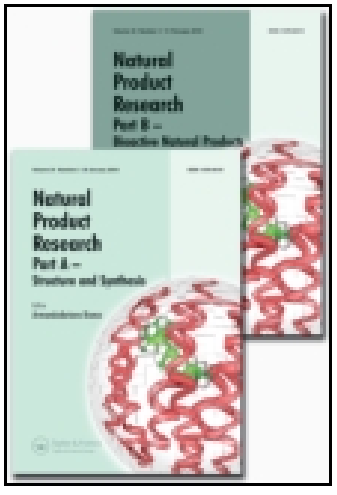

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Facile, economical and direct synthesis of 9-anilinoacridines

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Acridines are well-known group of compounds with a wide variety of biological properties. We describe herein an expeditious approach to prepare anilinoacridine derivatives from mefenamic acid. It is the first report of a one-pot approach to anilinoacridines in good to excellent yields.

Keywords: mefanamic acid; phosphorous oxytrichloride; 9-anilino-acridines; one-pot synthesis

1. Introduction

Acridines are known to have activities against numerous solid tumours i.e. sarcoma, myeloma, carcinoma, and melanoma (Bonse, Santelli-Rouvier, Barbe, & Krauth-Siegel, 1999; Kirk, Luedtke, & Tor, 2000; Lee et al., 1996; Lorente et al., 1995; Magiatis et al., 1999; Magiatis et al., 1999; McConnaughie & Jenkins, 1995). They have a wide spectrum of other important activities, such as antiplasmodial (Chavalitshewinkoon et al., 1993), antibactarial (Tabarrini et al., 1999), immunostimulating (Dzierzbicka, Kołodziejczyk, Wysocka-Skrzela, Myśliwski, & Sosnowska, 2001), antiallergic, anti-inflamatory (Lin, Chang, Tseng, & Wang, 2002), photosensitizing (in the photodynamic therapy of malignant cancers) (Mehta, Sambaiah, Maiya, Sirish, & Chatterjee, 1993), and antifeedant (Tringali, Spatafora, Calì, & Simmonds, 2001). For decades, a number of acridine derivatives have been discovered with potent biological activities, however, due to toxicity and other adverse side effects, most of them were not developed as therapeutic agents. Nevertheless, more recently various chemical modifications of these known active compounds have been carried out to enhance and modify their activity profiles and decrease toxicity (Skonieczny, 1980). The use of acridines as trypanocidal and antibacterial agents was first proposed by Ehrlich, Benda, and Browning in 1912/13, and the first clinical use of these agents started in 1917 (Wainwright, 2001). Due to the extensive clinical use of acridine chromophores, such as proflavine, euflavine, diflavine, sinflavin, flavicid, ethacridine, and aminacrine (Wainwright, 2001), we describe here a preparation of several new anilinoacridine derivatives from mefenamic acid. Previously, 9-anilinoacridines were synthesised *via*

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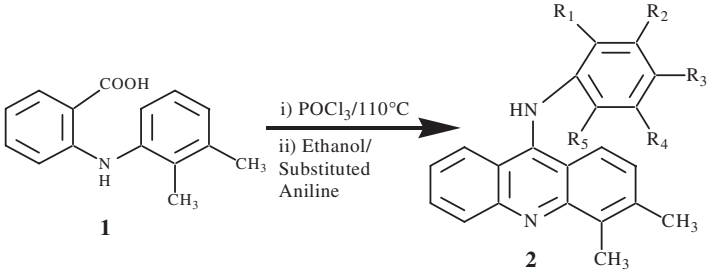
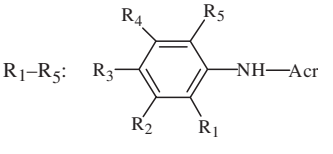
Ullmann reaction in 40–60% yield (Groundwater & Munawar, 1997; Sánchez, del Campo, Avendano, & Llama, 1990). Our one-pot reaction is carried out without isolating the intermediate 9-chloroacridine, as it is readily hydrolysed in neutral and acidic solutions (Wainwright, 2001) resulting in high yields.



2. Results and discussion

The synthetic pathway described here is based on the preparation of different derivatives of 9-anilinoacridine by the treatment of mefenamic acid (2,3-dimethyl-*N*-Phenyl-anthranilic acid) with appropriate anilines in the presence of $POCl_3$. This has resulted in the formation of 9-chloroacridines (Scheme 1). 9-Chloroacridine reacts smoothly with anilines resulting in the formation of 9-anilinoacridines in different yields, depending upon the substituents present on the aromatic ring. Anilines with electron-withdrawing groups at *ortho*, or *para* positions, such as those with nitro groups for the synthesis of compounds **4** and **14** decrease the nucleophilicity of the amino group and cause reduction of the yields. On the other hand, anilines with electron-donating groups in *ortho* or *para* positions, such as methyl, methoxy, or chloro substituents, facilitate the electron density at the amino group thus enhance the nucleophilicity and results in excellent yields. In case of *meta* substituents, inductively electron donating groups increase the reactivity of anilines that result in an increase in percent yields e.g., compounds **8** and **11** (Table 1).

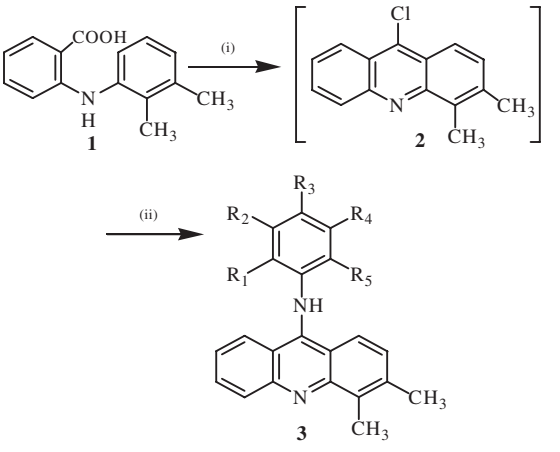
In conclusion, an efficient, economical, high yielding and simple one-pot method for the conversions of mefenamic acid into 9-anilinoacridines using phosphoryl chloride and respective anilines has been developed.



3. Experimental

3.1. *General*

Melting points were determined on a Büchi 434 melting point apparatus and are uncorrected. NMR was performed on a Bruker AM 300 MHz. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106 Italy. The ultraviolet spectra (UV) were recorded on Perkin-Elmer Lambda-5 UV/VIS spectrometer, the infrared spectra (IR) on JASCO IR-A-302 spectrometer and the electron impact mass spectra (EIMS) on



Scheme 1. (i) $POCl_3$/110°C; (ii) Ethanol/substituted aniline.

Table 1. Yields of the one-pot syntheses of 9-anilinoacridines.

Compound	R_1	R_2	R_3	R_4	R_5	Yield (%)
3	H	H	H	H	H	82
4	CH_3	H	H	H	NO_2	68
5	OCH_3	H	H	NO_2	H	78
6	H	H	CH_3	CH_3O	H	75
7	Cl	H	Cl	H	H	93
8	H	CH_3	H	CH_3	H	92
9	CH_3	H	CH_3	H	H	88
10	H	Cl	Cl	H	H	97
11	CH_3	H	H	CH_3	H	88
12	CH_3	CH_3	H	H	H	90
13	H	CH_3	CH_3	H	H	91
14	H	H	NO_2	H	H	63
15	Cl	H	H	H	Cl	93

Finnigan MAT-311A Germany. TLC was performed on precoated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualised by UV at 254 and 365 nm, respectively.

3.2. *General procedure for the preparation of compounds 3–15*

A mixture of mefenamic acid (0.1 g, 0.4 mmol) and phosphoryl chloride (0.5 mL, 3.2 mmol) was stirred at 110°C for completion of the reaction (TLC analysis), and then $POCl_3$ was evaporated under high-reduced pressure yielding air-sensitive residues. The residues were dissolved in anhydrous ethanol, and after adding an appropriate amount of differently-substituted anilines (0.8 mmol), the reaction was complete within 30 min (TLC analysis). The solvent was evaporated under reduced pressure, the residue suspended in water and extracted with dichloromethane (3 × 50 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure.

The obtained product, if solid, was recrystallised from ethanol and in case of liquid was distilled under reduced pressure.

3,4-Dimethyl-9-anilinoacridine **(3)** Yield 0.15 g (82%); $R_f = 0.65$ (hexane/ethyl acetate, 8: 2); m.p. 152–154°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 2H, $J = 6.2$ Hz, H-5,8), 7.6 (ddd, 1H, $J = 7.9$, $J = 6.9$, $J = 1.4$ Hz, H-6),ÿ 7.5 (br.s, 1H, N-H), 7.35 (ddd, 1H, $J = 7.9$, $J = 7.1$, $J = 1.5$ Hz, H-7), 7.24 (m, 5H, Ar-H), 6.81 (d, 2H, $J = 7.1$ Hz, H-1,2), 2.81 (s, 3H, CH_3), 1.57 (s, 3H, CH_3); IR (KBr) ν_{max} 3010, 2990, 1715, 1605, 1514, 1250, 1170, 1010 cm^{-1}; MS: m/z (%) = 298 (M^+), 222 (100), 204 (5), 281 (27), 84 (8), 82 (13); Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39; Found: C, 84.08; H, 6.16; N, 9.45.

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