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SYNTHESIS OF *N*-ALLYL AND *N*-PROPADIENYLACRIDONES USING PHASE-TRANSFER CATALYSIS

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Abstract- A convenient procedure for the synthesis of *N*-allyl substituted acridones under phase-transfer catalysis is reported using allyl bromide as alkylating agent. When propargyl bromide was used, in the same reaction conditions, no propynylacridone was detected in the reaction and only propadienylacridone was obtained in moderate yield.

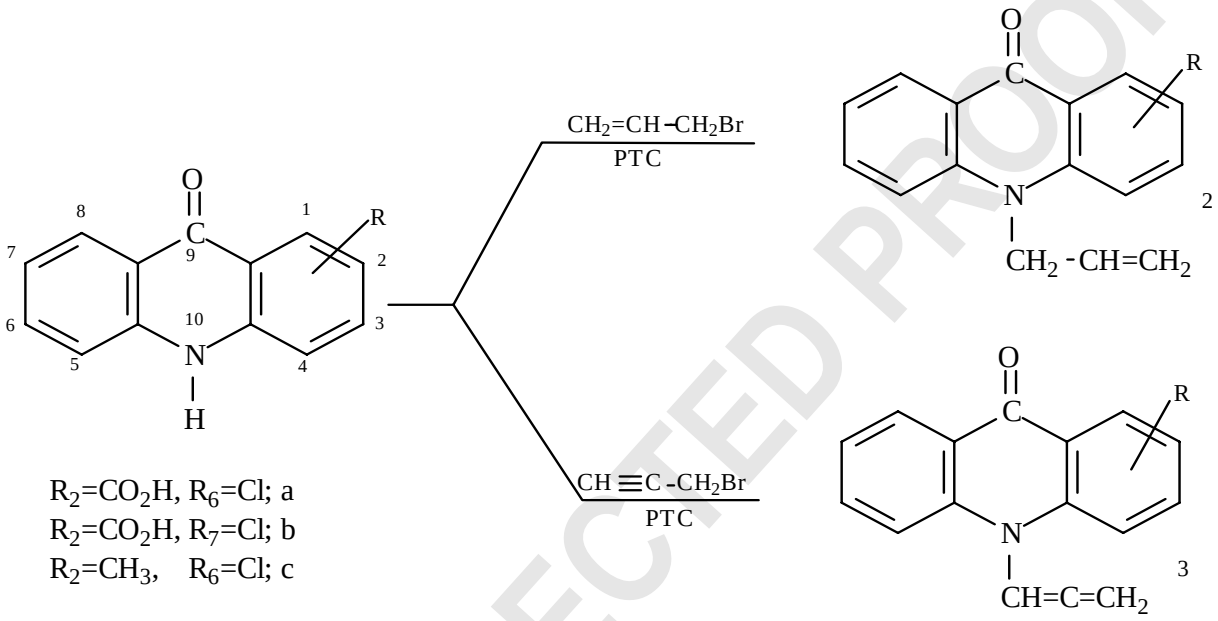
Recent biological studies concerning acridone derivatives has been reported, some of these compounds are antitumoral,[1-3] antiparasitic,[5-6]and antiviral agents.[7-9] Alkylation of acridones under phase-transfer catalysis has been previously studied.[10-11] We were interested in synthesizing a new series of *N*-substituted acridones in order to investigate the biological activities and in this paper we describe the synthesis of *N*-allyl and *N*-propadienyl substituted acridone derivatives. Phase-transfer catalysis was used in aqueous 50% potassium hydroxide using cetyltrimethylammonium bromide as catalyst and allyl bromide or propargyl bromide as an alkylating agent. In all cases the corresponding allylacridone derivatives were obtained and however, the use of propargyl bromide lead only the allenyl compound **(3)** but not the expected *N*-1-propynylacridone derivative.

The synthetic scheme for those compounds is outlined in Scheme 1 and data of the products are summarized in Tables 1 and 2. ^{1}HNMR spectra of the compounds **(3)** revealed the absence of the absorption signals corresponding to the propargilic protons[12] at δ= 2.5 ppm and δ= 3.9 ppm while exhibiting characteristic new absorption signals corresponding to allenic protons at δ= 5.7 ppm (d, H_{13} and δ=3.3 ppm (s, H_{11}) (Table 1). ^{13}C NMR spectra reveal three new signals at 200 ppm (quaternary C),

95 ppm (CH) and 80 ppm (CH_2) attributed to allenic carbons suggesting that allenic substitution product has taken place.

MS spectrum displays peaks (M^+) for the molecular ion as well as the base peak, and the loss of 39 unit (C_3H_3) in allenyl derivative and 41 unit for allyl compounds (Table 3). These results are consistent with the structure proposed in Scheme I.

Scheme 1



EXPERIMENTAL

Melting points were measured using a GALLENKANMP hot apparatus and are uncorrected. NMR spectra were recorded on a Bruker A 250 Z spectrometer at 300K. Chemical shifts are expressed in ppm relative to TMS as internal standard. MS were recorded with a spectrometer TRIO 1000 FISIONS Instruments by electronic impact (EI).

Preparation of 10-allylacridone (2). General procedure.

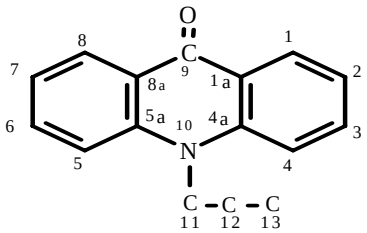
A stirred mixture of the 9(10-H)-acridone (**1**) (0.01 mol), allyl bromide (0.8 mL, 9.24 mmol), cetyltrimethylammonium bromide (0.08 g, 0.22 mmol), aqueous 50% potassium hydroxide (50 mL, 0.62 mol) and butanone (75 mL, 0.84 mol) was refluxed for 2.5 h. The butanone phase was separated, dried with sodium sulfate, and evaporated *in vacuo*. The residual product **(2c)** was recrystallized from ethanol or ethanol-water. The salts were dissolved in water and the acids (**2a, b**) were liberated by addition of 1% hydrochloric acid.

Preparation of 10-propadienylacridone (3). General procedure.

A stirred mixture of the 9(10-H)-acridone (**1**) (0.01 mol), propargyl bromide (0.8 mL, 8.98 mmol),

cetyltrimethylammonium bromide (0.08 g, 0.22 mmol), aqueous 50% potassium hydroxide (50 mL, 0.62 mol) and butanone (75 mL, 0.84 mol) was refluxed for 2.5 h. The butanone phase was separated, dried with sodium sulfate, and evaporated *in vacuo*. The residual product **(3c)** was recrystallized from ethanol. The salts were dissolved in water and the acids (**3a, b**) were liberated by addition of 1% hydrochloric acid.

Table1. Physical and ^{1}HNMR Data of 10-allylacridone (2a-c) and 10-propadienylacridone (3a-c)



Compound	R	Yield (%)	mp ^{0}C	^{1}H NMR (DMSO-d_6/TMS$_{int}$) δ, ppm; J, Hz
2a	**2-CO_2H, 6-Cl**	**78.8**	**>300**	8.80 (d, $J_{8,7}$=8.64, H_8); 8.20 (d, $J_{1,3}$=1.56, H_1); 8.11 (dd, $J_{3,4}$=8.55, $J_{3,1}$=1.56, H_3); 7.59 (d, $J_{4,3}$=8.55, H_4); 7.42 (d, $J_{5,7}$=1.86, H_5); 7.01 (dd, $J_{7,8}$=8.64 and $J_{7,5}$=1.86, H_7); 6.27 (m, $J_{12,13a}$=17.37 and $J_{12,13b}$=10.86, H_{12}); 5.20 (d, $J_{13b,13a}$=17.40, H_{13b}); 4.93 (d, $J_{13a,13b}$=17.40, $H_{13a,}$); 3.18 (CH_2).
2b	**2-CO_2H, 7-Cl**	**76.4**	**>300**	8.88 (dd, $J_{8,5}$=1.75 and $J_{8,6}$=2.50, H_8); 8.26 (d, $J_{1,3}$=2.62, H_1); 7.60 (d, $J_{3,4}$=9.00 and $J_{3,1}$=2.62, H_3); 7.84 (d, $J_{5,6}$=10.00, H_5); 7.50 (d, $J_{4,3}$=9.00, H_4); 7.32 (dd, $J_{6,8}$=2.50 and $J_{6,5}$=10.00, H_6); 6.17 (m, $J_{12,13a}$=17.15 and $J_{12,13b}$=11.18, H_{12}); 5.22 (d, $J_{13b,12}$=11.18 and $J_{13b,13a}$=17.06, H_{13b}); 4.95 (dd, $J_{13a,12}$=17.15 and $J_{13a,13b}$=17.06, H_{13a}); 3.03 (CH_2).
2c	**2-CH_3, 6-Cl**	**78.1**	**168-169**	8.32 (d, $J_{8,7}$=8.60, H_8); 8.12 (d, $J_{1,3}$=2.10, H_1); 7.65 (m, $J_{3,4}$=8.84 and $J_{3,1}$=2.10, H_3; H_4); 7.60 (d, $J_{5,7}$=1.60, H_5); 7.32 (dd, $J_{7,5}$=1.60 and $J_{7,8}$=8.60, H_7); 6.13 (m, $J_{12,13a}$=17.30, $J_{12,13b}$=11.74, H_{12}); 5.20 (dd, $J_{13b,12}$=11.74 and $J_{13b,13a}$=17.69, H_{13b}); 4.88 (dd, $J_{13a,12}$=17.30 and $J_{13a,13b}$=17.69, H_{13a}); 3.26 (CH_2); 2.42 (s,CH_3).
3a	**2-CO_2H, 6-Cl**	**69.5**	**>300**	8.83 (d, $J_{8,7}$=8.63, H_8); 8.35 (d, $J_{1,3}$= 1.71, H_1); 8.25 (dd, $J_{3,4}$=9.90 and $J_{3,1}$= 1.71, H_3); 7.06 (t, $J_{4,3}$=9.90, H_4); 7.60 (d, $J_{5,7}$=1.14, H_5); 7.39 (dd, $J_{7,5}$=1.14 and $J_{7,8}$=8.63, H_7); 5.75 (d, $J_{13,11}$=6.10, H_{13}); 3,30 (d, $J_{11,13}$=6.10, H_{11}).
3b	**2-CO_2H, 7-Cl**	**78.6**	**>300**	8.88 (dd, $J_{8,5}$=1.22, $J_{8,6}$=2.10, H_8); 8.26 (d, $J_{1,3}$=2.51, H_1); 7.60 (dd, $J_{3,1}$=2.51 and $J_{3,4}$=9.80, H_3); 7.04 (t, $J_{4,3}$=9.80, H_4); 7.50 (d, $J_{5,6}$=9.72, H_5); 7.32 (dd, $J_{6,5}$=9.72 and $J_{6,8}$=2.10, H_6); 5.22 (d, $J_{13,11}$=6.19, H_{13}); 3.33 (d, $J_{11,13}$=6.19, H_{11}).
3c	**2-CH_3, 6-Cl**	**81.1**	**175-176**	8.83 (d, $J_{8,7}$=8.56, H_8); 8.35 (d, $J_{1,3}$=2.10, H_1); 8.25 (dd, $J_{3,1}$=2.10 and $J_{3,4}$=8.75, H_3); 7.00 (t, $J_{4,3}$=8.75, H_4); 7.62 (d, $J_{5,7}$=1.90, H_5); 7.39 (dd, $J_{7,5}$=1.90 and $J_{7,8}$=8.56, H_7); 5.75 (d, $J_{13,11}$=6.30, $H_{13,}$); 3.36 (d, $J_{11,13}$=6.30, H_{11}); 2.40 (s,CH_3).

Recorder with a Bruker A 250 Z spectrometer

Table 2: Microanalysis Data of 10-allylacridones (2a-c) and 10-propadienylacridones (3a-c)

Compound	Calcd (%)			Found (%)		
	C	H	N	C	H	N
2a	65.17	3.83	4.47	65.15	3.90	4.45
2b	65.17	3.83	4.47	65.17	3.82	4.25
2c	72.08	4.95	4.95	72.24	4.93	4.95
3a	65.59	3.21	4.50	65.43	3.19	4.48
3b	65.59	3.21	4.50	65.62	3.24	4.53
3c	72.60	4.27	4.98	72.61	4.29	5.02

Table 3. ^{13}C-NMR Spectral Data of Compounds (2a-c) and (3a-c)

	Compound					
Carbon	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**
C_1	131.83	131.34	125.64	131.23	130.84	125.20
C_2	121.20	122.01	121.49	121.19	122.34	120.70
C_3	141.55	141.70	135.65	141.35	140.75	134.66
C_4	115.82	116.62	115.33	115.22	115.55	116.02
C_5	118.63	118.31	115.83	118.66	118.60	115.99
C_6	134.51	134.11	138.90	134.15	134.45	138.20
C_7	124.26	125.22	116.24	124.63	125.26	116.64
C_8	128.36	128.62	128.67	127.40	128.16	127.66
C_{1a}	119.18	119.13	119.94	118.95	119.10	119.90
C_{4a}	126.28	126.74	131.18	125.66	125.64	130.89
C_{8a}	115.96	116.23	139.25	116.32	116.02	139.20
C_{5a}	144.66	143.99	142.83	144.68	144.68	144.60
C_{11}	48.63	48.58	47.99	95.51	94.31	95.66
C_{12}	130.03	130.73	131.63	209.84	207.62	208.98
C_{13}	122.82	122.24	121.35	83.9	84.4	83.51
CO_2H	160.57	160.25	-	161.55	164.20	-
C=O	176.12	176.08	175.81	178.18	177.86	175.21
CH_3	-	-	20.08	-	-	20.22

Recorder with a Bruker A 250 Z spectrometer, DMSO-d_6 as solvent

Table 4. MS Spectrum of Compounds (2a-c) and (3a-c)

Compound	m/z, %I
2a	313/315 (M^+, 30.95/9.51); 296/298 (OH, 0.71/<0.3); 272/274 (C_3H_5; 18.51/5.63); 268/270 (COOH, 5.74/1.89); 255/257 (OH^-, 4.48/1.35); 244/246 (CO, 4.29/1.32); 227/275 (CO, 1.33/<0.5); 312 (M-1, 6.94/2.40); 268/270 (CO_2, 5.74/1.89); 232 (HCl, 1.44); 204 (CO, 2.40); 178 (C_2H_2, 0.95); 152 (C_2H_2, 2.64).
2b	313/315 (M^+, 30.23/9.45); 272/274 (C_3H_5, 42.49/12.95); 268/270 (COOH, 2.57/0.84); 255/257 (OH^-, 2.79/0.97); 244/246 (CO, 5.93/1.67); 227/229 (CO, 2.04/0.43); 312/314 (M-1, 2.38/0.61); 268/270 (CO_2, 2.57/0.84); 232 (HCl, 0.90); 204 (CO, 2.00); 178 (C_2H_2, 0.97).
2c	283/285 (M^+, 57.39/21.35); 268/270 (CH_3, 9.61/3.62); 256/258 (C_2H_3, 2.81/1.03); 242/244 (C_3H_5, 100/40); 228/230 (CO, 0.94<0.2); 214/216 (CO, 13.48/5.45); 178 (HCl, 14.03); 152 (C_2H_2, 7.70); 137 (CH_3, 1.03).
3a	311/313 (M^+, 14.46/5.95); 293/295 (OH 7.72/2.38); 266/268 (CO, 6.05/2.01); 238/240 (CO, 2.84/0.97); 202 (HCl, 5.95); 194 (HCl, 14.72); 176 (CN, 1.70), 166 (CO, 13.53).
3b	311/313(M^+, 16,95/6.01) ; 293/295 (OH, 6,54/2.36); 266/268 (CO, 5,88/2.02); 238/240 (CO, 1,52/0.44); 202 (HCl, 6,24); 194 (HCl, 8,62) y 166 (CO, 10,22).
3c	281/283 (M^+,40.29/13.33); 280/282 (M-1,100/35); 242/244 (C_3H_4, 9.50/3.25); 252/254 (CO, 7.64/2.80) 237/239 (CH_3, 1/<0.3); 236/238 (H , 0.66/<0.2); 216 (HCl, 6.33).

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