Novel Synthesis of Isoxazolo[5,4-*b*]quinolines [1]

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Isoxazolo[5,4-*b*]quinolines have been prepared by reacting 3-acyl or aroyl-2-chloro-6-alkoxy or 6,7-dialkoxyquinolines with hydroxylamine. The method is of general applicability for obtaining this class of compounds and involves the use of easily available starting materials.

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The only synthesis of 3-phenylisoxazolo[5,4-*b*]quinoline, reported by earlier workers [2], involves the reaction of 3-phenyl-2-isoxazolin-5-one with *o*-aminobenzaldehyde. The limiting factor for the general applicability of this reaction for obtaining substituted isoxazolo[5,4-*b*]quinolines is the elaborate synthesis of appropriately substituted *o*-aminobenzaldehydes [3-7] required as the starting materials and very often many of these aldehydes are fairly unstable. We, therefore, report herein a novel synthesis of substituted isoxazolo[5,4-*b*]quinolines.

Reaction of 2-chloro-3-formylquinolines **1a-1d**, prepared by the method of Cohn *et al* [8], with alkyl or aryl magnesium halide gave the tertiary alcohols **2a-f** which on oxidation with pyridinium chlorochromate yielded 3-acyl or aroyl-2-chloroquinolines **3a-f**. Oximation of **3a-f** with hydroxylamine hydrochloride in refluxing methanol in the presence of sodium acetate furnished the title compounds **4a-f** along with the oximes **5a-f**. In all of the cases the isoxazoloquinolines were obtained in 20-40% yield. These were separated by column chromatography over silica gel. As would be expected only the *Z*-oximes gave the isoxazoloquinolines and this helped in purifying the *E*-oximes.

EXPERIMENTAL

Melting points were determined on an electrically heated block and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 157 grating instrument. The ^{1}H nmr spectra were recorded on a Perkin-Elmer R-32 spectrometer using tetramethylsilane as internal reference.

6-Alkoxy or 6,7-Dialkoxy-2-chloro-3-[(α-alkyl or aryl)hydroxymethyl]-quinolines **2a-f**. General Procedure.

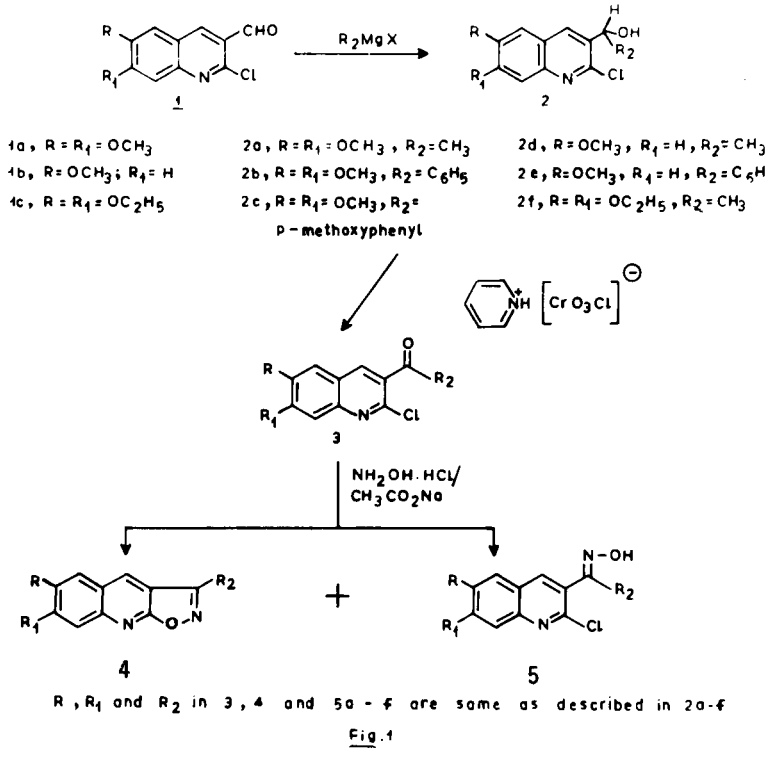

Fig. 1

Table

Physical, Analytical and Spectral Data

Compound	MP °C	Yield %	Molecular Formula	Analysis % Calcd./Found C	H	N	Spectral Data
2a	172-173	85	$C_{13}H_{14}ClNO_3$	58.31 58.70	5.23 5.29	5.23 5.00	ir: 3500 (OH) nmr (deuteriochloroform): 2.00 (d, 3H, CH_3, J = 6.3 Hz), 2.60 (bs, 1H, OH), 3.90 and 3.95 (2s, 6H, 2 × OCH_3), 5.25 (q, 1H, CHOH), 6.88 (s, 1H, C-8H), 7.28 (s, 1H, C-5H), 8.08 (s, 1H, C-4H)
2b	151-153	85	$C_{18}H_{16}ClNO_3$	65.55 66.00	4.85 4.90	4.24 4.00	ir: 3300 (OH) nmr (deuteriochloroform): 3.52 (bs, 1H, OH), 3.88 (s, 6H, 2 × OCH_3), 6.18 (s, 1H, CHOH), 6.88 (s, 1H, C-8H), 7.00-7.45 (m, 6H, C-5H and ArH), 8.11 (s, 1H, C-4H)
2c	80-81	70	$C_{19}H_{18}ClNO_4$	63.42 63.40	5.00 5.20	3.89 3.53	ir: 3400 (OH) nmr (deuteriochloroform): 3.70 (s, 3H, OCH_3), 3.90 (s, 6H, 2 × OCH_3), 6.12 (s, 1H, CHOH), 6.60-7.04 (m, 3H, C-8H and ArH), 7.10-7.40 (m, 3H, C-5H and ArH), 8.19 (s, 1H, C-4H)
2d	131-132	80	$C_{12}H_{12}ClNO_2$	60.63 60.80	5.05 4.89	5.89 5.61	ir: 3430 (OH) nmr (deuteriochloroform): 1.47 (d, 3H, -$CHCH_3$, J = 7.2 Hz), 3.80 (s, 3H, OCH_3), 5.18 (q, 1H, CHOH), 6.82 (d, 1H, C-5H, J_m = 2.7 Hz), 7.24 (dd, 1H, C-7H, J_o = 9.9 Hz, J_m = 3.6 Hz), 7.75 (d, 1H, C-8H, J_o = 9.9 Hz), 8.10 (s, 1H, C-4H)
2e	149-151	90	$C_{17}H_{14}ClNO_2$	68.11 67.68	4.67 4.98	4.67 4.60	ir: 3400 (OH) nmr (deuteriochloroform): 3.42 (bs, 1H, OH), 3.80 (s, 3H, OCH_3), 6.18 (s, 1H, CHOH), 6.92 (bs, 1H, C-5H), 7.10-7.50 (m, 6H, C-7H and ArH), 7.30 (d, 1H, C-8H, J_o = 9.0 Hz), 8.26 (s, 1H, C-4H)
2f	116-118	80	$C_{15}H_{18}ClNO_3$	60.91 60.60	6.09 6.30	4.77 5.09	ir: 3500 (OH) nmr (deuteriochloroform): 1.30-1.70 (m, 9H, CH_3 and 2 × OCH_2CH_3), 3.40 (bs, 1H, OH), 4.00 (2q, 4H, 2 × OCH_2CH_3), 5.22 (q, 1H, $CHCH_3$), 6.78 (s, 1H, C-8H), 7.12 (s, 1H, C-5H), 7.99 (s, 1H, C-4H)
3a	172	90	$C_{13}H_{12}ClNO_3$	58.75 58.95	4.51 4.86	5.27 5.47	ir: 1665 (C=O) nmr (deuteriochloroform): 2.72 (s, 3H, $COCH_3$), 3.94 and 3.99 (2s, 6H, 2 × OCH_3), 6.99 (s, 1H, C-8H), 7.26 (s, 1H, C-5H), 8.19 (s, 1H, C-4H)
3b	142-144	98	$C_{18}H_{14}ClNO_3$	65.95 65.70	4.27 4.06	4.27 3.91	ir: 1670 (C=O) nmr (deuteriochloroform): 3.92 and 3.98 (2s, 6H, 2 × OCH_3), 7.01 (s, 1H, C-8H), 7.28-7.60 (m, 4H, C-5H and 3 × ArH), 7.78 (dd, 2H, 2 × ArH, J_o = 8.1 Hz and J_m = 2.7 Hz), 7.99 (s, 1H, C-4H)
3c	168-170	80	$C_{19}H_{16}ClNO_4$	63.77 63.50	4.47 4.19	3.91 3.95	ir: 1635 (C=O) nmr (deuteriochloroform): 3.71 (s_4 3H, OCH_3), 3.94 and 3.98 (2s, 6H, 2 × OCH_3), 6.75-7.10 (m, 3H, C-8H and 2 × ArH), 7.30 (s, 1H, C-5H), 7.75 (d, 2H, 2 × ArH, J_o = 9.0 Hz), 7.95 (s, 1H, C-4H)
3d	100	85	$C_{12}H_{10}ClNO_2$	61.14 61.50	4.24 4.18	5.94 5.92	ir: 1690 (C=O) nmr (deuteriochloroform): 2.79 (s, 3H, $COCH_3$), 3.86 (s, 3H, OCH_3), 7.03 (d, 1H, C-5H, J_m = 3.6 Hz), 7.26 (dd, 1H, C-7H, J_o = 9.0 Hz, J_m = 1.8 Hz), 7.84 (d, 1H, C-8H, J_o = 9.0 Hz), 8.18 (s, 1H, C-4H)
3e	127-128	90	$C_{17}H_{12}ClNO_2$	68.57 68.50	4.03 3.88	4.70 4.86	ir: 1670 (C=O) nmr (deuteriochloroform): 3.88 (s, 3H, OCH_3), 7.06 (d, 1H, C-5H, J_m = 3.6 Hz), 7.28-7.64 (m, 5H, C-7H and 4 × ArH), 7.82 (dd, 3H, C-8H and 2 × ArH, J_o = 9.0 Hz, J_m = 3.6 Hz), 8.14 (s, 1H, C-4H)
3f	126-128	90	$C_{15}H_{16}ClNO_3$	61.32 61.60	5.45 5.89	4.77 5.09	ir: 1680 (C=O) nmr (deuteriochloroform): 1.49 (t, 6H, 2 × OCH_2CH_3), 2.71 (s, 3H, $COCH_3$), 4.14 (2q, 4H, 2 × OCH_2CH_3), 6.85 (s, 1H, C-8H), 7.19 (s, 1H, C-5H), 8.12 (s, 1H, C-4H)

Table (cont.)

Physical, Analytical and Spectral Data

Compound	MP °C	Yield %	Molecular Formula	Analysis % Calcd./Found C	H	N	Spectral Data
4a	153-154	20	$C_{13}H_{12}N_2O_3$	63.93 63.50	4.91 4.91	11.47 11.40	ir: 1640 (-C=N) nmr (deuteriochloroform): 2.98 (s, 3H, CH_3), 3.98 (s, 6H, 2 × OCH_3), 7.02 (s, 1H, C-8H), 7.30 (s, 1H, C-5H), 7.92 (s, 1H, C-4H)
4b	174-175 dec	40	$C_{18}H_{14}N_2O_3$	70.58 70.42	4.57 4.34	9.15 9.40	ir: 1620 (-C=N) nmr (deuteriochloroform): 3.91 and 3.94 (2s, 6H, 2 × OCH_3), 7.08 (s, 1H, C-8H), 7.29 (s, 1H, C-5H), 7.40-7.70 (m, 3H, ArH), 7.75-8.10 (m, 2H, ArH), 8.44 (s, 1H, C-4H)
4c [a]	165-166 dec	20	$C_{19}H_{18}N_2O_5$	64.40 64.30	5.08 5.02	7.90 7.70	ir: 1610 (-C=N) nmr (deuteriochloroform): 3.85 and 3.98 (2s, 9H, 3 × OCH_3), 6.90-7.40 (m, 4H, C-8, C-5H and ArH), 7.90 (d, 2H, ArH, J = 9.0 Hz), 8.48 (s, 1H, C-4H)
4d	185-186	20	$C_{12}H_{10}N_2O_2$	67.28 66.95	4.67 4.98	13.08 13.20	ir: 1620 (-C=N) nmr (deuteriochloroform): 2.56 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.05 (d, 1H, C-5H, J_m = 2.7 Hz), 7.40 (2d, 1H, C-7H, J_o = 9.0 Hz, J_m = 2.7 Hz), 7.92 (d, 1H, C-8H, J_o = 9.0 Hz), 8.21 (s, 1H, C-4H)
4e [b]	179-180	30	$C_{17}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$	71.57 71.87	4.56 4.65	9.82 9.57	ir: 1630 (-C=N) nmr (deuteriochloroform + deuteriodimethyl sulphoxide): 3.95 (s, 3H, OCH_3), 7.41 (d, 1H, C-5H, J_m = 2.7 Hz), 7.50-7.80 (m, 4H, C-7H and 3 × ArH), 7.85-8.20 (m, 3H, C-8H and 2 × ArH), 8.90 (s, 1H, C-4H)
4f	165-166	25	$C_{15}H_{16}N_2O_3$	66.17 66.40	5.50 5.88	10.29 10.00	ir: 1620 (-C=N) nmr (deuteriochloroform): 1.45 (t, 6H, 2 × OCH_2CH_3), 2.52 (s, 3H, CH_3), 4.14 (2q, 4H, 2 × OCH_2CH_3), 6.98 (s, 1H, C-8H), 7.20 (s, 1H, C-5H), 8.04 (s, 1H, C-4H)
5a	220-221	80	$C_{13}H_{13}ClN_2O_3$	55.61 55.35	4.63 4.57	9.98 9.72	ir: 3200 (OH), 1625 (-C=N) nmr (deuterochloroform + deuteriodimethyl sulphoxide): 2.20 (s, 3H, CH_3), 3.94 (s, 6H, 2 × OCH_3), 7.12 (s, 1H, C-8H), 7.29 (s, 1H, C-5H), 7.88 (s, 1H, C-4H), 8.00 (bs, 1H, OH)
5b	168-170	50	$C_{18}H_{15}ClN_2O_3$	63.06 62.75	4.37 4.00	8.17 8.42	ir: 3400 (OH), 1620 (-C=N) nmr (deuteriochloroform + deuteriodimethyl sulphoxide): 3.90 and 3.94 (2s, 6H, 2 × OCH_3), 7.12 (s, 1H, C-8H), 7.22-8.00 (m, 6H, C-5H and ArH), 8.10 (s, 1H, C-4H)
5c	138-140	75	$C_{19}H_{17}ClN_2O_4$	61.20 61.40	4.56 4.96	7.51 7.40	ir: 3400 (OH), 1600 (-C=N) nmr (deuteriochloroform): 3.78 (s, 3H, OCH_3), 3.98 (s, 6H, 2 × OCH_3), 6.70-7.50 (m, 6H, C-5, C-8H and 4 × ArH), 7.85 (s, 1H, C-4H)
5d	141-143	70	$C_{12}H_{11}ClN_2O_2$	57.48 57.40	4.39 4.20	11.17 11.30	ir: 3200 (OH), 1610 (-C=N) nmr (deuteriochloroform + deuteriodimethyl sulphoxide): 2.20 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.02 (d, 1H, C-5H, J_m = 2.7 Hz), 7.30 (dd, 1H, C-7H, J_o = 9.0 Hz, J_m = 2.7 Hz), 7.75 (d, 1H, C-8H, J_o = 9.0 Hz), 7.94 (s, 1H, C-4H)
5e [a]	198	60	$C_{17}H_{15}ClN_2O_3$	61.72 61.60	3.93 4.38	8.47 8.40	ir: 3450 (OH), 1630 (-C=N) nmr (deuteriochloroform + deuteriodimethyl sulphoxide): 3.83 (s, 3H, OCH_3), 7.12 (d, 1H, C-5H, J_m = 2.7 Hz), 7.21-7.65 (m, 4H, C-7H and 3 × ArH), 7.70-8.05 (m, 3H, C-8H and 2 × ArH), 8.00 (s, 1H, C-4H)
5f	190 dec	70	$C_{15}H_{17}ClN_2O_3$	58.91 58.50	5.51 5.40	9.07 9.20	ir: 3160 (OH), 1615 (-C=N) nmr (deuteriochloroform + deuteriodimethyl sulphoxide): 1.45 (t, 6H, 2 × OCH_2CH_3), 2.20 (s, 3H, CH_3), 2.51 (bs, 1H, OH), 4.13 (q, 4H, 2 × OCH_2CH_3), 7.02 (s, 1H, C-8H), 7.20 (s, 1H, C-5H), 7.89 (s, 1H, C-4H)

[a] Crystallized as the hydrate. [b] Crystallized as the hemihydrate.

To a suspension of alkyl- or arylmagnesium halide, prepared from magnesium turnings (0.02 g-aton) and alkyl or aryl halide (0.02 mole) in dry ether (50 ml), was added a solution of **1a-c** (0.01 mole) in THF (50 ml). The resulting suspension was stirred at this temperature for ten minutes. Ammonium chloride solution (10%, 100 ml) was then added to this suspension and the reaction mixture extracted with ethyl acetate. Usual work up of the organic layer yielded an oil which after addition of petroleum ether gave **2a-f** as solids. These were recrystallized from chloroform:petroleum ether mixture (30:70).

3-Acyl or Substituted Benzoyl-6-alkoxy- or 6,7-dialkoxy-2-chloroquinolines **3a-f**. General Procedure.

To a well stirred solution of **2a-f** (0.01 mole) in dry dichloromethane (50 ml) was added pyridinium chlorochromate (0.015 mole) and the mixture stirred at room temperature (30°) for 45 minutes. The suspension was extracted with dry diethyl ether (3 × 100 ml) and the ethereal extract after concentration was passed through a short band of florisil using a chloroform:ethyl acetate mixture (9:1) as eluent. Removal of the solvent gave **3a-f** as solids which were recrystallized from methanol.

6-Alkoxy or 6,7-Dialkoxy-3-alkyl or Arylisoxazolo[5,4-*b*]quinolines **4a-f** and 6-Alkoxy or 6,7-Dialkoxy-2-chloroquinoline-3-ketoximes **5a-f**. General Procedure.

A mixture of appropriately substituted ketone **3a-f** (0.0l mole), hydroxylamine hydrochloride (0.015 mole) and sodium acetate (0.015 mole) in methanol (50 ml) was refluxed under constant stirring for 4 to 6 hours. The reaction mixture was cooled, the solvent removed by distillation and the residual solid filtered, dried and purified by column chromatography over silica gel. Elution of the column with chloroform furnished isoxazoles **4a-f** which were recrystallized from methanol. Further elution of the column with chloroform:ethyl acetate (80:20) gave **5a-f**.

REFERENCES AND NOTES

[1] C.D.R.I. Communication No. 3448.

[2] S. Carlo and B. Eberhard, *Chem. Z.*, **102**, 264 (1978).

[3] T. K. Shanmugam and K. Kanakarajan, *Monatsch. Chem.*, **107**, 259 (1976).

[4] T. Kametani, Y. Fujimoto and M. Mizushima, *Chem. Pharm. Bull.*, **23**, 2025 (1975).

[5] T. Kametani, Y. Fujimoto and M. Mizushima, *Heterocycles*, **3**, 619 (1975).

[6] P. Shanmugam, R. Palaniappan, *Z. Naturforsch.*, **28**, 196 (1973).

[7] T. Kyosuke, I. Susumu, K. Masaaki, T. Ryuji and M. Tetsuo, *Chem. Pharm. Bull.*, **10**, 865 (1962).

[8] M. O. Cohn, B. Narine and B. Tarnowski, *Tetrahedron Letters*, 3111 (1979).