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A New Synthesis of Substituted Acridine-4-carboxylic Acids and the Anticancer Drug *N*-[2-(Dimethylamino)ethyl]acridine-4-carboxamide (DACA)

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***Abstract*:** A new synthesis of substituted acridine-4-carboxylic acids **2** from methyl 2-[*N*-(2-carboxyphenyl)amino]benzoates (**4**) is reported, *via* $NaBH_4$ reduction of the corresponding imidazolides (**5**), oxidation of the resulting alcohols **6** to aldehydes **7**, and cyclisation of these with trifluoroacetic acid to the methyl acridine-4-carboxylates (**8**), followed by base hydrolysis. Direct amidation of **8a** provides a new route to the clinical anticancer drug DACA (**3**) which avoids use of the irritant acid **2a**.
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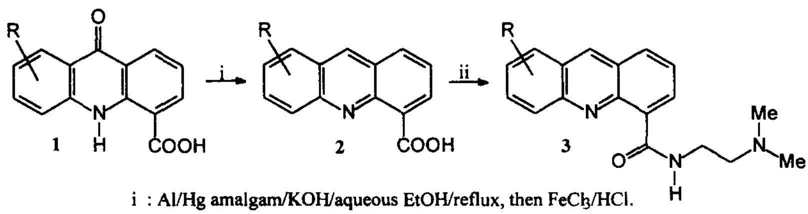
The acridine derivative *N*-[(2-dimethylamino)ethyl]acridine-4-carboxamide **3** (DACA; NSC 601316) is a new DNA-intercalating agent with inhibitory activity against the enzymes topoisomerase I and topoisomerase II.[1] It has a wide spectrum of activity against solid tumours in animals,[2,3] is relatively unaffected by P-glycoprotein-mediated multidrug resistance,[4] and is currently in clinical trial as an anticancer drug.[3] A small number of analogues of **3** bearing methyl, methoxy and chloro substituents have been reported, and many showed significant activity in a mouse solid tumour model.[2] For the synthesis of further analogues of **3**, we required the corresponding substituted acridine-4-carboxylic acids **2**. The existing route[2] (Scheme 1), from

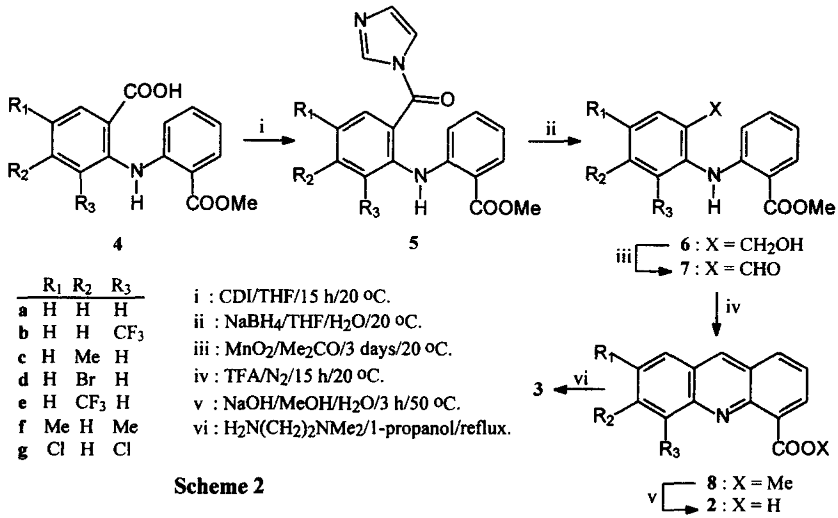


i : Al/Hg amalgam/KOH/aqueous EtOH/reflux, then $FeCl_3$/HCl.
Scheme 1 ii : CDI/DMF, then *N,N*-dimethylethylenediamine.

reduction of the corresponding acridones by aluminium/mercury amalgam, followed by re-oxidation of the resulting acridans with $FeCl_3$, has quite limited scope, requiring harsh reductive conditions. Even for the chloro derivatives reported, it was noted that some dechlorination took place.[2]

While mild acid-catalysed cyclisation of diphenylamine-2-aldehydes is a facile route to acridines,[5] the use of this procedure for the preparation of acridine-4-carboxylic acids has been precluded by the lack of a flexible synthetic route to suitably substituted precursors. However, a recent report[6] on the mild reduction of carboxylic acids to alcohols *via* imidazolides enabled us to develop a route from available[7,8] methyl 2-[*N*-(2-carboxyphenyl)amino]benzoates **4** (Scheme 2).

Thus, reaction of **4a** with CDI, followed by reduction of the resulting crude imidazolide **5a** with $NaBH_4$,[6] gave the alcohol **6a** in 83% yield. Oxidation of this with MnO_2 gave a quantitative yield of the aldehyde **7a**,



	R_1	R_2	R_3
a	H	H	H
b	H	H	CF_3
c	H	Me	H
d	H	Br	H
e	H	CF_3	H
f	Me	H	Me
g	Cl	H	Cl

i : CDI/THF/15 h/20 °C.
ii : $NaBH_4$/THF/H_2O/20 °C.
iii : MnO_2/Me_2CO/3 days/20 °C.
iv : TFA/N_2/15 h/20 °C.
v : NaOH/MeOH/H_2O/3 h/50 °C.
vi : $H_2N(CH_2)_2NMe_2$/1-propanol/reflux.

Scheme 2

which was cyclised in trifluoroacetic acid at room temperature to methyl acridine-4-carboxylate **8a** in 98% yield. Unlike the corresponding acid **2a**, the ester did not have lachrymatory or sternutatory properties, but was somewhat unstable to oxidation, slowly converting to the acridone. Mild base hydrolysis of **8a** under nitrogen gave an 87% yield of the desired acid **2a**. In contrast to **8a**, **2a** is essentially stable to oxidation.

To test the generality of this method, a series of substituted analogues of **2a** were also prepared, and the results (compound number and isolated yields) are given in Table 1.

This method thus provides a flexible and high-yielding route to acridine-4-carboxylic acids containing substituents sensitive to the reductive conditions used in the previous synthesis.[2] The availability of the intermediate methyl ester **8a** prompted us to explore its direct conversion to DACA **3** (Scheme 2), since the irritant properties of the corresponding acid **2a** makes its use in the conventional synthesis difficult on a large scale. Reaction of **8a** with *N*,*N*-dimethylethylenediamine in 1-propanol at reflux gave a 61% purified yield of **3**, suggesting this as a superior route for large-scale synthesis.

Table 1. Synthesis of substituted acridine-4-carboxylic acids **2** from substituted methyl 2-[*N*-(2-carboxyphenyl)amino]benzoates **4**.[a]

4	yield (4→7)	7	yield (7→2)	2
4a[b]	83%	**7a**[b]	87%	**2a**[b]
4b	100%	**7b**	76%	**2b**
4c	82%	**7c**	98%	**2c**
4d	67%	**7d**	100%	**2d**
4e	77%	**7e**	81%	**2e**
4f	60%	**7f**	99%[c]	**2f**
4g	44%	**7g**	92%[c]	**2g**

[a]All compounds had satisfactory spectroscopic and analytical properties. [b]ref. 2. [c]Yield for conversion **7→8** only (acids not made).

Experimental: Acridine-4-carboxylic acid 2a. A solution of methyl 2-[*N*-(2-carboxyphenyl)amino]-benzoate[7,8] **4a** (10 g, 36.9 mmol) in dry THF (200 mL) was treated with CDI (8.97 g, 55.4 mmol). The reaction mixture was allowed to stir at room temperature for 15 hours, then the THF solution was added slowly to a suspension of $NaBH_4$ (7.00 g) in H_2O (200 mL) without isolation of the intermediate imidazolide **5a**. The reaction was virtually instantaneous, and at the end of the addition the mixture was quenched with conc. HCl, partitioned between EtOAc (200 mL) and $NaHCO_3$ (200 mL), and the organic layer was dried with Na_2SO_4. Removal of the solvent and filtration of the residue through a plug of flash-grade silica gel in petroleum ether/EtOAc (4:1) gave methyl 2-[*N*-(2-hydroxymethylphenyl)amino]benzoate **6a**, (7.85 g, 83%), mp (CH_2Cl_2/petroleum ether) 69-71 °C. ^{1}H NMR ($CDCl_3$) δ 1.93 (br s, 1 H, OH), 3.91 (s, 3 H, $COOCH_3$), 4.72 (s, 2 H, CH_2OH), 6.74 (ddd, J = 8.0, 7.0, 1.1 Hz, 1 H, ArH), 7.08-7.44 (m, 6 H, H-3,3′,4,4′,5′,6′), 7.97 (dd, J = 8.1, 1.6 Hz, 1 H, ArH), 9.59 (br s, 1 H, NH).

A stirred solution of **6a** (7.74 g, 30 mmol) in Me_2CO (200 mL) was treated with a suspension of MnO_2 (10 g) for 3 days at room temperature, when all the starting material had been consumed. The MnO_2 was filtered off (Celite) and the Me_2CO was removed under reduced pressure to yield methyl 2-[*N*-(2-formylphenyl)amino]benzoate **7a** (7.70 g, 100%). A sample crystallised from EtOAc/petroleum ether had mp 110-112 °C. ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3 H, $COOCH_3$), 6.95-7.03 (m, 2 H, 2xArH), 7.41-7.45 (m, 2 H, 2xArH), 7.50 (br d, J = 8.5 Hz, 1 H, ArH), 7.61 (br d, J = 8.2 Hz, 1 H, ArH), 7.65 (dd, J = 7.7, 1.7 Hz, 1 H, ArH), 8.01 (dd, J = 7.9, 1.7 Hz, 1 H, ArH), 10.00 (s, 1 H, CHO), 11.26 (br s, 1 H, NH).

The aldehyde **7a** (210 mg, 0.82 mmol) was placed in a flask which was flushed with N_2, then TFA (10 mL) was added and the resultant solution was stirred for 24 h at room temperature. Solvent was removed under reduced pressure to give crude methyl acridine-4-carboxylate **8a** (183 mg, 94 %). The flask was flushed with nitrogen, and a degassed solution of NaOH in aqueous EtOH (1:1, 2 M) (35 mL) was added. The mixture was stirred for 3 h at 50 °C, when a clear solution was obtained, then neutralised with glacial AcOH. Extraction with EtOAc (3 x 50 mL) followed by chromatography on silica gel, eluting with EtOAc/petroleum ether (1:4), gave acridine-4-carboxylic acid (**2a**) (160 mg, 87%), mp (Me_2CO) 196-197 °C (lit.[2] mp 202-204 °C).

Direct preparation of 3 from from 8a. Aldehyde **7a** (2 g, 7.84 mmol) was cyclised in TFA as above, and the residue after removal of solvent was diluted with CH_2Cl_2 (100 mL), and neutralised with Et_3N. Solvents were removed under reduced pressure, and the residue was filtered through a short column of flash silica gel in EtOAc/petroleum ether (1:3) to give methyl acridine-4-carboxylate (**8a**) as an orange oil (1.83 g, 98%). ^1H NMR ($CDCl_3$) δ 4.12 (s, 3 H, $COOCH_3$), 7.53-7.58 (m, 2 H, H-2 and H-6 or H-7), 7.79 (ddd, J = 8.8, 6.6, 1.4 Hz, 1 H, H-7 or H-6), 8.00 (dd, J = 8.0, 1.0 Hz, 1 H, H-1), 8.12-8.14 (m, 2 H, H-5,8), 8.30 (dd, J = 8.7, 0.9 Hz, 1 H, H-3), 8.80 (s, 1 H, H-9).

A solution of **8a** (1.83 g, 7.72 mmol) and *N,N*-dimethylethylenediamine (3.40 g, 38.6 mmol) in 1-propanol (80 mL) was flushed with N_2, and the mixture was heated at reflux for three days under N_2. Solvent was then removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (100 mL) and 1M Na_2CO_3 (100 mL). The organic layer was evaporated and the residue chromatographed on alumina, eluting with CH_2Cl_2/MeOH (199:1) to give *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA; **3**) (1.38 g, 61%), mp (diHCl salt) 191-195 °C, identical with an authentic sample.[2]

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References

1. Schneider, E.; Darkin, S. J.; Lawson, P. A.; Ching, L-M.; Ralph, R. K.; Baguley, B. C. *Eur. J. Cancer Clin. Oncol.* **1988**, *24*, 1783: Finlay, G.J.; Riou, J.-F.; Baguley, B.C. *Eur. J. Cancer* **1996**, *32A*, 708.
2. Atwell, G. J.; Rewcastle, G. W.; Baguley, B. C.; Denny, W.A. *J. Med. Chem.* **1987**, *30*, 664.
3. Baguley, B. C.; Zhuang, L; Marshall, E. *Cancer Chemother. Pharmacol.* **1995**, *36*, 244.
4. Finlay, G. J.; Marshall, E.; Matthews, J. H. L.; Paull, K. D.; Baguley, B. C. *Cancer Chemother. Pharmacol.* **1993**, *31*, 401.
5. Rosevear, J.; Wilshire, J. F. K. *Aust. J. Chem.* **1981**, *34*, 839.
6. Sharma, R.; Voynov, G. H.; Ovaska, T .V.; Marquez, V.E. *Synlett* **1995**, 839.
7. Rewcastle, G. W.; Denny, W. A. *Synthesis* **1985**, 220.
8. Rewcastle, G. W.; Denny, W. A. *Synth. Commun.* **1987**, *17*, 309.

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