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One-pot derivatization of medicinally important 9-aminoacridines by reductive amination and S_NAr reaction

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ABSTRACT

A new highly efficient one-pot derivatization of medicinally important 9-aminoacridines (9-AA) at the amine position is described. Simple reductive amination and S_NAr reaction using easily accessible starting materials give a fast entry to novel 9-AA derivatives for biological screening.

The 9-aminoacridine (9-AA) core is a structure of interest to medicinal chemists and appears in many biologically active compounds, mostly with anticancer and antimalarial applications. 9-AA derivatives such as quinacrine[1] are able to intercalate with DNA, and consequently, can inhibit DNA transcription in parasites.[2] 9-Anilinoacridines have good antimalarial activities and are potent parasite DNA topoisomerase II inhibitors.[3] N-alkylated 9-AA analogs have been shown to be potent inhibitors of prion disease in cultured neuroblastoma cells, which also show inhibition by lysosomotropic agents and cysteine protease inhibitors.[4]

In the field of antitumor DNA-intercalating agents, 9-AA derivatives play an important role due to their antiproliferative properties.[5] Several cancer chemotherapeutics such as Amascrine and Ledakrin based on the 9-aminoacridine scaffold have been developed.[6a] In addition, a series of potential topoisomerase II-mediated anticancer 9-anilinoacridines, which are designed to avoid bioxidation and which possess long durations of drug action, have been reported.[7] Among these substances, 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA) (Fig. 1) and its alkylcarbamate derivatives have been developed for potential clinical application.[8]

9-Aminoacridines have also been investigated as potential photoaffinity labels[9] and as fluorescent probes used to detect cancer cells.[10]

Recently, 9-aminoacridine analogs, including the antimalarial drug quinacrine, were found to present strong induction of p53 function in renal cell carcinomas (RCCs) and other types of cancer cells.[11] Interestingly, induction of p53 function by these compounds does not involve genotoxic stress and is mediated by the suppression of NF-κB activity. Active NF-κB signaling provides selective advantages to tumor cells by inhibiting apoptosis and promoting proliferation by stimulating expression of antiapoptotic factors.

These findings, together with those mentioned above, indicate that 9-AA derivatives have potential for anticancer applications and this has inspired us to look for a short and efficient method for the derivatization of 9-AA suitable for the rapid generation of new compounds for evaluation.

Herein we report a new, highly-efficient, one-pot derivatization of 9-AA at the amine position by simple reductive amination or S_NAr reaction, using commercially available synthons. Reductive amination of aldehydes and ketones is an important and direct method for the transformation of these functionalities into amines.[12] In this carbon–nitrogen bond-forming process, the intermediate imine is not pre-formed.[13] Thus, the chosen reducing agent should be stable enough for the in situ formation of the imine and avoid undesirable carbonyl reduction to alcohol by-products. Mild $NaCNBH_3$ in a weak acidic media is a widely reported reducing reagent for reductive amination and was therefore employed as the reagent of choice. To demonstrate the synthetic potential of $NaCNBH_3$ in the reductive amination of 9-AA under standard conditions (1% AcOH in MeOH, rt, 3 h) we employed two classes of aldehydes: aromatic and aliphatic (Scheme 1), yielding *N*(9)-benzylacridines **1a–h** and 2-(acridin-9-ylamino)acetic acid **1i**, respectively, in moderate to good yields (Table 1).[14] The *N*(9)-aminobenzyl analogs synthesized bear representative electron-donating (ED) and electron-withdrawing (EW) groups as well as aryl and indolyl systems at various positions around the benzyl

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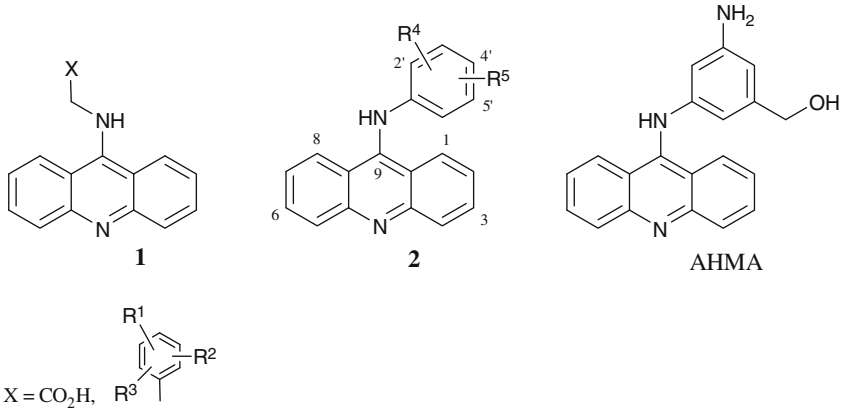
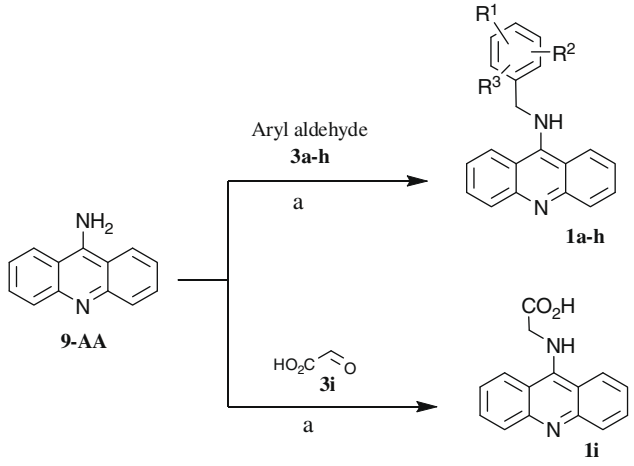


Figure 1. General structures of 9-aminoacridines.



Scheme 1. Synthesis of 9-aminoacridine derivatives **1** by reductive amination. Reagents and conditions: (a) $NaCNBH_3$, 1% AcOH in MeOH, 3 h, rt.

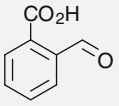
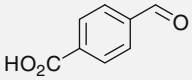
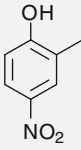
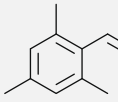
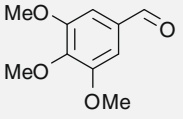
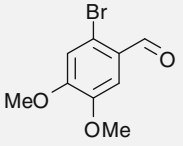
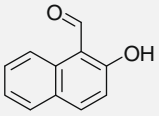
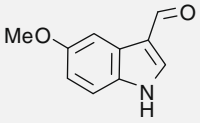
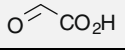
ring. Such syntheses are more difficult to accomplish using the classical 'reverse' synthetic approach in which 9-chloroacridine reacts with benzylamines,[15] due to the poor commercial availability of substituted benzylamines. The aliphatic analog **1i** was prepared in the same manner using the corresponding glyoxylic acid hydrate (**3i**).

In the context of exploring the rapid derivatization of the 9-AA scaffold we found that the amine (NH_2) at position nine is nucleophilic enough to take part in nucleophilic aromatic substitution (S_NAr) to give medicinally important 9-anilinoacridines.[16]

We successfully reacted representative electrophilic haloaryls **4a–e** (Scheme 2), bearing one or two strongly electron-withdrawing groups, with 9-AA in the presence of one equivalent (half molar ratio) of Cs_2CO_3 in DMF at 90 °C to afford the substituted 9-anilinoacridines **2a–e** in good yields (Table 2).[17] The uniqueness of this method is in its ability to form the anilino tether in 9-AAs with two EW groups which is very difficult to accomplish using the standard 'reverse' approach, namely nucleophilic substitution of the deactivated anilines on 9-chloroacridines.

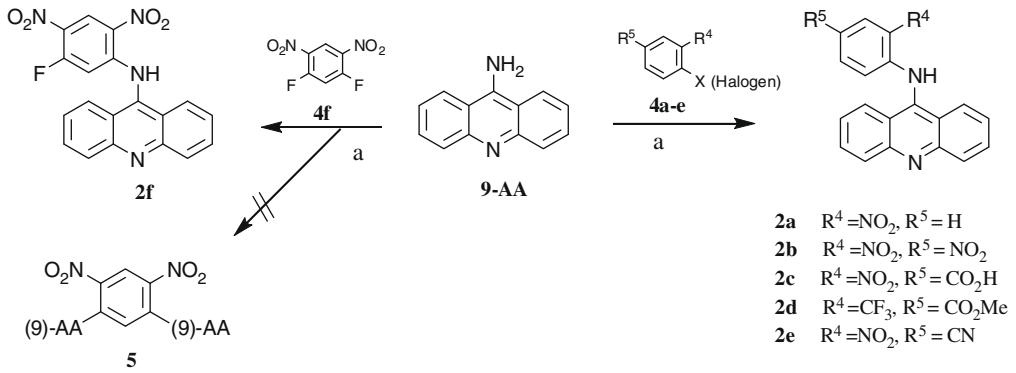
The anilinic amine in such a 'reverse' reaction is strongly deactivated by EW groups leading mostly to unreacted materials or black tars. The additional advantage of the S_NAr reaction with 9-AAs is the extensive commercial availability of appropriately substituted haloaryls. Interestingly, 4-chloro-3-nitrobenzoic acid

Table 1
Reaction data for reductive amination of 9-AA

Entry		Aldehyde	Product	Yield (%)
1	**3a**		**1a**	92
2	**3b**		**1b**	89
3	**3c**		**1c**	87
4	**3d**		**1d**	66[a]
5	**3e**		**1e**	68[a]
6	**3f**		**1f**	72[a]
7	**3g**		**1g**	83
8	**3h**		**1h**	58[a]
9	**3i**		**1i**	91

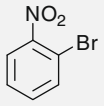
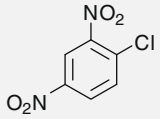
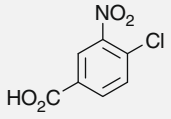
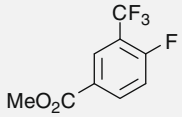
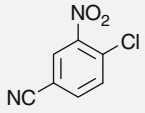
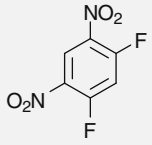
[a] After chromatography.

(**4c**) which bears an acidic CO_2H group smoothly undergoes the S_NAr reaction to give product **2c** even in the presence of basic Cs_2CO_3. Moreover, the CO_2H group in **2c** (as well as in the



Scheme 2. Synthesis of 9-aminoacridine derivatives **2** by S_NAr reaction. Reagents and conditions: (a) Cs_2CO_3, DMF, 90 °C, 12 h.

Table 2
Reaction data for S_NAr reaction of 9-AA

Entry		Haloarene	Product	Yield (%)
1	**4a**		**2a**[18]	73[a]
2	**4b**		**2b**	78[a]
3	**4c**		**2c**	86
4	**4d**		**2d**	76[a]
5	**4e**		**2e**	71[a]
6	**4f**		**2f**	52[a]

[a] After chromatography.

previously mentioned carboxy and hydroxy analogs **1a–c**, **g**, and **i**) could serve as a linking group to various carriers for possible delivery. Another attempt was made to obtain bis-9-AA **5** (Scheme 2) by reacting 2.5 equiv of 9-AA with 1 equiv of 1,5-difluoro-2,4-dinitrobenzene. Unfortunately, only the mono adduct **2f** was obtained in a moderate yield, most probably due to severe steric hindrance.

All the products synthesized in this work which possess acidic CO_2H or phenolic substitution (**1a**,**b**,**c**,**g**,**i**, and **2c**) precipitated from acetone as pure (more than 94% by HPLC) yellow solids, while unreacted starting materials and solvents were completely soluble in acetone. Such a phenomenon can be attributed to the formation of poorly soluble (in organic solvents) zwitterions. This hypothesis is supported by an observed low-field shift in the ^1H NMR spectrum for the anilinic H-2' in **2c**, *ortho* to the EW positively charged 9-aminoacridinium moiety (δ 7.76, J = 6.5 Hz, see data for **2c** in the Supplementary data). Typically, protons *ortho* to strongly electron-donating (ED) free amine bases, as in **2b** and **2d**, are shifted higher-field to δ 7.01 and δ 6.85, respectively (see Supplementary data for **2b**,**d**). Other one-pot derivatizations of 9-AA are under investigation.

In conclusion, we have developed a new method for the efficient one-pot derivatization of the medicinally important 9-aminoacridine (9-AA) scaffold. A simple reductive amination of 9-AA with aldehydes yielded a series of novel substituted *N*(9)-benzylaminoacridines and *N*(9)-alkylaminoacridines. An S_NAr reaction between 9-AA and halobenzenes that had strong EW groups gave novel *N*(9)-anilinoacridines. All the products were obtained from commercially available synthons in good yields. These synthetic routes provide easy and rapid access to novel 9-AA derivatives which can be further explored for their biological properties.

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The authors thank Dr. Alexandra Massarwa for the HRMS measurements of all new compounds.

Supplementary data

Supplementary data (selected ^1H and ^{13}C NMR, HRMS spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.020.

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14. *General procedure for the synthesis of* **1a–i** *via reductive amination*: 9-AA (0.194 g, 1 mmol) and the corresponding aldehyde (1 mmol) were added to 5 mL of MeOH/AcOH (99:1) and the mixture stirred at room temperature until the starting material dissolved (15 min). Then, $NaCNBH_3$ (0.09 g, 1.5 mmol) was added in small portions with stirring. After additional stirring for 3 h at room temperature, the solvent was evaporated and the residue was taken into acetone. The resulting precipitate was filtered under vacuum, washed with acetone, and dried to give the product as a yellow solid. Compounds that did not precipitate were purified by flash column chromatography on silica gel 60 (5% MeOH in EtOAc) to yield pure (yellow) products. Data for **1a** (0.3 g, 92% yield): ν_{max} (KBr): 3500–3180 (br, s), 1700 (C=O), 1640, 1290 cm^{-1}; HRMS (CI, *m*/*z*) calcd for $C_{21}H_{17}N_2O_2$ (MH^+) 329.121, found 329.102; ^1H NMR (300 MHz, DMSO-d_6): δ 8.50 (d, 2H, J = 7.0 Hz), 7.92 (d, 2H, J = 7.0 Hz), 7.77 (d, 1H, J = 6.8 Hz), 7.68–7.65 (m, 2H), 7.41–7.36 (m, 2H), 7.30–7.24 (m, 3H), 4.54 (s, 2H, –NH–CH_2–); ^{13}C NMR (75 MHz, $CDCl_3$): 171.9 (CO_2H), 168.7, 152.7, 146.5, 141.5, 139.0, 131.5, 130.6, 130.1, 128.6, 128.2, 126.3, 125.5, 123.6, 122.1, 64.1.
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17. *General procedure for the synthesis of* **2a–e** *via* S_NAr *reaction*: 9-AA (0.194 g, 1 mmol), haloaryl compound (1 mmol), and Cs_2CO_3 (0.161 g, 0.5 mmol) were heated in 5 mL of dry DMF at 90 °C for 12 h. While heating, the color of the reaction mixture changed to dark red. After completion of the reaction (TLC monitoring in CH_2Cl_2) the mixture was cooled and poured into water. In the case of **2c**, the pH was adjusted to 6 by careful addition of 0.1 N HCl. The resulting precipitate was collected by filtration, washed several times with water, and dried to give a crude orange solid. The products (except **2c** which precipitated in pure form) were purified by flash column chromatography on silica gel 60 (CH_2Cl_2). Data for **2a** (orange solid, 0.23 g, 73% yield): ν_{max} (KBr): 1670, 1650, 1190 cm^{-1}; HRMS (CI, *m*/*z*) calcd for $C_{19}H_{14}N_3O_2$ (MH^+) 316.101, found 316.061; ^1H NMR (300 MHz, $CDCl_3$): δ 9.32 (br s, 1, NH), 8.24 (d, 2H, J = 6.8 Hz), 8.01–7.88 (m, 3H), 7.71–7.53 (m, 4H), 7.33 (t, 1H, J = 7.0 Hz), 6.62 (d, 1H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 165.2, 154.3, 147.7, 144.1, 133.4, 130.0, 129.7, 128.7, 127.2, 125.6, 124.7, 122.3, 120.5.
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