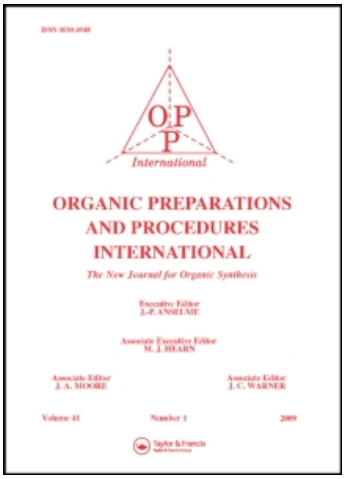

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SYNTHESIS OF 2-CHLORO-3-ALKYL- AND ARYLQUINOLINES

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SYNTHESIS OF 2-CHLORO-3-ALKYL- AND ARYLQUINOLINES

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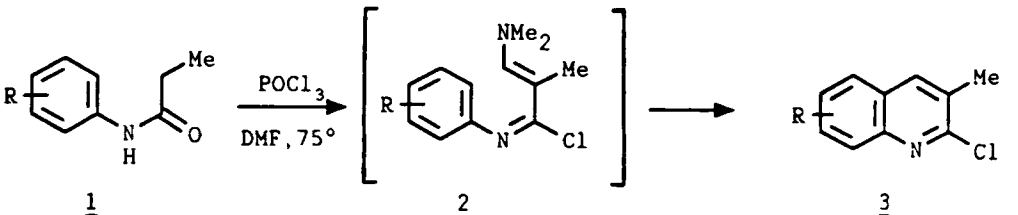
2-Chloro-3-substituted quinolines are useful intermediates for the synthesis of biologically active compounds.[1,2] Meth-Cohn and his coworkers elaborated a new synthesis of these quinolines from acylanilides under Vilsmeier conditions,[3,4] albeit only in cases where the aromatic substituents of the anilides were 3-methyl and 3-methoxy. These electron-donating substituents in the meta position behaved as activating groups in this electrophilic process. It was stated that cyclisation is regiospecific; only the formation of 7-substituted quinolines was observed.[3,4]



1 2 3

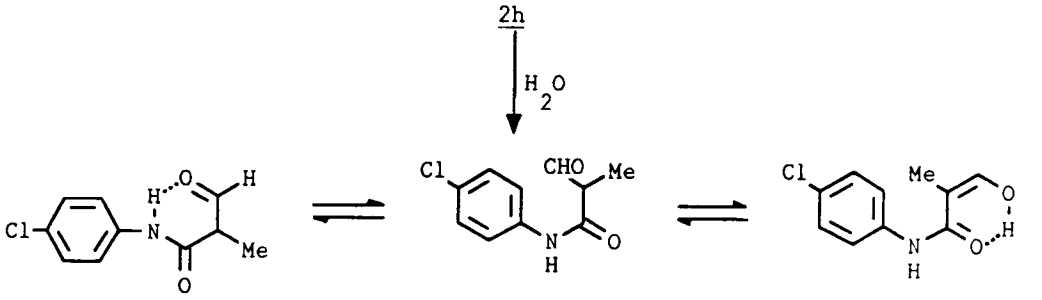
a)R = H b)R = 4-Me c)R = 2-Me d)R = 4-Et e)R = 2-Et f)R = 4-OMe
g)R = 2-OMe h)R = 4-Cl i)R = 4-Br j)R = 4-F k)R = 4-NO_2

Since we needed different 2-chloroquinolines as starting materials for further synthesis,[2] we attempted to extend the scope of the reaction to other anilides having substituents at different positions, and decided to study the selectivity of this reaction. Working under the reported conditions,[3,4] we followed each reaction by taking aliquot samples from the reaction mixture and working them up. In this fashion, we were able to establish the maximum yield for each compound but in this paper we only report the time required to reach 95% of the maximum yield (Tables 1 and 2). This reaction time qualitatively indicates the rate of the reaction and characterizes the activating or deactivating effect of the substituents.

We found that cyclisation occurred not only with methyl or methoxy substituents in the meta position, but in any other position. Using appropriate reaction time, mildly deactivated 3- and 4-haloanilides could be converted into quinolines in very high yields. However, 2-haloanilides could not be converted into quinolines. With the strongly electron withdrawing nitro group, the reaction is possible only when it is in the para position, but the yield is very low.

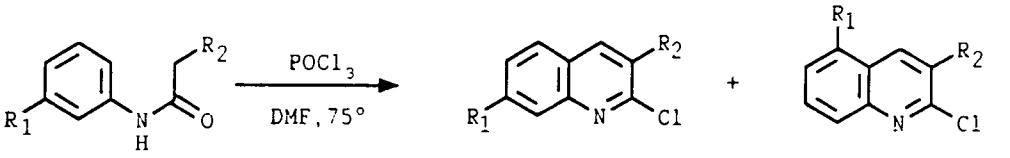
We verified the existence of intermediate 2h in the case of N-(4-chlorophenyl)propionamide (1h) by the isolation of N-(4-chlorophenyl)-2-methylformylacetamide (4h), which is clearly derived from the intermediate 2h on work-up; 4h exist in an approximately 1:1 ratio of two tautomers in deuteriochloroform

solution according to the ^{1}H-NMR spectrum. Mass spectral data further supported its structure.



A 4h B

In the course of our investigations, attention was paid to the formation of 5-substituted quinolines (7) as side-products from unsymmetrical anilides. Careful study of the prod-



5 6 7

a)R_1 = Me, R_2 = Me b)R_1 = Et, R_2 = Me c)R_1 = OMe, R_2 = Me
d)R_1 = Cl, R_2 = Me e)R_1 = Br, R_2 = Me f)R_1 = F, R_2 = Me
g)R_1 = Me, R_2 = Et h)R_1 = OMe, R_2 = Et i)R_1 = Cl, R_2 = Et
j)R_1 = Br, R_2 = Et k)R_1 = Me, R_2 = But l)R_1 = OMe, R_2 = But
m)R_1 = Cl, R_2 = But n)R_1 = Me, R_2 = Ph o)R_1 = OMe, R_2 = Ph
p)R_1 = Cl, R_2 = Ph

ucts revealed that the cyclisation is not regiospecific as had

been previously thought,[3,4] and the ratio of isomers depends on the substituents on the aromatic ring of the anilides and the nature of the acyl group of the anilides. The ratio of quinoline isomers was determined by GC and by characteristic signal of the isomers in the ^{1}H-NMR spectra of the products. In most cases, the isomers could be separated by column chromatography, and their structure was confirmed by elemental analysis and by their ^{1}H-NMR and mass spectral data.

TABLE 1. Cyclisation of o- and p-Substituted Propionanilides(1)

Prod.	Time	Yield[a]	mp[b]	Elemental analysis					
				Calculated (%)			Found (%)		
	(hrs)	(%)	(^{o}C)	C	H	N	C	H	N
3a	10	78	81-83	67.62	4.54	7.89	67.55	4.52	7.91
3b	10	79	99-101	68.94	5.26	7.31	68.90	5.25	7.35
3c	15	78	59-61	68.94	5.26	7.31	68.95	5.21	7.30
3d	8	83	47-49	70.07	5.88	6.81	70.25	5.93	6.82
3e	10	80	38-40	70.07	5.88	6.81	70.1	5.83	6.87
3f	16	77	91-93	63.62	4.85	6.75	63.51	4.84	6.78
3g	18	76	120-121	63.62	4.85	6.75	63.57	4.80	6.79
3h	16	85	143-145	56.63	3.33	6.60	56.79	3.34	6.65
3i	6	87	147-149	46.82	2.75	5.46	46.70	2.74	5.40
3j	20	75	106-108	61.36	3.60	7.16	61.31	3.56	7.17
3k	20	20	185-187	53.95	3.17	12.58	53.89	3.17	12.62

a)Yield of crude product; b)mps of recrystallized product (chloroform-ethanol)

TABLE 2. Cyclisation of m-Substituted Anilides (5)

Prod.	Time	Yield[a]	R[b]	mp[c]	Elemental analysis					
					Calculated (%)			Found (%)		
	(hrs)	(%)	(%)	(°C)	C	H	N	C	H	N
6a	7	75	88	91-93	68.94	5.26	7.31	68.76	5.30	7.39
7a			12							
6b	5	75	95	44-46	70.07	5.88	6.81	70.18	5.87	6.80
7b			5							
6c	3	85	89	94-96	63.62	4.85	6.75	63.71	4.80	6.72
7c			11	108-110	63.62	4.85	6.75	63.75	4.85	6.79
6d	6	86	76	124-126	56.63	3.33	6.60	56.61	3.30	6.57
7d			24	85-87	56.63	3.33	6.60	56.78	3.33	6.54
6e	3	85	80	128-130	46.82	2.75	5.46	46.88	2.76	5.48
7e			20	110-112	46.82	2.75	5.46	46.90	2.79	5.52
6f	5	86	84	96-98	61.36	3.60	7.16	61.23	3.55	7.20
7f			16							
6g	6	78	92	58-60	70.07	5.88	6.81	70.15	5.86	6.83
7g			8							
6h	4	76	90	64-66	65.02	5.46	6.32	65.14	5.47	6.22
7h			10	98-100	65.02	5.46	6.32	64.96	5.40	6.28
6i	5	80	83	76-78	58.43	4.01	6.19	58.31	4.07	6.11
7i			17	95-97	58.43	4.01	6.19	58.36	4.06	6.23
6j	5	76	85	85-87	48.83	3.35	5.18	48.89	3.31	5.20
7j			15	97-99	48.83	3.35	5.18	48.96	3.31	5.12
6k	7	79	94	36-38	71.94	6.90	5.99	71.73	6.87	6.06
7k			6							
6l	4	78	92	86-88	67.33	6.46	5.61	67.21	6.41	5.60
7l			8	44-46	67.33	6.46	5.61	67.39	6.43	5.57
6m	7	68	90	60-62	61.43	5.16	5.51	61.27	5.11	5.43
7m			10	44-46	61.43	5.16	5.51	61.34	5.19	5.48
6n	7	80	92	83-85	75.74	4.77	5.52	75.55	4.71	5.58
7n			8							
6o	4	82	92	128-130	71.25	4.48	5.19	71.20	4.53	5.13
7o			8	127-129	71.25	4.48	5.19	71.38	4.42	5.28
6p	8	65	86	102-104	65.72	3.31	5.11	65.49	3.30	5.19
7p			14	128-130	65.72	3.31	5.11	65.77	3.25	5.12

a) Yield of crude product (consist of two quinoline isomers only); b) Ratio of isomers in the crude product (determined by GC and NMR with satisfactory agreement); c) mps of 7-substituted isomers obtained by crystallization and 5-substituted isomers obtained by column chromatography.

TABLE 3. ^{1}H-NMR and Mass Spectral Data of Products (3,6,7)

Prod.	Chemical shifts of quinoline ring[a,b] hydrogens δ(ppm) ($CDCl_3$/TMS int.)					MS m/e(%)
	4-H	5-H	6-H	7-H	8-H	
3a	7.95(s)	7.73(dd)	7.50(m)	7.65(m)	7.98(dd)	177(M^+,100) 142(47)
3b	7.87(s)	7.45(d)		7.47(dd)	7.92(d)	191(M^+,100) 176(16)
3c	7.85(s)	[7.30———		———7.55](m)		191(M^+,100) 176(10)
3d	7.87(s)	7.50(d)		7.55(dd)	7.90(d)	205(M^+,46) 190(100)
3e	7.87(s)	[7.37———		———7.55](m)		205(M^+,76) 204(100)
3f	7.87(s)	7.00(d)		7.32(dd)	7.90(d)	207(M^+,100) 192(16)
3g	7.87(s)	7.02(dd)	7.42(m)	7.30(dd)		207(M^+,87) 178(100)
3h	7.87(s)	7.70(d)		7.60(dd)	7.92(d)	211(M^+,100) 176(50)
3i	7.87(s)	7.90(d)		7.73(dd)	7.83(d)	257(M^++2,100) 255(M^+,85)
3j	7.90(s)	7.37(dd)		7.43(m)	7.97(dd)	195(M^+,100) 160(45)
3k	8.17(s)	8.72(d)		8.45(dd)	8.10(d)	222(M^+,100) 176(38)
6a	7.90(s)	7.62(d)	7.35(dd)		7.75(d)	191(M^+,100) 176(17)
7a[c]	8.12(s)					
6b	7.90(s)	7.65(d)	7.38(dd)		7.80(d)	205(M^+,70) 190(100)
7b[c]	8.15(s)					
6c	7.88(s)	7.62(d)	7.17(dd)		7.32(d)	207(M^+,100) 192(10)
7c	8.35(s)		6.80(dd)	[7.50———	———7.60](m)	207(M^+,100) 192(32)
6d	7.85(s)	7.62(d)	7.42(dd)		7.90(d)	211(M^+,100) 176(66)
7d	8.35(s)		7.92(dd)	[7.52———	———7.62](m)	211(M^+,100) 176(55)
6e	8.17(s)		[7.57———	———7.63](m)	7.95(d)	257(M^++2,100) 255(M^+,63)
7e	8.30(s)		7.95(dd)	7.50(m)	7.75(dd)	257(M^++2,100) 255(M^+,71)
6f	7.95(s)	7.72(dd)	7.30(m)		7.60(dd)	195(M^+,100) 160(74)
7f[c]	8.20(s)					

TABLE 3. (continued)

6g	7.90(s)	7.65(d)	7.35(dd)		7.75(d)	205(M^+,61) 190(100)
7g[c]	8.10(s)					
6h	7.85(s)	7.65(d)	7.17(dd)		7.32(d)	221(M ,55) 206(100)
7h	8.35(s)		6.82(dd)	[7.50——7.60](m)		221(M^+,86) 206(100)
6i	7.95(s)	7.70(d)	7.50(dd)		8.00(d)	225(M^+,51) 210(100)
7i	8.35(s)		7.92(dd)	[7.53——7.63](m)		225(M^+,63) 210(100)
6j	8.15(s)	[7.57——7.63](m)			7.90(d)	271(M^++2,68) 269(M^+,53)
7j	8.32(s)		7.95(dd)	7.52(m)	7.80(dd)	271(M^++2,84) 269(M^+,54)
6k	7.85(s)	7.62(d)	7.32(dd)		7.72(d)	233(M^+,34) 190(100)
7k[c]	8.05(s)					
6l	7.85(s)	7.60(d)	7.15(dd)		7.30(d)	249(M^+,24) 206(100)
7l	8.35(s)		6.80(dd)	[7.50——7.60](m)		249(M^+,32) 206(100)
6m	7.90(s)	7.67(d)	7.45(dd)		7.95(d)	253(M^+,30) 210(100)
7m	8.32(s)		7.90(dd)	[7.53——7.63](m)		253(M^+,44) 210(100)
6n	8.05(s)	7.70(d)	7.40(dd)		7.85(d)	253(M^+,100) 218(39)
7n[c]	8.25(s)					
6o	8.00(s)	7.68(d)	7.20(dd)		7.40(d)	269(M^+,100) 226(32)
7o	8.55(s)		6.90(dd)	[7.60——7.70](m)		269(M^+,100) 226(34)
6p	8.08(s)	7.78(d)	7.55(dd)		8.05(d)	273(M^+,100) 238(42)
7p	8.50(s)		8.00(dd)	[7.60——7.70](m)		273(M^+,100) 238(66)

a) The hydrogens in the substituents (R_1,R_2) of the products (3, 6, 7) appeared in the following ranges $^2\delta$ (ppm): i) methyl hydrogens α, β and δ to the aromatic ring 2.48-2.73, 1.32-1.40 and 0.97-1.00 respectively; ii) methylene hydrogens α, β and γ to the aromatic ring 2.80-3.25, 1.70-1.75 and 1.42-1.50 respectively; iii) methoxy hydrogens 3.90-4.05; iv) phenyl hydrogens 7.43-7.58 b) The coupling constants between hydrogens on the quinoline ring were J_o=8-9 Hz, J_m=1-3 Hz c) Characteristic signal of the 5-substituted isomer in the ^{1}H-NMR spectrum of the isomer mixture.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Bruker WP-200 SY instrument at 200 MHz using TMS as internal standard and chemical shifts are expressed in ppm. Mass spectra were scanned on a VG 7035 instrument in EI mode at 70 eV. A Fractovap 2300 chromatograph (Carlo-Erba) was used for GC and DC-Allurole Kieselgel 60 F 254 (Merck) silica gel plates for TLC analysis. The separation of quinoline isomers was performed by column chromatography using Kieselgel 60 (0.063-0.2 mm) (Reanal, Hungary) packing and chloroform-hexane (1:1 v/v) eluent.

Anilides (1,5). General Procedures.

a) Propionanilides and Butyranilides.- To 1 mol of appropriate aniline, 1.1 mol of propionic or butyric anhydride was added with stirring and the mixture was boiled under reflux for 1 min. It was allowed to cool below 100°, 500 ml of water was added dropwise and the mixture was stirred at room temperature for 1 hr. The solid propionanilides were collected, washed with water and dried. The oily precipitated butyranilides were extracted with chloroform. The organic extract was dried (Na_2SO_4), concentrated, and the residual oil was purified by distillation under reduced pressure.

b) Caproylanilides and Phenylacetanilides.- To a stirred and cooled solution of 1 mol of appropriate aniline and 1.1 mol of triethylamine in 1 l chloroform, 1.1 mol caproyl or phenylacetyl chloride was added dropwise at room temperature. The mixture was stirred for 1 hr then was successively washed with water, aqueous sodium carbonate (10%), water, aqueous hydrochloric acid (1 mol), water and dried (Na_2SO_4). After evaporation of the solvent, anilides were obtained as dense oil, but phenylacetanilides solidified on standing at room temperature. All anilides prepared by these procedures were sufficiently pure for further use.

Quinolines (3,6,7). General Procedure.- To phosphoryl chloride (322 ml, 3.5 mol) at 0-5°, dimethylformamide (58 ml, 0.75 mol)

was added dropwise with stirring. To this solution, the appropriate anilide (0.5 mol) was added and the mixture was heated at 75° for the appropriate time (Tables 1 and 2). After evaporation of excess phosphorylchloride, the residue was poured into ice-water. The precipitated quinolines were collected, washed with water and dried.

Except for 3k, none of the crude products prepared by this general procedure contained any component other than quinoline according to GC and TLC analysis and ^{1}H-NMR spectra. 2-Chloro-3-methyl-6-nitroquinoline (3k) was extracted into chloroform (3x100 ml) from the solid precipitated upon pouring into ice-water, followed by removal of chloroform under reduced pressure.

Separation of Quinoline Isomers. General Procedure. - All quinolines may be crystallized from chloroform-ethanol (1:3 v/v) solvent. By crystallization of isomer mixtures prepared from meta-substituted anilides, 7-substituted isomers were obtained in pure form, and the mother liquor contained both isomers. It was concentrated and chromatographed on a silica gel column (2 g/100 g) using chloroform-hexane (1:1 v/v) eluent. Pure 5-substituted isomers could be obtained when the substituents on the homoaromatic ring (R_1) were Cl, Br or OMe; however the separation was not successful when they were F, Me or Et.

Preparation and Identification of N-(4-Chlorophenyl)-2-methylformylacetamide (4h).- N-(4-chlorophenyl)propionamide (18.4 g, 0.1 mol) was added to the Vilsmeier reagent prepared from 64.4 ml (0.7 mol) phosphoryl chloride and 11.6 ml (0.15 mol) dimethylformamide, and the reaction mixture was stirred at 75° for 1 hour or at 40° for 4 hours, then it was poured into ice-water. The clear solution was decanted from dense oil which precipitated immediately and was allowed to stand in the refrigerator overnight. The white crystalline product (12.7 g, 60 %), mp. 103-104°, was collected and washed with water.

^{1}H-NMR ($CDCl_3$): δ 2.04 [d, 3H, J = 7 Hz, Me(A)], 2.28 [s, 3H, Me(B)], 3.88 [q, 1H, J = 7 Hz, CH(A)], 7.50 [broad, 1H, NH(B)] 7.58 [s, 1H, CH(B)], 7.70-7.88 [m, 4H, Ar-H], 7.92-8.04 [m, 4H, Ar-H], 8.74 [broad, 1H, OH(B)], Mass: m/e (%) = 211 (M^+, 15), 183 (15), 153 (8), 127 (100), 85 (18).

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