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A Novel Synthetic Route to Morpholin-2,3-Diones from 2-Aminoalcohols.

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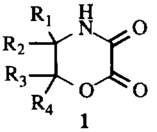
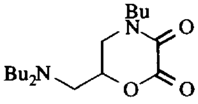
Abstract: Reaction of dimethyl acetylenedicarboxylate with 2-aminoalcohols possessing a primary amino group gives 3-methoxycarbonylmethylidinemorpholin-2-ones **5**. Subsequent ozonolysis furnishes morpholin-2,3-diones **1** in excellent yields. Copyright © 1996 Elsevier Science Ltd

Cyclic morpholin-2,3-dione formation provides a means for double protection of aminoalcohols and substrates **1** have been used as precursors to biologically active compounds including the β-adrenergic blocking agent *N*-butyl-6-[(dibutylamino)methyl]morpholin-2,3-dione **2**, which is an active local anaesthetic and analgesic.[1] Our interest focused on morpholin-2,3-diones derived from optically active aminoalcohols, readily prepared by either reduction of amino acids or amination of asymmetric epoxides.[2] In association with ongoing work, we required access to a range of structures **1** as potential templates for asymmetric induction.

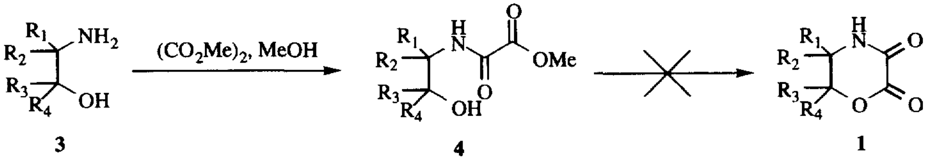


1



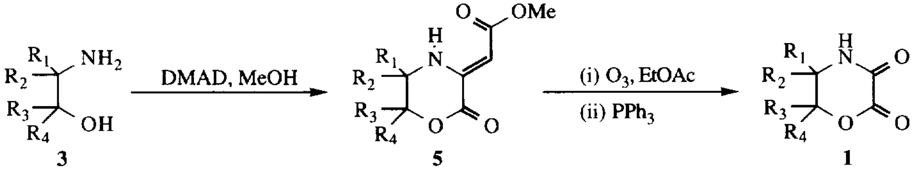
2

N-Alkyl-substituted morpholin-2,3-diones have been prepared from *N*-alkylated-2-aminoalcohols by palladium catalyzed double carbonylation[3] or treatment with dimethyl oxalate in refluxing methanol.[1] However, the first procedure is only described for substrates unalkylated on nitrogen and application of the latter methodology to such substrates was shown by Drefahl to yield only the corresponding oxamidic esters **4** (**Scheme 1**).[4] Failure to achieve cyclisation to structures **1** was attributed to conformational energy barriers inhibiting rotation around the secondary amide bond and formation of the *cisoid* dicarbonyl conformation with the result that the reacting conformation is highly disfavoured when the amide nitrogen is secondary.

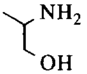
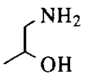
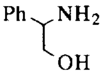
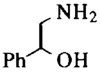
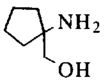
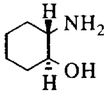
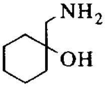
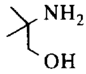
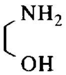
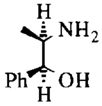


Scheme 1

The modification reported by Drefahl[4] to overcome this reactivity problem requires severe reaction conditions (refluxing with sodium in xylene) and furnishes the desired morpholin–2,3–diones **1** in only moderate yields. To circumvent the cyclisation problem we decided to couple the aminoalcohol with dimethyl acetylenedicarboxylate,[5] giving the corresponding morpholin–2–ones **5a–j** (**Scheme 2**). In all instances the IR and ^{1}H NMR spectra[6] of the isolated products suggested the presence of intramolecular hydrogen bonds, leading to the conclusion that *Z* –isomers had been formed.[7] Subsequent ozonolysis[8] of the exocyclic alkene and reductive work–up with triphenylphosphine[9] gave the desired morpholin–2,3–diones **1a–j** in excellent yields after chromatography (**Table**).



Scheme 2

3	5 Yield (%)	1 Yield (%)	3	5 Yield (%)	1 Yield (%)
a 	84	80	**f** 	81	78
b 	83	87	**g** 	67	70
c 	72	88	**h** 	94	80
d 	76	73	**i** 	69	86
e 	81	91	**j** 	70	81

Table

The range of amino alcohols used demonstrates that the two–step procedure described herein overcomes the conformational constraints observed in the direct derivatization with oxalate derivatives and permits a general, simple and rapid access to a range of morpholin–2,3–diones in which the ring nitrogen is immediately available for further functionalization.

General procedure

(a) Preparation of morpholin-2-ones 5a–j. To a stirred solution of the 2-aminoalcohol **3** (1 equiv.) in anhydrous methanol (3 mL mmol^{-1}) at room temperature under nitrogen was added dimethyl acetylenedicarboxylate (1 equiv.) dropwise over 10 min. The resulting yellow solution was stirred for a further 3 h. Concentration *in vacuo* and chromatographic purification (SiO_2, Et_2O–pentane) of the residue provided cyclic products **5a–j** as colourless solids.

(b) Preparation of morpholin-2,3-diones 1a–j. A stirred solution of the cyclic alkene **5** in ethyl acetate at –78°C was ozonized until the solution turned pale blue. Excess ozone was removed by purging the system with nitrogen until the blue colour was discharged. Triphenylphosphine (1 equiv.) was added and the reaction warmed to room temperature and stirred for a further 5 h. Concentration *in vacuo* and chromatographic purification (SiO_2, Et_2O–pentane) of the residue gave pure morpholin-2,3-diones **1a–j** as colourless solids.

Acknowledgements

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6. The NH 3350–3220 cm^{-1} and ester carbonyl 1680–1650 cm^{-1} stretching frequencies appeared at lower wavenumbers than expected for the isolated functionalities (3460–3400 cm^{-1} and 1730–1715 cm^{-1} respectively). The H–D exchange rate of the NH protons were also found to be very slow.
7. Spectroscopic data: **5a**; m.p. 53–54°C; ν_{max} (KBr disk) 3296, 1668, 1243, 771 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.24 (1H, bs), 4.40 (1H, dd, *J* 9, *J'* 3.3 Hz), 4.16 (1H, dd, *J* 9, *J'* 8 Hz), 3.85–3.71 (1H, m), 3.70 (3H, m), 1.28 (3H, d, *J* 6.5Hz); δ_C (500 MHz, $CDCl_3$) 170.40, 160.14, 143.89, 89.71, 72.33, 50.94, 44.16, 16.84; $C_8H_{11}NO_4$ requires 185.0688, found 185.0687. **5c**; m.p. 42–43°C; ν_{max} (KBr disk) 3310, 1666, 959, 775 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.41 (1H, bs), 5.62 (1H, s), 4.29 (2H, s), 3.70 (3H, s), 1.89–1.70 (8H, m); δ_C (500 MHz, $CDCl_3$) 170.51, 160.39, 143.70, 89.30, 74.38, 59.38, 50.87, 36.31, 23.65; $C_{11}H_{15}NO_4$ requires 225.1000, found 225.0999. **5d**; m.p. 79–80°C; ν_{max} (KBr disk) 3348, 1658, 962, 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.23 (1H, bs), 5.65 (1H, s), 7.31 (3H, s), 3.34 (2H, d, *J* 3.5 Hz), 1.93–1.37 (10H, m); δ_C (500 MHz, $CDCl_3$) 170.52, 160.31, 144.16, 89.15, 81.84, 50.89, 46.79, 34.06, 25.19, 21.42; $C_{12}H_{17}NO_4$ requires 239.1157, found 239.1148. **5e**; m.p. 80–82°C; ν_{max} (KBr disk) 3334, 1662, 1004, 774 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.35 (1H, bs), 5.68 (1H, s), 4.51 (1H, t, *J* 3.8 Hz), 3.71 (3H, s), 3.52 (2H, m); δ_C (500 MHz, $CDCl_3$) 170.04, 160.01, 144.46, 90.09, 67.33, 51.00, 38.53; $C_7H_9NO_4$ requires 171.0531, Found 171.0525. **5f**; m.p. 94–95°C; ν_{max} (KBr disk) 2977, 1669, 962, 777 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.26 (1H, bs), 5.60 (1H, s), 4.69 (1H, m), 3.65 (3H, s), 3.44 (1H, dt, *J* 3, *J'* 12 Hz), 3.36 (1H, dd, *J* 11, *J'* 12 Hz), 1.42 (3H, d, *J* 7Hz); δ_C (200 MHz, $CDCl_3$) 170.67, 160.95, 144.14, 89.48, 74.95, 50.92, 44.19, 17.87; $C_8H_{11}NO_4$ requires 185.0688, found 185.0686. **5g**; m.p. 104–105°C; ν_{max} (KBr disk) 3328, 1670, 1013, 773, 745 cm^{-1}; δ_H (500 MHz,

$CDCl_3$) 8.43 (1H, bs), 7.45–7.38 (5H, m), 5.75 (1H, s), 5.58 (1H, dd, *J* 4 Hz, *J'* 9.5 Hz), 3.73 (3H, s), 3.63–3.54 (2H, m); δ_C (500 MHz, $CDCl_3$) 170.44, 160.58, 143.85, 135.15, 129.33, 128.90, 126.16, 90.28, 79.79, 51.06, 45.11; $C_{13}H_{14}NO_4$ requires 248.0932, found 248.0932. **5h**; m.p. 47–48°C; υ_{max} (KBr disk) 3300, 1673, 1157, 774 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.13 (1H, bs), 5.64 (1H, s), 4.15–4.10 (1H, m), 3.70 (3H, s), 3.26–3.21 (1H, m), 2.16–1.33 (8H, m); δ_C (500 MHz, $CDCl_3$) 170.41, 160.82, 144.78, 89.38, 81.58, 53.09, 50.86, 29.66, 29.41, 23.35, 23.27; $C_{11}H_{15}NO_4$ requires 225.1000, found 225.0996. **5i**; m.p. 89–90°C; υ_{max} (KBr disk) 3307, 1660, 1620, 828, 744 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.25 (1H, bs), 5.61 (1H, s), 4.21 (2H, s), 3.69 (3H, s), 1.35 (6H, s); δ_C (500 MHz, $CDCl_3$) 170.44, 160.12, 143.15, 89.41, 76.00, 50.87, 48.56, 25.37; $C_9H_{13}NO_4$ requires 199.08444, found .**5j**; Found C, 64.10; H, 6.03; N, 5.08 $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36); υ_{max} 3300, 1747, 1666, 1619 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.56 (1H, br s), 7.49–7.30 (5H, m), 5.73 (1H, m), 5.70 (1H, d, *J* 3 Hz), 3.84 (1H, m), 3.72 (3H, s), 1.02 (3H, d, *J* 7 Hz); δ_C (250 MHz, $CDCl_3$) 15.3, 48.9, 51.0, 81.7, 90.0, 125.9, 128.7, 134.8, 143.3, 160.5, 170.5; $^{m}/_{z}$ (CI(NH_3)) 262 (100%, MH^+); $[\alpha]_D^{25.5}$ –40.9 (c 1.00, $CHCl_3$). **1a**; m.p. 63–64°C; υ_{max} (KBr disk) 3210, 1760, 1716, 1349, 1040, 764 cm^{-1}; δ_H (500 MHz, DMSO) 8.55 (1H, bs), 4.47 (1H, dd, *J* 3.4, *J'* 4.4 Hz), 4.27 (1H, dd, *J* 8.3, *J'* 3.4 Hz), 4.03 (1H, m), 1.35 (3H, d, *J* 6.7 Hz); δ_C (500 MHz, DMSO) 156.97, 154.68, 71.66, 46.36, 16.74; MH^+ requires 130.0504, found 130.0501. **1b**; m.p. 161–162°C; Found C, 62.54, H, 4.70, N, 7.19; $C_{10}H_9NO_3$ requires C, 62.81, H, 4.75, N, 7.33%; υ_{max} (KBr disk) 3265, 1753, 1717, 1689, 1046, 753; δ_H (250 MHz, DMSO) δ 9.53 (1H, s), 7.49–7.20 (5H, m), 5.01 (1H, m), 4.68 (1H, dd, *J* 12 Hz, *J'* 4 Hz), 4.57 (1H, dd, *J* 7, *J'* 12 Hz); δ_C (250 MHz, DMSO) δ 53.2, 71.1, 127.0, 128.5, 128.9, 137.0, 154.2, 157.9; $^{m}/_{z}$ (CI (NH_3)) 209 (90%, MNH_4^+), 138 (100%, M–59). **1c**; m.p. 166–167°C; υ_{max} (KBr disk) 3445 , 3297, 2950, 1766, 1704, 1409, 1175, 1024 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.65 (1H, bs), 4.33 (2H, s), 2.03–1.70 (8H, m); δ_C (500 MHz, $CDCl_3$) 157.05, 154.54, 73.64, 62.10, 36.07, 23.51; MH^+ requires 170.0817, found 170.80826. **1d**; m.p. 96–97°C; υ_{max} (KBr disk) 3226, 2934, 2863, 1751, 1710, 998, 723 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.27 (1H, bs), 3.55 (2H, d, *J* 3.4 Hz), 2.04–1.35 (10H, m); δ_C (500 MHz, $CDCl_3$) 157.07, 155.41, 82.19, 48.09, 34.12, 25.02, 21.27; MH^+ requires 184.0974, found 184.0981. **1e**; m.p. 155–156°C; υ_{max} (KBr disk) 3295, 1745, 1711, 1691, 1354, 1191, 1012 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.09 (1H, bs), 4.48 (2H, t, *J* 5.1 Hz), 3.49 (1H, dt, *J* 3.4 Hz, *J'* 5.1 Hz); δ_C (500 MHz, $CDCl_3$) 158.30, 154.22, 67.01, 39.07. **1f**; m.p. 108–109°C; υ_{max} (KBr disk) 3211, 1760, 1683, 1211, 959, 749 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.02 (1H, bs), 4.85 (1H, m), 3.39 (2H, m), 1.29 (3H, d, *J* 6.4 Hz); δ_C (500 MHz, $CDCl_3$) 158.08, 154.06, 74.70, 44.48, 17.49; MH^+ requires 130.0504, found 130.0504. **1g**; m.p. 78–79°C; υ_{max} (KBr disk) 3447, 3236, 3055, 1748, 1689, 1439, 1120, 723 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.51 (1H, bs), 7.40–7.31 (5H, m), 4.90 (1H, dd, *J* 3.6, *J'* 8.3 Hz), 3.79 (1H, ddd, *J* 12.7, *J'* 3.7, *J"* 3.4 Hz), 3.43 (1H, ddd, *J* 5, *J'* 8.3, *J"*12.7 Hz); δ_C (500 MHz, $CDCl_3$) 160.95, 156.83, 141.03, 128.74, 128.32, 125.77, 72.85, 53.63; MH^+ requires 192.0660, found 192.0651.**1i**; m.p. 135–134°C; υ_{max} (KBr disk) 3300, 1752, 1706, 1180, 722, 543 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85 (1H, bs), 4.30 (2H, s), 1.44 (6H, s); δ_C (200 MHz, $CDCl_3$) 157.38, 154.31, 75.49, 51.80, 25.05; MH^+ requires 144.0660, found 144.0654.

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