α-Pyranones; I. Reaction of 4-Ethoxy- and 4-Chloromethylene-2-phenyl-5(4*H*)-oxazolone with Ethyl 3-Oxo-4-(triphenylphosphoranylidene)butyrate: A New Synthesis of 2*H*-pyran-2-one Compounds

M.L. Gelmi,* D. Pocar

Istituto di Chimica Organica-Facoltà di Farmacia dell'Università, Via Venezian 21, I-20133 Milano, Italy

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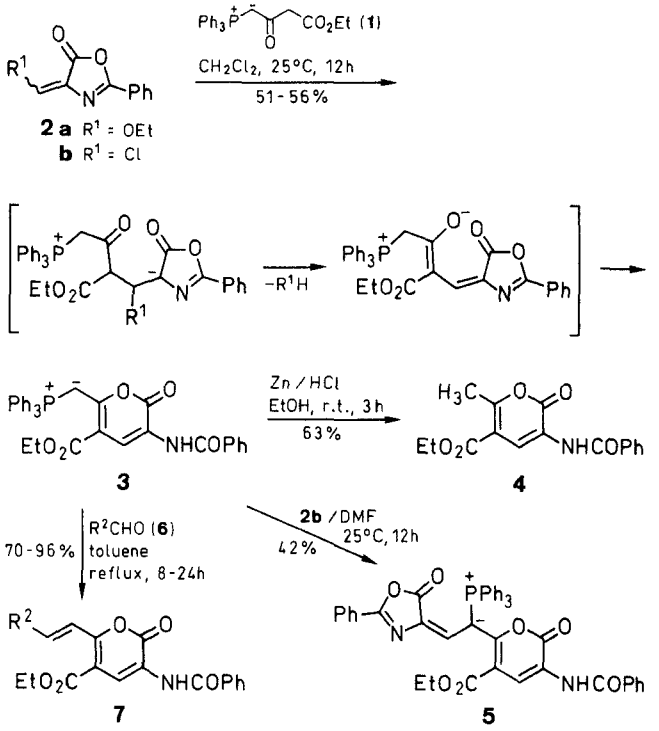
The reaction of 4-ethoxymethylene-5(4*H*)-oxazolone (**2a**) with ethyl 3-oxo-4-(triphenylphosphoranylidene)butyrate (**1**) affords ethyl 3-benzoylamino-2-oxo-6-triphenylphosphoranylidenemethyl-2*H*-pyran-5-carboxylate (**3**). Starting from the corresponding 4-chloromethylene compound **2b** and **1**, besides **3**, ethyl 3-benzoylamino-6-[2-(4,5-dihydro-5-oxo-2-phenyl-4-oxazolylidene)-1-(triphenylphosphoranylidene)ethyl]-2-oxo-2*H*-pyran-5-carboxylate (**5**) is formed. The phosphorane **3** is a reactive synthetic intermediate for the preparation of ethyl 6-(1-alkenyl)-3-benzoylamino-2-oxo-2*H*-pyran-5-carboxylates **7** through reaction with aldehydes.

Recently, as a part of our research in the synthetic employment of the reaction of oxazolone compounds with phosphorus ylides,[1] we described the synthesis of dihydrobenzoxazoles and 1,3-cyclohexadienone ylides from 4-alkylidene-5(4*H*)-oxazolones and ethyl 3-oxo-4-(triphenylphosphoranylidene)butyrate.[2] We now report on the use of oxazolones as starting materials for the preparation of pyran-2-one derivatives. There are several syntheses of 3-benzoylamino-2*H*-pyran-2-ones reported in the literature, recently, in particular, by reaction of 2-aminomethylene-1,3-diketones with 2-phenyl-5(4*H*)-oxazolones.[3,4] Another synthetic path to similarly substituted pyranone compounds is by reaction of 4-(ethoxymethylene)oxazolones with active methylene compounds.[5] However, all the above synthetic procedures do not allow easy functionalization of the 6 position in the 2*H*-pyran-2-one ring. This paper describes the reaction of the phosphorane **1** with 4-ethoxy- and 4-chloromethylene-2-phenyl-5-(4*H*)-oxazolones **(2a,b)** which affords a new useful synthetic intermediate for the preparation of several 2*H*-pyran-2-one derivatives bearing a substituted vinyl group in position 6.

Oxazolone **2a** reacted readily with **1** at room temperature in dichloromethane within 12 hours to give a satisfactory yield of ethyl 3-benzoylamino-2-oxo-6-triphenylphosphoranylidenemethyl-2*H*-pyran-5-carboxylate (**3**). Compound **3** was also formed in the reaction of **2b** with **1**, under similar reaction conditions, however a substantial amount of the deep red byproduct **5** was also formed. Compound **5**, which derives from the starting reactants **1** and **2b** in a 1 : 2 ratio, was shown in a separate experiment to arise from the reaction of the primary product, that is **3**, with **2b**.

The structure of **3** was confirmed by its reduction with metal zinc and hydrochloric acid to the known pyranone **4**.[5] Moreover, **3** and **5** were identified by analytical and spectroscopic techniques. In the IR spectrum of **3** two carbonyl absorptions (1700 and 1650 cm^{-1}) were present and correspond to the ester and amide functions, respectively. Noticeably, the expected 2*H*-pyran-2-one band[5] at about 1720 cm^{-1} was absent and there was evidence of extensive delocalization of the ylide negative charge on the carbonyl group through the π-system of the pyranone



6, 7	a	b	c	d	e
R^2	4-MeC_6H_4	2-HOC_6H_4	2-furyl	2-pyridyl	Pr

ring. In agreement with this, the 2*H*-pyran-2-one band (1720 cm^{-1}) was observed in the spectrum of **5**, where cross-conjugation exists, suggesting a major contribution of the delocalized system encompassing the oxazolone ring. This agrees with the lack of the typical lactone band (1760–1780 cm^{-1}) in the spectrum of **5**. The ^1H NMR spectrum of **5** showed the expected singlet associated with H-4[3,4] at δ = 8.9. The corresponding singlet for compound **3** was overlapped by the aromatic multiplet (δ = 7.4–7.8). The ylide hydrogen was associated with a doublet at δ = 5.5 (J_{P-H} = 18.5 Hz, exchangeable with D_2O). In the ^{13}C NMR spectrum the ylide carbons of **3** and **5** resonated at δ = 50.0 (J_{C-P} = 115 Hz) and 70.7 (J_{C-P} = 115 Hz), respectively.

The reaction proceeds by Michael addition of the 2-C of the ambident ylide **1**[6] to the exocyclic double bond of **2**. The initially formed addition anion readily eliminates ethanol or hydrogen chloride, which is followed by enolization of the ketone group. Accordingly, in the case of **2b**, an excess of ylide **1** was found to give better yields owing to its ability to neutralize the hydrogen chloride. A *trans*-lactonization reaction brings the formation of the pyrone ring.

Table. 2*H*-Pyran-2-ones **3, 5, 7** Prepared

Product	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (Nujol, cm^{-1})[c] ν_{NH}	ν_{CO}	^1H NMR (DMSO)[d] δ, J (Hz)
3	211–212 (acetone)	$C_{34}H_{28}NO_5P$ (561.5)	3400	1700, 1650	1.3 (t, 3H, J = 7, CH_3), 4.1 (q, 2H, J = 7, CH_2), 5.5 (d, 1H, J_{P-H} = 18.5, CH–P), 7.4–7.8 (m, 21H, H_{arom} and H-4), 9.2 (s, 1H, NH)
5	205 (dec) (*i*-PrOH)	$C_{44}H_{33}N_2O_7P$ (731.7)	3400	1720, 1700, 1640	1.1 (t, 3H, J = 7, CH_3), 4.1 (q, 2H, J = 7, CH_2), 7.0 (d, 1H, $J_{P=H}$ = 19.8, CH=), 7.2–8.0 (m, 25H_{arom}), 8.3 (s, 1H, NH), 8.9 (s, 1H, H-4)
7a	212–213 (toluene)	$C_{24}H_{21}NO_5$ (403.4)	3340	1720, 1690, 1670	1.4 (t, 3H, J = 7, $CH_2\underline{CH}_3$), 2.4 (s, 3H, CH_3), 4.4 (q, 2H, J = 7, CH_2), 7.3–8.0 (m, 11H, H_{arom} and CH=CH), 7.9 (s, 1H, NH), 8.6 (s, 1H, H-4)
7b	240–241 (toluene)	$C_{23}H_{19}NO_6$ (405.4)	3300 (br)[f]	1720, 1700, 1650	1.4 (t, 3H, J = 7, CH_3), 4.3 (q, 2H, J = 7, CH_2), 6.8–7.0, 7.4–7.7, 7.9–8.0 (m, 9H_{arom}), 7.7, 8.05 (AB system, 2H, J = 15.3, CH=CH), 8.5 (s, 1H, H-4), 9.7, 10.4 (two s, 2H, NH and OH)
7c	180–181 (toluene)	$C_{22}H_{18}N_2O_5$ (390.4)	3400	1720, 1700, 1670	1.4 (t, 3H, J = 7, CH_3), 4.4 (q, 2H, J = 7, CH_2), 7.2–7.9 (m, 9H, H_{arom}, H_{pyr} and =CH), 8.5 (d, 1H, J = 15.4, =CH), 8.6 (s, 1H_{pyr}), 8.7 (s, 1H, NH), 9.0 (s, 1H, H-4)
7d	180–183 (toluene)	$C_{21}H_{17}NO_6$ (379.4)	3340	1720, 1680, 1670	1.3 (t, 3H, J = 7, CH_3), 4.3 (q, 2H, J = 7, CH_2), 6.6–6.7 (m, 1H, H-3$_{fur}$), 6.9 (d, 1H, J = 6.4, H-4$_{fur}$), 7.4, 7.7 (AB system, 2H, J = 15.8, CH=CH), 7.5–7.6, 7.9–8.0 (m, 6H, H_{arom} and H-5$_{fur}$), 7.8 (s, 1H, NH), 8.5 (s, 1H, H-4)
7e	89–91 (CH_2Cl_2/ *i*-Pr_2O)	$C_{20}H_{21}NO_5$ (355.4)	3320	1720, 1700, 1640	0.9 (t, 3H, J = 7, CH_3), 1.3 (t, 3H, J = 7, $OCH_2\underline{CH}_3$), 1.4–1.6 (m, 2H, $CH_2\underline{CH}_2CH_3$), 2.2–2.4 (m, 2H, $C\underline{H}_2CH$), 4.3 (q, 2H, J = 7, CH_2), 6.7–6.8 (m, 1H, $CH_2C\underline{H}$), 7.2 (d, 1H, J = 15.4, =CH), 7.5–7.6, 7.8–7.9 (m, 5H_{arom}), 8.4 (s, 1H, H-4), 9.6 (s, 1H, NH)

Appendix: ^{13}C NMR ($CDCl_3$)[d] δ, J (Hz): **3** = 14.8 (CH_3), 50.0 (d, J_{P-C} = 114.5, CH–P), 59.6 (CH_2), 91.8 (d, J_{C-P} = 9.0, C-5), 107.3 (C-3), 125.0 (d, J_{C-P} = 92.3, C_{arom}), 127.0–134.0 (C-4 and CH_{arom}), 135.0 (C_{arom}), 159.1 (C-6), 165.1 (CONH), 166.3 ($\underline{C}OOC_2H_5$), 168.7 (C-2). **5** = 14.1 (CH_3), 61.2 (CH_2), 70.7 (d, J_{C-P} = 115, C–P), 113.3 (C-3), 115.4 (d, J_{C-P} = 16.5, C-5), 120.7 ($\underline{C}$=CH), 123.0 (d, J_{C-P} = 90.0, C_{arom}), 125.6–138.0 (C-4, =CH and CH_{arom}), 127.2 (C_{arom}), 152.5 (C=N), 158.9 (C-6), 163.8 (CONH), 165.9 ($\underline{C}OOC_2H_5$), 168.8 (C-2), 179.6 (CO_{oxaz}).
^{31}P-NMR ($CDCl_3$)[d] δ: **3** = 14.7. **5** = 23.4
MS, (FD), m/z:[g] **3** = 561 (M^+), 547, 278, 277. **5** = 732 (M^+), 588, 471, 454, 447, 318, 279, 278.

[a] Measured with Büchi 510 capillary apparatus.
[b] Satisfactory microanalyses obtained: C ±0.35, H ±0.20, N ±0.28.
[c] Recorded on a PYE UNICAM SP 3-200S Philips Infrared spectrophotometer.
[d] Obtained on a Bruker AC 200 spectrometer.
[e] $CDCl_3$ for compounds **5** and **7**.
[f] Overlapped with ν_{OH}.
[g] Recorded on a Varian MAT 311-A spectrometer.

Compound **3** is a reactive synthetic intermediate for the preparation of the 6-vinyl substituted 2*H*-pyran-2-ones **7**. Reaction of **3** with aldehydes **6** in refluxing toluene gave good yields of **7** by straightforward Wittig reaction. Nevertheless **3** appeared to be inert with respect to ketones which gave only a trace of products. In the IR spectra compounds **7** show a clear 2*H*-pyran-2-one band at 1720–1730 cm^{-1}. The ^1H NMR spectra were characterized by an AB-pattern associated with the CH=CH group. The reaction is highly stereoselective and the coupling constant of about 15 Hz confirms the *E* configuration.

Ethyl 3-oxo-4-(triphenylphosphoranylidene)butyrate **(1)**[6] and 5(4*H*)-oxazolones **2a,b**[7] (mixture of *E* and *Z* stereoisomers) are known compounds.

Ethyl 3-Benzoylamino-2-oxo-6-triphenylphosphoranylidenemethyl-2*H*-pyran-5-carboxylate (3):
A solution of ylide **1** (17.0 g, 43.6 mmol) and **2a** (9.4 g, 43.4 mmol) in CH_2Cl_2 (240 mL) was kept at 25 °C for 12 h. After solvent evaporation the residue was crystallized, filtered and washed with acetone (10 mL) to give pure **3** (12.5 g, 51 %).

Ethyl 3-Benzoylamino-6-methyl-2-oxo-2*H*-pyran-5-carboxylate (4):
To a stirred mixture of **3** (1.0 g, 1.8 mmol) and zinc (0.2 g, 3.0 mmol) in EtOH (30 mL), 10 M HCl (10 mL) was added dropwise over 30 min. The reaction was kept at 25 °C for 3 h. After solvent evaporation the residue was taken up with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), evaporated and recrystallized to give pure **4** (380 mg, 63 %); mp 136–138 °C (CH_2Cl_2/*i*-Pr_2O) (Lit.[5] mp 135–138 °C).

Ethyl 3-Benzoylamino-6-[2-(4,5-dihydro-5-oxo-2-phenyl-4-oxazolylidene)-1-(triphenylphosphoranylidene)ethyl]-2-oxo-2*H*-pyran-5-carboxylate (5):
Method A: Ylide **1** (6.2 g, 15.9 mmol) and oxazolone **2b** (3.3 g, 15.9 mmol) were dissolved in CH_2Cl_2 (100 mL) and kept at 25 °C for 12 h. After solvent evaporation the crude mixture was chromatographed. The first fraction was eluted with AcOEt/benzene (1:4), and contained compound **5** (810 mg, 7 %) which was obtained after crystallization as red crystals. After elution with MeOH a second fraction containing **3** (1.7 g, 20 %) was isolated.

Method B: The same reaction was carried out starting from **1** and **2b** in a 2:1 ratio. Compounds **5** and **3** were obtained in 9 and 56 % yields, respectively.

Method C: Compound **2b** (830 mg, 4.0 mmol) and **3** (2.2 g, 4.0 mmol) were dissolved in DMF (10 mL) and reacted at 25 °C for 12 h. The solvent was evaporated and the crude mixture was chromatographed with hexane/AcOEt (3:2). After crystallization pure **5** (1.2 g, 42 %) was isolated.

Ethyl 3-Benzoylamino-2-oxo-6-vinyl-2*H*-pyran-5-carboxylates (7); General Procedure:
A suspension of ylide **3** (4.5 g, 8.0 mmol) and aldehyde (**6a**: 8.8 mmol; **6b–d**: 8.0 mmol) was stirred and refluxed in toluene (100 mL) for 8–24 h until the starting materials had disappeared. After cooling, the yellow solid was filtered to give pure **7**. The mother liquor, after elimination of the solvent, was recrystallized from CH_2Cl_2/*i*-Pr_2O to give a further amount of **7**. Total yield for **7a**:

96%; **7b**: 90%; **7c**: 90%; **7d**: 95%. In the case of **7e** the reaction was carried out without solvent using an excess of butanal (40 mmol, 3.6 mL). The mixture was refluxed for 24 h, then, after elimination of the excess aldehyde, chromatographed with hexane/AcOEt (1:4) to give **7e** (70%).

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