Reactivity of the Acridine Ring: One-Pot Regioselective Single and Double Bromomethylation of Acridine and Some Derivatives

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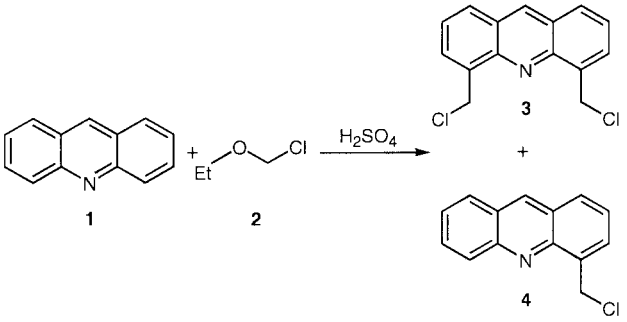
Abstract: We report here a new efficient regioselective synthetic route to 4-bromomethylacridine and to 4,5-bis-(bromomethyl)acridine, two interesting starting materials for various 4-methyleneacridine and 4,5-bis-(methylene)acridine derivatives, in one step by direct bromomethylation of acridine with bromomethylmethylether (BMME). We also describe some biologically interesting diesters derivatives from the corresponding 4,5-bis(hydroxymethyl)acridine precursor.

Key words: acridines, bromomethylation, electrophilic aromatic substitution, regioselectivity, reactivity



Scheme 1 Chloromethylation of acridine.

Regioselective functionalization of position 4 of the acridine ring has been poorly described in the literature. The first example reported by Hess in 1971 is about the synthesis of 4-phthalimidoacridines from acridine, involving a Tscherniac–Einhorn reaction.[1] This regioselective reactivity seems to be possible because of the protonation of the acridine ring nitrogen. We did recently optimize this method to synthesize various 4-amino- and 4-hydroxymethylacridine derivatives.[2] Halomethylacridines are also synthetic precursors of choice that were widely described in the literature and extensively used in our laboratory, but their synthesis generally involves many steps.[3] In search for an efficient method to get halomethylacridines, we decided to exploit the particular reactivity of the lateral phenylenes of protonated acridine. Many assays were carried out in order to functionalize directly the acridine ring, but classical chloromethylation methods,[4,5] involving formaldehyde, paraformaldehyde or trioxane with $HCl/ZnCl_2$ or H_2SO_4, under heating, microwave irradiation or sonication, were completely inefficient. Neither chloromethylacridines nor hydroxymethylacridines were obtained and the starting acridine was totally recovered every time.

Use of chloromethylethylether (CMEE, **2**) under strong acidic conditions gave some traces (less than 5% conversion) of product **3** and **4** that were isolated by column chromatography (Scheme 1). Because of these encouraging results, we decided to follow the halomethylether way.

Bromomethylmethylether (BMME, **5**) was the reagent of choice for this reaction. It has already been described by Taylor as an efficient bromomethylating agent of aromatic compounds.[5] As shown in Scheme 2, under strong acidic conditions, **5** reacts with acridine by electrophilic substitution regioselectively at position 4. Compound **6** was obtained in one step and under mild conditions[6] with a yield of 31%. In the previously reported synthetic route,[3b] **6** was obtained in 4 steps and with only 27% overall yield. However, unlike the results described in the Hess article, in which mono- or di-alkylation was depending only on the quantity of electrophile,[7] in the case of BMME reaction, monoalkylation was difficult to carry out in higher yield. It seems that the intermediate 4-bromomethylacridinium has a higher reactivity towards N-protonated **6** than acridinium, leading to 4,5-bis(bromomethyl)acridine as by-product. We decided to exploit this particular reactivity to get 4,5-bis(bromomethyl)acridine. Increasing BMME/acridine ratio at a controlled temperature was critical to get the bisfunctional product in good yield. This method afforded 4,5-bis(bromomethyl)acridine **7** with a suitable yield of 64%.[8]

4,5-Bis(bromomethyl)acridine was easily converted into the corresponding 4,5-bis(hydroxymethyl)acridine (**8**) using the classical $CaCO_3$ hydrolyzing method.[9] Yield after column chromatography (CH_2Cl_2/EtOAc, 5/5 v:v) was 92%.

Several diester derivatives **9a**–**h** (Scheme 3) were prepared using classical esterification methods with various acyl chlorides and DMAP as activator.[10] These compounds were synthesized because of their structural similarities with various anticancer and antileishmanian drugs.[11]

In conclusion, we have described for the first time the one-pot regioselective synthesis of 4-bromomethylacridine and 4,5-bis(bromomethyl)acridine by taking

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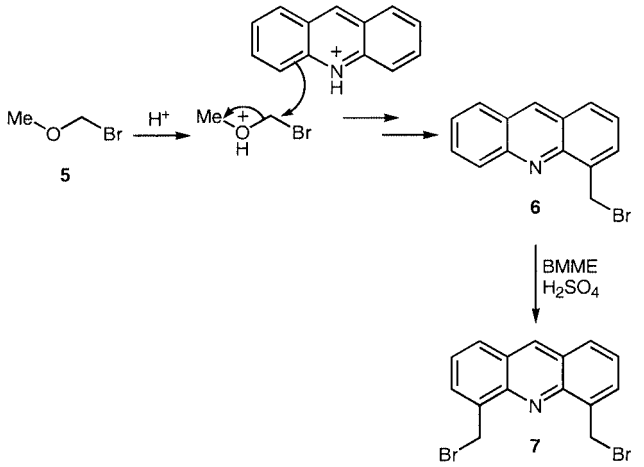
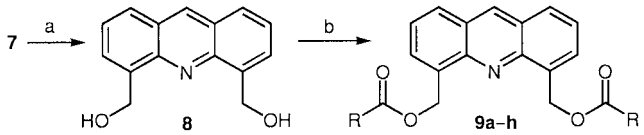


Scheme 2 Bromomethylation of acridine.



Scheme 3 a) $CaCO_3$, H_2O/Dioxane, reflux; b) RCOCl, DMAP, Et_3N, CH_2Cl_2.

Table 1 Yields and Melting Points of Diester Derivatives

Moiety	R	Yield (%)	Mp (°C)
a	Ph	79	160
b	4-Cl-C_6H_4	79	170
c	4-F-C_6H_4	82	186
d	4-MeO-C_6H_4	81	199
e	4-Me_2N-C_6H_4	67	263
f	CH_2=CH	32	104
g	4-Cl-Prop	65	–[a]
h	4-(Ph-N=N)-C_6H_4	42	218

[a] Compound **9g** is an oil.

advantage of the particular reactivity of position 4, respectively 5, of acridine enhanced by protonation of the central ring nitrogen. We also reported for the first time the 4,5-bis(hydroxymethyl)acridine, which undergoes esterification to give new 4,5-bisfunctional acridinic esters **9a**–**h** that are potential anticancer and antileishmanian drugs (Table 1).

References

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(6) **4-Bromomethylacridine 6**: Acridine **1** (1 g, 5.58 mmol) was dissolved in H_2SO_4 (20 mL) at 20 °C under N_2 and BMME **5** (1.05 g, 7,71 mmol) was added in one portion. The mixture was maintained at 20 °C for 17 h then it was poured into ice and stirred for 1 h. The precipitated was filtered off and dissolved in $CHCl_3$. The organic layer was then dried with $MgSO_4$, the solvent was removed under vacuo and the resulting yellow solid was chromatographed (silica gel, $CHCl_3$/cyclohexane, 7/3, v:v) to give **6** as a bright yellow powder (466 mg, 31%). Mp 166 °C, lit.[3b] 165 °C.

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(8) **4,5-Bis(bromomethyl)acridine 7**: Acridine **1** (2 g, 11.16 mmol) was heated in H_2SO_4 (25 mL) to 50 °C under N_2 and BMME **5** (6.08 g, 44.64 mmol) was added in one portion. The mixture was maintained at 50 °C for 12 h then it was poured into ice and stirred for 1 h. The precipitated was filtered off and dissolved in $CHCl_3$. The organic layer was then dried with $MgSO_4$, the solvent was removed under vacuo and the resulting yellow solid was recrystallized from dry Et_2O to give **7** as a bright yellow powder (2.49 g, 64%). Mp 156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.19 (s, 4 H), 7.95 (dd, 1 H, *J* = 8 Hz), 8.37 (d, 1 H, *J* = 8 Hz), 8.50 (d, 1 H, *J* = 8 Hz), 9.91 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.01, 126.94, 127.59, 128.81, 131.55, 137.83, 139.45, 151.22. Anal. Calcd for $C_{15}H_{11}Br_2N$: C, 49.35; H, 3.04; N, 3.84. Found: C, 49.49; H, 3,03; N, 3.83.

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(10) **(5-{[(4-Chlorobenzoyl)oxy]methyl}-4-acridinyl)methyl 4-Chlorobenzoate 9b**: A solution of 4-chlorobenzoyl chloride (471 mg, 2.75 mmol) in CH_2Cl_2 (10 mL) was added dropwise under N_2 to a stirred solution of **7** (300 mg, 1.25 mmol), Et_3N (0.44 mL, 3.17 mmol) and DMAP (383 mg, 3.14 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After complete addition, the mixture was allowed to stand at r.t. for 6 h. The organic layer was then washed with NaOH 1 N (2 × 35 mL), dried with $MgSO_4$ and the solvent was removed under vacuo. The resulting solid was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc, 99:1, v:v) to give **9b** as a yellow powder (515 mg, 81%). Mp 170 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6,21 (s, 4 H), 7.35 (m, 4 H), 7.53 (dd, *J* = 8.5, 6.9 Hz, 2 H), 7.84 (dd, *J* = 6.9, 0.8 Hz, 2 H), 7.97 (dd, *J* = 8.5, 0.8 Hz, 2 H), 8.02 (m, 4 H), 8.77 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 63.67, 125.50, 126.33, 128.26, 128.67, 128.73, 128.85, 131.10, 134.46, 136.18, 139.31, 146.13, 165.61. Anal. Calcd for $C_{29}H_{19}Cl_2NO_4$: C, 67.58; H, 3.71; N, 2.71. Found: C, 67.45; H, 3.70; N, 2.70.

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