A New Synthesis of 2,3,4-Substituted Quinolines

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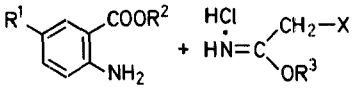
Recently, Harris[1] reported the use of ethyl 2-ethoxycarbonylacetimidate hydrochloride in the synthesis of 2-alkoxy-4-hydroxyquinolines by thermal cyclisation. In the course of our study in the field of heterocyclic chemistry we were interested in quinolines substituted by alkoxycarbonyl groups.

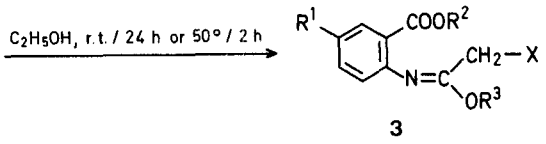
Imidates **3** were prepared in 50–60% yield by reaction of the corresponding methyl or ethyl anthranilate **1** with ethyl 2-ethoxycarbonylacetimidate hydrochloride (**2**) in ethanol solution at room temperature for 24 h or at 50° for 2 h.



1 **2**

$R^1 = H, CH_3$ $R^3 = CH_3, C_2H_5$

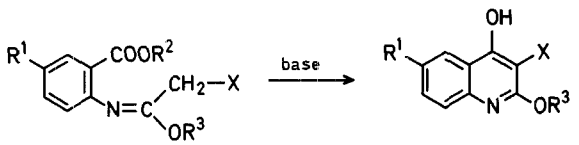
$R^2 = CH_3, C_2H_5$ $X = COOC_2H_5, CN$



3

The yields of imidates **3** were not as good as those for *ortho*-unsubstituted anilines[1]. The use of *o*-chloroaniline or *o*-methylaniline gives ethyl 2-ethoxycarbonyl-*N*-*o*-chlorophenylacetimidate (**3e**) or ethyl 2-ethoxycarbonyl-*N*-*o*-methylphenylacetimidate (**3f**) in approximately the same yields as obtained for compounds **3a** ($R^1=H$, $R^2=CH_3$, $X=COOC_2H_5$) and **3b** ($R^1=CH_3$, $R^2=C_2H_5$, $X=COOC_2H_5$).

Imidates **3** were treated with bases (see Table) at reflux or room temperature to give substituted quinolines **4a–d**. These quinolines were isolated in the 4-quinolinol form (keto-enol tautomerism was not observed[2]).



3 **4**

An excess of isopropylamine reacts with imidate **3a** to give **4e** ($R^1=H$, $R^3=C_2H_5$, $X=-CO-NH-C_3H_7$-*i*) which may also be obtained by reacting compounds **4a** or **4f** with isopropylamine; **4f** ($R^1=H$, $R^3=C_2H_5$, $X=COOCH_3$) [compound **4f** is obtained by basic hydrolysis of the ester group of compound **4a**[3] followed by esterification with boron trifluoride/methanol complex].

Treatment of imidates **3** with gaseous hydrogen chloride yields the hydrochloride of the initial anthranilate, **1**.

It is known[4] that condensation of methylhydrazine with methyl 2-ethoxymethyleneiminobenzoate leads to 3-methylamino-4(3*H*)-quinalozinone. The same reaction with imid-

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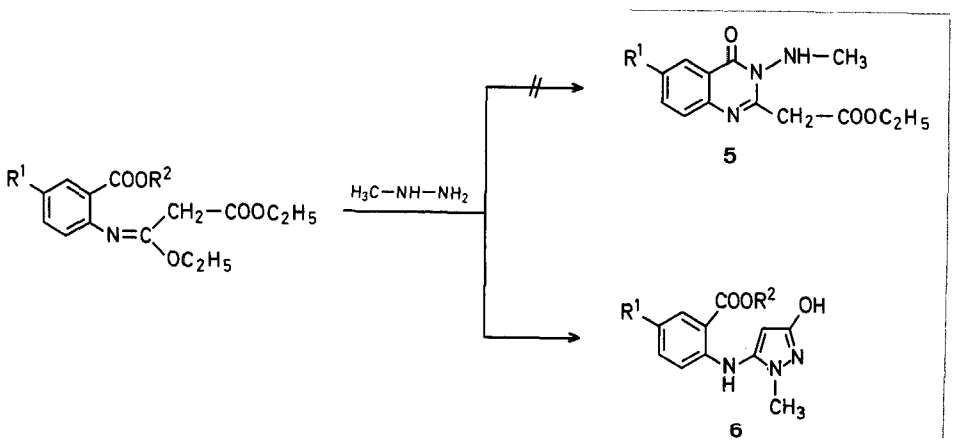
Table. Preparation of Imidates **3**, Quinolines **4**, and Pyrazoles **6**

Product No.	R^1	R^2	R^3	X	Yield [%]	b.p./ torr	Molecular formula[a]	M.S. *m/e* (M^+)	^{1}H-N.M.R. δ [ppm]
3a	H	CH_3	C_2H_5	$COOC_2H_5$	61	135°/2	$C_{15}H_{19}NO_5$ (293.3)	—	(CCl_4): 1.25 (m, 6H, $OCH_2C\underline{H}_3$); 3.02 (s, 2H, CH_2—CO—); 3.79 (s, 3H, OCH_3); 4.10 (m, 4H, OCH_2); 7.0 (m, $4H_{arom}$)
3b	CH_3	C_2H_5	C_2H_5	$COOC_2H_5$	52	130°/1	$C_{17}H_{23}NO_5$ (321.4)	—	(CCl_4): 1.30 (m, 9H, $OCH_2C\underline{H}_3$); 2.36 (s, 3H, CH_3); 3.02 (s, 2H, CH_2—CO—); 4.30 (m, 6H, OCH_2); 7.0 (m, $3H_{arom}$)
3d	H	CH_3	C_2H_5	CN	40	115°/2	$C_{13}H_{14}N_2O_3$ (246.3)	—	(CCl_4): 1.29 (m, 3H, O—$CH_2C\underline{H}_3$); 3.35 (s, 2H, CH_2—CN); 3.80 (s, 3H, OCH_3); 4.17 (m, 2H, OCH_2); 7.1 (m, $4H_{arom}$)
4a[3]	H	—	C_2H_5	$COOC_2H_5$	80–95	m.p. 101°	$C_{14}H_{15}NO_4$ (261.3)	261	($CDCl_3$): 1.45 (m, 6H, $OCH_2C\underline{H}_3$); 4.53 (m, 2H, OCH_2); 4.63 (m, 2H, $COOCH_2$); 7.6 (m, $4H_{arom}$); 13.4 (large, 1H, OH^b)[2]
4b	CH_3	—	C_2H_5	$COOC_2H_5$	65	m.p. 94°	$C_{15}H_{17}NO_4$ (275.3)	275	($CDCl_3$): 1.38 (m, 6H, $OCH_2C\underline{H}_3$); 2.42 (s, 3H, CH_3); 4.40 (m, 2H, OCH_2); 4.50 (m, 2H, $COOCH_2$); 7.7 (m, $3H_{arom}$); 13.3 (broad, 1H, OH^b)
4c	H	—	CH_3	CN	75	m.p. 264°	$C_{11}H_8N_2O_2$ (200.2)	200	(DMSO-d_6): 4.25 (s, 3H, OCH_3); 7.90 (m, $5H_{arom} + OH^b$)
4d	H	—	C_2H_5	CN	60–85	m.p. 265°	$C_{12}H_{10}N_2O_2$ (214.2)	214	(DMSO-d_6): 1.45 (m, 3H, $OCH_2C\underline{H}_3$); 4.60 (m, 2H, OCH_2); 7.60 (m, $5H_{arom}$ + OH^b)
4e	H	—	C_2H_5	CO—NH—C_3H_7-*i*	70–77	m.p. 67°	$C_{15}H_{18}N_2O_3$ (274.3)	274	($CDCl_3$): 1.28 [d, 6H, $CH(C\underline{H}_3)_2$]; 1.40 (m, 3H, $OCH_2C\underline{H}_3$); 4.26 [m, 1H, $C\underline{H}(CH_3)_2$]; 4.55 (m, 2H, OCH_2); 8.35 (broad, 1H, NH); 16.05 (s, 1H, OH^b)
4f	H	—	C_2H_5	$COOCH_3$	50	m.p. 93°	$C_{13}H_{13}NO_4$ (247.3)	247	($CDCl_3$): 1.45 (m, 3H, $OCH_2C\underline{H}_3$); 3.95 (s, 3H, $COOC\underline{H}_3$); 4.55 (m, 2H, $OC\underline{H}_2CH_3$); 13.4 (broad, 1H, OH^b)
6a	H	CH_3	—	—	53	m.p. 226°	$C_{12}H_{13}N_3O_3$ (247.3)	247	(DMSO-d_6): 3.45 (s, 3H, N—CH_3); 3.90 (s, 3H, OCH_3); 5.40 (s, 1H, =C—H); 7.20 (m, $4H_{arom}$); 9.15 (s, 1H, N—H^c)[d]; 9.62 (broad, 1H, OH^b)[d]
6b	CH_3	C_2H_5	—	—	55	m.p. 198°	$C_{14}H_{17}N_3O_3$ (275.3)	275	(DMSO-d_6): 1.35 (m, 3H, $OCH_2C\underline{H}_3$); 2.25 (s, 3H, CH_3); 3.40 (s, 3H, N—CH_3); 4.35 (m, 2H, OCH_2); 5.35 (s, 1H, =C—H); 7.0 (m, $3H_{arom}$); 9.05 (s, 1H, N—H^c)[d]; 9.1 (broad, 1H, OH^b)[d]

[a] All products gave satisfactory microanalyses (C ±0.31%, H ±0.19%, N ±0.20%).
[b] Undergoes rapid exchange.
[c] Undergoes slow exchange.
[d] The chemical shifts of NH and OH protons were assigned by comparison of N.M.R. spectra of similar pyrazoles, **6e, f**, obtained from **3e, f** and methylhydrazine.

ates **3a, b** does not give the expected quinalozinones **5** but rather compounds **6a**, 3-hydroxy-5-(2-methoxycarbonylphenylamino)-1-methylpyrazole and **6b**, 3-hydroxy-5-(4′-methyl-2′-ethoxycarbonylphenylamino)-1-methylpyrazole, respectively.

Compounds **6a, b** were obtained by initial displacement of the ethoxy group of the imino ether by the *N*-methyl group of methylhydrazine[5]. No reaction was observed with 1,1-dimethylhydrazine under the same conditions. Compounds **6a, b** exist in the enol form.



In order to prevent the cyclisation reaction with methylhydrazine occurring on the ester group of the alkyl chain, compounds **3c, d** were prepared; **3c** ($R^1=H$; $R^2=R^3=CH_3$; $X=CN$); **3d** ($R^1=H$, $R^2=CH_3$; $R^3=C_2H_5$; $X=CN$). In basic media compounds **3c, d** reacted to give 2-alkoxy-4-hydroxy-3-quinolinecarbonitriles **4c, d** in good yields (Table). Unfortunately, compounds **3c, d** do not cyclize to give the quinalozinone or the pyrazolone on treatment with methylhydrazine.

General Method for the Preparation of Ethyl *N*-(2′-Ethoxycarbonylphenyl)-2-ethoxycarbonylacetimidates (3):
Ethyl 2-ethoxycarbonylacetimidate hydrochloride (**2**; 0.12 mol) is added to a solution of the anthranilate ester (**1**; 0.1 mol) in ethanol (200 ml). The mixture is stirred for 24 h at room temperature, filtered, and the solid washed with ethanol. The combinated filtrates are evaporated and the residue is slurried in benzene. After evaporation of the solvent, the product is obtained by vacuum distillation; **3a**, yield: 61 %, b.p. 135°/2 torr; **3b**, yield: 52 %, b.p. 130°/1 torr; **3e**, yield: 55 %, b.p. 122°/0.5 torr; **3f**, yield: 52 %, b.p. 115°/0.2 torr.

Preparation of 2-Alkoxy-4-hydroxy-3-quinolinecarboxylate Esters 4:
Method A: Potassium *t*-butoxide (15 mmol) is added to a solution of **3a, b** (10 mmol) in *t*-butyl alcohol (50 ml). The mixture is heated under reflux for 2 h, then hydrolysed, and evaporated. The residue is dissolved in water (25 ml), acidified to pH 1, the solid collected by filtration, and recrystallised from benzene; **4a**, yield: 84 %, m.p. 101° (Lit.[3] m.p. 103°); **4b**, yield: 65 %, m.p. 94°.

Method B: As above using sodium ethoxide in ethanol; **4a**, yield: 80 %.

Method C: Sodium amide (18 mmol) is added to a solution of **3a, b** (10 mmol) in benzene (20 ml). The suspension is stirred for 2 h at room temperature, then cautiously hydrolysed; the aqueous layer is acidified to pH 1 and the solid collected; **4a**; yield: 2.48 g (95 %); **4d**, yield: 60 %.

Methyl 2-Ethoxy-4-hydroxy-3-quinolinecarboxylate (4f):
2-Ethoxy-4-hydroxy-3-quinolinecarboxylic acid[3] (5 mmol) is dissolved in boron trifluoride/methanol complex (25 ml) and stirred for 24 h at room temperature; water (100 ml) is added and a solid precipitates from the solution at pH 3–4; **4f**; yield: 1.21 g (50 %); m.p. 93°.

2-Ethoxy-4-hydroxy-*N*-isopropyl 3-quinolinecarboxamide (4e):
Compound **3a** (10 mmol) is dissolved in an excess of isopropylamine (5 ml) and heated under reflux for 8 h. Excess isopropylamine is then distilled and the solid residue recrystallised from benzene; **4e**; yield: 2.11 g (77 %); m.p. 67°.

By heating compound **4a** (10 mmol) in isopropylamine (5 ml) under reflux for 8 h, compound **4e** is obtained; yield: 1.01 g (74 %).

Compound **4f** (5 mmol) is dissolved in isopropylamine (10 ml) and stirred for 48 h at room temperature; the excess isopropylamine is removed in vacuo and the solid recrystallised from benzene; **4e**; yield: 0.96 g (70 %).

Preparation of Substituted Pyrazoles 6a, b:
Methylhydrazine (10 mmol) is added to a solution of compound **3a** or **3b** (5 mmol) in ethanol (10 ml). After 36 h at room temperature the precipitated solid is filtered and recrystallised from ethanol; **6a**, yield: 1.31 g (53 %), m.p. 226°; **6b**, yield: 1.51 g (55 %), m.p. 198°.

Ethyl *N*-(2-Alkoxycarbonylphenyl)-2-cyanoacetimidates (3c, d):
Prepared by using ethyl 2-cyanoacetimidate hydrochloride[6] and the corresponding anthranilate ester, in manner similar to that used for compounds **3a, b**. Compounds **3c, d** are sometimes gated cyano group in the raw material and in the distillate; **3c**, yield: 38 %, b.p. 115°/2 torr; **3d**, yield: 40 %, b.p. 115°/2 torr.

2-Alkoxy-4-hydroxy-3-quinolinecarbonitriles (4c, d):
Preparation identical to that of compounds **4a, b; 4c**, yield: 75 %, m.p. 264°; **4d**, yield: 85 %, m.p. 265°.

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