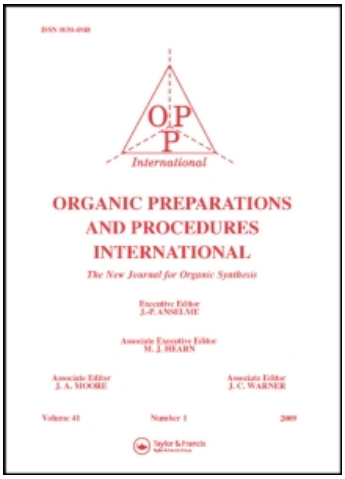

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A NEW SYNTHETIC METHOD FOR THE 2-SUBSTITUTION OF PYRROLE†

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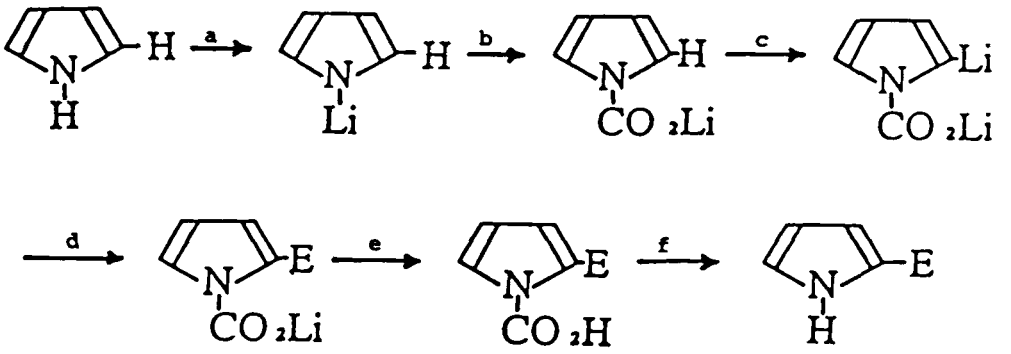
Carbon-carbon bond formation reactions using intermediate organolithium species[1] are familiar in strategic approaches for introducing new functionalities. Such advantageous methodology has enabled the synthesis of many key compounds.[2] In the context of our general study of methodologies for the α- or β-functionalization of amines and alcohols, we have already reported a procedure for introducing a 2-substituent into indole[3] by using carbon dioxide for the protection. We have now extended this proceedure to the



a: n-BuLi/THF, hexane, -70 to 25°C, **b**: CO_2, 25°C, 3 mins., **c**: t-BuLi/THF, pentane, -70°C, -25°C, 1hr, **d**: E^+, -70 to 25°C, **e,f**: H^+/H_2O, 0°C, 5 mins.

lithiation of the lithium pyrrole-1-carboxylate, easily derived from pyrrole. This is an extension of the scope of our previously reported protection methodology to a one-pot synthetic sequence for the α-functionalization of N-H pyrroles. The basic concept of the methodology and the experimental procedures are almost the same as those described earlier,[3] including the sequence divided into five operations: **(i) Protection. (ii) Lithiation. (iii) Carbon-Carbon bond formation. (iv) Deprotection** and **(v) Work-up.** The electrophiles utilized and the compounds synthesized are listed in the Table.

TABLE. One-Pot Preparations of 2-Substituted Pyrroles from Pyrrole

Electrophile	2-Subst.	Yield(%)[a]	mp(°C)	lit.mp(°C)
CO_2	$-CO_2H$	95	207-208 (dec.)	208.5(dec.)[4]
C_6H_5NCO	$-CONHC_6H_5$	69	155.5-157	---
$(C_6H_5)_2CO$	$-C(OH)(C_6H_5)_2$	60	80-82	81-82[4]
$4-CH_3C_6H_5SO_2F$	$-SO_2C_6H_4CH_3-p$	55	186-187	---
$(CH_3)_2NCHO$	-CHO	50	42.5-43.5	50-51[4]

a) Isolated overall yield based on pyrrole

Whereas N-alkylpyrroles can be C-lithiated,[5,6] N-unsubstituted pyrroles form unreactive pyrrole N-anions.[6b] Previously proposed N-protecting groups each require the isolation and purification of two intermediates: the protected pyrrole, and the 2-substituted 1-protected pyrrole:

(i) The CO_2Bu-t[7a] group was introduced with pivaloyl azide and these compounds require lithiation with lithium 2,2',6,6'-tetramethylpiperidie; the overall yields were 0-49 %.

(ii) N-(Dimethylamino)pyrrole[7b] was prepared from 2,5-dimethoxytetrahydrofuran and unsym-dimethylhydrazine. Deprotection requires $Cr_2(OAc)_4 \cdot 2H_2O$ which affects many functionalities at the 2-position. This method is thus not general.

(iii) The benzenesulfonyl group[7a] was stated to be easily cleaved during lithiation.

(iv) The recently reported use of 2-trimethylsilyethoxymethyl group[7c] gave only two examples of deprotection and the best overall yield was less than 30%.

In contrast, we have synthesized 2-substituted pyrroles in one-pot sequences by the reaction of pyrrole-1-carboxylate with t-butyllithium as a key step. The particular ease of introduction and of removal which characterize our use of carbon dioxide as a protecting group offer considerable advantages over all the previously reported N-protection methodologies.

EXPERIMENTAL SECTION

Mps of the products were measured on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. IR spectra are of KBr discs using a Perkin-Elmer 283 B. ^{1}H NMR spectra were obtained with a Varian EM 360 L and using tetramethylsilane as an internal standard. Elemental analyses were carried out under the supervision of Dr. R. King of this Department. Pyrrole was purchased from Eastman Kodak Chemical Co. and was used after distillation. n-Butyllithium and t-butyllithium (Aldrich) were used without further purification. Tetrahydrofuran, reagent grade from Fisher Chemical Co, was dried with calcium hydride and used directly after distillation under dry argon. Carbon dioxide (Matheson) was used after drying with calcium sulfate. Processes (i) to (iii) were carried out under dry argon.

α-Functionalization of Pyrrole.- A two-necked flask was evacuated and was flushed with dry argon three times. Pyrrole (2.00 ml, 28.8 mmol) was placed into the flask and tetrahydrofuran (40.0 ml) added to give a homogeneous solution. The solution was cooled to -70°C, and n-butyllithium (11.6 ml of a

2.5 M hexane solution) was slowly added at -70°C. The cooling bath was removed to allow the solution to warm to 25°C within 10 mins. Carbon dioxide gas was passed into the solution for 3 mins with vigorous stirring; a pale yellow homogeneous solution resulted. After aging for 5 mins at 25°C, the solvent was removed below 25°C on a rotary evaporator using a vacuum pump to give a colorless solid. The flask was evacuated thoroughly, flushed with dry argon three times and tetrahydrofuran (60.0 ml) was added. The solution was cooled to -70°C, and t-butyllithium (20.0 ml of a 1.7 M pentane solution) was slowly added at -70°C to give a yellow solution. This solution was aged at the same temperature for 1 hr. The electrophile in tetrahydrofuran (5.0 ml) was then added at -70°C. The solution was kept at the same temperature for 2 hrs., and then slowly quenched with aqueous ammonium sulfate, at -70°C. The solution was allowed to reach 25°C within 1 hr, and 2N sulfuric acid (20.0ml) was slowly added at 0°C, gas was evolved. The solution was neutralized with aqueous sodium hydroxide solution, was extracted twice with diethyl ether, washed with water, dried with anhydrous magnesium sulfate, filtered, and the solvent evaporated on a rotary evaporator under reduced pressure to give the crude product. The products were purified by column chromatography or recrystallization.

Pyrrole-2-carboxylic Acid: ^{1}H NMR ($CDCl_3$-DMSO_D6, TMS): δ 6.28-6.32 (m, 1H, Pyr-H), 6.99-7.06 (m, 2H, Pyr-H), and 11.63 (bs, 2H, $-CO_2H$, =NH).

2-(N-Phenylcarbamoyl)pyrrole: ^{1}H NMR ($CDCl_3$, TMS): δ 6.13-6.30 (m, 1H, Pyr-H), 6.97-7.53 (m, 5H, Pyr-H, ArH), 7.77-7.97 (m, 2H, ArH), 9.8 (s, 1H, -CONH), and 11.73 (bs, 1H, =NH).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04
Found: C, 70.72; H, 5.60; N, 14.96

α,α-Diphenyl-2-pyrroylmethanol: ^{1}H NMR ($CDCl_3$, TMS): δ 2.52-3.45 (bs, 1H, -OH), 5.78-6.45 (m, 2H, Pyr-H), 6.68-6.88 (m, 1H, Pyr-H), 7.05-7.98 (m, 10H, ArH), and 8.05-8.98 (bs, 1H, =NH).

2-Pyrroyl p-tolyl sulfone: ^{1}H NMR ($CDCl_3$, TMS): δ 2.40 (s, 3H, $-CH_3$), 6.17-6.33 (m, 1H, Pyr-H), 6.83-7.07 (m, 2H, Pyr-H), 7.37 (d, 2H, ArH), 7.93 (d, 2H, ArH), and 12.37 (bs, 1H, =NH).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C; 59.71, H; 5.01, N; 6.33

Found: C; 59.61, H; 5.13, N; 6.08

2-Formylpyrrole: ^{1}H NMR ($CDCl_3$, TMS): δ 6.33-6.47 (m, 1H, Pyr-H), 7.07-7.30 (m, 2H, Pyr-H), 9.70 (s, 1H, -CHO), and 11.37 (bs, 1H, =NH). IR (KBr, cm^{-1}) 3260 (N-H), 1640 (C=O).

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