

EFFICIENT SYNTHESIS OF 1,1'-METHYLENEBIS-1H-PYRROLE DERIVATIVES[†]

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Abstract - The title compounds may be prepared efficiently by the reaction of methylene chloride with the pyrrolyl anion generated under phase-transfer conditions. The spectral characteristics of these relatively unknown compounds are discussed.

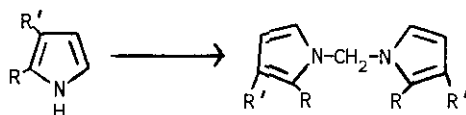
The N-alkylation of pyrroles by means of phase-transfer technique is a well-established synthetic method in pyrrole chemistry¹ and is probably the most convenient way to prepare N-alkyl derivatives. In the course of some phase-transfer alkylation studies in our laboratory, we inadvertently discovered that in the absence of a more reactive alkylating agent, methylene chloride, often used as a solvent in such reactions, will alkylate two molecules of the pyrrolyl anion, thus giving 1,1'-methylenebis-1H-pyrrole derivatives in high yield.

Although C,C'-methylenebis-1H-pyrroles of various types are well-known compounds described in the literature², the N,N'- or 1,1'-methylenebis-1H-pyrroles are members of a less studied class of compounds. A search of the literature reveals that apparently only two such compounds have been prepared. The parent compound (4), mp 112°C, was first made by Pictet and Rilliet in 1907³ by the reaction of pyrrolyl potassium with methylene chloride at 130°C. The corresponding 2,2'-methylenebis-1H-pyrrole was also formed in this reaction. Later, Scott allegedly prepared the same 1,1'-methylene compound (27% yield) by treatment of pyrrole with sodium amide and methylene chloride⁴, although a very different melting point (47°C) is reported. Most recently Burger and Dreier have prepared and fully characterized (4), mp 105°C, by the reaction of pyrrolyl lithium with methylene chloride in HMPA (85% yield)⁵. The corresponding 2,2'-bis-acetyl derivative, mp 180-181°C, has also been prepared in an analogous way from the pyrrolyl potassium derivative⁶.

In the present work various pyrroles and indole were reacted in methylene chloride with aqueous sodium hydroxide and a standard phase-transfer catalyst at reflux. The results are reported in Table 1. A typical procedure is as follows: 2-Formylpyrrole (0.500 g) and tetrabutylammonium iodide (1.942 g) were dissolved in 20 ml methylene chloride. To this solution was added 5 ml 50% sodium hydroxide solution and the mixture was gently refluxed with vigorous stirring for 5 h. Upon cooling the mixture was diluted with 50 ml water and extracted with 50 ml methylene chloride three times. The combined organic phases were washed with water to neutrality, dried over sodium

sulfate and evaporated to dryness. The crude product was percolated through a short silica gel column, eluting with hexane-ethyl acetate (7:3) to give pure 1,1'-methylenebis-2-formylpyrrole, 0.522 g (98%), which was homogeneous on tlc. Recrystallization from hexane-methylene chloride gave an analytical sample, mp 144.5-145.0°C.

TABLE 1: The reaction of pyrrolyl anions with methylene chloride



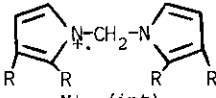
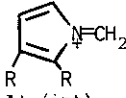
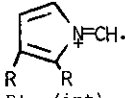
	R	R'	mp ⁹ (°C)	% yield	time of reaction (h)
1.	C ₆ H ₅ CO-	H	159°	100	4
2.	HCO-	H	144.5-145°	98	5
3.	CH ₃ S-	H	53.5-54.5°	50	5
4.	H	H	106-107°	20	90
5.	-CH ₂ CH ₂ CH ₂ CO-		250° (dec.)	86	4
6.	-CH=CH-CH=CH-		116-117°	43	15

TABLE 2: ¹H 300 MHz nmr spectral parameters of 1,1'-methylenebispyrroles
measured in CDCl₃

COMPOUND	N-CH ₂ -N	H-3	H-4	H-5	J ₄₅	J ₃₅	J ₃₄
1	7.17	6.78	6.16	7.57	3.2	1.7	3.9
2	6.90	6.96	6.23	7.58	3.0	2.0	4.4
3	6.18	6.40	6.16	6.94	2.9	1.8	3.6
4	5.73	(6.70)	6.16	6.70	a	a	a
5 ^b	5.85	----	6.58	6.67	3.2	---	---
6	6.26	----	6.51 ^c	7.13 ^d	3.3 ^e	---	---

a) Compound 4 exhibits two unsymmetrical triplets as the result of an AA'BB' system with apparent J values of 2.0 and 2.2 Hz for each triplet. b) Measured in CDCl₃-CD₃OD for reasons of poor solubility in CDCl₃. c) H-3 by indole numbering. d) H-2 by indole numbering. e) J₂₃ by indole numbering.

TABLE 3: Important mass spectral fragmentation of 1,1'-methylenebispyrroles

COMPOUND	 M^+ (int)	 A^+ (int)	 B^+ (int)
1	354 (4%)	184 (67%)	183 (100%)
2	202 (42%)	108 (100%)	107 (78%)
3	238 (15%)	126 (41%)	-----
4	146 (45%)	80 (100%)	79 (2%)
5	282 (41%)	148 (100%)	147 (68%)
6	246 (25%)	130 (100%)	129 (2%)

The structures of all compounds were confirmed on the basis of their 300 MHz proton nmr spectra (Table 2) which exhibit the characteristic $N-CH_2-N$ singlet as well as the expected pyrrole proton chemical shifts and coupling constants⁷. All compounds fragment in the mass spectrometer in the expected manner⁶ (Table 3), giving strong peaks at m/e values corresponding to fragmentation of one $N-CH_2$ bond (A^+), as well as one mass unit less in the case of the carbonyl derivatives (B^+). Though the latter ion has been proposed to originate via proton abstraction from the $N-CH_2-N$ by the oxygen in a 6-membered transition state prior to fragmentation⁶, compound 5, for which such rearrangement is geometrically impossible, also shows a strong peak of the type B^+ . Finally, the ir spectra of all compounds indicate the absence of the $N-H$ band of the starting pyrrole.

The present work, though not efficient for the synthesis of the parent system 4, does offer an extremely easy and efficient means of preparing 1,1'-methylenebis-1H-pyrroles which does not require the use of organometallic bases nor anhydrous conditions for the generation of the pyrrolyl anion. Such double alkylation of substrates by methylene chloride under phase-transfer conditions has precedent in the formation of methylene diesters of carboxylic acids⁸. This observation, together with those of the present work, point to the need for judicious choice of the solvent in phase-transfer alkylations when the alkylating agent is relatively unreactive.

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