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Regio and diastereoselective lactonisation of enolisable 1,3-dicarbonyls by reaction with mesoionic 1,3-oxazolium-5-olates†

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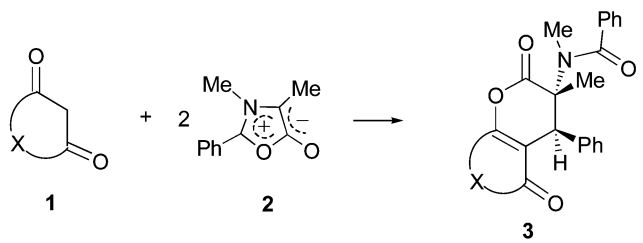
The one-pot reaction of enolisable 1,3-dicarbonyls and *N*-methyl-1,3-oxazolium-5-olate derivatives provided enol lactones directly in good yield and with excellent regio- and diastereocontrol.

The search for convenient and selective methods of synthesising enol lactones has attracted a great deal of interest because of their applicational importance. These functionalized subunits are a key structural feature in a wide range of natural products and artificial molecules, many of which often exhibit a variety of interesting biopharmacological activities.[1] It is not, therefore, surprising that numerous routes have been devised over the years to construct the enol lactone system,[2] and the cyclisation of readily available alkynoic acids is the most attractive and straightforward synthetic approach.[3]

In the course of our studies of the reactivity of mesoionic oxazole,[4] we unexpectedly found a new route which allows the construction of an endocyclic enol lactone ring in good yield and with excellent regio- and diastereocontrol *via* the reaction of enolisable 1,3-dicarbonyls and *N*-methyl-1,3-oxazolium-5-olates.

Here we report the results of this study which, beyond its obvious synthetic interest, describes unprecedented behaviour in the above mentioned mesoionic derivatives commonly called münchnones.

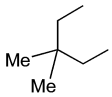
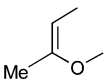
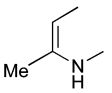
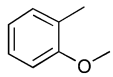
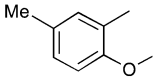
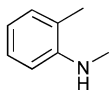
Treatment of 4,5-dimethyl-2-phenyl-1,3-oxazolium-5-olate (DMPO) **2**, generated *in situ* from *N*-benzoyl-*N*-methylalanine (2.2 mmol) and acetic anhydride (4 mmol),[5] with dicarbonyls **1** (1 mmol) in dioxane at reflux for 1 h gave enol lactones **3** in 56–74% yield as single diastereomers (Table 1). The reactions proceeded with excellent chemo-, regio- and distereoselectivity and in all cases compound **3** was formed directly as the only isolated reaction product.



The structure of **3** was determined from analytical and spectral data‡ and the relative stereochemistry was proven by NOE experiments. Thus, methyl and phenyl groups at the α and β positions in the enol lactone ring are *cis* to each other and could be assigned *R** and *S** as their corresponding absolute configurations. This structural characterisation was subsequently secured by X-ray crystallographic analysis carried out on **3a** (Fig. 1)§ and **3e**.[6]

† Electronic supplementary information (ESI) available: 3-D rotatable structure of **3a**. See http://www.rsc.org/suppdata/cc/b3/b304560a/

Table 1 Reactions of 1,3-dicarbonyls **1** and DMPO **2** to afford **3a–f**[a]

Entry	X	Starting material	Product (% yield)[b]
1		**1a**	**3a** (67)
2		**1b**	**3b** (60)
3		**1c**	**3c** (74)
4		**1d**	**3d** (71)
5		**1e**	**3e** (68)
6		**1f**	**3f** (56)

[a] The reactions were carried out according to the general procedure described in the text. [b] Yield of pure isolated product.

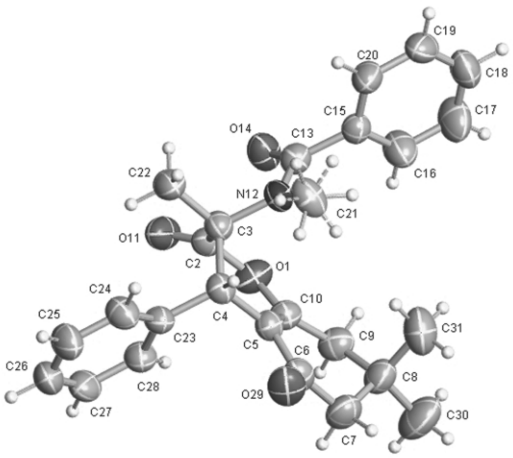


Fig. 1 Molecular structure of **3a** with the thermal ellipsoids at 30% probability while the hydrogen size is arbitrary. Selected bond lengths (Å) and angles (°): O1–C10 1.378(3), O1–C2 1.402(3), C2–C3 1.520(4), C3–C4 1.566(3), C4–C5 1.507(3), C5–C10 1.338(4), C5–C6 1.462(4), C6–C7 1.503(4), C7–C8 1.527(4), C8–C9 1.521(4), C9–C10 1.487(4), C2–O11 1.188(3), C13–O14 1.225(3), C2–C3–C4 103.6(2), O1–C2–C3 113.9(2), C10–O1–C2 118.3(2), C5–C10–C9 126.3(3), O1–C10–C9 111.6(2), C5–C6–C7 117.5(2).

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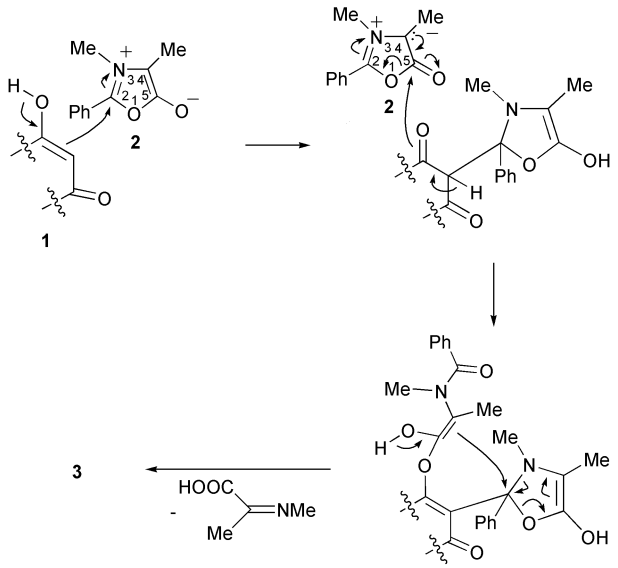

Scheme 1

Unexpectedly and in contrast with the results obtained using the same starting materials **1** and mesoionic *N*-unsubstituted 5(4*H*)-oxazolone (in which fused pyrrole derivatives were obtained),[7] this reaction does not produce cycloadducts between 1,3-dicarbonyls and DMPO. The fact that the carboxyl ester and the imidate ester linkages of mesoionic 1,3-oxazolium-5-olates are potential reaction sites for nucleophilic attack is well documented however.[8]

On this basis a plausible mechanism for the formation of **3** is suggested in Scheme 1: unusual double attack of the binucleophile **1** in enolic form on the two electrophilic centres C-5 and C-2 of two different DMPO molecules and subsequent facile closure to the enol lactone ring with loss of the α-amino acidic fragment.

In conclusion, we have demonstrated a new approach to the construction of an important functionalised substructure found in the skeletons of the neoflavonoid and coumarin families. Use of these results in the diastereocontrolled synthesis of natural products is presently under investigation.

Notes and references

‡ **3a**: m.p. 201–202 °C. ν_{max}/cm^{-1} 1797, 1665, 1645. δ_H (300 MHz, $CDCl_3$): 1.15 (s, 3H), 1.23 (s, 3H), 1.40 (s, 3H), 2.33 (s, 2H), 2.58 (part of AB system, J_{AB} 18 Hz, 1H), 2.65 (part of AB system, J_{AB} 18 Hz, 1H), 2.93 (s, 3H), 4.55 (s, 1H), 7.12–7.44 (m, 10H). Analysis: Found C, 74.93; H, 6.61; N, 3.22%. Calc. C, 74.80; H, 6.52; N, 3.35% for $C_{26}H_{27}NO_4$. **3b**: m.p. 189–190 °C. ν_{max}/cm^{-1} 1803, 1705, 1639. δ_H (300 MHz, $CDCl_3$): 1.43 (s, 3H), 2.30 (s, 3H), 2.91 (s, 3H), 4.55 (s, 1H), 6.08 (s, 1H), 7.11–7.40 (m, 10H). Analysis: Found C, 71.58; H, 5.36; N, 3.31%. Calc. C, 71.45; H, 5.25; N, 3.47% for $C_{24}H_{21}NO_5$. **3c**: m.p. 251–252 °C. ν_{max}/cm^{-1} 3554, 1804, 1656, 1625. δ_H (300 MHz, $CDCl_3$): 1.45 (s, 3H), 2.18 (s, 3H), 2.86 (s, 3H), 4.67 (s, 1H), 5.97 (s, 1H), 7.13–7.38 (m, 10H). Analysis: Found C, 71.53; H, 5.43 ; N, 6.81%. Calc. C, 71.63; H, 5.51; N, 6.96% for $C_{24}H_{22}N_2O_4$. **3d**: m.p. 171–172 °C. ν_{max}/cm^{-1} 1801, 1724, 1645. δ_H (300 MHz, $CDCl_3$): 1.49 (s, 3H), 2.93 (s, 3H), 4.69 (s, 1H), 7.07–7.96 (m, 14H). Analysis: Found C, 73.91; H, 4.92; N, 3.08%. Calc. C, 73.79; H, 4.82; N, 3.19% for $C_{27}H_{21}NO_5$. **3e**: m.p. 159–160 °C. ν_{max}/cm^{-1} 1805, 1716, 1642. δ_H (300 MHz, $CDCl_3$): 1.51 (s, 3H), 2.41 (s, 3H), 2.96 (s, 3H), 4.71 (s, 1H), 7.11–7.46 (m, 12H), 7.77 (s, 1H). Analysis: Found C, 74.29; H, 5.21; N, 3.20%. Calc. C, 74.16; H, 5.11; N, 3.09% for $C_{28}H_{23}NO_5$. **3f**: m.p. 233–234 °C. ν_{max}/cm^{-1} 1782, 1656, 1625. δ_H (300 MHz, d_6-DMSO): 1.40 (s, 3H), 2.80 (s, 3H), 4.91 (s, 1H), 6.91–7.97 (m, 14H), 12,02 (s, 1H). Analysis: Found C, 73.79; H, 4.98; N, 6.27%. Calc. C, 73.96; H, 5.06; N, 6.39% for $C_{27}H_{22}N_2O_4$.

§ *Crystal data for* **3a**: $C_{26}H_{27}NO_4$ (298 K). M = 417.49, monoclinic, space group $P2_1$, a = 10.3788(9), b = 6.4952(7), c = 16.451(2) Å, β = 92.587(8)°, V = 1107.9(2) Å^3, Z = 2, $\rho_{calc.}$ = 1.251 g cm^{-3}, absorption coefficient = 0.084 mm^{-1}. 3734 reflections (2771 unique with R_{int} = 0.013) were collected at room temperature on a Bruker P4 diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SIR97), and refined against all F^2 data (SHELXL-97). All non-hydrogen atoms were refined with anisotropic thermal parameters while hydrogen atoms were treated by the "reading model" method. One terminal methyl showed rotational disorder. In the chiral space group the Flack parameter did not converge for both the possible enantiomers and the crystal was treated as a racemic twin. GOF = 1.048, R_1 = 0.0409/0.0638 and wR_2 = 0.0842/0.0961 (for 2114 $I > 2\sigma(I)$ and all data, respectively). Residual electron density ranges from −0.176 up to 0.175 e Å^{-3}. CCDC 209308. See http://www.rsc.org/suppdata/cc/b3/b304560a/ for crystallographic data in CIF or other electronic format.

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