Acetylene Chemistry. Part 29 [1]. A Convenient Synthesis of 9-(*N*-Alkynyl)acridinamines *via* a Nucleophilic Displacement Reaction Between 9-Chloroacridine and *N*-Alkynyl Amines

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Received February 16, 1993

Three new 9-(*N*-alkynyl)acridinamines **5**, **6** and **7** have been synthesized from 9-chloroacridine using a simple aromatic nucleophilic substitution reaction.

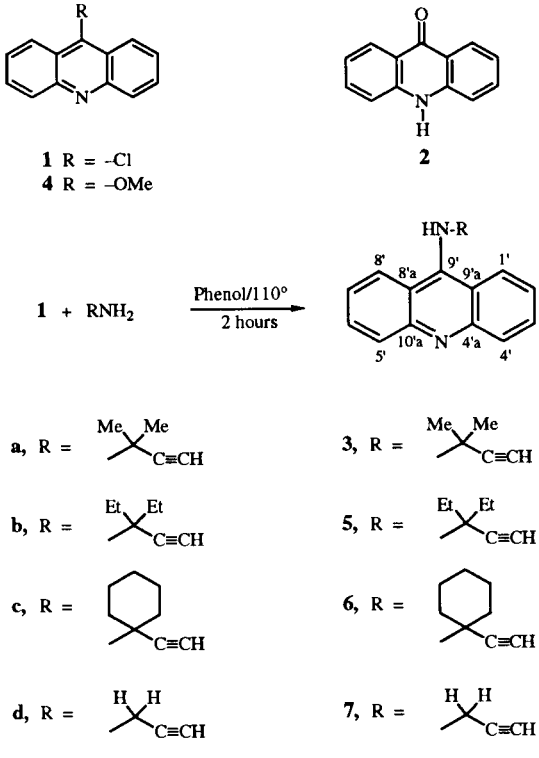
J. Heterocyclic Chem., **30**, 1677 (1993).

Various *N*-substituted-9-acridinamines show an array of biological activities such as anti-inflammatory, anti-tumor, anti-Alzheimer's, anti-HIV and cytostatic activity [2-7]. 9-(*N*-Alkynyl)acridinamines were left out from these investigations so far. Therefore an investigation was launched to synthesize some *N*-alkynyl-9-acridinamines with potential biological activity, as a continuation of our studies on acridinones and acetylenes [8].

Synthesis of *N*-alkynyl-9-acridinamines involves 9-chloroacridine (**1**) as the starting material, which is moisture (water) labile. It is a well known fact that **1** undergoes ready nucleophilic attack by moisture (water) at C-9 to produce more stable 9(10*H*)-acridinone (**2**) [9].

Thus usage of 9-chloroacridine (**1**) in a synthesis involving strong nucleophiles and having many steps was considered to be non desirable. *N*-(Acridin-9′-yl)-3-methylbut-1-yn-3-amine (**3**) has been synthesized by us [10] using 9-methoxyacridine (**4**) as the starting material. Here again **4** was synthesized from **3** *via* nucleophilic displacement. In order to obtain good yields of **4** one has to employ completely anhydrous conditions through out the reaction pathway even at the isolation stages of the compound **4**.

The method described in this paper uses 9-chloroacridine, as the starting material for the production of *N*-alkynyl-9-acridinamines, and involves a single step [11]. Primarily purified 9-chloroacridine (**1**) was heated with phenol at 110° until it dissolves and the alkynyl amines, **a-d** were added at 110°. The amine acts as the nucleophile and replaces the chloro substituent of the acridine nucleus to produce 9-(*N*-alkynyl)acridinamines **3**, **5**, **6** and **7** (see Scheme).



Scheme. Synthesis of 9-(*N*-Alkynyl)acridinamines

Table

^{13}C NMR Assignments (δ ppm in $CDCl_3$ at 50.28 MHz) 9-(*N*-Alkynyl)acridinamines, **3**, **5**, **6** and **7**

C	**3**	**5**	**6**	**7** [b]
1′ 8′	130.01	129.91	130.12	134.51
2′ 7′	124.97	124.89	124.99	124.97
3′ 6′	129.57	129.44	129.55	119.64
4′ 5′	124.32	123.98	124.19	123.85
4′a 10′a	148.45	149.00	148.66	140.44
8′a 9′a	123.69	123.31	123.12	112.73
9′	149.64	149.47	149.39	165.77
-*C*≡C-H	88.94	86.40	86.75	77.93
-C≡*C*-H	72.12	74.97	75.52	74.92
Others [a]	53.35	61.27	58.19	37.79
	(-*C*-NH)	(-*C*-NH)	(-*C*-NH)	(-*C*H$_2$-NH)
	31.55 (CH_3)	33.09 (CH_2)	40.09)))	
		8.98 (CH_3)	25.21)))	CH_2 of
			23.29)	

[a] Possible assignments are in parenthesis. [b] Recorded in $CDCl_3$ containing CD_3OD due to low solubility in $CDCl_3$.

The ^1H nmr and ^{13}C nmr spectral data of all the compounds prepared were found to be consistant with the expected structures. Unambiguous assignment of ^{13}C nmr data of these compounds were possible by comparison with the published data on *N*-(acridin-9'-yl)-3-methylbut-1-yn-3-amine (**3**) [10] (see Table).

EXPERIMENTAL

Melting points were determined on Kofler hot stage apparatus and are uncorrected. The ^1H nmr and ^{13}C nmr spectra were recorded in deuteriochloroform with tetramethylsilane as internal reference on Varian Gemini 200 spectrometer at 200 MHz and 50.28 MHz respectively. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV and high resolution mass spectra were measured on a Finnigan MAT 312 spectrometer at 70 eV.

9-Chloroacridine was purchased from Eastman Kodak Co. (USA) and purified over a short column of silica gel (eluant: dry dichloromethane) before utilisation.

Preparation of 9-(*N*-Alkynyl)acridinamines **3**, **5**, **6** and **7**.

9-Chloroacridine (0.106 g, 0.5 mmole) was fused with crystalline phenol (0.6 g) at 110° and the amines **a** to **d** were added in 2-fold excess. The heating was continued for 2 hours and the reaction mixture was allowed to cool, stirred with 2 *M* aqueous potassium hydroxide solution (25 ml), then extracted with diethyl ether. The ether layer was dried over anhydrous sodium sulphate and solvent was removed under *vacuo*. The resultant solid was chromatographed over preparative tlc (6% methanol in dichloromethane x 3) to obtain the title aminoacridine derivatives.

N-(Acridin-9'-yl)-3-methylbut-1-yn-3-amine (**3**).

This compound was obtained as a yellow amorphous solid (0.083 g, 64%), mp 93-94°; ^1H nmr: δ 8.46 (dd, 2H, J = 1.4 and 8.8 Hz, 4'-H, 5'-H), 8.18 (dd, 2H, J = 1.2 and 8.7 Hz, 1'-H, 8'-H), 7.73 (ddd, 2H, J = 1.4, 6.5 and 8.7 Hz, 2'-H, 7'-H), 7.47 (ddd, 2H, J = 1.2, 6.5 and 8.8 Hz, 3'-H, 6'-H), 2.33 (s, 1H, C≡C-*H*), 1.62 (s, 6H, 2 x C*H*$_3$); ^{13}C nmr: (see Table); ms: m/z (relative intensity, %) 260 (22, M$^+$), 245 (12), 209 (12), 194 (100), 166 (25), 140 (12) and 67 (17); hrms Calcd. for $C_{18}H_{16}N_2$ 260.13135. Found: 260.1318.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.08; H, 6.15; N, 10.76.

N-(Acridin-9'-yl)-3-ethylpent-1-yn-3-amine (**5**).

This compound was obtained as a yellow oil (0.060 g, 42%); ^1H nmr: δ 8.45 (dd, 2H, J = 1.4 and 8.7 Hz, 4'-H, 5'-H), 8.16 (dd, 2H, J = 1.3 and 8.7 Hz, 1'-H, 8'-H), 7.71 (ddd, J = 1.4, 6.5 and 8.7 Hz, 2'-H, 7'-H), 7.44 (ddd, 2H, J = 1.3, 6.5 and 8.7 Hz, 3'-H, 6'-H), 2.36 (s, 1H, C≡C-*H*), 1.85 (ddq, 4H, J = 28.8 and 7.5 Hz, -C*H*$_2$CH$_3$), 1.05 (t, 6H, J = 7.5 Hz, CH$_2$C*H*$_3$); ^{13}C nmr: (see Table); ms: m/z (relative intensity, %) 288 (20, M$^+$), 273 (7), 259 (12), 194 (100), 166 (10), 129 (10), 97 (10) and 67 (25); hrms Calcd. for $C_{20}H_{20}N_2$: 288.16265. Found: 288.1632.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71. Found: C, 83.33; H, 6.94; N, 9.72.

N-(Acridin-9'-yl)-1-ethynylcyclohexanamine (**6**).

This compound was obtained as a yellow semisolid (0.060 g, 40%); ^1H nmr: δ 8.50 (dd, 2H, J = 1.3 and 8.7 Hz, 4'-H, 5'-H), 8.18 (dd, 2H, J = 1.2 and 8.7 Hz, 1'-H, 8'-H), 7.73 (ddd, 2H, J = 1.3, 6.5 and 8.7 Hz, 2'-H, 7'-H), 7.47 (ddd, 2H, J = 1.2, 6.5 and 8.7 Hz, 3'-H, 6'-H), 2.43 (s, 1H, C≡C-*H*), 1.85-1.60 (m, 10H, 5 x C*H*$_2$); ^{13}C nmr: (see Table); ms: m/z (relative intensity, %): 300 (14, M$^+$), 257 (5), 194 (100), 166 (11), 140 (6), 79 (5) and 67 (22); hrms Calcd. for $C_{21}H_{20}N_2$: 300.1626. Found: 300.1620.

Anal. Calcd. for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 84.00; H, 6.66; N, 9.33.

N-(Acridin-9'-yl)-propyn-3-amine (**7**).

This compound was obtained as a yellow amorphous solid (0.069 g, 57%), mp 218-220°; ^1H nmr: δ 8.54 (d, 2H, J = 8.7 Hz, 4'-H, 5'-H), 7.94 (d, 2H, J = 8.6 Hz, 1'-H, 8'-H), 7.77 (dd, 2H, J = 6.8 and 8.6 Hz, 2'-H, 7'-H), 7.44 (dd, 2H, J = 6.8 and 8.7 Hz, 3'-H, 6'-H), 4.78 (brs, 2H, C*H*$_2$-C≡C), 2.69 (t, 1H, J = 2.4 Hz, C≡C-*H*); ^{13}C nmr: (see Table); ms: m/z (relative intensity, %) 232 (100, M$^+$), 217 (9), 193 (39), 166 (76), 140 (17), 115 (23), 102 (18), 75 (20) and 63 (14); hrms Calcd. for $C_{16}H_{12}N_2$: 232.1000. Found: 232.0995.

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.76; H, 5.17; N, 12.07.

Acknowledgement.

We thank Mrs. I. Meinert for typing the manuscript, Deutsche Forschungsgemeinschaft (DFG) and Natural Resources, Energy and Scientific Authority (NARESA), Sri Lanka for financial assistance and DAAD for the award of a fellowship to G.M.K.B.G.

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