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Novel 2-pyrone synthesis via Michael addition of mandelic acid enolate to *trans*-1,2-diaroylethenes

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This paper is dedicated to the memory of Dr. Juan Carlos del Amo, member of the RSEQ, deceased in the 11-M terrorist attack in Madrid

Abstract—4-Aroyl-6-aryl-3-phenyl-2-pyrones are prepared in a three-step procedure involving the Michael addition of a *cis*-2,5-disubstituted-1,3-dioxolan-4-one, derived from mandelic acid, to *trans*-1,2-diaroylethenes, cyclisation to a furan under acidic conditions and lactonisation. The 2-pyrones can be also obtained directly from the Michael products under prolonged or strong acidic treatment with little decrease in yield.

1. Introduction

2-Pyrones have found a wide variety of applications in organic synthesis as dienes in Diels–Alder reactions[1] and as precursors to other carbo-[2] and heterocyclic systems.[3] The 2-pyrone moiety is also present in a large number of biologically active compounds[4] and recently, low molecular weight 2-pyrones as well as 4-hydroxy-2-pyrones have been shown to be potent HIV-1 protease inhibitors.[5] 4-Alkenyl/alkynyl-2-pyrones are associated with antimicrobial, human ovarium carcinoma (A2780) and human chronic myelogenous leukaemia (K562) inhibitory properties as well.[6] Consequently the synthesis of 2-pyrones with different substitution patterns presents an interesting challenge that has deserved considerable efforts.

Further to the introduction of substituents into the preformed 2-pyrone ring[7] a number of methods for the construction of this moiety either by traditional approaches[8] or by procedures involving transition metal catalysed reactions[9] have been reported. A number of these methods involve the lactonisation of 4-alkynoic acids promoted by palladium[10] or by electrophilic reagents.[11] In many cases these procedures lead to γ-alkylidene butenolides instead of pyrones and when carried out with nonsymmetric alkynes two 2-pyrone regioisomers may be obtained. Recently, a K_2CO_3-catalysed 1,4-addition of malonic esters to allenic ketones to give β,γ-unsaturated enones, which are lactonised to 2-pyrones has been reported.[12]

As part of our recent research[13] we have reported the Michael reaction of the enolate of a mandelic acid dioxolanone with simple α,β-unsaturated ketones to give α-hydroxy-γ-ketoacids, which were transformed into chiral 1,4-dicarbonyl compounds.[13c]

In this communication we report the Michael addition of the enolate of a mandelic acid dioxolanone to *trans*-1,2-diaroylethenes and the transformation of the resulting compounds into 4-aroyl-2-pyrones. Despite the fact that an acyl group at this position seems an excellent precursor for further functionalisation, the number of procedures for the preparation of 4-acyl-2-pyrones is very scarce.

The first step in our synthetic sequence (Scheme 1) is the Michael addition of the enolate of *cis*-2,5-disubstituted-1,3-dioxolan-4-one **1**, prepared from mandelic acid and pivalaldehyde,[14] to *trans*-1,2-diaroylethenes **2**, which can be obtained by Friedel–Crafts acylation of aromatic compounds with fumaroyl chloride.[15]

Keywords: Dioxolanone; Lactones; Enones; Hydroxyacids.
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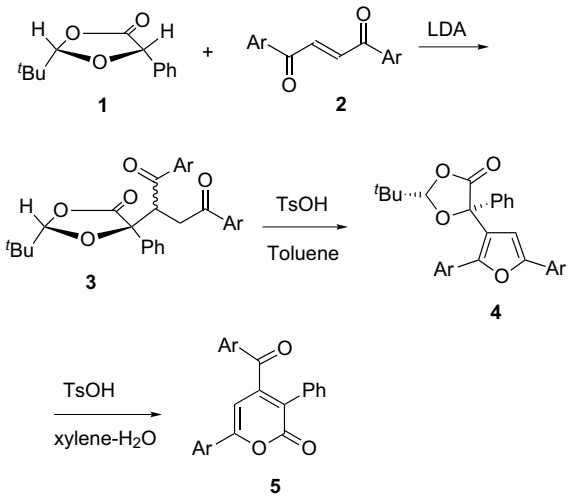


Scheme 1.

1,2-Di-(4′-toluoyl)ethene **2a** was used as test substrate for the Michael addition. The addition of **2a** to a preformed solution of the lithium enolate of dioxolanone **1** at −78 °C gave a mixture of two Michael products **3a**, with 90% yield, in a 74:26 diastereomeric ratio. NOEs experiments carried out with the major product showed interaction between the signal at δ 0.93 (s), corresponding to the *t*-Bu group, and the signal at δ 7.78 (dd, $J = 8.2$, 1.5 Hz) corresponding to the 2-H of the phenyl group. Also, irradiation at the signal of the C–H of the dioxolanone ring (δ 5.53) gave NOE with the signal of a 4-toluoyl proton at δ 8.01 (d, $J = 8.1$ Hz). Similarly for the minor product, NOEs between the signals at 0.73 and at δ 7.70 (dd, $J = 8.1$, 1.5 Hz), as well as between the signals at δ 5.15 (s) and at δ 8.02 (d, $J = 8.2$ Hz) were observed. These results indicate that in both cases the *t*-Bu and phenyl groups are in *cis* disposition. The two diastereomers differ in the configuration of the newly created stereogenic centre of the side chain[16] and result from the approach of the enedione from the less hindered face of the enolate, opposite to the *t*-Bu group, as expected according to the principle of self-regeneration of stereocentres by Seebach et al.[17] The presence of HMPA and the inversion in the order of addition of the reagents, which were crucial for the yield and diastereoselectivity in the addition of the enolate of **1** to simple enones,[13c] resulted in this case in a lower yield.

Under the optimised conditions, a number of diaroylethenes **2** reacted with the enolate of **1** to give the corresponding products **3** with good yields and diastereoselectivities (Table 1). It is worth remarking that the diastereoselectivity of the reaction increases with the presence of electron-releasing groups on the aromatic ring of the diaroylethene.

By acid treatment of compounds **3**, a lactonisation reaction by nucleophilic attack of the side chain ketone group enol to the dioxolanone carbonyl group (1,5-dicarbonyl system) and dehydration would lead to 4-aroyl-2-pyrones **5**. However the possibility of a cyclisation process through the 1,4-dicarbonyl system to give a furan **4** could not be excluded. In fact either compound **4** or **5** can be obtained by acid treatment of compound **3** depending on the reaction conditions. So when compound **3a** was heated in boiling benzene or toluene with a Dean–Stark apparatus a product identified as furan **4a** was obtained in 71% yield. Under prolonged treatment a new product appeared in the reaction mixture, which was identified as the 2-pyrone **5a**. This product was most probably formed from furan **4a** through an equilibrating open ring enol form (Scheme 2). Addition of water (1–10 equiv) did not prevent the formation of the furan although it seemed to speed up the formation of the 2-pyrone product. Treatment of Michael adduct **3a** with TsOH–H_2O in xylene–H_2O at reflux gave directly the 2-pyrone **5a** in a one-pot procedure (45% yield), still through the intermediate furan **4a**, which was observed by TLC of the reaction mixture. On the other hand, treatment of isolated furan **4a** under similar conditions also gave the 2-pyrone **5a** with a 72% yield. The overall yield of 2-pyrone obtained in this way, through the isolated furan, was 51% from **3a**, somehow higher than the yield obtained in the one-pot procedure (45%).

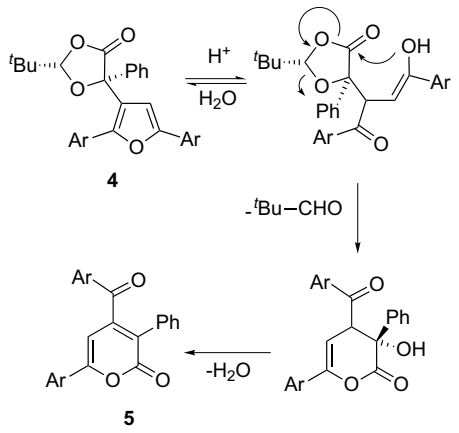
Thus the final procedure that we have carried out involved three steps, namely Michael addition of the enolate of **1** to the diaroylethene **2**, cyclisation to the furan ring **4** and lactonisation to the 2-pyrone **5**. The results of these reactions for different compounds are shown in Table 1.

In summary, we present a new method for the synthesis of substituted 2-pyrones. The presence of an aroyl group at position **4** of the pyrone ring thus formed should allow further functional modification at this position. This procedure is short and simple and the starting materials are readily available. The extension of this methodology to other Michael acceptors and/or hydroxyacids for the preparation of 2-pyrones with different substitution patterns is under study.

Table 1. Synthesis of compounds **3**, **4** and **5**

Entry		Ar	Yield **3** (%)	**3** dr	Yield **4** (%)	Yield[a] **5** (%)
1	**a**	4-Toluoyl	90	83:17	71	72 (45)
2	**b**	Phenyl	97	74:26	88	64 (48)
3	**c**	3,4-Dimethylphenyl	95	84:16	73	73 (46)
4	**d**	4-Methoxyphenyl	80	90:10	67	64 (37)
5	**e**	4-Fluorophenyl	91	71:29	64	60 (30)
6	**f**	4-Chlorophenyl	63	67:33	72	58 (36)

[a] Yields in brackets refer to compound **5** obtained directly from **3** in one step (xylene–H_2O).



Scheme 2.

2. Typical experimental procedure

2.1. Michael addition of *cis*-2,5-disubstituted-1,3-dioxolan-4-one 1 to *trans*-1,2-di-(4′-toluoyl)ethene 2a

A solution of dioxolanone (*S*,*S*)-**1** (220 mg, 1 mmol) in 1.5 mL of dry THF was added to a −78 °C pre-cooled solution prepared from 0.625 mL of a 2 M commercial solution of LDA in heptane–THF–ethylbenzene (1.25 mmol) and 2 mL of THF. After 30 min, a solution of **2a** (303 mg, 1.15 mmol) in 1.5 mL of THF was added dropwise and 10 min after, the reaction was quenched with the addition of saturated aqueous NH_4Cl (3 mL). The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous NH_4Cl (2 × 10 mL) and brine (2 × 10 mL) and dried. Column chromatography with hexane–EtOAc gave 362 mg (75%) and 74 mg (15%) of two diastereomeric products **3a**. Major diastereomer: mp 70–72 °C (hexane–EtOAc); $[\alpha]_D^{25}$ +95 (*c* 0.4, $CHCl_3$); MS (EI) 484 (M^+, 1), 466 (5), 219 (16), 144 (14), 119 (100); HRMS 484.2246, $C_{31}H_{32}O_5$ required 484.2250; ^{1}H NMR ($CDCl_3$): δ 0.93 (9H, s), 2.37 (3H, s), 2.42 (3H, s), 3.19 (1H, dd, J = 18.0, 4.0 Hz), 3.71 (1H, dd, J = 18.0, 8.0 Hz), 4.82 (1H, dd, J = 8.0, 4.0 Hz), 5.53 (1H, s), 7.18 (2H, d, J = 8.1 Hz), 7.20–7.50 (5H, m), 7.67 (2H, d, J = 8.1 Hz), 7.78 (2H, dd, J = 8.2, 1.5 Hz), 8.01 (1H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$): δ 21.6 (q), 21.7 (q), 23.6 (q), 35.1 (s), 37.0 (t), 50.2 (d), 81.7 (s), 110.2 (d), 125.4 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.9 (d), 129.0 (d), 129.3 (d), 133.5 (s), 134.3 (s), 137.2 (s), 144.1 (s), 144.3 (s), 172.2 (s), 196.3 (s), 199.9 (s). Minor diastereomer: mp 85–87 °C (hexane–EtOAc); $[\alpha]_D^{25}$ −84 (*c* 0.3, $CHCl_3$); MS (EI) 484 (M^+, 1), 466 (6), 381 (10), 144 (11), 119 (100); HRMS 484.2253 $C_{31}H_{32}O_5$ required 484.2250; ^{1}H NMR ($CDCl_3$): δ 0.73 (9H, s), 2.38 (3H, s), 2.42 (3H, s), 3.56 (1H, dd, J = 18.4, 7.2 Hz), 3.67 (1H, dd, J = 18.4, 4.9 Hz), 4.94 (1H, dd, J = 7.2, 4.9 Hz), 5.15 (1H, s), 7.17 (2H, d, J = 8.2 Hz), 7.20–7.40 (5H, m), 7.66 (2H, d, J = 8.2 Hz), 7.70 (2H, dd, J = 8.1, 1.5 Hz), 8.02 (1H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$): δ 21.5 (q), 21.6 (q), 23.3 (q), 35.0 (s), 37.3 (t), 51.2 (d), 81.6 (s), 110.3 (d), 125.8 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.9 (d), 129.0 (d), 129.3 (d), 133.3 (s), 133.9 (s), 137.4 (s), 144.1 (s), 144.3 (s), 172.7 (s), 195.6 (s), 200.1 (s).

2.2. Cyclisation to furan 4a

A solution containing compound **3a** (diastereomer mixture) (249 mg, 0.51 mmol) and $TsOH{\cdot}H_2O$ (24 mg, 0.13 mmol) in benzene (30 mL) was heated at reflux in a Dean–Stark system for 24 h. After this time, the solvent was removed under reduced pressure and the residue chromatographed using hexane–diethyl ether to give 169 mg (71%) of furan **4a**: mp 62–65 °C (hexane–EtOAc); $[\alpha]_D^{25}$ +107 (*c* 1.8, $CHCl_3$); MS (EI) 466 (M^+, 32), 336 (14), 57 (100); HRMS 466.2104, $C_{31}H_{30}O_4$ required 466.2144; ^{1}H NMR ($CDCl_3$): δ 0.88 (9H, s), 2.28 (3H, s), 2.34 (3H, s), 5.01 (1H, s), 6.85 (1H, s), 7.05 (2H, d, J = 7.8 Hz), 7.18 (2H, d, J = 7.8 Hz), 7.30–7.40 (3H, m), 7.47 (2H, d, J = 8.4 Hz), 7.54 (2H, dd, J = 8.1, 1.5 Hz), 7.60 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 21.2 (q), 21.3 (q), 23.5 (q), 33.9 (s), 82.1 (s), 107.3 (d), 107.6 (d), 116.3 (s), 123.8 (d), 127.1 (d), 127.3 (s), 128.4 (d), 128.5 (d), 128.9 (d), 129.5 (d), 137.7 (s), 137.8 (s), 137.9 (s), 152.0 (s), 152.8 (s), 172.6 (s).

2.3. Lactonisation to 2-pyrone 5a

A solution containing furan **4a** (57 mg, 0.12 mmol), $TsOH{\cdot}H_2O$ (13 mg, 0.07 mmol) and water (40 μL, 2.2 mmol)[18] in xylene (7 mL) was heated at reflux (140 °C) for 40 h. After this time, the solvents were removed under reduced pressure and the residue chromatographed using hexane–diethyl ether to give 34 mg (72%) of compound **5a**: mp 202–204 °C (hexane–EtOAc); MS (EI) 380 (60), 352 (100), 261 (15), 119 (65); HRMS 380.1406, $C_{26}H_{20}O_3$ required 380.1412; ^{1}H NMR ($CDCl_3$): δ 2.33 (3H, s), 2.41 (3H, s), 6.69 (1H, s), 7.13 (2H, d, J = 8.1 Hz), 7.15–7.25 (3H, m), 7.27 (2H, d, J = 8.1 Hz), 7.34 (2H, dd, J = 8.1, 1.8 Hz), 7.66 (2H, d, J = 8.1 Hz), 7.77 (2H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$): δ 21.5 (q), 21.8 (q), 100.4 (d), 122.6 (s), 125.6 (d), 128.0 (s), 128.1 (d), 128.7 (d), 129.4 (d), 129.7 (d), 129.8 (d), 129.9 (d), 131.9 (s), 132.6 (s), 141.8 (s), 145.5 (s), 150.8 (s), 160.1 (s), 161.9 (s), 194.5 (s).

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16. The configuration of this stereogenic centre was not determined because it was found that both diastereomers led to the same furan or pyrone and that they could be used in the following step as a mixture.
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18. Although the TsOH used in this reaction is a hydrate, additional amounts of water were required to speed up the lactonisation reaction. Probably, the presence of water facilitates the equilibrium between the furan and the open ring enol intermediate (Scheme 2).