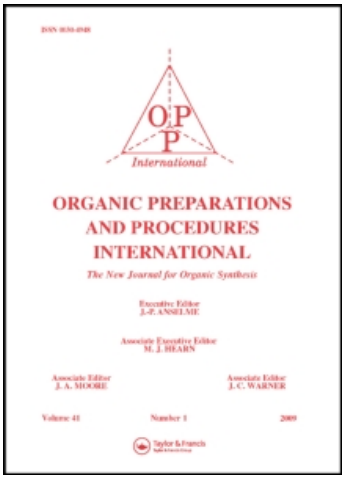

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A NEW EFFICIENT SYNTHESIS OF 3-AMINO-1-PHENYLPYRROLE

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4. The ratio of starting material, 4-chloro-, 5-chloro- and 4,5-/3,4-dichlorothiophenecarboxaldehyde isomers was determined by HPLC to be 3:90:4:3 (cf. 6); Surprisingly, when the Friedel-Crafts chlorination was carried out in 1,2-dichloroethane the ratio of chlorothiophene aldehydes formed was 17:61:17:5.

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6. HPLC conditions: Column: silica, 3.9x150mm Waters Nova-Pak®; Mobile Phase: 0.1% THF/hexane; Flow Rate: 1mL/min; Injection volume: 20ul; UV detection @254nm.

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A NEW EFFICIENT SYNTHESIS OF 3-AMINO-1-PHENYLPYRROLE

Submitted by (08/03/94)

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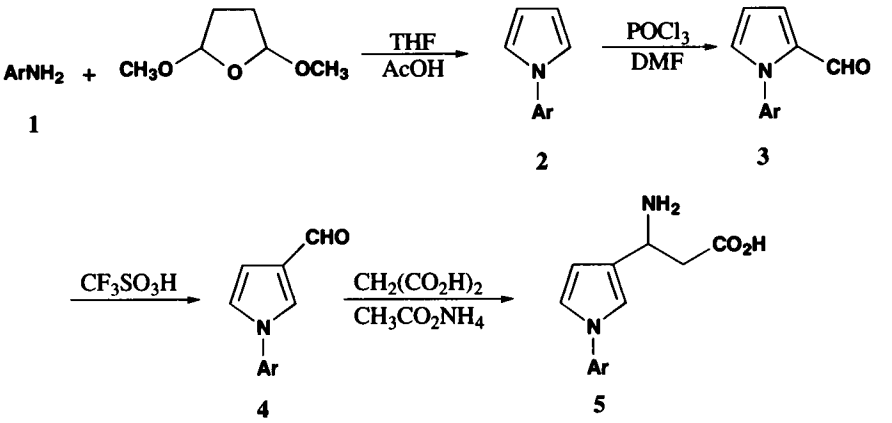
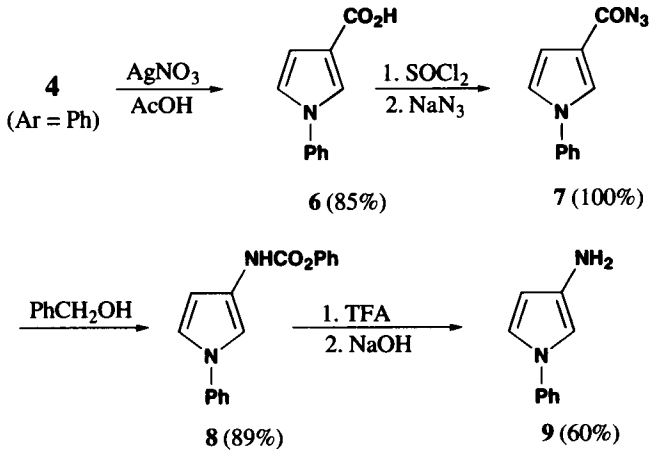
Despite the great interest in 3-aminopyrrole derivatives as building blocks in heterocyclic chemistry, access to these compounds remains quite difficult and the methods described fail for large scale. For example, only one synthesis of 3-amino-1-phenylpyrrole (**9**) has been reported;[1] it involves nitration of 1-phenylpyrrole (**2**), separation of the 2- and 3-nitropyrrole isomers, and subsequent hydrogenation of the latter to **9**. The overall yield and spectrometric data were not reported. In the course of our work concerning the synthesis of new pyrrole derivatives of therapeutic interest, we needed reasonable quantities of 3-amino-1-phenylpyrrole (**9**) and we wished to develop a convenient synthesis on a multigram scale. The results of this study are reported herein.

We recently described an efficient synthesis of 1-arylpyrrole-3-carboxaldehydes (**4**) by acidic transposition of their 2-isomers (**3**),[2] and pointed out their importance for the preparation of new β-aminoacids **5** (Scheme 1).[3] 1-Phenylpyrrole-3-carboxaldehyde (**4**), obtained in 93% yield from aniline **1** was then oxidized to the corresponding carboxylic acid **6** in 85% yield, using silver nitrate and sodium hydroxide in refluxing methanol (Scheme 2). The synthesis of **6** had been previously described in 6 steps starting from 2-buten-1,4-diol in 12% yield but without spectral data. [4] Treatment of **6** with thionyl chloride and followed by sodium azide in acetone gave the carboxylic acid azide **7** in quantitative yield. Curtius rearrangement of **7** in a mixture of dichloroethane and benzyl alcohol



Scheme 1



Scheme 2

afforded the carbamate **8** in 89% yield. Although the synthesis of other carbamates as the corresponding ethyl carbamate was successful, their hydrolysis failed. Hydrolysis of **8** in trifluoroacetic acid followed by treatment with aqueous sodium hydroxide solution gave the free base **9**, in 60% yield.

This synthetic pathway has been carried on a multigram scale and gave **9** (7 g) in an overall yield of 42% from aniline. This method will be extended to the synthesis of substituted phenylpyrrole derivatives, and it should have considerable utility in the syntheses of new heterocyclic systems with potential therapeutic interest.

EXPERIMENTAL SECTION

Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded as KBr pellets on a Philips PU 9716 apparatus. Nmr spectra were obtained on a Jeol FX 200 in DMSO-d_6 using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

1-Phenylpyrrole-3-carboxylic Acid (6).- A 6N aqueous sodium hydroxide solution (100 mL) was added to a solution of phenylpyrrole-3-carboxaldehyde **4** (16.5 g, 0.096 mol) in methanol (100 mL). Silver nitrate (24.5 g, 0.15 mol) was then added to the reaction mixture which was refluxed for 2 hrs. The solution was filtered and methanol was removed under reduced pressure. The aqueous layer was washed twice by ether (2x100 mL) and then acidified to pH 1 with conc. hydrochloric acid. The precipitate was collected, washed with water (100 mL) and dried to give **6** as a white solid (15.3 g, 85%), mp 126° (ether-petroleum ether). IR : 3150-2500 (OH), 1660 (CO) cm^{-1}. ^1H NMR: δ 7.91 (s, 1H, H-2), 7.66 (d, 2H, *J* = 7.8 Hz, H-2' and H-6'), 7.49 (dd, 2H, *J* = 7.8 and 7.8 Hz, H-3' and H-5'), 7.42 (s, 1H, H-5), 7.34 (d, 1H, *J* = 7.8 Hz, H-4'), 6.60 (s, 1H, H-4), 3.5 (br, 1H, OH). ^{13}C NMR : 165.50 (CO), 139.46 (C-1'), 130.05 (C-2' and C-6'), 126.78 (C-3' and C-5'), 124.10 (C-3), 120.94 (C-2), 120.36 (C-5), 118.72 (C-4'), 111.72 (C-4).

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.76; H, 4.73; N, 7.47

1-Phenylpyrrole-3-carboxylic acid Azide (7).- 1-Phenylpyrrole-3-carboxylic acid **6** (15.3 g, 0.082 mol) was added portionwise at room temperature to thionyl chloride (50 mL). The reaction mixture was refluxed for 30 min and then evaporated to dryness under reduced pressure to give an oily residue which was immediately dissolved in acetone (50 mL). An aqueous solution (5 mL) of sodium azide (5.9 g, 0.090 mol) was added to the solution and the reaction mixture was stirred at room temperature for 30 min. The solution was then poured into water (400 mL) and extracted twice with ether (2 x 200 mL). The ethereal extracts were collected, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give **7** as a brown solid (17.4 g, 100%), mp 65° (dec.), which was used without other purification. IR : 2130 (N_3), 1670 (CO) cm^{-1}. ^1H NMR: δ 8.12 (s, 1H, H-2); 7.6 (m, 2H, H-2' and H-6'); 7.5 (m, 3H, H-3', H-4' and H-5'); 7.38 (s, 1H, H-5); 6.70 (s, 1H, H-4).

3-Benzyloxycarbonylamino-1-phenylpyrrole (8).- Benzyl alcohol (9.3 mL, 0.090 mol) was added to a solution of 1-phenylpyrrole-3-carboxylic acid azide **7** (17.4 g, 0.082 mol) in 1,2-dichloroethane (250 mL). The reaction mixture was refluxed for 4 hrs and the solvent was then removed under reduced pressure to give **8** as a yellow solid (21.3 g, 89%), mp 96° (ether-petroleum ether). IR : 3260 (NH), 1700 (CO) cm^{-1}. ^1H NMR: δ 9.56 (s, 1H, NH), 7.4 (m, 11H, 2Ph and H-5), 7.22 (s, 1H, H-2), 6.17 (s, 1H, H-4), 5.12 (s, 2H, CH_2).

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 10.95. Found: C, 73.89; H, 5.65; N, 10.60

3-Amino-1-phenylpyrrole (9).- A solution of 3-benzyloxycarbonylamino-1-phenylpyrrole **8** (21.3 g, 0.073 mol) in trifluoroacetic acid (50 mL) was refluxed for 4 hrs. The reaction mixture was evaporated to dryness and the oily residue was taken up in ether (100 mL). The mixture was stirred at room temperature for 3 hrs and the resulting solid was collected, washed with ether (50 mL), dried and then dissolved into water (50 mL). Sodium hydroxide pellets were added to bring the pH of the aqueous solution to 10. The precipitate formed was collected, washed with water (20 mL) and dried to give **9** as a yellow solid (7g, 60%), mp 109° (ether-petroleum ether). IR : 3360, 3300 (NH_2) cm^{-1}. ^1H NMR: δ 7.3 (m, 4H, H-2', H-3', H-5'and H-6'), 7.1 (m, 2H, H-5 and H-4'), 6.61 (s,1H, H-2), 5.79 (s, 1H, H-4), 3.9 (br, 2H, NH_2). ^{13}C NMR : 140.04 (C-1'), 135.02 (C-3), 129.30 (C-2' and C-6'); 123.57 (C-3'

and C-5'), 117.50 (C-5), 116.65 (C-4'), 104.00 (C-4), 102.08 (C-2).
Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.76; H, 6.34; N, 17.26

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A PRACTICAL METHOD FOR THE SYNTHESIS OF N-FLUORENYLMETHOXYCARBONYL DIAMINES

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Monoprotected alkyldiamines are extremely important homobifunctional reagents needed as spacers in many applications in biotechnology. Such linkers are used to attach complex drugs to proteins for the development of antibodies, to link antigens and antibodies to solid supports for use in affinity chromatography, and for the regioselective attachment of drugs to monoclonal antibodies for site specific delivery.[1,2] Desirable monoprotected diamine linkers would allow connection of costly biological and chemical moieties *via* carboxylic acid groups in a controlled, predictable fashion and in high yield. The choice of groups useful for amine protection is rather limited, since the conditions required for *de*protection denature proteins such as monoclonal antibodies and enzymes. Complex antigens (macrocyclic lactones, glycosides, quassinoids, etc.) also contain numerous structural features which render them sensitive to reduction and hydrolysis under acidic or basic conditions. The fluorenylmethoxycarbonyl (FMOC) group, however, is cleavable under a variety of mild conditions[3,4] and is thus an excellent choice for such applications. The synthesis of stable mono-fluorenylmethoxycarbonyl diamines has not been previously described. We report here a simple, practical synthesis of mono-fluorenylmethoxycarbonyl diamines.

The N-*tert*-butoxycarbonyl diamine[5] was first protected by acylation with fluorenylmethyl chloroformate in aqueous tetrahydrofuran in the presence of sodium carbonate as an acid scavenger[6]