FIRST SYNTHESIS OF 4-AMINO-4,5-DIHYDRO-1-PHENYL-CYCLOPENTA[*b*]PYRROL-6(1*H*)-ONES

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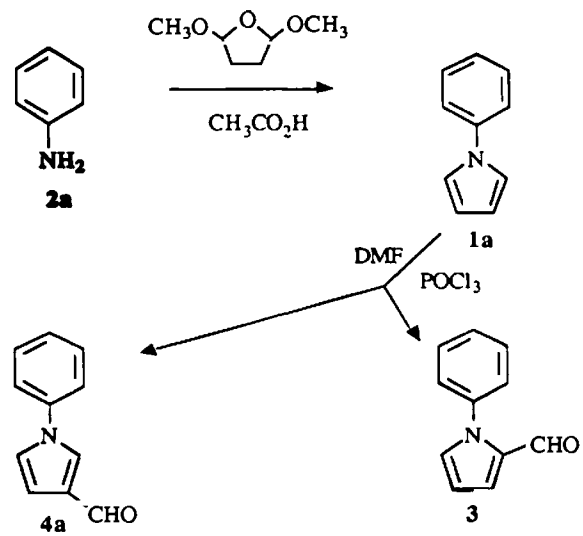
Abstract : Aminophenylcyclopenta[*b*]pyrrolones are synthesized in four steps starting from various substituted anilines via N-phenylpyrrole-3-carboxaldehydes and corresponding aminopyrrolylpropionic acids using trifluoroacetic acid and trifluoroacetic anhydride.

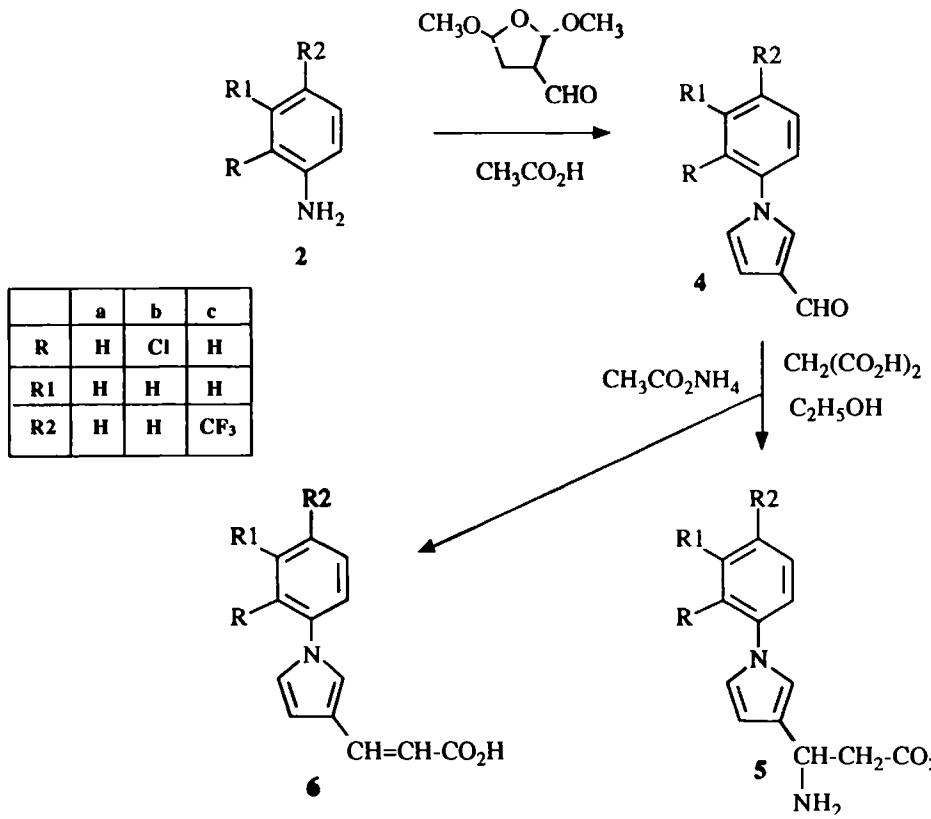
We previously emphasized the chemical interest of several β-aminoarylpropionic acids and their ability to lead to new homo- and heterocyclic systems in thienyl (1), furyl (2) and phenyl (3) series. We describe here the access, starting from anilines, to some 3-amino-3-[(1-phenyl)pyrrol-3-yl]propionic acids and their subsequent cyclization into 4-amino-4,5-dihydro-1-phenylcyclopenta[*b*]pyrrol-6(1*H*)-ones which represent a new heterocyclic system with potent pharmacological interest especially in virology field (4).

Vilsmeier-Haack formylation of 1-arylpyrroles leads predominantly to α formylated products. Starting from 1-phenylpyrrole **1a**, synthesized by treatment of aniline **2a** with 2,5-dimethoxytetrahydrofuran (5), the reaction affords a mixture of **3** and **4a** isomers with a 9:1 ratio (Scheme 1) (6).



Scheme 1

Use of 2,5-dimethoxytetrahydrofuran-3-carboxaldehyde in the Clauson-Kaas reaction allows the selective synthesis, starting from alkyl- or arylanilines, of 1-substituted pyrrole-3-carboxaldehydes (7).We applied this method to aniline **2a**, 2-chloroaniline **2b** and 4-trifluoromethylaniline **2c** in boiling acetic acid. Reaction led to 1-phenylpyrrole-3-carboxaldehydes **4a-c** in about 80% yield (Scheme 2).



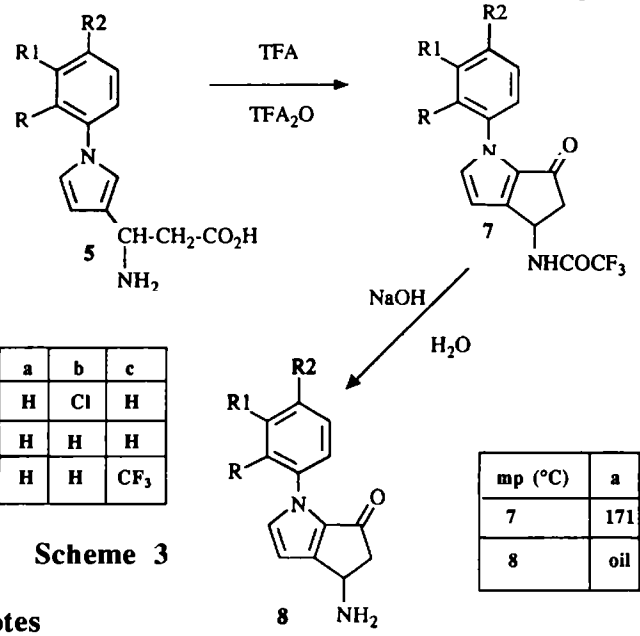
	a	b	c
R	H	Cl	H
R1	H	H	H
R2	H	H	CF_3

Scheme 2

Treatment of **4a-c** with ammonium acetate and malonic acid in refluxing ethanol afforded the expected β-aminoacids **5a-c** (8) in low yield (10-15%). Reaction gave also the acrylic acids **6a-c** as by-products (40-45%).

We have previously reported the use of trifluoroacetic acid and trifluoroacetic anhydride in the one-pot cyclization of some 3-amino-3-arylpropionic acids (9). The 3-amino-3-[(1-phenyl)pyrrol-3-yl]propionic acids **5a-c** were also cyclized according to this method (Scheme 3). They were first dissolved in a small volume of trifluoroacetic acid at room temperature and then an equivalent amount of trifluoroacetic anhydride was added. The reaction mixture was refluxed for 3 hours. The 4-trifluoroacetylamino-4,5-dihydro-1-phenylcyclopenta[*b*]pyrrol-6(1*H*)-ones **7a-c** (10) were obtained in quantitative yield. Hydrolysis of the amido group of **7a-c** was achieved in alkaline medium to give the titled free bases **8a-c** (11) in quantitative yield.

This 4 steps synthesis of *N*-substituted cyclopenta[*b*]pyrroles starting from anilines, could be applied to numerous other aryl- and alkylamines.



	a	b	c
R	H	Cl	H
R1	H	H	H
R2	H	H	CF_3

mp (°C)	a	b	c
7	171	180	132
8	oil	108	108

Scheme 3

References and notes

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(8) 5a. mp >260°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 7.47 (s, H-Φ), 7.34 and 7.26 (m, H-2 and H-5), 6.40 (m, H-4), 4.76 (t, CH), 2.60 (d, CH_2).

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(10) 7a. mp 171°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 9.92 (d, NH), 7.88 (d, H-2), 7.7 (m, H-2' and H-6'), 7.5 (m, H-3' and H-5'), 7.4 (m, H-4'), 6.40 (d, H-3), 5.31 (ddd, H-4), 3.31 (dd, H-5a), 2.83 (dd, H-5b).

(11) 8a. oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4 (m, H-Φ and H-2), 9.92 (d, NH), 6.39 (d, H-3), 4.47 (broad, H-4), 3.34 (dd, H-5a), 2.65 (dd, H-5b), 2.2 (broad, NH_2).

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