SYNTHESIS OF 2,3-DISUBSTITUTED 4-OXOQUINOLINES AND 3-SUBSTITUTED FUSED 4-OXOQUINOLINES

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Abstract- Seven 2,3-disubstituted 4-oxoquinolines were prepared *via* two methods. In the first one 2,3-disubstituted 4-oxoquinolines were prepared *via* the condensation of 2-amino-α-cyanoacetophenone with substituted phthalic anhydrides, while in the second method the fused isoindolo[2,1-*a*]quinolines and pyrrolo[1,2-*a*]quinolines were first prepared and then converted to 4-oxoquinolines. X-Ray crystal structure analysis of ethyl 2-[3-cyano-4-oxo-2-quinolyl]benzoate is reported.

INTRODUCTION

Due to the biological importance of some of the quinoline derivatives,[1] in particular, the 4-oxoquinoline-3-carboxylic acid (known as quinolones), a large number of these derivatives have been prepared and tested for their antibacterial activity.[2,3]

In continuation of our interest in these kind of compounds,[4] we report here the preparation of 2,3-disubstituted 4-oxoquinolines as well as 6-substituted isoindolo[2,1-*a*]quinoline-5,11-dione and 4-substituted pyrrolo[1,2-*a*]quinoline-1,5-dione.

RESULTS AND DISCUSSION

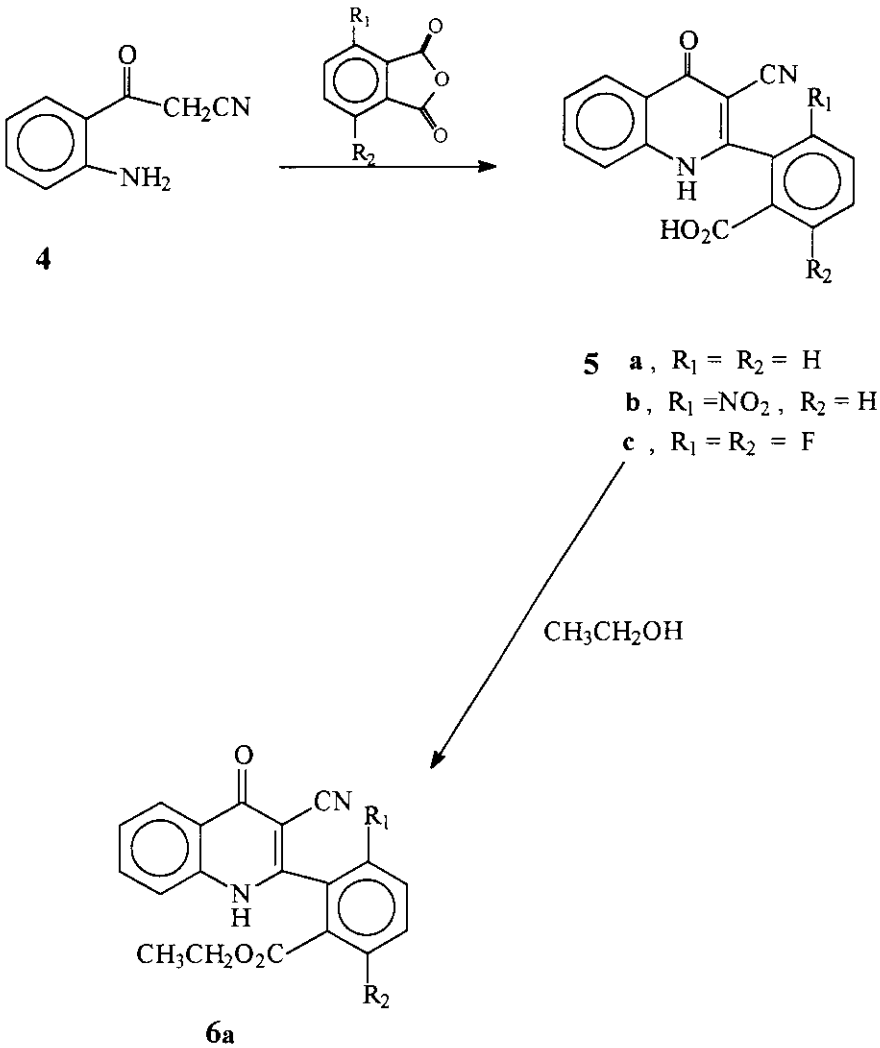
The first part of this study is directed toward the synthesis of 2,3-disubstituted 4-oxoquinolines. 2-Amino-α-cyanoacetophenone (**4**) [which was prepared in four steps from 2-aminoacetophenone, see

Experimental] reacted with phthalic, 3-nitrophthalic and 3,6-difluorophthalic anhydrides under basic conditions to give the 2,3-disubstituted 4-oxoquinolines (**5a, 5b** and **5c**) respectively (Scheme 1) . These compounds isolated in the cases of compounds (**5a**) and (**5b**) as the triethylammonium salts show in their IR spectra wide absorbance in the region 3250-2450 cm^{-1} in addition to two carbonyl group absorbances at 1626 and 1560 cm^{-1}. It should be mentioned here that although the reaction of compound (**4**) with 3-nitrophthalic anhydride could produce two isomers [compound (**5b**) and its isomer where R_1 = H, and R_2 = NO_2] only one isomer was obtained which was identified as **5b**. The structure of **5b** was determined based upon the following two observations. First, there are two resonance signals at δ 7.9 and 8.1 in the ^1H NMR spectrum of compound (**5b**) which were assigned to the protons ortho to the carboxyl and nitro groups, respectively. In the other possible isomer there will be no ortho proton to the carboxyl group and the signal at δ 7.9 will shift upfield. Second, we have previously observed from an earlier work that when 3-nitrophthalic anhydride is involved in similar cyclizations, the carbonyl group which takes part in the formation of the newly formed six membered ring is the one adjacent to the nitro group,[5] which in the present case will lead to the formation of **5b**.

As a proof of the proposed structures of the latter compounds, compound (**5a**) was treated with ethanol to give the ester derivative (**6a**). The IR spectrum of compound (**6a**) shows absorbances for two carbonyl groups at 1711 cm^{-1} (ester) and 1630 cm^{-1} (ketone),[6] while the ^{13}C NMR spectrum shows a noticeable upfield shift in the resonance signal of position (3) when compared with the unsubstituted ring system. In the unsubstituted ring system position (3) appears at δ 106.7[7] while in compound (**6a**) this position appears at δ 95.05. The structure of the latter compound was unequivocally confirmed by X-Ray single crystal diffraction study (see later in the text).

Further analogs of compound (**6a**) were prepared using another approach. Isoindolo[2,1-*a*]quinoline derivatives were first prepared followed by the treatment with sodium ethoxide to give the desired compounds (Scheme 2). The starting material (**7**) was prepared in two steps from 2-aminoacetophenone.[4] The treatment of this compound with BuLi in DMF afforded compound (**8**). The MS spectrum of this compound shows the molecular ion at m/z 325 (100%) with an M+2 peak at 327(94%). The loss of CO and bromide radical represent the main fragmentation pathway.[8,9] Treatment of compound (**8**) with sodium ethoxide gave the ester (**10**). On the other hand, when compound (**7**) was treated with sodium azide, the azido derivative (**9**) was obtained as the sole product. The MS spectrum of compound (**9**) shows the molecular ion at m/z 288 (4%) with the loss of N_2 representing a major fragment at m/z 260 (97%). Although the azido analog of **7** (where N_3 is in place of Br) was not isolated,[10] it is nevertheless a logical

Scheme 1



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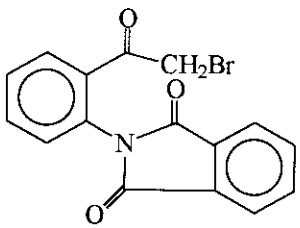
5 **a**, $R_1 = R_2 = H$
b, $R_1 = NO_2$, $R_2 = H$
c, $R_1 = R_2 = F$

6a

Scheme 2



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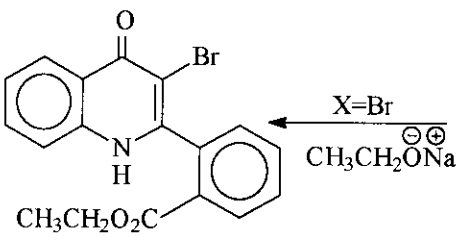
A



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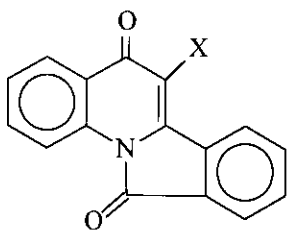
X=Br

$CH_3CH_2\overset{\ominus}{O}\overset{\oplus}{Na}$

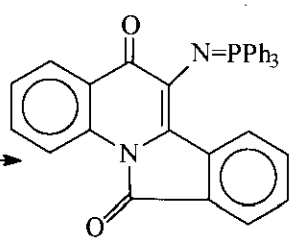


$A = n\text{-}C_4H_9Li$; X= Br, **8**

$= NaN_3$; X= N_3 , **9**

X= N_3

Ph_3P



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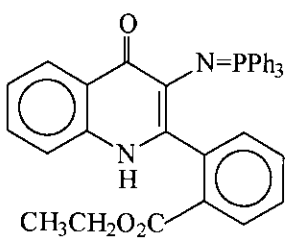
$CH_3CH_2\overset{\ominus}{O}\overset{\oplus}{Na}$



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intermediate between compounds (**7**) and (**9**). It was observed that neither the unbrominated analog of **7** [*N*-(2-acetylphenyl)phthalimide] nor compound (**8**) reacted with sodium azide under the same conditions used for the transformation of **7** to **9** . The involvement of the azide ion in this cyclization was investigated. The reaction of compound (**7**) with sodium azide was conducted under different molar ratios of the azide. 5, 2 and 1 equivalents of sodium azide were used. If the azide ion is playing the role of a nucleophile and a base in the same time then at least two equivalents of this reagent will be necessary to complete the reaction. It was found, however, that the yield was not affected by the change in the molar ratio of sodium azide.

The treatment of compound (**9**) with triphenylphosphine afforded the iminophosphorane (**11**). The CI MS spectrum of compound (**11**) shows the molecular ion at m/z 522 (58%) with an M+1 peak at m/z 523 (23%). This iminophosphorane compound is stable enough that it did not react with acetone or benzaldehyde under conditions suitable for the aza-Wittig reaction. It was, however, converted to the 2,3-disubstituted 4-quinolone (**12**) when treated with sodium ethoxide.

Finally, another derivative of 2,3-disubstituted 4-quinolone was prepared using the approach outlined in Scheme 3. Compound (**13**) was prepared from *N*-[2-acetylphenyl]pyrrolidine-2,5-dione using the procedure previously described.[4] The treatment of compound (**13**) with sodium azide afforded the fused 4-quinolone derivative (**14**). This latter compound did not show a molecular ion in its MS spectrum, instead the loss of N_2 represents a major fragment at m/z 212 (71%). The treatment of compound (**14**) with triphenylphosphine resulted in the formation of compound (**15**) which when treated with sodium ethoxide gave the 2,3-disubstituted 4-quinolone (**16**).

X-Ray Crystal-Structure Determination of Compound (6a).

Single crystals suitable for X-Ray structural analysis were grown by slow evaporation from ethanol solution. The structure was solved by direct methods using SHELXS86[11] and refined by full-matrix least-squares technique using SHELXL93.[12] The non-H-atoms were refined with anisotropic temperature factors and the H-atoms with individual isotropic temperature factors. Details of crystal data, intensity data collection parameters and structure refinement results are summarized in Table 1. A view of the molecule is shown in Figure 1. The atomic coordinates of non-Hydrogen atoms are listed in Table 2 while selected bond lengths and angles are given in Table 3. The quinoline ring N(1), C(1) through C(9) is essentially planar, the maximum deviations from the quinoline least-square plane (l.s.p.) are 0.024(2) and -0.012(2) Å for C(8) and C(7) respectively. The C(10), N(2), O(1) and H(1) atoms are displaced out of the quinoline plane by 0.044(4), 0.046(5), -0.063(3) and -0.12(3) Å respectively. The l.s.p. of the phenyl ring of the ethyl benzoate moiety makes an angle of 75.27(7)° with the quinoline plane while it makes an angle of

Scheme 3

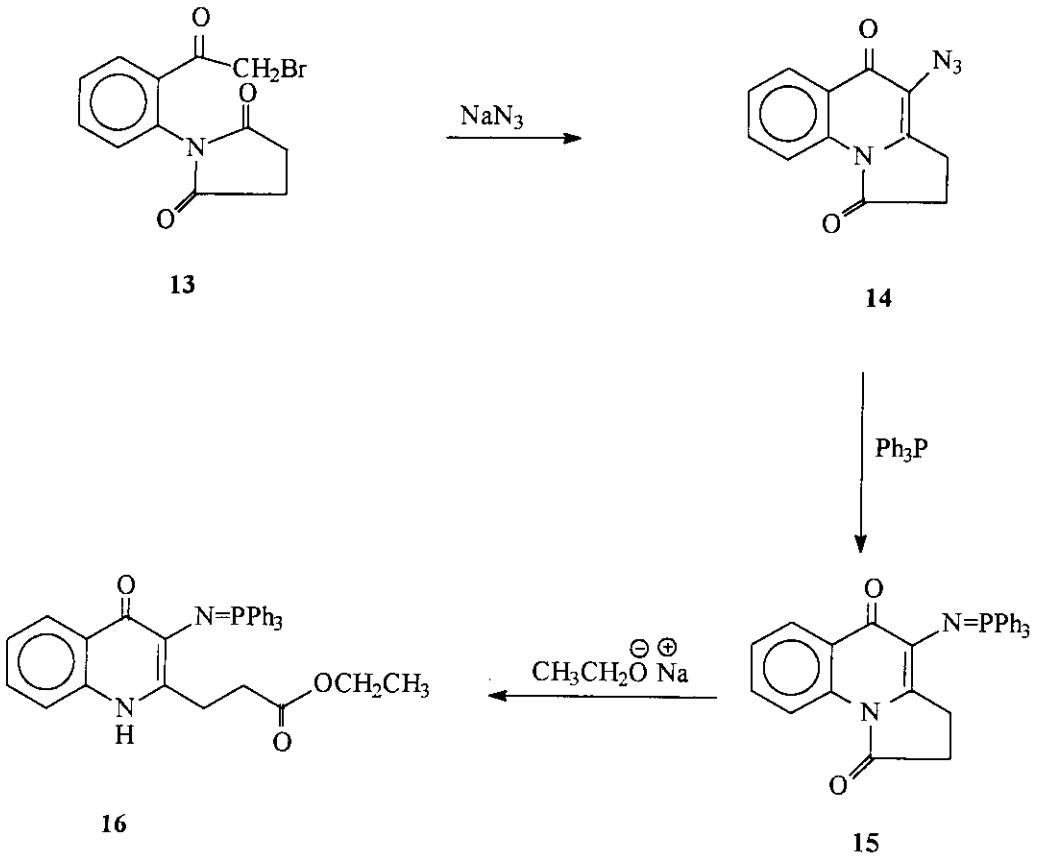

Figure 1. Prespective view of compound (**6a**). Displacement elliposides are drawn at the 50% probability level

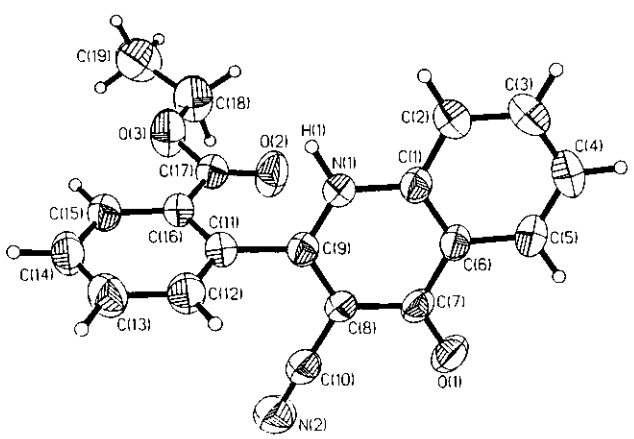

Table 1. Crystal Data, Intensity Measurement and Structuer Refinement for compound **(6a)**

Empirical formula	$C_{19}H_{14}N_2O_3$	$F(000)$	664
Formula weight	318.32	Diffractometer/scan	Siemens P4/ω
Color, habit	colorless, tabular	Radiation: graphite monochromater	Mo$K\alpha$ (λ = 0.71073Å)
Crystal dimentions [mm]	0.10 x 0.30 x 0.60	Decay of standard reflections	1.3%
Crystal system	monoclinic	2θ range [°]	$2 \leq 2\theta \leq 45$
Space group	$P2_1/c$	Independent reflections	2191
Cell constants: from 27 reflections	$19.67 \leq 2\theta° \leq 24.44$	Observed reflections $[F_o > 4\ \sigma(F_o)]$	1379
a [Å]	15.454(2)	Parameters varied	274
b [Å]	8.754(1)	Refinement on	F^2
c [Å]	12.546(3)	Reflections used in refinement	2190
β [°]	99.40(1)	$R = \Sigma \mid\mid F_o \mid - \mid F_c \mid\mid / \Sigma \mid F_o \mid$	0.046
V [Å^3]	1674.5(5)	Extinction coefficient	0.005(1)
Z	4	GOF	1.036
D_{calc} [Mg m^{-3}]	1.263	Final maximum Δ/σ	0.0004
μ_{calc} [mm^{-1}]	0.087	Max., min. residual electron [e$^-$Å^{-3}]	0.28, -0.17

Table 2. Fractional atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for compound (**6a**).

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$$

atom	x	y	z	U_{eq}
O(1)	1999(1)	1000(3)	559(2)	59(1)
O(2)	2191(2)	-116(3)	4511(2)	70(1)
O(3)	2875(1)	-549(3)	6192(2)	72(1)
N(2)	4101(2)	-75(4)	1900(2)	76(1)
N(1)	2116(2)	3004(3)	3521(2)	46(1)
C(1)	1368(2)	3225(3)	2750(2)	44(1)
C(2)	685(2)	4129(4)	3023(3)	59(1)
C(3)	-49(3)	4345(5)	2255(3)	72(1)
C(4)	-118(3)	3719(5)	1227(4)	75(1)
C(5)	553(2)	2839(4)	963(3)	60(1)
C(6)	1315(2)	2577(3)	1724(2)	45(1)
C(7)	2039(2)	1649(4)	1461(2)	45(1)
C(8)	2784(2)	1520(3)	2307(2)	42(1)
C(9)	2796(2)	2155(3)	3318(2)	42(1)
C(10)	3521(2)	641(4)	2084(2)	52(1)
C(11)	3569(2)	2023(3)	4205(2)	44(1)
C(12)	4308(2)	2887(4)	4110(3)	57(1)
C(13)	5043(2)	2845(4)	4907(3)	63(1)
C(14)	5044(2)	1932(4)	5799(3)	58(1)
C(15)	4323(2)	1055(4)	5904(3)	49(1)
C(16)	3574(2)	1086(3)	5116(2)	42(1)
C(17)	2812(2)	87(4)	5209(3)	48(1)
C(18)	2177(3)	-1627(5)	6376(4)	79(1)
C(19)	2381(4)	-2101(6)	7536(4)	89(1)

Table 3. Selected bond lengths (Å) and bond angles (°) for compound (**6a**).

O(1)-C(7)	1.259(3)	C(6)-C(7)	1.463(4)
O(2)-C(17)	1.202(3)	C(7)-C(8)	1.438(4)
O(3)-C(17)	1.342(3)	C(8)-C(9)	1.382(4)
O(3)-C(18)	1.479(4)	C(8)-C(10)	1.438(4)
N(1)-C(9)	1.345(4)	C(9)-C(11)	1.498(4)
N(1)-C(1)	1.395(4)	C(11)-C(12)	1.392(4)
N(1)-H(1)	0.95(3)	C(11)-C(16)	1.405(4)
N(2)-C(10)	1.148(4)	C(12)-C(13)	1.386(5)
C(1)-C(2)	1.405(4)	C(13)-C(14)	1.374(5)
C(1)-C(6)	1.397(4)	C(14)-C(15)	1.376(4)
C(2)-C(3)	1.376(5)	C(15)-C(16)	1.395(4)
C(3)-C(4)	1.389(5)	C(16)-C(17)	1.488(4)
C(4)-C(5)	1.376(5)	C(18)-C(19)	1.496(6)
C(5)-C(6)	1.408(4)	H(1)···O(1)^{i}	1.79(3)
C(9)-N(1)-C(1)	122.0(3)	C(8)-C(9)-N(1)	120.2(3)
C(9)-N(1)-H(1)	119(2)	N(1)-C(9)-C(11)	117.0(3)
C(1)-N(1)-H(1)	118(2)	C(8)-C(9)-C(11)	122.7(3)
N(1)-C(1)-C(6)	120.0(3)	N(2)-C(10)-C(8)	179.0(4)
N(1)-C(1)-C(2)	118.7(3)	C(9)-C(11)-C(12)	117.4(3)
C(6)-C(1)-C(2)	121.4(3)	C(9)-C(11)-C(16)	123.2(3)
C(1)-C(2)-C(3)	118.2(4)	C(16)-C(11)-C(12)	119.4(3)
C(2)-C(3)-C(4)	121.7(4)	C(11)-C(12)-C(13)	120.7(3)
C(3)-C(4)-C(5)	119.9(4)	C(12)-C(13)-C(14)	119.6(4)
C(4)-C(5)-C(6)	120.5(4)	C(13)-C(14)-C(15)	120.6(3)
C(5)-C(6)-C(1)	118.4(3)	C(14)-C(15)-C(16)	120.8(3)
C(1)-C(6)-C(7)	120.1(3)	C(15)-C(16)-C(11)	118.8(3)
C(5)-C(6)-C(7)	121.5(3)	C(11)-C(16)-C(17)	120.5(3)
C(6)-C(7)-C(8)	115.3(3)	C(15)-C(16)-C(17)	120.6(3)
C(6)-C(7)-O(1)	121.7(3)	O(2)-C(17)-O(3)	122.6(3)
O(1)-C(7)-C(8)	123.0(3)	O(2)-C(17)-C(16)	125.3(3)
C(7)-C(8)-C(9)	122.3(3)	O(3)-C(17)-C(16)	112.2(3)
C(7)-C(8)-C(10)	117.5(3)	C(17)-O(3)-C(18)	117.6(3)
C(9)-C(8)-C(10)	120.1(3)	O(3)-C(18)-C(19)	106.6(4)
N(1)-H(1)···O(1)^{i}	176(3)		

Symmetry code: *i*) x, -y+1/2, z+1/2

11.0(3)^{o} with the l.s.p. of the ester moiety. A point worth mentioning here is that although the 4-quinolone system clearly exist in the keto form, the bond length of the carbonyl group C(7)-0(1), 1.259(3) Å, is elongated due to the expected resonance with the quinoline nitrogen in addition to an intermolecular H-bonding with H1; H(1)....O(1)^{i} 1.79(3) Å and the N(1)-H(1)....0(1)^{i} 176(3)^{o}. There is no intramolecular hydrogen bonding between O(2) and H(1) ; C(17)-O(2) 1.202(3) Å and O(2)....H(1) 3.05(3) Å which comes as a result of the benzoate moiety being rotated from the plane of the quinoline ring.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer as KBr pellets. NMR spectra were recorded on a Jeol FX-100 (100 MHz) and EX-400 (400 MHz) with TMS as internal standard in the indicated solvents and reported in the δ (ppm) values. The MS spectra were recorded on a Fisons Trio-1 VG masslab with methane as the carrier gas in the CI technique. Microanalysis was performed at KACST research laboratories.

N-[2-(Bromoacetyl)phenyl]acetamide (2)

To a refluxing suspension of $CuBr_2$ (10.0 g, 44.74 mmol) in ethyl acetate (50 mL) was added dropwise a solution of *N* -[2-acetylphenyl]acetamide (**1**)[4] (3.90 g, 22.25 mmol) in chloroform (50 mL). Reflux was continued for 8 h (or until a white precipitate was formed). The solvent was evaporated and the remaining solid was boiled in 100 mL of a 1:1 mixture of ethanol and chloroform and filtered off while hot. The filtrate was left to cool down and the resulting solid was collected. 68% yield (3.8 g), white solid, mp 129 ^{o}C (ethanol and chloroform). ^{1}H NMR (100 MHz, $CDCl_3$): 2.25 (s, 3H), 4.5 (s, 2H). 7.2 (m, 1H) 7.6 (m, 2H), 8.8 (d, J = 7.8 Hz, 1 H), 11.0 (br s, 1H). Anal. Calcd for $C_{10}H_{10}NO_2Br$: C, 46.90; H, 3.94; N, 5.47. Found: C, 46.62; H, 3.82; N, 5.18.

2-Amino-α-bromoacetophenone (3)

To a solution of compound (**2**) (0.5 g, 1.95 mmol) in ethanol (50 mL) was added 4 mL of concd HCl and the mixture was heated at 80 ^{o}C for 2 h. The solution was neutralized with 2N NaOH followed by extraction with chloroform (3x50 mL). The organic layer was dried over anhydrous magnesium sulfate and then evaporated under vacuum. The resulting solid was collected and recrystallized from ethanol. 55% yield (0.23 g), white solid, mp 107 ^{o}C. IR: (ν, cm^{-1}) 3400, 3300, 1640, 1590, 1570, 1450. ^{1}H NMR (100 MHz, DMSO-d_6): 3.5 (br s, 2H), 5.0 (s, 2H), 6.5 (m, 1H), 6.7 (d , J=8.5 Hz, 1H), 7.2 (m, 1H), 7.6 (dd, J=8.2, 1.4 Hz, 1H). ^{13}C NMR: 47.4, 114.0, 114.4, 117.0, 131.5, 134.7, 151.5, 192.3. Anal. Calcd for C_8H_8NOBr: C, 44.89; H, 3.77; N, 6.44. Found: C, 44.71; H, 3.61; N, 6.56.

2-Amino-α-cyanoacetophenone (4)

To a suspension of potassium cyanide (1.30 g, 19.97 mmol) in DMF (20 mL) was addded dropwise a solution of compound (**3**) (0.86 g, 4.01 mmol) in DMF (20 mL). After stirring for 2 h at rt, the mixture was poured into a saturated solution of ammonium chloride and then extracted with chloroform (3x50 mL). The organic layer was dried over anhydrous magnesium sulfate and then evaporated to dryness. The resulting solid was collected and recrystallized from ethanol. 52% yield (0.33 g), white solid, mp 90 °C. IR: (ν, cm^{-1}), 3434, 3324, 2242, 1651, 1619, 1550, 1486. ^{1}H NMR (100 MHz, $CDCl_3$): 4.1 (s, 2H), 5.9 (br s, 2H), 6.7 (m, 2H), 7.4 (m, 2H), ^{13}C NMR: 39.0, 114.4, 115.0, 117.7, 134.4, 135.7, 151.4, 188.2. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.73; H, 4.83; N, 17.26.

2-[3-Cyano-4-oxo-1*H*-2-quinolyl]benzoic acid triethylammonium salt (5a)

A solution of compound (**4**) (1.0 g, 6.25 mmol), phthalic anhydride (1.10 g, 7.43 mmol) and 1 mL (7.17 mmol) of triethylamine in xylene (150 mL) was refluxed at 130 °C for 4 h. After evaporation of the solvent under vacuum, the resulting solid was recrystallized from acetonitrile. 48% yield (1.1 g) white solid, mp 272 °C. IR: (ν, cm^{-1}) 3250-2450, 2220, 1699, 1626, 1560. ^{1}H NMR (400 MHz, DMSO-d_6): 1.05 (t, J=7.3 Hz, 9H), 2.85 (q, J=7.3 Hz, 6H), 7.5 (br dt, 1H), 7.6 (m, 2H), 7.7 (m, 2H), 7.75 (dt, J=8.8, 1.1 Hz, 1H), 8.05 (dd, J=6.8, 1.0 Hz, 1H), 8.15 (dd, J=6.8, 1.0 Hz, 1H). ^{13}C NMR: 8.65, 45.2, 88.8, 116.75, 119.3, 124.1, 124.8, 125.1, 128.5, 129.8, 130.5, 133.05, 140.95, 168.9, 191.65. Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.58; H, 6.4; N, 10.73. Found: C, 71.02; H, 6.05; N, 10.35.

2-[3-Cyano-4-oxo-1*H*-2-quinolyl]-3-nitrobenzoic acid triethylammonium salt (5b)

This compound was obtained analogously from compound (**4**) and 3-nitrophthalic anhydride. 40% yield, white solid, mp 195 °C (acetonitrile). ^{1}H NMR (100 MHz, DMSO-d_6): 1.1 (t, J = 7.1 Hz, 9H), 3.0 (q, J=7.1 Hz, 6H), 7.75 (m, 5H), 7.9 (m, 1H), 8.1 (d, J=7.5 Hz, 1H). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.29; H, 5.54; N, 12.83. Found: C, 63.61; H, 5.38; N, 12.64.

2-[3-Cyano-4-oxo-1*H*-2-quinolyl]-3,6-difluorobenzoic acid (5c)

This compound was obtained analogously from compound (**4**) and 3,6-difluorophthalic anhydride. 32% yield, white solid, mp 288 °C (acetonitrile). ^{1}H NMR (100 MHz, DMSO-d_6): 7.4 (m, 3H), 7.8 (m, 2H), 8.15 (d, J=7.69 Hz, 1H), 12.2 (br s, 1H). Anal. Calcd for $C_{17}H_8N_2O_3F_2$: C, 62.58; H, 2.47; N, 8.58. Found: C, 62.82; H, 2.29; N, 8.35.

Ethyl 2-[3-cyano-4-oxo-1*H*-2-quinolyl]benzoate (6a)

A solution of compound (**5a**) (0.50 g, 1.28 mmol) in absolute ethanol (50 mL) was refluxed (with or without drops of concd HCl) for 3 h. The solvent was evaporated and the resulting solid was recrystallized

from ethanol. 86% yield (0.35 g), white solid, mp 275 °C. IR: (ν, cm^{-1}), 3290, 3037, 2230, 1711, 1630, 1550. ^1H NMR (100 MHz, DMSO-d_6) : 1.05 (t, J=7.4 Hz, 3H), 4.15 (q, J=7.4 Hz, 2H), 7.6 (m, 6H), 8.2 (m, 2H). ^{13}C NMR: 13.75, 61.4, 95.05, 116.1, 119.1, 124.5, 125.3, 129.7, 130.3, 130.9, 132.6, 133.1, 133.3, 139.1, 157.8, 164.95, 175.4. MS (CI): m/z (%) 319.17 (M+1, 6.7), 273(55), 272(100), 246(6), 244(82), 216(20), 215(40),188(20), 76(10). Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.68; H, 4.43; N, 8.79. Found: C, 71.46; H, 4.44; N, 8.67.

***N*-[2-(Bromoacetyl)phenyl]phthalimide (7)**

This compound was prepared from *N*-[2-acetylphenyl]phthalimide in a procedure similar to that described for compound (**2**). 82% yield, white solid, mp 194°C (lit., 192°C).[4]

6-Bromo-5*H*,11*H*-isoindolo[2,1-*a*]quinoline-5,11-dione (8)

To a stirred solution of compound (**7**) (1.0 g, 2.90 mmol) in DMF (20 mL), n-BuLi (3.60 mmol of 1.6 M in hexane) was added dropwise at rt. The mixture was then heated at 80 °C for 3 h and then at 125 °C for another 3 h. The resulting solid was collected and recrystallized from ethanol and chloroform to give 0.68 g of compound (**8**) (72% yield), mp 226 °C. IR: (ν, cm^{-1}) 1751, 1656, 1612, 1480, 1380. ^1H NMR (100 MHz, $CDCl_3$): 7.4 (t, J=8.1 Hz, 1H), 7.6-7.9 (m, 4H), 8.3 (dd, J=8.1, 1.0 Hz, 1H), 8.8 (br dd, 1H), 9.1 (dd, J=8.1, 1.0 Hz, 1H). ^{13}C NMR: 102.85, 117.8, 122.6, 124.95, 125.5, 126.1, 126.5, 127.55, 132.45, 134.7, 146.85, 152.0, 171.5. MS (EI): m/z (%) 327 (M+2, 94), 325(M^+, 100), 299(37), 297 (36), 246(23), 218(19), 190(98). Anal. Calcd for $C_{16}H_8NO_2Br$: C, 59.00; H, 2.50; N, 4.30. Found: C, 59.03; H, 2.45; N, 4.14.

6-Azido-5*H*,11*H*-isoindolo[2,1-*a*]quinoline-5,11-dione (9)

A mixture of compound (**7**) (1.0 g, 2.90 mmol) and sodium azide (0.28 g, 4.30 mmol) in acetone (50 mL) and water (50 mL) was refluxed for 6 h. The resulting solid was collected and recrystallized from ethanol and chloroform (this experiment could be carried out in DMF (50 mL), but work up with ammonium chloride and extraction is necessary). 76% yield (0.64 g), white solid, mp 126 °C. IR: (ν, cm^{-1}) 2125, 1743, 1631, 1483, 1412, 1313. ^1H NMR (100 MHz, $CDCl_3$): 7.4-7.9 (m, 5H), 8.2 (m, 2H), 9.1 (d, J=8.2 Hz, 1H). ^{13}C NMR: 110.9, 117.65, 122.4, 125.1, 125.6, 125.9, 126.55, 130.25, 131.3, 134.65, 145.2, 149.2, 175.4, 178.6. MS (EI): m/z (%) 288(M^+, 4), 260(97), 234(24), 204(98), 177(100), 102(91), 76(94). Anal. Calcd for $C_{16}H_8N_4O_2$: C, 66.67; H, 2.80; N, 19.44. Found: C, 67.05; H, 2.92; N, 19.18.

Ethyl 2-[(3-Bromo-4-oxo-2-quinolyl]benzoate (10)

A solution of Na (85.0 mg, 3.70 mmol) in 10 mL of absolute ethanol was added dropwise (under N_2

atmosphere) to a solution of compound **(8)** (1.0 g, 3.06 mmol) in 30 mL of absolute ethanol . After refluxing for 2 h, water was added (100 mL) followed by extraction with chloroform (2x50 mL). The organic fractions were collected, dried over anhydrous magnesium sulfate and evaporated to dryness. Recrystallization of the resulting solid from ethanol afforded compound **(10)**, 82% yield (0.93 g), white solid, mp 225 °C. IR: (ν, cm^{-1}), 3060, 2972, 1719, 1627, 1584, 1462, 1429. ^1H NMR (400 MHz, DMSO-d_6): 0.9 (t, J=7.1 Hz, 3H), 4.1 (q, J=7.1 Hz, 2H), 7.4 (br dt, 1H), 7.6 (d, J=7.8 Hz, 2H), 7.7 (m, 2H), 7.8 (m, 1H), 8.1 (d, J=7.8 Hz, 1H), 8.2 (d, J=7.7 Hz, 1H), 12.4 (br s, 1H) ^{13}C NMR: 13.5, 60.85, 105.4, 118.3, 123.1, 123.9, 125.25, 129.2, 130.2, 130.6, 132.0, 132.9, 135.6, 138.95, 150.45, 164.95, 171.6. Anal. Calcd for $C_{18}H_{14}NO_3Br$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.93; H, 3.77; N, 3.87.

***N*-[(5*H*,11*H*-Isoindolo[2,1-*a*]quinoline-5,11-dione)-6-yl]iminotriphenylphosphorane (11)**

A solution of compound **(9)** (0.50 g, 1.70 mmol) and Ph_3P (0.50 g, 1.90 mmol) in dry THF (100 mL) was heated to reflux for 3 h. The resulting solid was collected and recrystallized from ethanol and chloroform. 70% yield (0.63 g), white solid, mp 303 °C. IR: (ν, cm^{-1}), 1708, 1618, 1487, 1426, 1333. ^1H NMR (100 MHz, $CDCl_3$/DMSO-d_6): 7.2-8.0 (m, 21H), 8.6 (m, 1H), 9.15 (d, J=8.2 Hz, 1H). ^{13}C NMR: 117.6, 124.95, 125.3, 125.9, 126.6, 127.25, 128.3, 128.85, 129.35, 130.0, 130.5, 131.9, 132.3, 132.9, 133.3, 134.95, 137.1, 145.2, 155.2, 174.05, 180.0. MS (CI): m/z (%) 523 (M+1, 23), 522 (M^+, 58), 445(14), 288(12), 272(100), 263(32), 260(16), 215(25), 204(15), 183(96), 107(34). Anal. Calcd for $C_{34}H_{23}N_2O_2P$: C, 78.15; H, 4.44; N, 5.36. Found: C, 78.66; H, 4.43; N, 5.57.

Ethyl 2-[4-Oxo-3-((triphenylphosphoranylidne)amino)-2-quinolyl]benzoate (12)

This compound was obtained from compound **(11)** in a procedure similar to that described for compound **(10)**. 67% yield, mp 292 °C (ethanol). IR: (ν, cm^{-1}), 3053, 2987, 1717, 1620, 1590, 1438. ^1H NMR (400 MHz, $CDCl_3$/DMSO-d_6): 1.2 (t, J=7.6 Hz, 3H), 3.7 (q, J=7.6 Hz, 2H), 7.5 (m, 8H), 7.55 (m, 5H), 7.7 (m, 10H). ^{13}C NMR: 12.8, 56.8, 128.1, 128.25, 131.6, 131.7, 132.65. Anal. Calcd for $C_{36}H_{29}N_2O_3P$: C, 76.07; H, 5.14; N, 4.92. Found: C, 76.40; H, 4.96; N, 4.62.

***N*-[2-(Bromoacetyl)phenyl]pyrrolidine-2,5-dione (13)**

This compound was prepared according to the procedure previously described.[4]

4-Azido-2,3-dihydro-1*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,5-dione (14)

This compound was prepared from compound **(13)** in a procedure similar to that described for compound **(9)**. 62% yield, mp 115 °C. IR: (ν, cm^{-1}), 2118, 1769, 1613, 1597, 1484. ^1H NMR (100 MHz, $CDCl_3$):

2.9 (m, 2H), 3.1 (m, 2H), 7.6 (m, 2H), 8.4 (br d, 1H), 9.1 (d, J=8.0 Hz, 1H). ^{13}C NMR: 21.0, 29.4, 109.65, 117.7, 126.3, 126.6, 126.9, 133.1, 144.15, 154.4, 175.2, 178.5. MS (EI): m/z (%) 213(15), 212 (M^+-N_2, 71), 185(20), 184(18), 156(55), 155(57), 129(52), 104(62), 76(55), 57(65), 55(100). Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.35; N, 23.32. Found: C, 60.21; H, 3.47; N, 23.13.

_N_-[2,3-Dihydro-1_H_,5_H_-pyrrolo[1,2-_a_]quinoline-1,5-dione)-4-yl]iminotriphenylphosphorane (15)

This compound was obtained from compound (**14**) in a procedure similar to that described for compound (**11**). 63% yield, mp 271 °C (ethanol and chloroform). IR: (ν, cm^{-1}), 1731, 1620, 1580, 1475, 1429, 1368. ^{1}H NMR (100 MHz, $CDCl_3$): 3.0 (m, 2H), 3.5 (m, 2H), 7.2-8.1 (m, 18H), 9.1 (d, J=8.2 Hz, 1H). ^{13}C NMR: 22.2, 30.55, 117.5, 124.7, 126.7, 127.9, 128.3, 130.8, 131.0, 131.35, 132.35, 132.7, 139.85, 140.2, 146.95, 178.9, 182.3. MS (EI): m/z (%) 474 (M^+, 75), 445(6), 397(12), 288(28), 262(77), 183(100), 108(62), 77(33). Anal. Calcd for $C_{30}H_{23}N_2O_2P$: C, 75.93; H, 4.88; N, 5.90. Found: C, 75.49; H, 4.68; N, 5.78.

Ethyl 3-[4-Oxo-3-((triphenylphosphoranylidene)amino)-2-quinolyl]propanoate (16)

This compound was obtained from compound (**15**) in a procedure similar to that described for compound (**10**). 46% yield, mp 171 °C (ethanol). IR: (ν, cm^{-1}), 3058, 2940, 1717, 1639, 1565, 1480, 1436. ^{1}H NMR (100 MHz, $CDCl_3$): 1.2 (t, J=7.1 Hz, 3H), 2.9 (m, 2H), 3.2 (m, 2H), 3.7 (q, J=7.1 Hz, 2H), 7.5 (m, 11H), 7.7 (m, 8H). Anal. Calcd for $C_{32}H_{29}N_2O_3P$: C, 73.83; H, 5.61; N, 5.38. Found: C, 73.43; H, 5.36; N, 5.08.

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