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Direct cyclization of *ortho*-(1*H*-pyrrol-1-yl)aryl and heteroaryl carboxylic acids into fused pyrrolizinones

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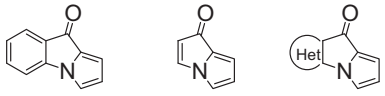
ABSTRACT

A series of fused heterocyclic compounds based on a pyrrolizinone structure have been prepared from *ortho*-(1*H*-pyrrol-1-yl)aryl and heteroaryl carboxylic acids by intramolecular Friedel–Crafts acylation promoted by bis(trichloromethyl) carbonate, in generally good yield without using Lewis acid catalysts.

Derivatives of fluorazone (9*H*-pyrrolo[1,2-*a*]indol-9-one) (**1a**) and some of its isosteres, bearing the same 1*H*-pyrrolizin-1-one framework **2** annelated to a heterocycle **3** (Fig. 1), show a broad spectrum of biological activities including antidiabetic,[1] psychostimulant,[2] antitubulin,[3] photosensitizing,[4] and hence are an important class of nitrogen-containing heterocycles, and useful intermediates in organic synthesis.[5]

Furthermore, we have recently found that some *N*′-heteroacyl-9*H*-pyrrolo[1,2-*a*]indol-9-hydrazones, directly obtained from fluorazone **1a**, show noticeable activity against a colon cancer cell line.[6] As a result, a number of synthetic strategies have been developed for the preparation of (un)substituted-fluorazones and analogs to be further elaborated into biologically active agents. Among the numerous synthetic methods discovered for the synthesis of basic fluorazone,[7] those involving 2-(1*H*-pyrrol-1-yl)benzoic acid as starting material appear as the most appealing, offering the possibility to be in general extended to the conversion of easily accessible *ortho*-(1*H*-pyrrol-1-yl)aryl carboxylic acids into fused pyrrolizinones.[8–12] All the existing methods suffered however from many drawbacks such as low yield, additional activation of the carboxylic function before cyclization or sensitivity of the pyrrole ring to the reagents employed. In order to avoid any intermediate manipulation, which would limit the general utility of the methods, we decided to reinvestigate the one-step Friedel–Crafts cyclization of 2-(1*H*-pyrrol-1-yl)benzoic acid to find conditions suitable to produce the cyclic ketone, and analogs thereof, in good yield. It is known that the intramolecular Friedel–Crafts acylation of aromatic rings is of particular value in building up cyclic systems. This reaction generally requires two steps starting from carboxylic acids, namely the formation of the intermediate acyl chloride and the subsequent cyclization catalyzed by a Lewis acid. However, the use of the catalyst can be avoided when particularly reactive substrates, such as heterocycles, are involved. Based on our previous experience,[13] we decided to attempt the intramolecular cyclization of 2-(1*H*-pyrrol-1-yl)benzoic acid **4a** to fluorazone **1a** (Fig. 2) by use of an aprotic chlorinating reagent inert to the pyrrole ring, but potentially capable of sufficiently activating enough of the carboxylic function to be in situ nucleophilically attacked from the pyrrole α-carbon.



1a **2** **3**

Figure 1. Reference structures.

4a-h[a] **1a-h**

Figure 2. Cyclization reaction. [a]See Table 1.

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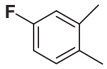
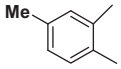
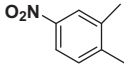
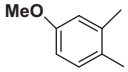
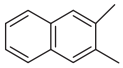
Table 1
Chemical structures, reaction time, yield and melting point of compounds **1a–h**

Compd	Ar	Reaction time (h)	Yield (%)	Mp (°C)
1a		24	80	121–123 [lit.[10a] 119.5–121.5]
1b		24	70	123 [lit.[12] 124]
1c		18	64	111 [lit.[12] 110–111]
1d		18	71	200 [lit.[12] 200–201]
1e		24	50	[lit.[12] 124–125]
1f		18	75	192
1g		24	58	[lit.[16] 112]
1h		24	77	131 [lit.[17] 130]

Among the common chlorinating agents, bis(trichloromethyl) carbonate (triphosgene), a crystalline phosgene substitute,[14] was selected as the most suitable for our purposes. A smooth conversion of 2-(1*H*-pyrrol-1-yl)benzoic acid **4a** to fluorazone **1a** was so achieved with the use of an equimolar amount of bis(trichloromethyl) carbonate in toluene at reflux for 24 h (Table 1).

Under such conditions, no detectable quantities of pyrrole-chlorinated side-products could be observed, while the final ketone **1a** was isolated in an 80% yield after a simple work-up and silica gel column chromatography purification.

The procedure was then extended to analogous acids (**4b–e**) variously substituted on the phenyl ring, to give the corresponding substituted-ketones (**1b–e**) in 50–71% yield. To further explore the generality of the method, we attempted the above conditions for the cyclization of 3-(1*H*-pyrrol-1-yl)naphthalene-2-carboxylic acid (**4f**), from which the hitherto unknown 11*H*-naphtho[2,3-*b*]pyrrolizin-11-one (**1f**) was obtained in a 75% yield.[15] The effectiveness of the method was so confirmed for the cyclization of *ortho*-(1*H*-pyrrol-1-yl)aryl carboxylic acids. On the other hand, it is known that classical Friedel–Crafts conditions are not effective for the intramolecular acylation of *ortho*-(1*H*-pyrrol-1-yl)heteroaryl carboxylic acids. As an example, Rault et al.[16] did not succeed to directly cyclize the 3-(1*H*-pyrrol-1-yl)thiophene-2-carboxylic acid **4g** into 8*H*-thieno[2,3-*b*]pyrrolizin-8-one **1g**, although they reported the synthesis of this latter compound using the Vilsmeier–Haack fashion.[3] Furthermore, Lauderée and Robba[17] did not manage to obtain 5*H*-pyrido[3,2-*b*]pyrrolizin-5-one **1h**, a further isostere of fluorazone, by Friedel–Crafts intramolecular acylation. Under our conditions, both these tricyclic compounds were smoothly obtained from acid precursors **4g,h** by action of triphosgene. Triphosgene thus proved to act as a selective and ideal reagent for uncatalyzed intramolecular acylation of pyrrole. The value of the reagent in promoting such cyclization reactions has to be attributed to its effectiveness in selectively chlorinating the carboxylic group, giving rise to an intermediate prone to the direct attack from the nucleophilic pyrrole, at the toluene reflux temperature. The utility of the present procedure lies also in the easy preparation of the starting materials **4a–h** from corresponding amino aryl or amino heteroaryl carboxylic acids, or esters thereof, according to the method of Clauson–Kaas, which involves the installation of the pyrrole ring through condensation of the amino group with 2,5-dimethoxytetrahydrofuran, followed by alkaline hydrolysis, in the case of esters.[3,12]

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15. Typical procedure for cyclization of *ortho*-(1*H*-pyrrol-1-yl)aryl and heteroaryl carboxylic acids. 11*H*-Naphtho[2,3-*b*]pyrrolizin-11-one (**1f**). To a solution of 3-(1*H*-pyrrol-1-yl)naphthalene-2-carboxylic acid (0.100 g, 0.42 mmol) in dry toluene (1 mL) cooled to 0 °C, was added bis-(trichloromethyl)-carbonate (0.125 mg, 0.42 mmol) in one portion. The mixture was heated to reflux for 18 h under argon. The solvent was evaporated and the residue obtained was dissolved in ethyl acetate (5 mL). The organic solution was washed with water (3 × 3 mL). The solid obtained after drying and evaporation of the solvent was purified by silica gel column chromatography (diethyl ether/hexanes, 1:3 as eluent) to give pure compound **1f** as a yellow solid. The yield, after recrystallization from cyclohexane, was 0.69 g (75% yield). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 8.05 (s, 1H), 7.82 (d, 1H, J = 7.6 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.50 (t, 1H, J = 6.9 Hz), 7.37 (m, 2H), 7.20 (m, 1H), 6.80 (m, 1H), 6.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 25 °C), δ: 177.96, 135.39, 132.84, 131.18, 130.69, 130.47, 129.54, 129.18, 128.01, 126.08, 125.83, 119.06, 116.98, 112.97, 106.85. IR (KBr discs) 1884, 1643 cm^{-1}. MS (CI) m/z 220 (MH^+). Anal. Calcd for $C_{15}H_9NO$: C, 81.18; H, 4.14; N, 6.39. Found: C, 81.11; H, 4.07; N, 6.55. Mp: 192 °C.
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