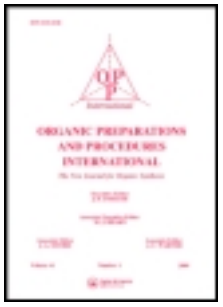

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A CONVENIENT SYNTHESIS OF OXAZOLO[3,2-a]QUINOLONES

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A CONVENIENT SYNTHESIS OF OXAZOLO[3,2-a]QUINOLONES

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(02/05/96)

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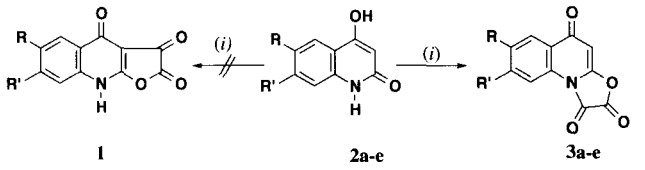
In view of the biological activity of compounds incorporating the α-diketo group,[1] the preparation of novel 2,3-furandiones seemed warranted. As a continuation of our investigation of these systems,[2] we attempted to prepare furoquinoline systems of type **1**. However, the reaction of 4-hydroxyquinolines[3] (**2a-e**) with oxalyl chloride gave only oxazolo[3,2-a]quinolones (**3a-e**) in 65-85% yields, without any by-products such as chlorinated and/or open-chain compounds.[4]



(1)

1 **2a-e** **3a-e**

i) ClCOCOCl *ii)* H_2O *iii)* R"NH_2

1-3 a) R = R' = H b) R = CH_3, R' = H c) R = Cl, R' = H
d) R = H, R' = CH_3 e) R = H, R' = Cl

4 a) R" = C_6H_5
b) R" = *p*-$CH_3C_6H_4$
c) R" = $CH_2C_6H_5$

The structure of these oxazoloquinolones was assigned based on their spectral properties and elemental analysis (Table 1). The IR spectra of **3a-e** displayed characteristic C=O stretching vibrations at 1835-1845 cm^{-1} and 1770 cm^{-1}. The ^1H NMR spectra of **3a-e** showed the presence of a singlet

TABLE 1. Mps, Yields, Elemental Analysis and Spectral Data of Oxazolo[3,2-a]quinolones (**3a-e**)

Cmpd	mp. (°C)	Yield (%)	Analysis Calcd (Found) C	H	N	IR (cm^{-1})	^1H and ^{13}C NMR (δ)
3a	215	85	61.43 (61.28	2.33 2.60	6.51 6.50)	1835cm^{-1}, 1770 $cm^{-1}$and 1650 cm^{-1}	6.19 (s, 1H, CH), 7.10-8.85 (m, 4H, arom.). 180.02, 165.40, 164.30, (C=O), 154.0 (=CNO), 116.50 (=CH).
3b	230	80	62.88 (62.87	3.07 3.24	6.10 6.24)	1845cm^{-1}, 1770 cm^{-1} and 1650cm^{-1}	2.55(s,3H,CH_3), 6.19 (s, 1H, CH), 7.59-8.70 (m, 3H,arom.).
3c	238	65	52.93 (53.00	1.62 1.97	5.61 5.97)	1840cm^{-1}, 1770 cm^{-1} and 1670cm^{-1}	6.19 (s, 1H,CH), 7.26-8.73 (m, 3H, arom.).
3d	232	83	62.88 (62.87	3.07 3.24	6.10 6.24)	1840cm^{-1}, 1770 cm^{-1} and 1660cm^{-1}	2.50 (s, 3H, CH_3), 6.19 (s, 1H, CH) 7.61-8.65 (m, 3H, arom.).
3e	240	68	52.93 (52.73	1.62 1.83	5.61 5.78)	1840cm^{-1}, 1770 cm^{-1} and 1670cm^{-1}	6.19 (s,1H,CH), 7.20-8.65(m, 3H, arom.).

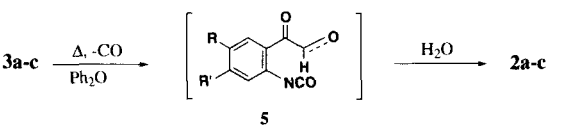
at δ 6.19 for (=C-H) and the ^{13}C NMR spectrum of **3a** exhibited signals at d 180.02, 165.40, 164.30, 154.0 and 116.50 (3 -C=O, -C(N-)O-, =CH-).

To examine the reactivity of oxazoloquinolones **3a-c** towards nucleophiles, their reactions with water, aromatic and aliphatic amines were performed. Compounds **3a-c** were easily hydrolyzed by a mixture of acetone/water at RT to give 4-hydroxyquinolones **2a-c** in 88-94% yield and oxalic acid (1). This behavior agrees well with similar finding from prolonged hydrolysis of 4-benzoyl-5-phenylfuran-2,3-dione.[5] Similarly, amines react with oxazoloquinolones **3a-c** to give oxalic acid diamide derivatives **4a-c** and 4-hydroxyquinolones **2a-c** (Table 2).

TABLE 2. Yields and mps of Hydrolysis and Aminolysis of **3a-c**

Cmpd	Hydrolysis		Aminolysis			
	2 (%)	Oxalic Acid (%)	2 (%)	Diamide (%)	mp. (°C)	Lit. mp. (°C)
3a	90	38	85	83	246	247-8 lit[8a]
3b	94	35	87	90	274	276 lit[8b]
3c	88	30	80	85	196	198 lit[8c]

The thermal decomposition in the solid state Flash Vacuum Pyrolysis (FVP) or in solution (boiling xylene) of 4,5-unsaturated furan(pyrrol)-2,3-diones in general is reported to form α-oxoketene intermediates which dimerize [6] or undergo further decarboxylation to yield pyran or quinolone derivatives. [2a,7]



5 (2)

However, heating of oxazoloquinolones **3a-c** above their melting points (259°) gave only 4-hydroxyquinolone derivatives **2a-c** whose formation may be viewed as proceeding *via* heterocumulene intermediates **5** with addition of adventitious water during work up, under Flash Vacuum Pyrolysis (FVP) conditions (450°, 10^{-3} m bar), no ketene intermediate could be isolated.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer (KBr). The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer in DMSO with TMS as internal reference. Chemical shifts are expressed as δ ppm. Analytical data were performed on C,H,N-Elemental Analyzer Carlo Erba 1106 in Karl-Franzens University, Graz, Austria.

Oxazolo[3,2-a]quinolones 3a-e. General Procedure.- Heating of 4-hydroxyquinolone derivatives **2a-e** (15 mmol) with oxalyl chloride (15.5 mmol) at 65° in dry benzene for 2 hrs gave the yellow oxazolo[3,2-a]quinolones **3a-e**, which were recrystallized from dry acetonitrile (Table 1).

Hydrolysis of Oxazolo[3,2-a]quinolones 3a-c. General Procedure.- Oxazolo[3,2-a]quinolone **3a-c** (1 mmol) was dissolved in a mixture of 20 mL acetone and two drops of water, the reaction mixture

was stirred at 20° for 24 hrs.The precipitate was collected to give the crude 4-hydroxyquinolones **2a-c**, which were washed with water, and the mother liquor was evaporated at reduced pressure to give oxalic acid (see Table 2).

Reaction of Amines with Oxazolo[3,2-a]quinolones 3a-c. General Procedure.- To the oxazolo[3,2-a]quinolone **3a-c** (1 mmol) in 15 mL of acetone, was added a solution of amine (2 mmol) in 5 mL of acetone. The crude oxalic acid diamide derivatives **4a-c** were formed immediately. After 2 hrs, the product was collected and crystallized from ethanol to yield the corresponding oxalic acid diamide derivatives **4a-c** (see Table 2). The formation of **4** was established by comparison of their IR spectra and mps. with these of authentic samples.[8]

Thermal Decomposition of Oxazolo[3,2-a]quinolones 3a-c. General Procedure.- The oxazolo[3,2-a]quinolone **3a-c** (1 mmol) was heated in 15 mL of diphenylether at 259° for 20 min. The solution was cooled and 20 mL of *n*-hexane was added. The precipitated solid was crystallized from DMF to afford 4-hydroxyquinolone derivatives **2a-c**.

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SYNTHESIS OF DIETHYL 3-ARYL-3-OXOPROPYLPHOSPHONATES

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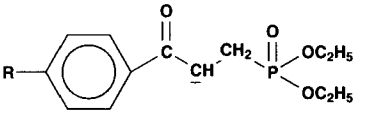
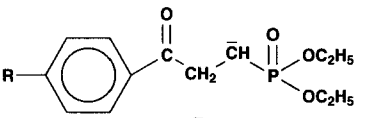
γ-Ketophosphonate **2** provides dual sites[1] for reaction with base, either with the formation of **A** or **B**.[2] Since *p*-substituents on the phenyl group may affect the stability of the enolate ion and thus



A



B

be important with the formation of **B** in competitive reactions, we sought a better route to prepare some of γ-ketophosphonates. A series of γ-ketophosphonates **2** containing some phenyl derivatives has been prepared in low to moderate yields from the Mannich reaction of the 1-diethylamino-3-aryl-propan-3-one hydrochloride or methiodide with triethyl phosphite (TEP).[3] Previous procedures require multiple steps with expensive reagents. For example, the addition of methyl iodide to form the quaternary salt of a Mannich intermediate and followed by reaction with TEP gave γ-ketophosphonates **2** in low yields.[3a] Furthermore the crude product required further purification. The parent compound (**2a**, R = H) was prepared (73%) by the reaction of **1a** with TEP in diglyme after prolonged reflux (15 hrs).[4] Other procedures for the related alkyl γ-ketophosphonates utilized the Michael addition of TEP to the α,β-unsaturated ketones in alcohol[5] or with a dialkylphosphite in alkoxide solution.[6] Another route involved the condensation of the haloethyl ketones with sodium dialkylphosphite.[7] One alkylation of α-copper(I) alkanephosphonates with dihalopropenes for γ-ketophosphonates was also reported.[8]

We now report the formation of *p*-substituted phenyl γ-ketophosphonates **2** *via* the Arbuzov reaction in excellent yields by simple reflux in TEP as reagent and solvent with the corresponding β-chloroethyl ketones **1** (Tables 1 and 2). The progress of the reaction was monitored by g.l.c. and the