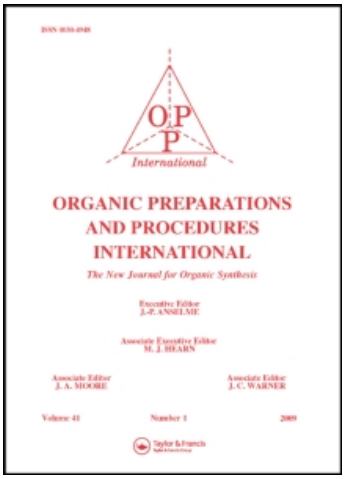

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A NEW APPROACH TO ALKYL 2-OXOQUINOLINE-3-ACETATES BY TRIPHENYLPHOSPHINE-INDUCED CYCLIZATION OF ALKYL *O*-FORMYLMALEANILATES

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1 H, OH). ^{13}C NMR ($CDCl_3$): δ 21.08, 27.52, 56.62, 98.94, 100.98, 101.71,116.0, 142.75, 156.10, 159.27, 167.13, 168.50, 171.19, 199.50. MS m/z (relative abundance): 262 (M^+, 32), 247 (14), 219 (6), 205 (100), 150 (8), 95 (11), 84 (6), 69 (25), 67 (5), 57 (9).

Anal. Calcd. for $C_{13}H_{10}O_6$: C, 59.54; H, 3.82. Found: C, 59.55; H, 3.56

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A NEW APPROACH TO ALKYL 2-OXOQUINOLINE-3-ACETATES BY TRIPHENYLPHOSPHINE-INDUCED CYCLIZATION OF ALKYL *o*-FORMYLMALEANILATES†

Submitted by (07/13/93)

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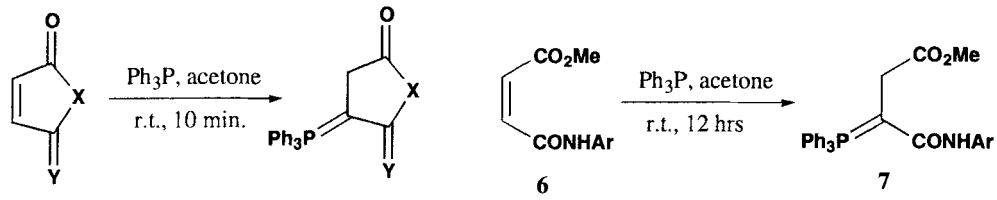
Suitably *ortho*-substituted maleanilic acids and their derivatives are useful for the synthesis of a variety of heterocyclic skeletons of structural[1] and biological interest.[2] We now report an application of alkyl *o*-formylmaleanilates (**9c-f**) for the synthesis of quinoline derivatives (**10c-f**). Maleic anhydride (**1**) reacts with triphenylphosphine (TPP) to generate triphenylphosphoranylidene succinic anhydride (**4**),[3] while maleimides (**2**) and isomaleimides (**3**) yield triphenylphosphoranylidene succinimides (**5**).[3] These phosphoranes have been used for syntheses of butenolides,[4] furans,[5] intermediates

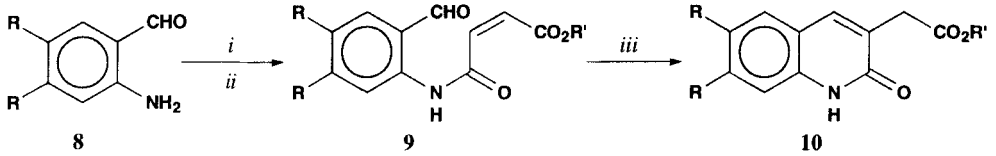


1, X = Y = O
2, X = NAr, Y = O
3, X = O, Y = NAr

4, X = Y = O
5, X = NAr, Y = O

6 7

to lysergic acid[6] and showdomycin.[7] The observation that alkyl maleanilates (**6**) on treatment with equimolar amounts of TPP in acetone at room temperature yielded triphenylphosphoranylidene succinanilates (**7**)[8] exclusively (activation by CO_2R prevailing over that of CONHAr) has led to a new and facile synthesis of 2-oxoquinolines (**10**). Esterification of *o*-formylmaleanilic acids (**9a**, **9b**) obtained from *o*-aminobenzaldehydes (**8a**,[9a] **8b**[9]) and maleic anhydride furnished the respective formyl esters (**9c-f**) in 70-75% yields. The behavior of these esters in their reaction with TPP was different from that of the simple maleanilic esters. The *o*-formyl esters failed to give the expected phosphorane **7** (Ar = *o*-$OHCC_6H_4$-) when mixed with TPP in acetone at RT; only the starting material was recovered. When repeated in refluxing ethanol, the reaction led directly to quinoline derivatives (**10c-f**) whose



8 **9** **10**

a) R = H
b) R = OMe

a) R = R' = H
b) R = OMe, R' = H
c) R = H, R' = Me
d) R = H, R' = Et
e) R = OMe, R' = Me
f) R = OMe, R' = Et

i) Maleic anhydride, Et_2O, r.t., 10 min. *ii*) R'OH, HCl gas, r.t., 30 min. *iii*) Ph_3P, EtOH, reflux, 4 hrs

structures were established on the basis of their analytical and spectral data (Table 1). None of the phosphorane intermediates could be isolated. Easy routes available for diverse substitutions in *o*-aminobenzaldehydes should make our approach to substituted quinolines attractive.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded as nujol mulls on a Perkin-Elmer R-37 spectrometer; ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on WH-90FT spectrometer using TMS as an internal standard (chemical shifts in δ ppm). Mass spectrum for **10e** (m/e for M^+ : 277, 50%) was recorded on a CEC-2-110B double focussing mass spectrometer at 70eV. Satisfactory neutralization equivalents were obtained for **9a** (calc. 219; obs. 215) and **9b** (calc.279; obs.276).

***o*-Formylmaleanilic Acid (9a).-** An equimolar mixture of powdered maleic anhydride (0.980 g; 0.01 mol) and *o*-aminobenzaldehyde (1.21 g; 0.01 mol) was stirred in anhydrous ether (15 ml) for 15 min.

The reaction mixture was kept at room temperature for an additional 5 min. The solid was collected, washed with ether and recrystallized from ethanol. Compound **9b** was prepared similarly using **8b** and maleic anhydride.

Table 1. Analytical and Spectral Data of **9a-f** and of **10c-f**

Cmpd.	mp. (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	Elemental Analyses (Found) C	H	N
9a	170-171	90	3400 1700 1685	— — —	60.27 (60.35)	4.10 (3.79)	6.39 (6.43)
9b	192-193	90	3420 1710 1700	— — —	55.91 (55.71)	4.66 (4.48)	5.02 (4.94)|
9c	110-111	75	3240 1725 1700 1670	3.83 (s, 3H), 6.90 (d, 1H, J = 10Hz), 7.16 (d, 1H, J = 10Hz), 7.32 (dd, 1H, J = 2, 8Hz), 7.67 (dt, 2H, J = 2, 8Hz), 9.97 (s, 1H), 11.56 (s, 1H, exch)	61.80 (61.77)	4.72 (4.77)	6.00 (5.89)
9d	75-77	70	3250 1730 1700 1670	1.30 (t, 3H, J = 7Hz), 4.30 (q, 2H, J = 7Hz), 6.80 (d, 1H, J = 13Hz), 7.15 (d, 1H, J = 13Hz), 7.47 (dd, 1H, J = 2, 8Hz), 7.77 (dt, 2H, J = 2,7Hz), 8.77 (dd, 1H, J = 2, 8Hz), 9.95 (s, 1H), 11.47 (s, 1H, exch.)	63.16 (63.24)	5.26 (5.15)	5.66 (5.51)
9e	180-181	70	3200 1730 1700 1600	3.82 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 6.84 (d, 1H, J = 10Hz), 7.04 (s, 1H), 7.13 (d, 1H, J = 10Hz), 8.51 (s, 1H), 9.75 (s, 1H), 11.71 (s, 1H, exch.)	57.33 (57.24)	5.12 (5.42)	4.78 (4.73)
9f	175-177	75	3200 1730 1715 1680	1.30 (t, 3H, J = 7Hz), 3.83 (s, 3H), 3.87 (s, 3H), 4.23 (q, 2H, J = 7Hz), 6.67 (d, 1H, J = 12.5Hz), 7.2 (d, 1H, J = 12.5Hz), 7.40 (s, 1H), 7.73 (s, 1H), 9.90 (s, 1H), 11.10 (s, 1H, exch.)	58.63 (58.44)	5.53 (5.42)	4.56 (4.69)
10c	231-233	60	3300 1730 1670	3.60 (s,2H), 3.71 (s, 3H), 7.73 (m, 4H), 7.80 (s, 1H), 11.47 (s, 1H, exch.)	66.36 (66.56)	5.07 (4.98)	6.45 (6.32)

Table 1. (cont'd)

Cmpd.	mp. (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	Elemental Analyses (Found) C	H	N
10d	186-188	60	3300 1730 1670	1.25 (t, 3H, J = 7Hz), 3.57 (s, 2H), 4.13 (q, 2H, J = 7Hz), 6.93-7.63 (m, 4H), 7.70 (s, 1H), 11.73 (s, 1H, exch.)	67.53 (67.84)	5.63 (5.29)	6.06 (5.94)
10e	258-260	65	3300 1735 1670	3.49 (s, 2H), 3.60 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 6.84 (s, 1H), 7.13 (s, 1H), 7.71 (s, 1H), 11.60 (s, 1H, exch.)	60.64 (60.65)	5.41 (5.36)	5.05 (5.15)
10f	225-226	60	3300 1730 1670	1.20 (t, 3H, J = 7Hz), 3.53 (s, 2H), 3.83 (s, 6H), 4.07 (q, 2H, J = 7Hz), 6.83 (s, 1H), 7.13 (s, 1H) 7.40 (s, 1H), 11.13 (s, 1H, exch.)	61.85 (61.58)	5.84 (5.63)	4.81 (4.63)

The esterification of the above acids was performed by passing a stream of HCl into a solution of the compound in excess (10 fold) of MeOH or EtOH for 30 minutes at room temperature.

Methyl 2-Oxoquinoline-3-acetates (10c-f).- A mixture of methyl *o*-formylmaleanilate (**9c,** 0.865g, 0.005 mol) and TPP (1.44 g, 0.0055 mol) was refluxed in EtOH for 4 hrs and allowed to cool to room temperature. The separated solid **10c** was filtered off, washed with ethanol and recrystallized from AcOH. Similarly, **10d, 10e** and **10f** were prepared by using the appropriate *o*-formylmaleanilates and TPP.

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EFFICIENT REGIOSELECTIVE ALKYLATION OF 2-CARBOXAMIDOPIPERAZINE. APPLICATION TO THE SYNTHESIS OF THE NMDA COMPETITIVE ANTAGONIST (±)-CPP

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The search for selective competitive antagonists at the NMDA-subtype of the excitatory amino acid (EAA) receptors has lead in the recent past to the synthesis of several compounds having therapeutic potential as antiexcitotoxins.[1] Among the new compounds so far introduced 2-carboxy-4-(3-phosphonopropyl)piperazine (CPP; **4**) is one of the most frequently employed tools for biochemical and behavioral studies.[2-4] Very recently, a synthesis of CPP[5] overcame some of the problems of selectivity which had emerged in the first procedures.[6] Furthermore, new NMDA-antagonists have been presented which bear a tetrazole group linked through an alkyl chain to the N-4 piperazine nitrogen.[7]

Compounds **2a-d** (Scheme) were suitable intermediates for the synthesis of the NMDA-antagonists and were obtained in low yields (28-37%)[8] from the corresponding ω-bromoalkanenitrile and 2-carboxamidopiperazine. Under suitable experimental conditions (e. g. DMF, K_2CO_3, 50°, 3 hrs), the N-4 alkylation is nearly regiospecific[9] and can be accomplished in good yields (50-67%). This observation seems to be of general value in the N-4 alkylations of 2-carboxamidopiperazine.