), 121.1, 126.5, 127.6, 128.4, 128.7, 130.2 and 130.4 (7 CH, 2 Ph), 135.3 (C_{ipso}, Me_2Ph), 136.5 (C_{ipso}-Br, Ph), 136.8 (C_{ipso}-N, *p*-BrPh), 137.5 (C_{ipso}-N, Me_2Ph), 161.8, 172.8 and, 182.1 (3 C═O) ppm. NMR data for the minor isomer (40%): ^{1}H NMR: $\delta = 1.42$ and 1.55 (6H, 2 s, CMe_2), 2.05 and 2.24 (6H, 2s, Me_2Ph), 4.51 (1H, 1 s, CH), 7.1–7.51 (7H, m, Ph); 9.08 (1H, s, OH) ppm; ^{13}C NMR: $\delta = 17.7$ and 20.0 (CMe_2), 27.7 (Me_2Ph), 44.0 (CMe$_2$), 57.2 (CH), 121.1, 126.5, 127.6, 128.4, 128.7, 130.0 and 130.5 (7 CH, Ph), 135.3 (C_{ipso}, Me_2Ph), 136.5 (C_{ipso}-Br), 136.8 (C_{ipso}-N, *p*-*B*rPh), 137.5 (C_{ipso}-N, Me_2Ph), 167.0, 174.7 and 183.0 (3 C═O) ppm.

Compound **4d**

White powder; mp 145–147°C, IR (KBr), $\bar{\nu} = 3420$ (OH), 1724, 1742, 1772 (3 C═O) cm^{-1}; MS: m/z (%) = 416 (M^+, 4), 186 (12), 159 (99), 130 (30), 83 (100), 55 (46), 57 (44). Anal. calcd. for $C_{25}H_{24}N_2O_4$ (416.47): C, 72.04; H, 5.76; N, 6.72, Found: C, 71.75; H, 5.45; N, 6.50%. ^{1}H NMR: $\delta = 1.64$, 1.76 (6H, 2 s, CMe_2), 2.06, 2.07 (6H, 2 s, Me_2Ph), 4.13 (1H, 1 s, CH), 7.1 (3H, s, C_6H_3), 7.34–9.05 (7H, m, naphthyl), 11.02 (1H, s, OH) ppm; ^{13}C NMR: $\delta = 17.7$ (CMe$_2$), 30.7 (Me_2-Ar). 43.3 (CMe$_2$), 51.2 (CH), 120.0, 122.2, 123.0, 126.6, 126.6, 126.9, 127.1, 127.2, 127.6, 128.1 and 131.3 (11 CH, phenyl and naphthyl), 135.1 (C_{ipso}-N, naphthyl), 135.8 (C_2-naphthyl), 140.9 (C_{ipso}-N, $PhMe_2$), 164.4, 164.9 and 174.9 (3 C═O) ppm.

Compound **4e**

White powder; mp 195–197°C. IR (KBr): $\bar{\nu} = 3289$ (OH), 1715 and 1771, (C═O) cm^{-1}. MS: m/z (%) = 470 (M^+, 12), 264 (12), 183 (58), 182 (56), 159 (38), 143 (78), 120 (100), 115 (54). Anal. calcd. for $C_{29}H_{30}N_2O_4$ (470.57): C, 73.95; H, 6.38; N, 5.95%. Found: C, 73.5; H, 6.15; N, 5.74%. ^{1}H NMR: $\delta = 1.41$–1.96 (10H, m, C_6H_{10}), 2.07 (6H, 1 s, Me_2Ph), 4.13 (1H, 1 s, CH), 7.01 (3H, s, C_6H_3), 7.62–9.10 (7H, m, naphthyl), 11.26 (1H, s, OH) ppm. ^{13}C NMR: $\delta = 17.7$ (*C*Me$_2$), 30.7 (Me_2Ph), 43.3 (CMe$_2$), 51.2 (CH), 120.0, 122.2, 123, 126. 6, 126.6, 126.9, 127.1, 127.2, 127.6, 128.1 and

131.3 (11 CH, phenyl and naphthyl), 135.1 (C_{ipso}-N, naphthyl), 135.8 (C_2-naphthyl), 140.9 (C_{ipso}-N, $PhMe_2$), 164.4, 164.9 and 174.9 (3 C═O) ppm.

Compound **4f**

White powder; mp 205–207°C. IR (KBr): $\bar{\nu} = 3381$ (OH), 1700 and 1715 (C = O) cm^{-1}. MS: m/z (%) = 499 (M^+, 9), 298 (14), 159 (100), 143 (48), 123 (46), 83 (62), 57 (82), 55 (100). Anal. calcd. for $C_{25}H_{27}BrN_2O_4$ (499.40): C, 60.07; H, 5.41; N, 5.61%. Found: C, 59.5; H, 5.30; N, 5.40%. ^{1}H NMR: $\delta = 1.60–2.10$ (10H, m, C_6H_{10}), 2.0, (6H, 1 s, Me_2Ph), 4.78 (1H, 1 s, CH), 7.03–7.85 (7H, m, 2 Ph), 11.61 (1H, s, OH) ppm. ^{13}C NMR: $\delta = 17.7$ (CMe_2), 32.2 (Me_2Ph), 48.3 (CMe$_2$), 53.5 (CH), 121.2, 126.7, 126.9 128.6, 129.6, 130.1 and 131.4 (7 CH, 2 phenyl), 131.4 (C_{ipso}, Me_2Ph), 135.1 (C_{ipso}-N, *p*-BrPh), 135.8 (C_{ipso}-Br, Ph), 140.9 (C_{ipso}-N, $PhMe_2$), 166.4, 167.9 and 174.1 (3 C═O) ppm.

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