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Convenient synthesis of fluorazone derivatives by one-pot pyrrolation/cyclization of anthranilic acids

Francesca Aiello *, Antonio Garofalo, Fedora Grande

Dipartimento di Scienze Farmaceutiche, Università della Calabria, Edif. Polifunzionale, Arcavacata di Rende 87036, Cosenza, Italy

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ABSTRACT

A series of fused heterocyclic compounds based on a fluorazone structure has been prepared from anthranilic or *ortho*-aminoheteroaryl carboxylic acids by one-pot sequential pyrrolation/cyclization catalyzed by 4-chloropyridine hydrochloride, in generally good yield.

Introduction

Fluorazone (9*H*-pyrrolo[1,2-*a*]indol-9-one) and its analogues, characterized by a benzo fused ring substituted or replaced for a heterocycle **1** (Fig. 1), represent valuable intermediates in organic synthesis. They have been extensively studied in relation to a variety of biological activities showed by many of their functionalized derivatives including anticancer,[1] psychostimulant,[2] photosensitizing.[3]

A number of synthetic strategies have been therefore developed for the preparation of (un)substituted-fluorazones and analogues to be further elaborated into biologically active agents. Amongst the numerous synthetic methods discovered, the most appealing appear those deriving from *ortho*-(1*H*-pyrrol-1-yl)aryl and heteroaryl carboxylic acids, in turn obtained by pyrrolation of *ortho*-aminoaryl (anthranilic) and *ortho*-aminoheteroaryl carboxylic acids, respectively.[4–6] However the complete synthetic elaboration of starting aromatic *ortho*-aminoacids to the final ketones usually requires too many reaction steps, which unavoidably results in time-consuming processes, waste of materials as well as lowering of overall yields. Typically, the reaction sequence implies: (*a*) transformation of the aminoacid into the aminoester, often via an intermediate isatoic anhydride;[7] (*b*) pyrrolation on the amino group under Clauson–Kaas conditions; (*c*) hydrolysis of the ester group to reinstate the free carboxylic function or its transformation into an amide; (*d*) activation of the carboxylic function to an acyl chloride; (*e*) cyclization under different conditions; (*f*) hydrolysis in the case of amide intermediates.[8] Only in a few instances steps *a* (then *c*) and/or *d* can be bypassed. In fact, the pyrrolation of amino group with 2,5-dimethoxytetrahydrofuran (DMTHF) is now preferentially carried out in 1,4-dioxane with 4-chloropyridine hydrochloride as the acid catalyst,[8] without taking into account if the carboxyl group was protected or not; whereas the classical refluxing acetic acid conditions, which, according to our own experience, generally require the carboxyl group protection to be effective. This way, steps *a* and *c* of the above sequence can be avoided. Also, we recently exploited a convenient procedure for the direct intramolecular acylation of *ortho*-(1*H*-pyrrol-1-yl)aryl carboxylic acids by the action of triphosgene, demonstrating that cyclization to ketones could take place directly, under conditions requiring no preliminary carboxylic activation (namely step *d* of the sequence).[6]

We herein investigated the possibility of converting anthranilic acids **2a–h** into fluorazones **1a–h**, through a sequential one-pot pyrrole formation/cyclization (Scheme 1), with the aim of discoveing straightforward alternative methods to reach compounds of formula **1**. Since both reactions were catalyzed by acids, we attempted the transformation of anthranilic acid **2a** by using DMTHF and 4-chloropyridine hydrochloride as the acid catalyst, in a 1:1:2 ratio, in 1,4-dioxane at reflux, after different experimental techniques. Fluorazone **1a** was so obtained in variable yields, strictly depending on reflux time and modalities of mixing the reagents. The use of an excess of both reactants with respect to the amount of the starting acid **2a** did not seem to considerably influence the reaction course. Thus, the best results were obtained by dissolving 4-chloropyridine hydrochloride in hot dioxane and then adding a solution of anthranilic acid **2a** and DMTHF in the same solvent. A smooth conversion to fluorazone **1a** was obtained through the

* Corresponding author. Tel.: +39 0984493154; fax: +39 0984493298.
E-mail address: francesca.aiello@unical.it (F. Aiello).

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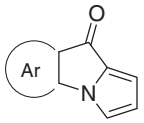
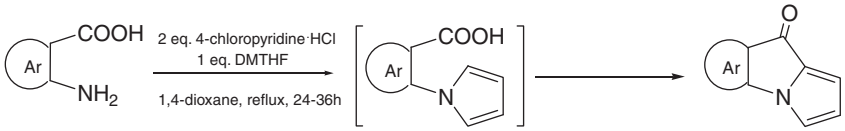


1

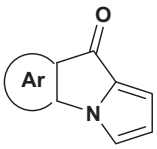
Figure 1. Fluorazone derivative general structure.

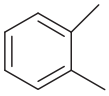
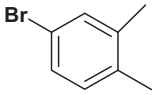
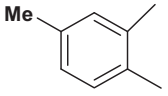
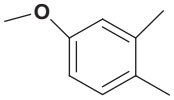
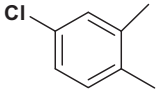
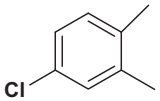
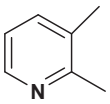
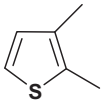


2a-h[a] 3a-h 1a-h

Scheme 1. One-pot pyrrolation/cyclization reaction. [a]See Table 1.

Table 1
Chemical structures, reaction time, yield and melting point of compounds **1a–h**



Compd	Ar	Reaction time (h)	Yield (%)	Mp (°C)
1a		36	23	121–123 [lit.[4a] 119.5–121.5]
1b		24	89	176
1c		24	36	[lit.[6] 110–111]
1d		36	34	[lit.[6] 124–125]
1e		24	75	[lit.[11] 140–141]
1f		24	62	180–181 [lit.[11] 179–180]
1g		24	83	131 [lit.[12] 130]
1h		24	44	[lit.[13] 123]

formation of intermediate 2-(1*H*-pyrrol-1-yl)benzoic acid **3a**, as confirmed by TLC and GC monitoring of the reaction. In some instances, small aliquots of catalyst were added time to time in order to drive the reaction to completion, although variable amounts of intermediate 2-(1*H*-pyrrol-1-yl)benzoic acid **3a** were recovered even after prolonged reaction times. The yield, however, reached only a 23%, after chromatographic purification. The procedure was then extended to analogous acids **2b–f** variously substituted on the phenyl ring, to give the corresponding substituted-ketones **1b–f** in 40–90% yield (Table 1).[9] Somewhat surprisingly, the conversion of the unsubstituted acid **2a** remained the least productive in the series. The generality of this method was also confirmed by the good results achieved by the synthesis of two hetero-isosteres of fluorazone, namely, 5*H*-pyrido[3,2-*b*]pyrrolizin-5-one **1g** and 4*H*-thieno[3,2-*b*]pyrrolizin-4-one **1h**, which were obtained in 83% and 44% yield, starting from 2-aminonicotinic acid **2g** and 2-aminothiophene-3-carboxylic acid **2h**, respectively. It is worth noting that 2-aminonicotinic acid **2g** was reported to fail to react under classical Clauson–Kaas conditions to give 2-(1*H*-pyrrol-1-yl)pyridine-3-carboxylic acid **3g**, unless previously transformed into an ester.[10]

In conclusion, 4-chloropyridine hydrochloride proved to act as the ideal catalyst for both pyrrolation on amino groups and intramolecular acylation of resulting pyrrole by a free carboxylic function, at the dioxane reflux temperature. This allows the preparation of fluorazone based derivatives from *ortho*-aminoaryl and heteroaryl carboxylic acids in generally good yield, after a simple work-up. A further advantage of the present procedure lies in the easy availability of the starting aminoacids **2a–h**, most of which are commercial reagents.

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9. Typical procedure for the pyrrolation/cyclization of *ortho*-aminoaryl carboxylic acids. 7-Bromo-9*H*-pyrrolo[1,2-*a*]indol-9-one (**1b**). To a hot solution of 4-chloropyridine hydrochloride (42 mg, 0.280 mmol) in 1,4-dioxane (1 mL), was added a solution of 5-bromo anthranilic acid (30 mg, 0.140 mmol) and 2,5-dimethoxytetrahydrofuran (18.14 μL, 0.140 mmol) in 1,4-dioxane (600 μL). The reaction was stirred at reflux for 24 h, then filtered on Celite®. The residue

obtained after evaporation of the solvent was dissolved in ethyl acetate (5 mL) and the resulting solution was washed with $NaHCO_3$ saturated solution. The solid obtained after drying and evaporation of the solvent was purified by silica gel column chromatography (ethyl acetate/hexanes, 3/7 as eluent) to give pure compound **1b** as a yellow solid. The yield, after recrystallization from cyclohexane, was 89% (31 mg). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.69 (d, 1H, J = 1.8 Hz), 7.55 (dd, 1H, J = 8.1 and 1.9 Hz), 7.07 (d, 1H, J = 2.5 Hz), 7.01 (d, 1H, J = 8.1 Hz), 6.82 (d, 1H, J = 3.7 Hz), 6.34 (t, 1H, J = 2.7 Hz). ^{13}C NMR ($CDCl_3$, 25 °C), δ: 177.90, 142.43, 136.40, 134.22, 131.88, 127.71, 119.82, 118.44, 116.48, 114.73, 111.72. IR (KBr discs) 1690 cm^{-1}. MS (EI) m/z 247 (M^+). Anal. Calcd for $C_{11}H_6BrNO$: C, 53.26; H, 2.44; N, 5.65; Br, 32.21. Found: C, 53.31; H, 2.28; N, 5.37; Br, 32.08. Mp: 176 °C.

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