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Simple and convenient conversion of acridones into 9-unsubstituted acridines via acridanes using borane tetrahydrofuran complex

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ABSTRACT

A new method for the synthesis of 9-unsubstituted acridines from acridones using mild conditions is described. Various acridines bearing reduction-sensitive group(s) have been synthesized from the corresponding acridones using a two-step procedure that involved a commercially available borane complex reduction followed by an acridane oxidation.

1. Introduction

Acridine derivatives were primarily used as stains for dye manufacturing (e.g., acridine orange) until their fluorescence and chemiluminescence properties found numerous other applications (e.g., acridinium salts, lucigenin).[1,2] In addition to these optical properties, this interesting heterocyclic family also displays a broad range of biological properties including antibacterial,[3] antiparasitic,[4] and antitumor activities.[5] Intensive research into this last area has shown that the substitution on the heterocycle is crucial to specific biological activity, especially in oncology. Depending on the substituted function introduced, the acridinic antitumor derivatives include not only DNA-intercalating agents but also hypoxia-specific drugs (e.g., nitracrine), topoisomerase I and/or II (e.g., amsacrine, DACA), and telomerase inhibitors.[6]

Most routes to acridines and their derivatives proceed through the corresponding acridones (Scheme 1) via a Jourdan–Ullman[7] or Buchwald–Hartwig[8] amination reaction. Among the other acridine synthesis methods that do not involve an acridone step, the most widely used is the Bernthsen reaction[9] between a diphenylamine and a carboxylic acid in the presence of zinc chloride, and the intramolecular cyclization of diphenylamine-2-carboxaldehyde derivatives.[10] The final steps of all these methods require harsh conditions such as strong acidic media, high temperatures and/or, drastic reductive agents. Consequently, the sensitive functional groups are usually introduced later on, at specific and limited positions.

As part of our ongoing research program to develop new targeting agents for radionuclide therapy[11] of melanoma, we needed to synthesize various iodoacridine-4-carboxylic acids. The literature reports only a small number of 9-unsubsituted iodoacridines, all essentially obtained by direct electrophilic iodination of acridines bearing activated substituents[12,13] or by diazotization and nucleophilic displacement with the iodide ion of the corresponding aminoacridines.[12] However, the most satisfactory route to access to these derivatives appeared to be the two-step transformation from acridones **1** to acridines **3** via the 9,10-dihydroacridines (or 'acridanes') **2** (Scheme 1). Unfortunately, this approach, which required direct reduction of the corresponding acridone with aluminum,[7] magnesium,[14] phenylphosphine,[15] or sodium[16] amalgam in alkali, appeared unsuitable for the synthesis of functionalized acridines incorporating reduction-sensitive functional groups. We observed that iodo-substituted acridones led to dehalogenated derivatives, as previously noted by Atwell for the synthesis of chloroacridine-4-carboxylic acids.[7] To overcome this problem, we developed an efficient protocol for the conversion of iodoacridones to iodoacridines using borane tetrahydrofuran complex,[11]

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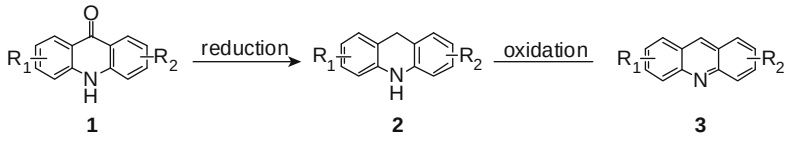
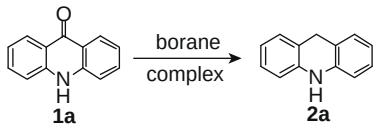


Scheme 1.

Table 1
Optimization of the reduction of acridone (**1a**) into acridane (**2a**) using different borane complexes



Entry	**1a** (M)	Borane complex (equiv)	Temperature (°C)	Time (h)	Yield[a] **2a** (%)
1	0.51	BH_3/SMe_2 (1.2)	Reflux	3	61
2	0.51	BH_3/diethyl aniline (1.2)	Reflux	18	10[b]
3	0.51	BH_3/diethyl aniline (2.4)	Reflux	48	21[b]
4	0.51	BH_3/diethyl aniline (3.2)	Reflux	5	54
5	0.51	BH_3/THF (1.2)	Reflux	1	75
6	0.51	BH_3/THF (1.2)	40	1	70
7	0.51	BH_3/THF (1.2)	rt[c]	12	NR[d]
8	0.10	BH_3/THF (1.2)	Reflux	1	52
9	0.80	BH_3/THF (1.2)	Reflux	1	58
10	0.51	BH_3/THF (2.4)	Reflux	1	71

[a] Isolated yields after column chromatography (SiO_2, CH_2Cl_2).
[b] Predominantly start product.
[c] rt = room temperature.
[d] NR = no reaction.

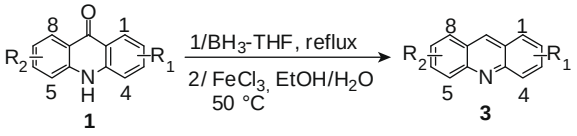
which is commonly used as regio-, chemo-, and stereoselective reducing agents for a wide range of functional groups. Based on this initial success, the protocol was tested on other acridone substrates bearing sensitive functional groups, and the results are reported here.

2. Results and discussion

The reaction was first carried out with commercially available acridone and with the three commercially available borane complex solutions (Table 1, entries 1–5). Results clearly indicated that borane tetrahydrofuran complex gave the fastest and highest-yield reaction. In this study, borane diethyl aniline complex was the least reactive, requiring 3.2 equiv to complete the reaction (Table 1, entries 2–4). Gradually decreasing the reaction temperature resulted in decreasing yields (Table 1, entries 6 and 7), whereas changes in the concentrations of acridone (**1a**) or borane tetrahydrofuran complex did not give better yields (Table 1, entries 8–10).

With the optimized conditions in hand, the reduction of various acridone compounds was studied, and the results are summarized in Table 2.[17] Preparation of acridines **3a–l** was performed by the addition of a solution of BH_3–THF to refluxing tetrahydrofuran solution of compounds **1a–l**. The reactions were maintained at reflux for 1 h and then hydrolyzed. The resulting unstable 9,10-dihydroacridines **2a–l** were classically oxidized to acridines **3a–l** with $FeCl_3$ in yields ranging from 44% to 90%. A quick column chromatography for 9,10-dihydroacridines **2a–l** compounds was necessary to obtain pure acridines **3a–l**. This method is compatible with various substituents such as iodo, chloro, nitro, and ester groups on the acridone moiety. The high yields and fairly simple reaction combined with the functional selectivity achieved with borane reagents make the BH_3–THF complex a promising reducing agent for the conversion of acridones into synthetically and biologically potent acridines. Moreover, this inexpensive and commercially available complex is environmentally friendly, whereas aluminum or sodium amalgams are synthesized in the presence of mercuric chloride, which is very toxic and an environmental hazard.

Table 2
Reduction of acridones with borane tetrahydrofuran complex



Entry	Substrate	Product[a]	R_1	R_2	Yield[b] (%)
1	**1a**	**3a**	H	H	59
2	**1b**[18]	**3b**[19]	2-Cl	H	47
3	**1c**[20]	**3c**[21]	2-Br	H	48
4	**1d**[22]	**3d**[23]	2-I	H	83
5	**1e**[24]	**3e**[25]	1-NO_2	H	50
6	**1f**[26]	**3f**[25]	2-NO_2	H	54
7	**1g**[27]	**3g**	1-CO_2Et	H	44[28]
8	**1h**[27]	**3h**	3-CO_2Et	H	73
9	**1i**[29]	**3i**	4-CO_2Me	7-Br	70
10	**1j**[11]	**3j**[11]	4-CO_2Et	1-I	65
11	**1k**[11]	**3k**[11]	4-CO_2Et	6-I	90
12	**1l**[11]	**3l**[11]	4-CONH$(CH_2)_2NEt_2$	3-I	44

[a] All known compounds were characterized by ^{1}H NMR and ^{13}C NMR and their spectroscopy profiles were identical to those reported in the literature. For the others, see Ref. 17.
[b] Isolated yields after two steps and column chromatography.

References and notes

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17. General procedure for the synthesis of acridines **3**. The appropriate 9,10-dihydro-9-oxoacridine (acridone) **1** (0.69 mmol) was dissolved in anhydrous tetrahydrofuran (2.6 mL) under a slowly flowing argon gas. A 1 M borane tetrahydrofuran complex solution (0.83 mL, 0.83 mmol) was added dropwise to the stirred reflux reaction. The mixture was refluxed for 1 h. After cooling to room temperature, aqueous 3 N hydrochloric acid solution (5 mL) was added dropwise and the reaction mixture was basified with an aqueous saturated sodium carbonate solution (20 mL) before being extracted with dichloromethane (3×20 mL). The organic phases collected were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The crude unstable product was quickly chromatographed (SiO_2, CH_2Cl_2) to give the corresponding 9,10-dihydroacridine (acridane) **2**. This acridane (0.38 mmol) was stirred in a mixture of ethanol (10 mL), water (2 mL), and iron chloride hexahydrate (0.30 g) for 30 min at 50 °C. After cooling to room temperature, an aqueous saturated sodium bicarbonate solution (20 mL) was added and the mixture was extracted with dichloromethane (3×30 mL). The organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the expected acridine **3** which could be used without further purification (except for **3g**: obtained by chromatographic purification over alumina (CH_2Cl_2–MeOH 98:2, v/v)). Spectroscopic data of the final acridines **3**: 2-iodoacridine (**3d**): mp 191–193 °C; IR (KBr) 2365, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (t, 1H, $J = 8$ Hz), 7.84 (m, 1H), 7.96 (m, 3H), 8.22 (d, 1H, $J = 9$ Hz), 8.38 (s, 1H), 8.61 (s, 1H). Ethyl acridine-1-carboxylate (**3g**): mp: 115–117 °C; IR (KBr) 1705, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51 (t, 3H, $J = 7$ Hz), 4.53 (q, 2H, $J = 7$ Hz), 7.58 (t, 1H, $J = 8$ Hz), 7.80 (m, 2H), 8.08 (d, 1H, $J = 9$ Hz), 8.23 (d, 1H, $J = 9$ Hz), 8.34 (d, 1H, $J = 9$ Hz), 8.43 (d, 1H, $J = 9$ Hz), 10.03 (s, 1H). Ethyl acridine-3-carboxylate (**3h**): mp: 109–111 °C; IR (KBr) 1703, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (t, 3H, $J = 7$ Hz), 4.46 (q, 2H, $J = 7$ Hz), 7.55 (t, 1H, $J = 7.5$ Hz), 7.79 (t, 1H, $J = 7.5$ Hz), 7.98 (m, 2H), 8.07 (d, 1H, $J = 9$ Hz), 8.23 (d, 1H, $J = 9$ Hz), 8.74 (s, 1H), 8.98 (s, 1H). Methyl 7-bromoacridine-4-carboxylate (**3i**): highly unstable compound; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 4.02 (s, 3H), 7.66 (m, 1H), 7.90 (d, 1H, $J = 9$ Hz), 8.06 (m, 2H), 8.26 (d, 1H, $J = 9$ Hz), 8.36 (s, 1H), 9.02 (s, 1H).
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28. In addition to compound **3g**, the following by-product was routinely observed: $R_1 = CH_2OH$, $R_2 = H$, 1-hydroxymethylacridine. Yield: 45%; mp: 169–171 °C; IR (KBr) 3200–3000, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.26 (s, 2H), 7.55 (m, 2H), 7.67 (m, 1H), 7.79 (m, 1H), 8.02 (d, 1H, $J = 8.5$ Hz), 8.15 (d, 1H, $J = 9$ Hz), 8.21 (d, 1H, $J = 9$ Hz), 9.10 (s, 1H).
29. This compound was obtained from the acid 7-bromo-9,10-dihydro-9-oxoacridine-4-carboxylic (Spicer, J. A.; Gamage, S. A.; Atwell, G J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 1919) according to the procedure developed for the synthesis of methyl 9,10-dihydro-7-nitro-9-oxoacridine-4-carboxylate described in Ref. 11a. Methyl 9,10-dihydro-7-bromo-9-oxoacridine-4-carboxylate (**1i**): yield 60%; mp: 214–216 °C; IR (KBr) 3266, 1691, 1593, 1518, 1277, 1138, 1129 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.99 (s, 3H), 7.40 (t, 1H, $J = 7.8$ Hz), 7.90 (m, 2H), 8,27 (br s, 1H), 8.45 (dd, 1H, $J = 7.6$, 1.6 Hz), 8.53 (d, 1H, $J = 7.8$ Hz), 11.67 (s, 1H).