Research Journal of Pharmaceutical, Biological and Chemical Sciences

N-Alkylation of 1, 3-substituted Acridones by Microwave Irradiation

N.K. Sathish[1]*, Y.C. Mayur[2]

[1]Medicinal Chemistry Research Division, SAC College of Pharmacy, BG Nagara, Mandya-571448, Karnataka, India.

[2]Medicinal Chemistry Research Division, V.L.College of Pharmacy, Raichur-584103, Karnataka, India.

ABSTRACT

N-Alkylation of 1,3-disubstituted acridones has been done under microwave irradiation in absence of solvent. Various dimethyl and diacetoxy substituted acridones have been alkylated at N^{10}-position with alkyl halides (1-bromo, 3-chloro propane and 1-bromo, 4-chloro butane) by using $NaOH/K_2CO_3$ adsorbed on Al_2O_3 in the presence of TBAB under microwave irradiation. The compound 3a with 1,3-dimethyl substitution, showed good yield.

Keywords: 1,3-substituted acridone, N-alkylation, Microwave, TBAB, Tetrabutylammoniumbromide.

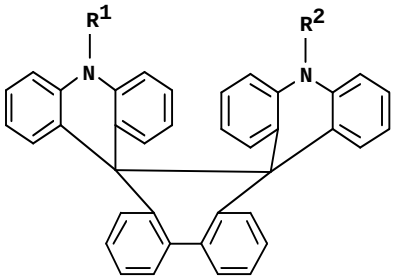
*Corresponding author

E-mail: nksathish76@yahoo.com
Mobile: +919448711684

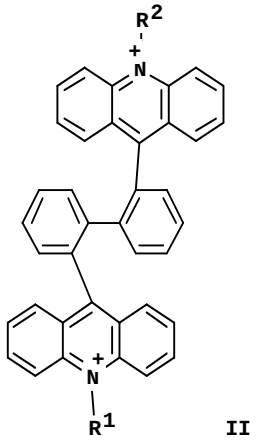
INTRODUCTION

Multidrug resistance (MDR) is one of the main obstacles limiting the efficacy of chemotherapy treatment of tumors. 10-Acridone and its 4-methoxy derivatives were prepared by the Ullmann reaction followed by cyclization and N-alkylation [1].

The biacridans I are synthsized by lithiation of (dihalogeno)biphenyl(s), coupling of the lithiated biphenyls with N-protected unsubstituted acridones, deprotection of the coupled products, protonation, alkylation, arylation, or benzylation of the resulting bisacridines, and reduction of the resulting bisacridinium compounds II [2].



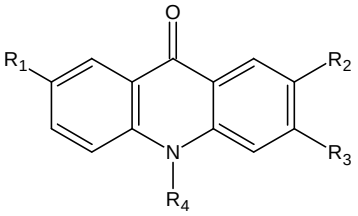
I



II

R_1, R_2 = H, alkyl, aryl, benzyl

A convenient procedure for the synthesis of N-allyl- and N-allenylacridones III under phase-transfer catalysis, using allyl and propargyl bromides as alkylating agents. When propargyl bromide was used, no propynylacridone was detected in the reaction, only propadienylacridone was obtained in moderate yield [3].

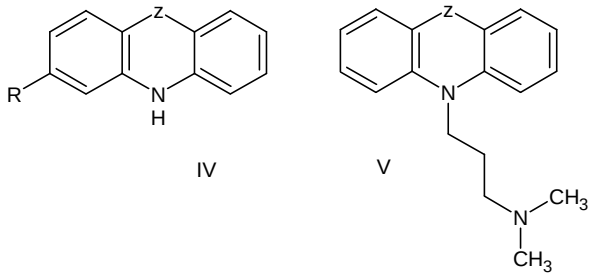


III

(R_1 = CO_2H; R_2 = Cl; R_3 = H; R_4 = $CH_2CH{=}CH_2$, $CH{=}C{=}CH_2$; R1 = CO_2H, Me; R_2 = H; R_3 = Cl),

The influence of the solvent in the alkylation reaction of 2-carboxy-6-chloro-9(10H)-acridone and 2-carboxy-6-chloro-7-nitro-9(10H)-acridone was done, obtaining the N-ethyl ester derivative of the alkylated products. Using the liquid-liquid phase transfer catalysis only the N-alkylated derivative was obtained in both cases with an improved yield [4]. N-alkyl acridones also done by liquid-liquid phase transfer catalysis [5].

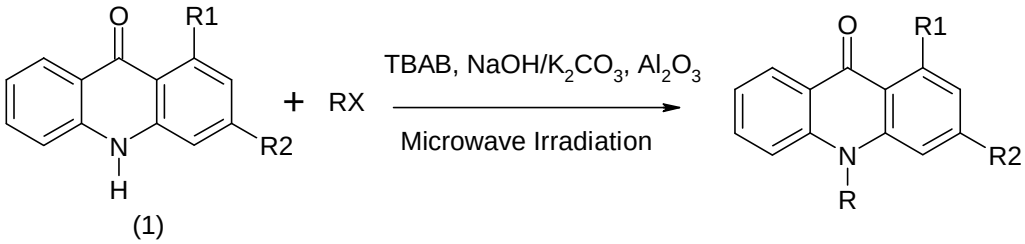
Many compounds such as Carbazole, indole, and fused tricyclic compounds IV were N-alkylated to yield N-[3-(dimethylamino)propyl]carbazole and -indole and N-aminopropyl derivatives using solid liquid two phase system. Thus, indole was treated with $CH_2N(CH_2)_3Cl$, 18-crown-6, K_2CO_3, and KOH to give 1-[3-(dimethylamino)propyl]indole, Phenothiazine, $CH_2N(CH_2)_3Cl$, $Bu_4N^+ HSO_4^-$, K_2CO_3, and NaOH gave V (Z = S) [6].



R = H, Cl; Z = S, SO2, CO, O

Wang, Cunde et al reported that N-Alkylacridones were effectively synthesized in few minutes by reaction of acridone and alkyl halides with $NaOH/K_2CO_3$ absorbed on Al_2O_3 in the presence of TBAB under microwave irradiation without solvent [7].

The 1,3-disubstituted acridones were synthesized by condensation of anthranilic acid and substituted phenols [8]. A survey of chemical literature has revealed that the N-alkylation of 1,3-dimethyl and diacetoxy acridones has not been reported. Hence, we planned to synthesize a rapid N-alkylation of 1,3-disubstituted acridones in dry media under microwave irradiation using different conditions with improved yield (Scheme).



$R_1=CH_3$, $R_2=CH_3$ **(1a)**

$R_1=OCOCH_3$, $R_2=OCOCH_3$ **(1b)**

Comp.	R
(1a)	$-CH_2-CH_2-CH_2-Cl$ **(2a)**, $-CH_2-CH_2-CH_2-CH_2-CH_2-Cl$ **(3a)**
(1b)	$-CH_2-CH_2-CH_2-Cl$ **(2b)**, $-CH_2-CH_2-CH_2-CH_2-CH_2-Cl$ **(3b)**

EXPERIMENTAL

Reactions were monitored by TLC, Column Chromatography utilized silica gel Merck Grade 60 (230–400 mesh, 60 Å). Melting points were recorded on a Tempirol hot-stage with microscope and are uncorrected. Elemental analysis was performed and found values are within 0.4% of theoretical values unless otherwise noted. ^{1}H-NMR spectra were recorded in $CDCl_3$ solution in a 5-mm tube on a Bruker DRX 300 Fourier transform spectrometer with tetramethylsilane as internal standard. Chemical shifts were expressed as δ (ppm) values. Mass spectra were recorded on Micromass Q-TOF and Shimadzu LCMS 2010A Mass spectrometry.

General Procedure for the Preparation of Compounds

A mixture of 0.9 g substituted acridone, alkyl halide (7.5–75 mmol) and 0.16 g TBAB (0.5 mmol) and 0.4 g NaOH (10 mol)/0.69 g K_2CO_3 (5 mol) adsorbed on 5 g Al_2O_3 (300 m) was introduced into a Galanz WP 750A domestic microwave oven in a 25 mL beaker. Microwave irradiation was performed for the appropriate time and at the power indicated (see Table-1). The mixture was cooled to ambient temperature, the product was obtained directly by silica gel column chromatography, using petroleum ether (60–90°C)–ethyl acetate–dichloromethane as

eluent. The structures of all products were identified on the base of elemental analytical data, ^{1}H-NMR and Mass spectral data.

10-(3-chloropropyl)- 1,3-dimethyl-10H-acridin-one (2a)

M.p: 180-190° C.^{1}H-NMR (DMSO-d_6) δ =6.7-8.45 (m, 6H, Ar-H), 2.05 (m, 2H, H_l), 3.99 (t, 2H, H_k J=2H_Z), 3.55 (t, 2H, H_m J=6Hz), 2.36, 2.88 (2s, 2CH_3), MS *m/z*: 299 $[M]^+$. Anal. Calcd for $C_{18}H_{18}$ ClNO: C, 72.11; H, 6.05; N, 4.67. Found: C, 72.08; H, 5.95; N, 4.56.

10-(4'-Chlorobutyl)- 1,3-dimethyl-10H-acridin-one (3a)

Mp: 130°C. ^{1}H-NMR (DMSO-d_6) δ = 6.7-8.45 (m, 6H, Ar-H), 2.05 (m, 2H, H_l), 3.75 (t, 2H, H_k J=6Hz), 4.2 (t, 2H, H_n J=8Hz), 1.6-2.26 (m, 4H, H_l and H_m), 2.4, 2.9 (2s, 2CH_3);
MS *m/z*: 313 $(M)^{+\cdot}$ Anal. Calcd for $C_{19}H_{20}$ ClNO: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.60; H, 6.33; N, 4.35.

10-(3-chloropropyl)-1,3-diacetoxy-10H-acridin-one (2b)

M.p: 150-155° C.^{1}H-NMR (DMSO-d_6) δ =7.39-8.33 (m, 6H, Ar-H), 2.05 (m, 2H, H_l), 3.99 (t, 2H, H_k, J=2H_Z), 3.55 (t, 2H, H_m, J=6Hz), 2.19 (s, 2$COCH_3$), MS *m/z*: 387.1 (M^+). Anal. Calcd for $C_{20}H_{18}$ $ClNO_5$: C, 61.94.39; H, 4.68; N, 3.61. Found: C, 61.89; H, 4.62; N, 3.58.

10-(4'-Chlorobutyl)- 1,3-diacetoxy-10H-acridin-one (3b)

Mp: 120^{0}C. ^{1}H-NMR ($CDCl_3$) δ = 6.21-8.34 (m, 6H, Ar-H), 2.05 (m, 2H, H_l), 3.61 (t, 2H, H_k,J=6Hz), 4.21 (t, 2H, H_n J=8Hz), 1.6-2.26 (m, 4H, H_l and H_m), 2.3 (s, 6H, 2$COCH_3$); MS *m/z*: 400.9 (M^+). Anal. Calcd for $C_{21}H_{20}ClNO_5$: C, 62.77; H, 5.02; N, 3.49. Found: C, 62.66; H, 4.98; N, 3.35.

RESULTS AND DISCUSSION

The reactions were carried out by simple mixing of 1,3-disubstituted acridones, alkyl halide, a catalytic amount of tetrabutylammonium bromide (TBAB) and NaOH/K_2CO_3 adsorbed on to Al_2O_3, and then by irradiating in an open vessel in a domestic microwave oven for 2–6 min. Effects of incident power as well as those of reaction times are checked. The optimum conditions and yields are given in Table 1. The reactions proceeded smoothly. Reaction time varied from 2 to 6 min. N-alkyl substituted acridones were isolated by silica gel column chromatography, using petroleum ether (60–90%)–ethyl acetate–dichloromethane as eluent. However, the yield depended largely on the kind of alkyl halide and the strength of base (Table 2). Comparing the yields of Entries 1–5, it can be found easily that the reactions in the presence of the mixed base KOH–K_2CO_3, NaOH–K_2CO_3 gave better yields than those in the presence of the base KOH, NaOH, or K_2CO_3. The effects of power and time of microwave irradiation for the synthesis of 3a are also studied. The results are summarized in Tables 3 and 4.

Table-1: Preparation of the compounds with isolated yield.

Compound	MW Power(W)	Irradiated time	Yield (%)	Melting point °C
2a	225	6	71	180-185
3a	300	5	88	130
2b	200	4	65	150-155
3b	225	5	69	120

Table-2: The effect of base in *N*-alkylation of substituted acridones

Entry	Base	Yield (%) of compound 3a
1	KOH	76
2	NaOH	70
3	NaOH-K_2CO_3	88
4	KOH-K_2CO_3	81
5	K_2CO_3	64

Table-3: Effect of the power of microwave irradiation on the synthesis of 3a in 3 minutes

Microwave power (W)	200	225	300	400	500
Compound 3a yield (%)	65	71	75	88	73

Table-4: Effect of the time of microwave irradiation on the synthesis of 3a at MW 300

Reaction time (min)	2	3	4	5	6
Compound 3a yield (%)	65	75	79	88	76

CONCLUSION

A rapid procedure for the efficient preparation of N-alkyl 1,3 substituted acridones has been developed in 65–88% yield from 1,3-disubstituted acridones and alkyl halides using TBAB as phase transfer catalysis in the presence of the mixed base NaOH/K_2CO_3.

ACKNOWLEDGEMENT

NK Sathish thanks to UGC for the award of RGNJRF and Management of Academy of Medical Education, Raichur, India for providing necessary facilities.

REFERENCES

[1] Ravi Hegde, Thimmaiah P, Mayur YC, Krishnegowda G, Thimmaiah KN, Houghton P J. European J Med Chem 2004; 39:161-177.

[2] Suzuki T, Tsuji T, Fujiwara N, Kawai H, Higuchi H, Uda A, Ota K. Biacridans and bisacridinium compounds, their manufacture, and environmentally friendly electrochemical fluorescent imaging and electrochromic materials, Jpn. Kokai Tokkyo Koho, 2005, pp 17

[3] Xuarez Lisbet, Pellon Rolando F, Fascio Mirta, Montesano Veronica. Heterocycles 2004; 63(1): 23-28.

[4] Marill LX, Comdom Rolando FP. Synthetic Communications 2001; 31(14):2159- 2167.

[5] Mayur YC, Padma T, Parimala BH, Chandramouli KH, Jagadeesh S, Made Gowda NM, Thimmaiah KN. Med Chem 2006; 2: 63-69.

[6] Schmolka SJ, Zimmer Hans. Synthesis 1984;1:29-31.

[7] Wang Cunde, Hang Tianlong, Zhang Hui. Synthetic Communications 2003;33(3): 451-456.

[8] Hlubucek J, Ritchie E and Taylor WC. Aust J Chem 1970; 23:1881-90.