SHORT PAPER

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Structural studies on bioactive compounds. Part 33.‡ Synthesis of 9-arylacridines by palladium-mediated couplings†

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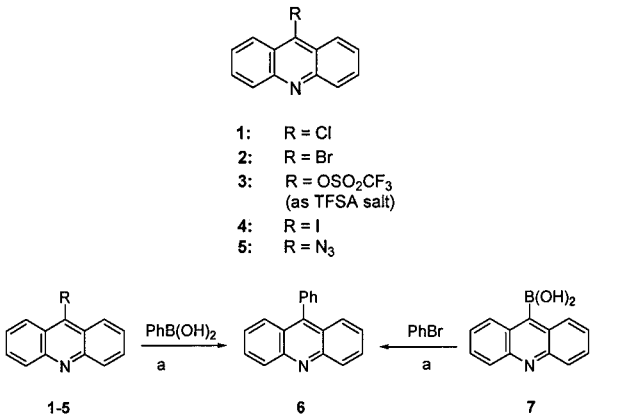
9-Halogenoacridines undergo Suzuki cross-coupling reactions with a range of arylboronic and thienyl-3-boronic acids to yield substituted 9-arylacridines and 9-(thien-3-yl)acridines.

The first synthesis of 9-halogenoacridines dates back to the early days of the nineteenth century[1,2] and 9-chloroacridine **1** in particular has been used as a starting material for the synthesis of antibacterial 9-aminoacridines[3] and antitumour 9-anilinoacridines.[4] As part of a study to explore the biological properties of novel polycyclic acridines[5] we required a versatile synthesis of 9-arylacridines and considered that 9-halogenoacridines could be substrates for Suzuki cross-coupling reactions. At the outset two potential problems were envisaged: (1) a halogen atom at the 9-position of acridine is activated to nucleophilic displacement (*i.e.* hydrolysis) by the electron-withdrawing π-deficient pyridine ring; and (2) hydrogen atoms in the *peri*-positions (1,8) could sterically hinder formation of the acridine-palladium-halogen intermediate and its subsequent encounter with an arylboronic acid. Selection of the appropriate 9-halogenoacridine was seen as the key to successful Suzuki reactions.

9-Chloroacridine is conveniently synthesized from 2-anilinobenzoic acid and phosphorus oxychloride.[3] Interaction of acridone and a mixture of bromine/phosphorus pentabromide gave a mixture of bromoacridines from which 9-bromoacridine **2** could be obtained in 76% yield.[6] Singer and Mass[7] reported the conversion of acridone to the trifluoromethanesulphonic acid (TFSA) salt of 9-trifluoromethanesulphonyloxyacridine **3** and this synthesis gave a 90% yield of product in our hands. The salt was reacted with sodium iodide in acetonitrile at 25 °C, followed by basification with diisopropylethylamine, to give 9-iodoacridine **4** in 85% yield. The same displacement method, using sodium chloride or sodium azide, gave **1** (40%) and 9-azidoacridine **5** (26%) respectively. Azide **5** was more conveniently prepared from **1** and sodium azide in aqueous acetone.[4]

Alternative routes to 9-iodoacridine **4** from chloroacridine **1** and HI/NaI, or from 9-aminoacridine and isoamyl nitrite/CH_2I_2 were inefficient, giving the iodoacridine in only 8 and 11% yields, respectively. In pilot experiments acridines **1–5** were coupled with benzeneboronic acid in the presence of diacetato[1,1'-bis(diphenylphosphino)ferrocene]palladium [Pd(dppf)$(OAc)_2$] catalyst. The highest yield of 9-phenylacridine 6 (60%) was obtained from 1; 9-azidoacridine gave no coupled product (Scheme 1). Alternatively, acridin-9-ylboronic acid **7**, prepared (65%) from 9-bromoacridine/*n*-BuLi/THF/triethyl borate/- 78 °C followed by HCl quench, was coupled with bromobenzene but the yield was only 23%.

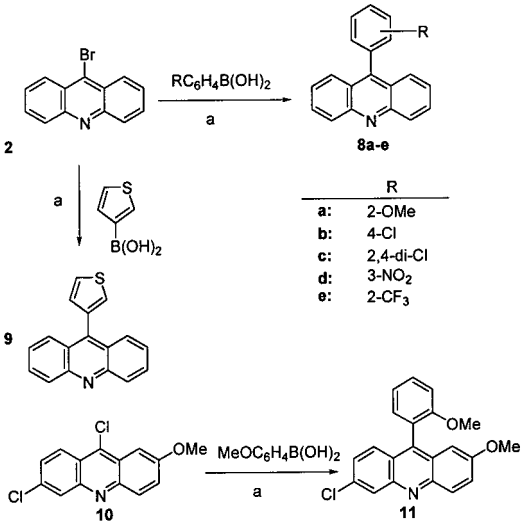


Yields of 9-phenylacridine **6**: from **1** (60%); **2** (50%); **3** (30%); **4** (38%); **5** (0%); **7** (23%)

[a]Reagents and conditions: a, Pd(dppf)$(OAc)_2$, Na_2CO_3, DMF or DME, 16 h at 110°C under N_2

Scheme 1

9-Bromoacridine **2** was coupled with a range of arylboronic acids and thienyl-3-boronic acid in the presence of Pd(dppf)$(OAc)_2$ (Scheme 2). Boronic acids bearing electron-donating substituents gave higher yields of 9-arylacridines, *e.g.* **8a**, **9** and **11**. However, yields overall were only poor to modest reflecting steric impediments imposed by interactions



[a]Reagents and conditions: a, Pd(dppf)$(OAc)_2$, Na_2CO_3, DMF or DME, 16 h at 110°C under N_2

Scheme 2

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

‡ Part 32. G. Wells, A. Seaton and M.F.G. Stevens, *J. Med. Chem.* in press

Table 1 Yields and physical characteristics of 9-substituted acridines formed from 9-bromoacridine **(2)**

Compound	Yield (%)	mp (°C)	Formula	% Found (required)			LRMS[a] M +1 Found (required)
				C	H	N	
8a	55	190–191	$C_{20}H_{15}NO$	84.20 (84.19)	5.29 (5.30)	4.90 (4.91)	286.3 (286.1)
8b	32	210–212	$C_{19}H_{12}ClN$	78.72 (78.76)	4.16 (4.17)	4.97 (4.83)	290.1 (290.1)
8c	30	220–221	$C_{19}H_{11}Cl_2N$	70.52 (70.39)	3.38 (3.42)	4.47 (4.32)	324.1 (324.0)
8d	21[b]	262–263	$C_{19}H_{12}N_2O_2$	76.08 (75.99)	3.94 (4.03)	9.38 (9.33)	301.2 (301.1)
8e	28[c]	208–211	$C_{20}H_{12}F_3N$	74.25 (74.30)	3.60 (3.74)	4.19 (4.33)	324.2 (324.1)
9	55	163	$C_{17}H_{11}NS$	77.87 (78.13)	4.26 (4.24)	5.49 (5.36)	262.2 (262.1)
11	48	150–152	$C_{21}H_{16}ClNO_2$	72.18 (72.10)	4.72 (4.61)	4.28 (4.00)	350.2 (350.1)

[a]APCI. [b]From starting material **3**. [c]From starting material **4**.

with *peri*-hydrogen atoms in the acridine ring (Table 1). Presumably acridine **11** exists as an enantiomeric (atropisomeric) mixture because of restricted rotation round the pivotal acridine-aryl bond.

This rotation was simulated using a semi-empirical AM1 model of the compound **11**. The torsion (dihedral) angle ϕ formed between the acridine ring and the benzene ring was changed in 10° steps and the geometrical optimization was performed (restraint force constant of the angle ϕ = 10^5 kcal/mol deg^2 and RMS gradient = 0.1 kcal/Å mol). The energy difference between the conformer with the lowest energy (ΔH_f = 19.735 kcal/mol; ϕ = –80°) and the highest energy conformers (ΔH_f = 40.343 kcal/mol; ϕ = -180° and ΔH_f = 42.708 kcal/mol; ϕ = 0°) are 20.608 kcal/mol and 22.973 kcal/mol respectively. These energy barriers should be high enough to allow the existence of two stable enantiomeric forms of the compound **11** at ambient temperature.

A further study was made using ^{1}H NMR spectroscopy. The mixture of the paramagnetic shift reagents Silver-fod; [(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)silver] and Europium-tfc; [tris[3-trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III)] was added (in molar ratio 1:1) to a $CDCl_3$ solution of the compound **11** (in molar ratio 1.2 : 1 to the acridine compound). Splitting of the band of the methoxy group in the ^{1}H NMR spectrum at 3.64 ppm to a doublet indicates the presence of two stable conformers of compound **11**.

The new 9-arylacridines were tested against human MCF-7 and SKBr-3 mammary carcinoma cells *in vitro* and gave IC_{50} values in the range 5-30 μM. This contrasts with values of 0.075 and 0.058 μM against these cell lines for the 9-anilinoacridine *m*-AMSA which is a potent inhibitor of mammalian topoisomerase-II.[8]

Representative experimental method: Palladium (II) acetate was heated at 50 °C with 1,1'-bis(diphenylphosphino) ferrocene (0.084 g) in DMF (5 mL) under nitrogen for 15 min. 9-Chloroacridine (0.50 g), benzeneboronic acid (0.34 g), dry Na_2CO_3 (0.60 g) and DMF (2 mL) were added and the mixture was heated at 100–110 °C for 16 h. The mixture was filtered, insoluble material washed with acetone and the organic filtrates were diluted with water. The precipitated solid was collected, purified by flash chromatography (silica gel and hexane/ethyl acetate 1:1) and crystallised from aqueous ethanol to afford 9-phenylacridine 6 (0.36 g, 60 %), mp 186-187 °C (Lit.,[3] mp 182-183 °C).

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