Diborane Reduction of Pyrrole Ester Groups

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Our interest in screening halogen derivatives of methyl pyrrole-2-carboxylate and other simple pyrroles for trail-following behavior on the leaf-cutting ant, *Atta texana* (Buckley) (1) led us to examine diborane reduction of some brominated pyrrole esters. Although we had expected to observe reductive removal of the halogen (2) we found rapid reduction of the carbomethoxy group to methyl in certain instances instead. Reduction of pyrrole aldehydes (3), ketones (3), and hydroxymethyl groups (4) with diborane has been described. Although reduction of aliphatic ester groups occurs slowly (5), the carboxylic ester groups of the pyrroles previously reported (3,4), have survived the reduction.

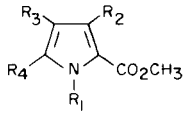
An approximate measure of the rapidity of this reduction was obtained by treating each compound with a measured excess of diborane in THF under nitrogen at ambient temperature. After 24 hours, ethylene glycol was injected and the amount of hydride (B-H) consumed per millimole of the reactant was assessed by collecting the evolved hydrogen and correcting with a blank. These results are given in Table I. The crude product was analyzed by glpc and nmr.

Replacement of bromine with hydrogen was not observed under these conditions. The effect of bromine substitution on the ring was to enhance the rate of reduction of the ester function. In fact, **5** was completely and quantitatively converted to 2-methyl-3,4,5-tribromopyrrole in less than 15 minutes, while **3** required several days for complete conversion to 2-methyl-4-bromopyrrole. Ring methyl, however, slowed this reduction. This was very marked in the case of the *N*-methylated compound, **11**, which gave no reaction at all. If the reduction proceeds through a hydroxymethyl stage, this stage undergoes reduction very rapidly, for dipyrrylmethanes were not found among the products (3).

Contrastingly, LAH reduction of **3** proceeded rapidly

TABLE I

Reaction of Pyrroles with Diborane



Compound	R_1	R_2	R_3	R_4	mm BH/mmole compound	Products
1	H	H	H	H	1.9	**1** + 2-methylpyrrole (77:23)
2	H	H	H	CH_3	2.0	**2** + 2,5-dimethylpyrrole (85:15)
3	H	H	Br	H	2.5	**3** + 4-bromo-2-methylpyrrole (50:50)
4	H	H	Br	Br	3.3	Reacted immediately upon isolation
5	H	Br	Br	Br	3.2	2-methyl-3,4,5-tribromopyrrole
6(a)	H	H	Br	CH_3	1.5	60% recovered **6**; no evidence for another product
7	H	Br	Br	CH_3	2.3	62% recovered **7**; no evidence for another product
8	H	H	H	CHO	3.6	53% isolated yield of **2**
9	H	Br	H	CHO	2.5	70% isolated yield of methyl 3-bromo-5-hydroxy= methylpyrrole-2-carboxylate
10	H	Br	CH_3	Br	4.1	Reacted immediately upon isolation
11	CH_3	Br	Br	Br	-----	90% recovered **11**; no evidence for another product

(a) ~9% of **7** present.

to the hydroxymethyl stage (nmr) and only slowly thereafter to methyl. Synthetically either reagent is satisfactory for transforming carbomethoxy into methyl and both appear to suffer limitations in the case of *N*-methylated esters. Interestingly, although diborane reduction of **8** gave primarily the methyl product, **2**; the reaction of **9** stopped at the hydroxymethyl stage. In these instances the ester group survived reduction and the formyl group underwent partial or complete reduction.

Several of these esters were treated with diborane-THF under reflux for 3 hours. Compound **11** was essentially inert, while **6** gave a few per cent of the debrominated compound **2**.

Clearly the reducibility of the pyrrole ester group is highly dependent on the nature and position of the other ring substituents. However, the data given are insufficient for any detailed mechanistic analysis.

EXPERIMENTAL

General.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded by a Perkin-Elmer 137 spectrophotometer as nujol mulls. Nmr spectra were determined with Varian T-60 and HA-100-A spectrometers. Analyses of reaction mixtures were carried out by means of gas-liquid partition chromatography using an Aerograph Model A-700 instrument equipped with a 6'x 1/8" stainless steel column packed with 5% silicone oil (SE-30) on acid-washed chromosorb W. Chemical analyses were determined by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Starting Materials.

Compounds **1** (1b), **2** (6), **3** (7), **4** (8), **5** (9), **6** (10), and **8** (11) were prepared as described in the literature.

General Procedure for Brominations of **2**,**8** and Methyl 3-Methylpyrrole-2-carboxylate (**1b**).

In a 100-ml. three-neck flask equipped with a magnetic stirring bar, condenser, and thermometer, was placed 0.005 mole of starting material in 40 ml. of dichloroethane (DCE). A solution of 0.005 mole of bromine (for converting **8** to **9**) or 0.010 mole of bromine (for converting **2** to **7** or methyl 3-methylpyrrole-2-carboxylate to **10**) in 10 ml. of DCE was added all at once, and then the mixture was allowed to stand overnight at room temperature. For **10**, the mixture was warmed to 50° overnight. The reaction mixture was stripped on a flash evaporator and the product was recrystallized from benzene-hexane. The products were: compound **7** (72%), m.p. 199-201° dec.; nmr (DMSO-d_6) 2.25 (s, 3, aryl CH_3), 3.70 (s, 3, ester CH_3).

Anal. Calcd. for $C_7H_7Br_2NO_2$: C, 28.32; H, 2.38; Br, 53.81; N, 4.72. Found: C, 28.31; H, 2.28; Br, 53.79; N, 4.68. Compound **9** (89%), m.p. 190-191°; nmr (DMSO-d_6)3.88 (s, 3, ester CH_3), 6.98 (s, 1, aryl H), 9.85 (s, 1, CHO).

Anal. Calcd. for $C_7H_6BrNO_3$: C, 36.23; H, 2.61; Br, 34.44; N, 6.04. Found: C, 36.17; H, 2.52; Br, 34.60; N, 6.06.

Compound **10** (84%), m.p. 172-172.5°; nmr (DMSO-d_6) 1.97 (s, 3, aryl CH_3), 3.83 (s, 3, ester CH_3).

Anal. Calcd. for $C_7H_7Br_2NO_2$: C, 28.32; H, 2.38; Br, 53.81; N, 4.72. Found: C, 28.52; H, 2.37; Br, 53.95; N, 4.76. The assignment for **9** is based on the known greater deactivating power of formyl as opposed to carbomethoxy (12).

N-Methylation of Methyl 3,4,5-tribromopyrrole-2-carboxylate (**5**) to Compound **11**.

Sodium hydride (22.8 mmoles) was washed three times with hexane and placed under nitrogen. Dimethylformamide (DMF) (20 ml.) was added, the slurry was cooled in an ice bath, and a solution of 13.8 mm of **5** in 20 ml. of DMF was added slowly. The mixture was then stirred for fifteen minutes without cooling and then chilled again while 23 mmoles of methyl iodide was injected into the mixture through a rubber serum cap at such a rate as to keep the temperature of the mixture below 20°. The reaction mixture was allowed to stand overnight, diluted with ice water, and extracted several times with ether. The ether extract was washed twice with water and dried over magnesium sulfate. The product, **11**, was obtained by removal of the solvent and recrystallization from isooctane (67%), m.p. 84-85°; nmr (carbon tetrachloride) 3.83 (s,3); 3.95 (s,3).

Anal. Calcd. for $C_7H_6Br_3NO_2$: C, 22.37; H, 1.61; Br, 63.78; N, 3.72. Found: C, 22.17; H, 1.75; Br, 6.370; N, 3.59.

General Procedure for the Diborane Reductions.

A 25 ml. three-neck flask fitted with a rubber serum cap and a reflux condenser was dried by flaming and placed under dry nitrogen. The compound, 1.00 mmole, was placed in the flask and 2 ml. of dry dimethoxyethane (molecular sieves) was injected. Diborane (~ 1.0 M in THF) 5 ml. was then injected. After 22-24 hours, ethylene glycol was injected and the hydrogen gas was collected over water. Appropriate corrections were made for temperature, vapor pressure of water and a blank run. In order to analyze the products, the reaction mixtures were worked up by diluting with water and then extracting with ether. The ether extracts were washed with water, dried (magnesium sulfate) and concentrated either on the steam bath (if volatiles such as 2-methylpyrrole were expected) or on the flash evaporator.

The nmr spectra of the new compounds obtained (DMSO-d_6) were as follows: *4-bromo-2-methylpyrrole:* 2.17 (s, 3, CH_3), 5.77 (m, 1, H3), 6.64 (m, 1, H5); *2-methyl-3,4,5-tribromopyrrole:* 2.18 (s, 3, CH_3); *methyl 3-bromo-5-hydroxymethylpyrrole-2-carboxylate:* 3.77 (s, 3, CH_3), 4.47 (s after addition of a trace of piperidine, 2, CH_2O), 6.77 (s, 1, H4). The hydroxymethyl derivative gave m.p. 139.5-140.5° (benzene).

Anal. Calcd. for $C_7H_8BrNO_3$: C, 35.92; H, 3.44; Br, 34.14; N, 5.98. Found: C, 36.21; H, 3.38; Br, 33.90; N, 5.89.

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