Synthesis of Functionalized 5-Oxo-2,5-dihydro-1*H*-pyrroles from Primary Alkylamines, Oxalyl Chloride, and Dimethyl Acetylenedicarboxylate

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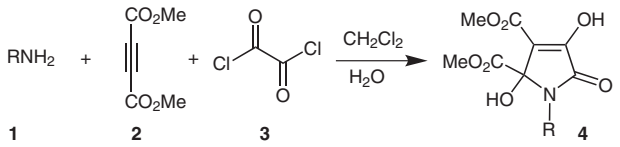
Abstract: An efficient synthesis of dimethyl 1-alkyl-2,4-dihydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates is described via a three-component reaction between primary alkylamines, oxalyl chloride, and dimethyl acetylenedicarboxylate.

Key word: oxalyl chloride, 3-pyrroline-2-one, enaminone, acetylenic ester, multicomponent reaction, alkylamines

The importance of substituted pyrrolidines in the chemical synthesis of biologically interesting molecules is well recognized.[1,2] The development of new synthetic procedures for preparation of 3-pyrrolin-2-ones has gained great interest in organic synthesis. The most investigated approaches to polysubstituted 3-pyrrolin-2-ones rely on multicomponent reactions.[3–5] Other recently reported methodologies include cyclization of α,β-unsaturated γ-aminoesters,[6] rearrangement of chlorinated pyrrolin-2-ones,[7] ruthenium-catalyzed cyclocarbonylation of α-allenic sulfonamides,[8] cyclization of 3-phenylsulfanyl-2-propenamides,[9] reaction of γ-keto thioesters with amines,[10] oxidative cyclization of phenacyl amide in the presence of atmospheric oxygen,[11] alkaline hydrolysis of N-substituted 2-acetoxypyrroles,[12] intramolecular aldol condensation,[13] and cyclization of 3-aryl-4,4-dichlorobutanamides.[14]

As part of our current studies on the development of new routes in heterocyclic synthesis,[15] we report an efficient synthetic route to 1,5-dihydro-2*H*-pyrrole-2-ones. Thus, the reaction between alkylamines **1**, dimethyl acetylenedicarboxylate (DMAD, **2**), and oxalyl chloride (**3**) in CH_2Cl_2 led to dimethyl 1-alkyl-2,4-dihydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates (**4**) in good yields[16] (Scheme 1).



1 2 3 4

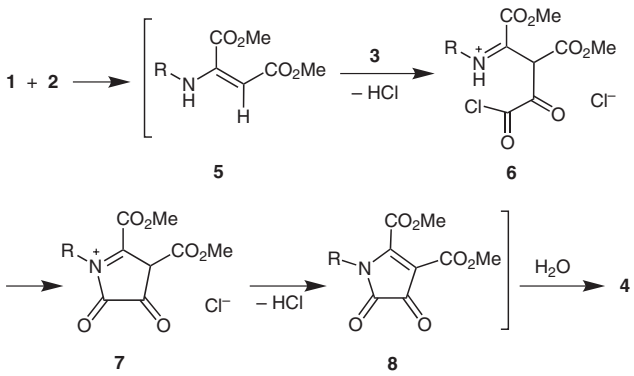
1, 4	R	Yield (%) of 4
a	Bn	90
b	4-$MeC_6H_4CH_2$	95
c	4-$MeOC_6H_4CH_2$	95
d	4-$ClC_6H_4CH_2$	90
e	2-$ClC_6H_4CH_2$	95
f	1-Naphthylmethyl	98
g	*n*-Bu	90

Scheme 1

The structures of compounds **4a–g** were apparent from their mass spectra, which showed, in each case, the molecular ion peak at the appropriate *m/z* value. The ^{1}H NMR and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed four singlets for methoxy (δ = 3.19 and 3.73 ppm) and OH (δ = 4.77 and 9.09 ppm) protons. The ^{13}C NMR spectrum of **4a** exhibited thirteen signals in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section.[16] The ^{1}H NMR and ^{13}C NMR spectra of **4b–g** are similar to those for **4a** except for the alkyl moieties, which showed characteristic resonances in appropriate regions of the spectrum.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of enaminoester **5** from the alkylamine and DMAD,[9,10] which is subsequently attacked by oxalyl chloride to produce **6**. Intermediate **6** undergoes cyclization to produce **7**, which is converted to **8** by elimination of HCl. Compound **4** is apparently formed by addition of adventitious water to **8**.

In conclusion, we have described a convenient route to functionalized 3-pyrroline-2-ones, from oxalyl chloride and DMAD in the presence of primary alkylamines. The advantage of the present procedure is that the reaction is



Scheme 2

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performed under neutral conditions by simple mixing of the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of functionalized 3-pyrroline-2-ones.

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(16) **Dimethyl 1-Benzyl-2,4-dihydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylate (4a)**
To a stirred solution of DMAD (0.34 g, 2.4 mmol) and alkylamine (0.20 g, 2 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.17 mL, 2 mmol) at r.t. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the precipitate was purified by recrystallization from Et_2O to give **4a**.
Compound **4a**: white powder; 170–171 °C (decomp.); yield 0.57 g (90%). IR (KBr): ν_{max} = 3360, 3135, 1741, 1705, 1674, 1425, 1311 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.19 (3 H, s, OMe), 3.73 (3 H, s, OMe), 4.28 (1 H, d, ^3J = 15.5 Hz, CH), 4.77 (1 H, br s, OH), 4.80 (1 H, d, ^3J = 15.5 Hz, CH), 7.24–7.30 (5 H, m, CH), 9.09 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 42.7 (NCH_2), 51.8 (OMe), 53.2 (OMe), 85.7 (C-OH), 112.4 (C), 128.2 (CH), 129.0 (CH), 129.3 (CH), 137.4 (C), 156.4 (=COH), 163.3 (C=O), 164.6 (C=O), 169.7 (CON) ppm. MS: *m/z* (%) = 321 (8) [M^+], 262 (70), 244 (100), 91 (50), 77 (64). Anal. Calcd (%) for $C_{15}H_{15}NO_7$ (321.28): C, 56.08; H, 4.71; N, 4.36. Found: C, 56.31; H, 4.82; N, 4.39.
Similarly, the following compounds were prepared. All compounds gave satisfactory analytical and spectroscopic data.
Compound **4b**: white powder; 150–152 °C (decomp.); yield 0.63 g (95%). IR (KBr): ν_{max} = 3380, 3140, 1744, 1699, 1671, 1429, 1388, 1234 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.29 (3 H, s, Me), 3.17 (3 H, s, OMe), 3.80 (3 H, s, OMe), 4.13 (1 H, d, ^3J = 14.6 Hz, CH), 4.74 (1 H, br s, OH), 4.93 (1 H, d, ^3J = 14.6 Hz, CH), 7.06 (2 H, d, ^3J = 7.9 Hz, CH), 7.15 (1 H, d, ^3J = 7.9 Hz, CH), 9.07 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 20.4 (Me), 41.5 (NCH_2), 51.6 (OMe), 53.0 (OMe), 83.5 (COH), 110.2 (C), 128.3 (CH), 128.4 (CH), 131.6 (C), 137.0 (C), 157.9 (=COH), 162.5 (C=O), 163.6 (C=O), 169.3 (CON) ppm. MS: *m/z* (%) = 335 (18) [M^+], 276 (70), 244 (100), 91 (50), 77 (64). Anal. Calcd (%) for $C_{16}H_{17}NO_7$ (335.31): C, 57.31; H, 5.11; N, 4.18. Found: C, 57.46; H, 5.06; N, 4.23.
Compound **4c**: white powder; 157–158 °C (decomp.); yield: 0.63 g (90%). IR (KBr): ν_{max} = 3363, 3130, 1745, 1710, 1674, 1425, 1308, 1236 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.23 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.76 (3 H, s, OMe), 4.21 (1 H, d, ^3J = 15.2 Hz, CH), 4.70 (1 H, br s, OH), 4.74 (1 H, d, ^3J = 15.2 Hz, CH), 6.85 (2 H, d, ^3J = 8.5 Hz, CH), 7.19 (1 H, d, ^3J = 8.5 Hz, CH), 9.09 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 42.2 (NCH_2), 51.8 (OMe), 53.3 (OMe), 55.5 (OMe), 85.6 (COH), 112.3 (C), 114.4 (CH), 129.2 (C), 130.8 (CH), 156.3 (C), 160.1 (=COH), 163.4 (C=O), 164.4 (C=O), 169.8 (CON) ppm. MS: *m/z* (%) = 351 (18) [M^+], 292 (70), 244 (100), 91 (50), 77 (64). Anal. Calcd (%) for $C_{16}H_{17}NO_8$ (351.31): C, 54.70; H, 4.88; N, 3.99. Found: C, 54.50; H, 4.96; N, 4.08.
Compound **4d**: white powder; 160–162 °C (decomp.); yield 0.64 g (90%). IR (KBr): ν_{max} = 3365, 3135, 1743, 1700, 1671, 1428, 1310, 1237 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.27 (3 H, s, OMe), 3.81 (3 H, s, OMe), 4.17 (1 H, d, ^3J = 15.3 Hz, CH), 4.72 (1 H, br s, OH), 4.88 (1 H, d, ^3J = 15.3 Hz, CH), 7.22 (2 H, d, ^3J = 8.3 Hz, CH), 7.27 (2 H, d, ^3J = 8.3 Hz, CH), 9.10 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 42.5 (NCH_2), 53.1 (OMe), 54.7 (OMe), 84.9 (COH), 111.8 (C), 129.4 (CH), 131.2 (CH), 134.7 (C), 156.4 (C), 159.6 (=COH), 163.8 (C=O), 165.1 (C=O), 170.8 (CON) ppm. MS: *m/z* (%) = 355 (18) [M^+], 296 (100), 276 (70), 91 (50), 77 (64). Anal. Calcd (%) for $C_{15}H_{14}ClNO_7$ (355.72): C, 50.65; H, 3.97; N, 3.94. Found: C, 50.52; H, 4.03; N, 3.91.
Compound **4e**: white powder; 160–164 °C (decomp.); yield 0.64 g (90%). IR (KBr): ν_{max} = 3310, 3305, 1747, 1680, 1675, 1462, 1430, 1400 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.39 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.64 (1 H, d, ^3J = 16.3 Hz, CH), 4.70 (1 H, d, ^3J = 16.3 Hz, CH), 4.75 (1 H, br s, OH), 7.26–7.29 (3 H, m, CH), 7.39 (1 H, m, CH), 9.12 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 40.5 (NCH_2), 51.9 (OMe), 53.4 (OMe), 86.1 (COH), 112.8 (C), 127.8 (CH), 129.8 (CH), 130.1 (CH), 130.4 (CH), 133.6 (C), 134.4 (C), 156.1 (=COH), 163.4 (C=O), 164.7 (C=O), 169.5 (CON) ppm. MS: *m/z* (%) = 355 (18) [M^+], 296 (100), 276 (70), 91 (50), 77 (64). Anal. Calcd (%) for $C_{15}H_{14}ClNO_7$ (355.72): C, 50.65; H, 3.97; N, 3.94. Found: C, 50.73; H, 4.02; N, 3.90.
Compound **4f**: white powder; 166–167.5 °C (decomp.); yield 0.72 g (98%). IR (KBr): ν_{max} = 3330, 3140, 1747, 1676, 1671, 1462, 1399, 1363 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 2.54 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.59 (1 H, d, ^3J = 14.9 Hz, CH), 4.81 (1 H, br s, OH), 5.63 (1 H, d, ^3J = 14.9 Hz, CH), 7.39–7.57 (4 H, m, CH), 7.84 (2 H, m, CH), 8.15 (1 H, m, CH), 9.18 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 41.2 (NCH_2), 52.1 (OMe), 52.8 (OMe), 84.5 (COH), 111.2 (C), 124.0 (CH), 125.0 (CH), 126.1 (CH), 126.8 (CH), 128.3 (CH), 129.3 (CH), 129.4 (CH), 129.9 (C), 131.6 (C), 133.6 (C), 158.8 (=COH), 162.7 (C=O), 164.3 (C=O), 169.4 (CON) ppm. MS: *m/z* (%) = 371 (18) [M^+], 312 (100), 276 (70), 91 (50), 77 (64). Anal. Calcd (%) for $C_{19}H_{17}NO_7$ (371.34): C, 61.46; H, 4.61; N, 3.77. Found: C, 61.59; H, 4.65; N, 3.82.
Compound **4g**: white powder; 132–133 °C (decomp.); yield 0.51 g (90%). IR (KBr): ν_{max} = 3350, 3140, 1745, 1674, 1670, 1460, 1389, 1360 cm^{-1}. ^1H NMR (500.1 MHz,

$CDCl_3$): δ = 0.85 (3 H, t, ^3J = 7.0 Hz, Me), 1.26 (2 H, q, ^3J = 7.3 Hz, CH_2), 1.42 (2 H, m, CH_2), 3.23 (2 H, m, CH_2), 3.78 (3 H, s, OMe), 3.79 (3 H, s, OMe), 4.77 (1 H, s, OH), 9.12 (1 H, br s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.5 (CH_3), 20.0 (CH_2), 30.1 (CH_2), 39.5 (NCH_2), 52.1 (OMe), 54.1 (OMe), 85.3 (COH), 110.5 (C), 157.4 (=COH), 163.7 (C=O), 163.8 (C=O), 170.4 (CON) ppm. MS: *m/z* (%) = 287 (18) [M^+], 276 (70), 228 (100), 91 (50), 77 (64). Anal. Calcd (%) for $C_{12}H_{17}NO_7$ (287.26): C, 50.17; H, 5.96; N, 4.88. Found: C, 50.00; H, 5.91; N, 4.92.