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ELECTROPHILIC SUBSTITUTIONS ON 2-TRICHLOROACETYLPYRROLE

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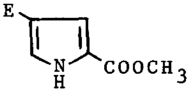
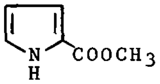
Summary: 2-Trichloroacetylpyrrole is a useful substrate leading to 4-substituted-2-trichloroacetylpyrrole as electrophilic substitutions occur exclusively at the position 4.

An interest in the preparation of various quantities of methyl 4-substituted-pyrrole-2-carboxylates 1 led to a thorough examination of the literature for a simple route amenable to preparation of large quantities of such derivatives (1,2).

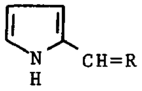
Methyl pyrrolecarboxylate 2 is not a very efficient intermediate since electrophiles attack non-selectively positions 4 and 5, leading to mixtures not readily separable by chromatography (3). The use of bulky groups in the 2 position did not improve the regioselectivity (4), although it reduces the attack on position 3. Formylpyrrole 3a is a more attractive starting material since on reaction with electrophiles a greater selectivity for attack at the 4 position is found (5), although the 5 position is still somewhat reactive (6). The most promising method currently available is that of Sonnet (7) who has shown that pyrrolidonium perchlorates 3b undergo electrophilic substitutions in an essentially regioselective manner. The usefulness of this approach is, however, limited by the number of steps required to achieve the conversion of the 4-substituted-pyrrolidonium perchlorate to the corresponding ester 1.



1



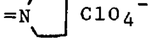
2



3

a) R = =O

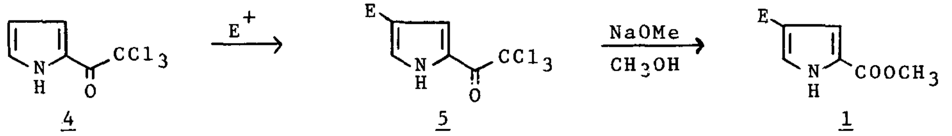
b) R =



We have found that with 2-trichloroacetylpyrrole 4, electrophilic substitution occurs at the 4 position cleanly and efficiently with essentially no substitution at the 5 position. The reaction is applicable to a wide variety of electrophiles and thus provides a convenient intermediate for obtaining compounds of the type 1 in good yields. Some attempts to achieve Friedel-Crafts reaction with alkyl halides were not successful and were not investigated further. Equation 1 summarizes the preparation of 1. Results obtained are given in Table I.

A typical procedure for the substitution is as follows: To 2-trichloroacetylpyrrole (8) (22 g, 0.1 mole) in 100 ml chloroform-d or methylene chloride-d_2 at 0°C is added dropwise an equivalent amount of an electrophile, monitoring the reaction by NMR after the addition is over for the disappearance of the 4-proton located at 6.33 ppm as a pair of doublets J=3 Hz, J=5 Hz. The reaction is then poured on ice, extracted with methylene chloride, washed with water until neutral and dried to yield the corresponding 4-substituted-2-trichloroacetylpyrrole 5, characterized in the NMR by aromatic proton signals observed as doublets with coupling constants of 2 Hz. With 5-substituted derivatives, the coupling constant is about 4 Hz (3).

Their structure is also well established by converting these derivatives to the well known corresponding esters. This is simply carried out by adding them to a solution of sodium methoxide in methanol at room temperature. The reaction is quenched with water after 15 minutes and the resulting esters are removed by filtration.



(1)

Our data together with published results indicate that the electron withdrawing character of the 2-substituent greatly affects the direction of the electrophilic attack. Pyrrole usually undergoes substitution on the alpha carbon (1). However, deactivation of the ring by electron withdrawing groups in the 2 position tends to direct electrophiles to the 4 position. CNDO calculations show that the 4-carbon is not influenced at all by groups in position 2, whereas the 5-carbon is greatly deactivated by an electron withdrawing group in the 2 position (9).

Table 1

		5		1	
E	Conditions	% Yield	m.p. °C	% Yield[a]	m.p. °C
$-NO_2$	90% HNO_3, -50°C, 1 hr.	77[b]	188-189	89	196-197[d] (197)[11]
$-Cl$	SO_2Cl_2, 0°C, $CHCl_3$, 10 min.	89	115-116.5	81	97-98.5 (101.5-103)[3]
$-Br$	Br_2, 0°C, $CHCl_3$, 10 min.	75	134-136	86	98.5-100 (98.5-100.5)[3]
$-I$	$AgOCOCF_3-I_2$, 22°C, 1 hr, $CHCl_3$	73	128-130	85	85-86 (87-89)[13]
$-CHO$	$CHCl_2OCH_3-AlCl_3$, CH_2Cl_2, 22°C, 18 hr.	3	136-137	85	120-122 (121-122)[13]
$-COCH_3$	$CH_3COCl-AlCl_3$, CH_2Cl_2, 0°C, 1 hr.	94	193-194	93	109-110
$-SCF_3$	CF_3SCl-pyridine reflux	-[c]	-	52	108-110[e]

[a] Yield for conversion of 5 to 1

[b] 5-NO_2 substitution also obtained; 5-NO_2; oil

[c] N substitution only

[d] 5-NO_2 derivative, m.p. 178-179°C (178°C)[11]

[e] Obtained by reaction of CF_3SCl on 2-carbomethoxypyrrole

The pyrrolidonium group is such a powerful electron withdrawing group that some weak electrophiles such as iodine do not undergo substitution readily (10). The trichloroacetyl group has electron withdrawing properties which allow weak electrophiles such as iodine or methoxychloromethyl to react readily. Trifluoromethylthiosulfenyl chloride behaves differently than the other electrophiles studied. This reagent reacts with trichloroacetylpyrrole to yield N-substitution exclusively.

In summary, a facile method has been developed for the preparation of methyl 4-substituted-pyrrole-2-carboxylates with a simple and good yielding sequence suitable for preparation of large quantities.

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