Novel Substituent Orientation in Reimer-Tiemann Reactions of Pyrrole-2-carboxylates

Kevin M. Smith,* Frank W. Bobe, Ohannes M. Minnetian, Håkon Hope, and Michael D. Yanuck

Department of Chemistry, University of California, Davis, California 95616

Received August 21, 1984

Reimer-Tiemann formylation reactions (base/$CHCl_3$) on 5-substituted pyrrole-2-carboxylates (**1**, **6**, **8**, **9**, **11**, and **13**) afford 2-formylpyrroles (**5**, **7**, **10**, **12**, and **14**) in which the formyl group is situated in the position originally occupied by the carboxylate function, and not, as had been expected, in the 5-unsubstituted site. These observations are confirmed by X-ray crystal structures of compounds **5**, **7**, and **10** and by nuclear Overhauser enhancement experiments for pyrroles **7**, **10**, and **14**.

Introduction

The Reimer-Tiemann reaction has been used extensively for preparation of aldehydes from electron-rich compounds such as phenols[1] and pyrroles.[2] The reactants are usually the appropriate substrate together with chloroform and a base, and dichlorocarbene has been clearly demonstrated to be an intermediate in the formylation.[3] During the final workup, the corresponding dichloromethyl intermediate is hydrolyzed to give the aldehyde. Anomalous Reimer-Tiemann reactions have also been observed and studied, and in these, ring expansion products are often produced; thus, pyrroles, for example, afford chloropyridines (Scheme I).[1,2] Yields of formylated products from Reimer-Tiemann reactions are rarely high,[1,2] and so, at least in the case of pyrroles, the methods of choice for formylation are the Vilsmeier, Gattermann, or orthoformate/trifluoroacetic acid routes.[2,4]

Results and Discussion

During the course of a study on the Vilsmeier formylation of benzyl 3-methylpyrrole-2-carboxylate (**1**) it was observed that both the 4-formyl- and 5-formylpyrroles (**3** and **4**) were produced. The well-established[2] greater nucleophilicity of the unsubstituted 2- and 5-positions in pyrroles was obviously being reduced by the fact that the 2-benzyl ester was conjugated with the vacant 5-position, thereby affecting the relative nucleophilicities at the 4- and 5-positions in **1**.

Since no studies of orientation of formylation of pyrroles by the Reimer-Tiemann method had been published, and because it was possible that more selectivity might be achieved by using the carbene method (most reports describe only 2- or 5-formylation of pyrroles with unsubstituted positions[2]), it was decided to investigate the Reimer-Tiemann formylation of **1**. When **1** was treated with chloroform and sodium or potassium hydroxide, a 16% yield of a single formylpyrrole was obtained; though the NMR spectrum clearly indicated the presence of a formyl proton (9.70 ppm), the resonances expected for the benzyl ester were missing, and the product still possessed *two* unsubstituted positions, evidenced by one-proton peaks (each a doublet of doublets) at 7.03 and 6.12 ppm. The product from this reaction appeared to be either 5-formyl-3-methylpyrrole (**4**) or 2-formyl-3-methylpyrrole (**5**). At first sight, compound **4** seemed the more likely product, obtained by "formylation" at the 5-position, followed by hydrolysis and decarboxylation of the 2-benzyl ester.

Scheme I

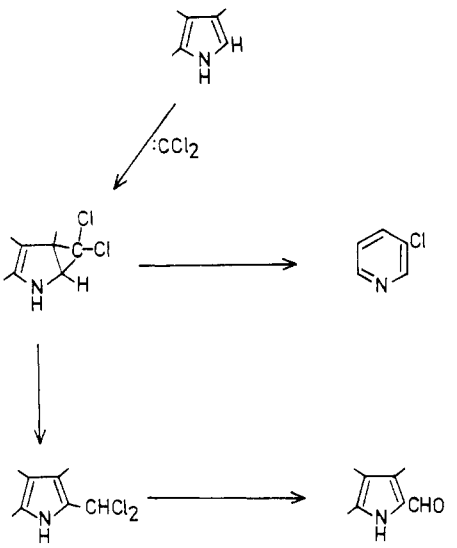
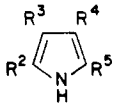


Table I. Structures of Pyrroles Studied



no.	R^2	R^3	R^4	R^5
1	$PhCH_2O_2C$	Me	H	H
2	$PhCH_2O_2C$	Me	CHO	H
3	$PhCH_2O_2C$	Me	H	CHO
4	H	Me	H	CHO
5	CHO	Me	H	H
6	$PhCH_2O_2C$	Me	Et	H
7	CHO	Me	Et	H
8	$PhCH_2O_2C$	Me	Cl	H
9	CO_2H	Me	Cl	H
10	CHO	Me	Cl	H
11	EtO_2C	Me	Br	H
12	CHO	Me	Br	H
13	$PhCH_2O_2C$	Me	CHO	H
14	CHO	Me	CHO	H
15	t-BuO_2C	Et	Me	H

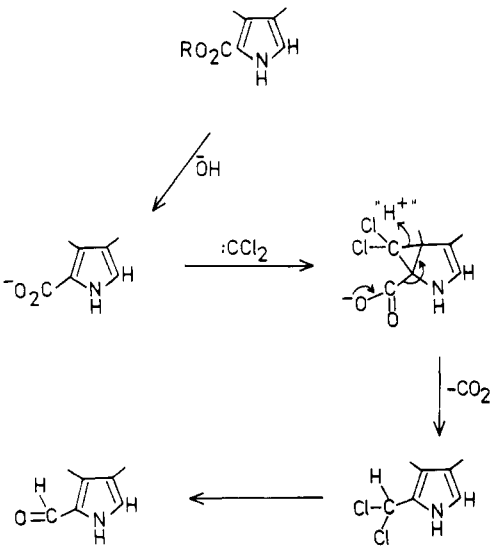
However, decarboxylation of the intermediate 5-formyl 2-carboxylic acid should not be facile, and melting point comparisons (Experimental Section) suggested that the product was 2-formyl-3-methylpyrrole (**5**), indicating that the aldehyde group had simply displaced the benzyl ester.

The structural problem was solved by X-ray crystallographic methods (vide infra), and the product was determined to be 2-formyl-3-methylpyrrole (**5**) (supplementary material). Repetition of the reaction with other pyrrole-2-carboxylates (**6**, **8**, **11**, and **13**) and a 2-carboxylic acid **9** (Table I) revealed that this unexpected substituent

(1) Wynberg, H. *Chem. Rev.* **1960**, *60*, 169-184.
(2) Gossauer, A., "Die Chemie der Pyrrole"; Springer: Berlin, 1974.
(3) Hine, J.; van der Veen, J. M. *J. Am. Chem. Soc.* **1959**, *81*, 6446-6449.
(4) Newkome, G. R.; Paudler, W. W. "Contemporary Heterocyclic Chemistry"; Wiley: New York, 1982.

0022-3263/85/1950-0790$01.50/0

Scheme II



orientation was common to all of the products; in every case the aldehyde function was sited in place of the 2-ester or 2-carboxylic acid. Confirmation was obtained in two more X-ray studies [of compounds **7** (from **6**) and **10** (from **8** and **9**)], and for three (**7**, **10**, and **14**) the orientation of the substituents was established by using nuclear Overhauser enhancement (NOE) NMR experiments; both of the analytical procedures (X-ray and NOE) were internally consistent for compounds **7** and **10**.

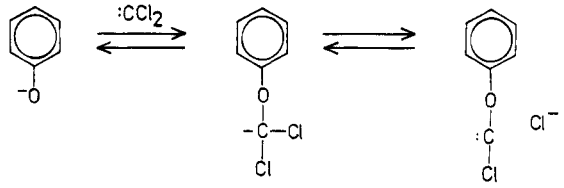
In a typical NOE study [(supplementary material), compound **7**, obtained from **6** with potassium hydroxide and chloroform], irradiation of the 3-methyl at 2.29 ppm gave a positive NOE for the 2-formyl proton (9.58 ppm), consistent with the methyl and formyl groups being adjacent to each other. Similarly, irradiation of the 3-methyl (2.33 ppm) in **10** gave a NOE for the 2-formyl proton (9.59 ppm), while irradiation of the 3-methyl (2.65 ppm) in **14** gave two positive ehancements, a large one to the 2-formyl group (9.76 ppm) and a somewhat smaller enhancement for the 4-formyl proton (at 9.94 ppm).

Attempts to use other bases, such as potassium *tert*-butoxide, failed to increase the yield of the product.

X-ray Crystallographic Studies. The structures of formylpyrroles **5**, **7**, and **10** were determined by X-ray methods. The pyrrole rings and nearest attached atoms are coplanar, and the oxygen atoms deviate by less than 0.15 Å from their respective ring planes. All C–C distances are essentially equal at 1.39 Å. N–C bonds are 1.38 and 1.34 Å, respectively; the longer distance is adjacent to the formyl group, as predicted from resonance considerations. The internal angle at C(4) varies with the substituent: 107.7 (2)° for **5**, 106.6 (1)° for **7**, and 109.4 (4)° for **10**. Again, this confirms to expectation: an electron-withdrawing substituent (Cl in **10**) opens the angle, and an electron-releasing one (ethyl in **7**) narrows it. All three compounds exhibit NH·O hydrogen bonding; compounds **5** and **10** form centrosymmetric dimers, while **7** forms chains. Thermal ellipsoid plots and crystallographic data for **5**, **7**, and **10** can be found in the supplementary material.

Mechanistic Implications. Because the reaction proceeds with the same relative orientation of the formyl group in both esters (e.g., **8**) and carboxylic acids (e.g., **9**), it seems most likely that the first step in the mechanistic sequence (Scheme II) is hydrolysis of the ester (if present) to give the corresponding carboxylate anion. Further evidence in favor of this is the fact that the *tert*-butyl pyrrole-2-carboxylate **15** failed to yield formylpyrrole from the Reimer–Tiemann reaction, presumably due to resistance to saponification of the *tert*-butyl ester. The hydrolysis step to produce the carboxylate anion effectively removes the electron-withdrawing effect of the 2-substituent and facilitates attack by the electron-deficient dichlorocarbene.

Scheme III



It should be mentioned that Reimer–Tiemann formylation[1,5] of salicylic acid and *p*-hydroxybenzoic acid affords formyl carboxylic acid products with the expected structure, as well as compounds in which the carboxylic acid function has been directly replaced by an aldehyde group; both "prior" or "subsequent" decarboxylation were suggested[1] for the mechanism. In the pyrrole case, prior decarboxylation (to give, e.g., 3-methylpyrrole) would certainly result eventually in a mixture of formylpyrroles being produced; thus, we prefer "subsequent" decarboxylation as shown in Scheme II. We propose that the step following carboxylate formation is attack at the 2–3 double bond by dichlorocarbene, the regioselective attack possibly being directed by an interaction between the carboxylate anion and the carbene. Interactions of this type in the Reimer–Tiemann reaction have been documented, for example[1] (Scheme III), in the reaction of phenol with dichlorocarbene. Finally, (Scheme II), decarboxylation is the driving force for transformation of the carbene adduct into the 2-(dichloromethyl)pyrrole, which is hydrolyzed under the basic conditions to give formylpyrrole.

Experimental Section

Melting points were measured on a hot-stage apparatus and are uncorrected. Silica gel 60 (Merck, 70–230 mesh) was used for column chromatography, and preparative TLC was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1 mm thick). Analytical TLC was performed with Merck silica gel 60 F 254 precoated sheets (0.2 mm). Elemental analyses were performed at the Berkeley Microchemical Analysis Laboratory, UC Berkeley.

Proton NMR spectra were measured at 360 MHz with a Nicolet NT-360 spectrometer or at 90 MHz with a Varian EM-390 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. NOE experiments were performed by narrowing down the sweep width of the Nicolet NT-360 instrument to +/− 2000 Hz, then obtaining a 32K spectrum with resolution of 0.3 Hz. The decoupler was set at a chosen frequency at the downfield end of the spectrum (reference) and the second frequency was set to saturate the 3-methyl peak in the pyrrole. The pulse width was set to zero (hetero mode) and the output level was 28 dB. A delay of about four times the acquisition time preceeded a 45° pulse (6.00 μs) in order to obtain maximum build up of the NOE. The decoupler was off during sixteen acquisitions used to obtain the two spectra. Fourier transformation, followed by subtraction of the reference spectrum from the NOE spectrum gave the corresponding difference spectra.

X-ray data for compounds **5**, **7**, and **10** were collected on a Syntex $P2_1$ diffractometer equipped with a locally modified Syntex LT-1 gas stream cooling device. The structures were solved by direct methods and refined by least-squares techniques using the Nicolet SHELXTL system. Hydrogen atoms were included and refined as parts of rigid groups. All calculations were performed on a Data General Eclipse computer. Experimental details are tabulated in the supplementary material.

(5) Reimer, K. L.; Tiemann, F. *Chem. Ber.* **1876**, *9*, 824–828.

Benzyl 4-Formyl-3-methylpyrrole-2-carboxylate (2) and Benzyl 5-Formyl-3-methylpyrrole-2-carboxylate (3). Benzyl 3-methylpyrrole-2-carboxylate[6] (1) (1.48 g) in dichloromethane (25 mL) was added at 0 °C to the Vilsmeier complex previously prepared from phosphoryl chloride (1.28 mL) and dimethylformamide (1.06 mL). The solution was stirred for 40 min at 40 °C until TLC monitoring showed complete formation of the imine salt. Aqueous sodium acetate (20 mL) was cautiously added, followed by aqueous sodium bicarbonate until pH 8. The mixture was stirred at 40 °C for 2 h and then diluted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a residue which was chromatographed on a silica column (elution with 20% ethyl acetate in *n*-hexane) and afforded two isomeric products. The faster moving product (1.2 g, 72%) was the 5-formylpyrrole (**3**), obtained from dichloromethane/hexane as white needles: mp 82.5–83 °C; NMR δ 10.52 (1 H, br s, NH), 9.58 (1 H, s, CHO), 7.33 (5 H, s, Ph), 6.68 (1 H, d, 4-H), 5.32 (2 H, s, CH_2Ph), 2.33 (3 H, s, 3-Me).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69,13; H, 5.38; H, 5.76. Found: C, 69.13; H, 5.45; N, 5.72.

The slower moving chromatographic band gave the 4-formylpyrrole (**2**) (448 mg, 28%), obtained as white needles from dichloromethane/hexane: mp 110.5–111 °C; NMR δ 9.96 (1 H, br s, NH), 9.90 (1 H, s, CHO), 7.42 (1 H, d, 5-H), 7.38 (5 H, s, Ph), 5.32 (2 H, s, CH_2Ph), 2.60 (3 H, s, 3-Me).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.38; N, 5.76. Found: C, 69.08; H, 5.46; N, 5.74.

2-Formyl-3-methylpyrrole (5). Benzyl 3-methylpyrrole-2-carboxylate[6] (**1**) (1.0 g) was dissolved in *tert*-butyl alcohol (6.0 mL) and water (3.7 mL) containing potassium hydroxide (2.76 g) and then heated at 60 °C with vigorous stirring while chloroform (11.1 mL) was added dropwise. After complete addition the mixture was stirred at 60 °C for 15 h, then cooled, diluted with water (20 mL), and extracted with chloroform (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated to dryness, and the oily residue was chromatographed (silica, elution with 30% ethyl acetate/*n*-hexane). Three bands were isolated; the first contained benzyl alcohol, the second yielded starting material (110 mg), and the third afforded the required formylpyrrole after recrystallization from dichloromethane/hexane to give white needles (78 mg, 16%): mp 91–92 °C (lit.[7] mp 92 °C). [The literature melting point[8] for the isomeric 2-formyl-4-methylpyrrole (**4**) is 47–48 °C.] NMR δ 10.00 (1 H, br s, NH), 9.70 (1 H, s, CHO), 7.03 (1 H, dd, 5-H), 6.12 (1 H, dd, 4-H), 2.38 (3 H, s, Me). The identity of the product, **5**, was further established by an X-ray crystal structure. When the experiment was performed with pyrrole **1**, chloroform, potassium hydroxide, and ethanol as solvent, a 14% yield of pyrrole **5** was obtained.

4-Ethyl-2-formyl-3-methylpyrrole (7). In an exactly analogous manner, benzyl 4-ethyl-3-methylpyrrole-2-carboxylate (**6**) (600 mg) was transformed into the title pyrrole, obtained from dichloromethane/hexane as white needles (40 mg, 12%): mp 77 °C; NMR δ 9.58 (1 H, s, CHO), 9.61 (1 H, br s, NH), 6.87 (1 H, d, 5-H), 2.43 (2 H, q, CH_2CH_3), 2.29 (3 H, s, Me), 1.18 (3 H, t, CH_2CH_3). The structure of this pyrrole was further confirmed in X-ray and NOE studies. When methanol was used as the solvent in the reaction, the product, **7**, was obtained in 12% yield.

4-Chloro-2-formyl-3-methylpyrrole (10). (A) From the Benzyl Pyrrole-2-carboxylate 8. The pyrrole ester **8** (1.0 g) in ethanol (4.0 mL) and chloroform (6.4 mL) containing sodium hydroxide (2.4 g) was transformed, as described above, into the 2-formylpyrrole **10** (62 mg, 11%) obtained as white needles from dichloromethane/hexane: mp 112–113 °C; NMR δ 9.59 (1 H, s, CHO), 9.50 (1 H, br s, NH), 7.02 (1 H, d, 5-H), 2.33 (3 H, s, Me). The structure of this material was further confirmed in X-ray and NOE studies.

(B) From the Pyrrole-2-carboxylic Acid 9. The pyrrole carboxylic acid **9** (870 mg) in ethanol (4.0 mL) and chloroform (10.0 mL) containing sodium hydroxide (3.27 g) was transformed, as described above, into the 2-formylpyrrole **10** (81 mg, 10%) obtained as white needles from dichloromethane/hexane. This product was identical, in all respects, with the product obtained from Method A.

4-Bromo-2-formyl-3-methylpyrrole (12). This pyrrole was likewise prepared from ethyl 4-bromo-3-methylpyrrole-2-carboxylate (**11**) (600 mg) in ethanol (5.0 mL) containing chloroform (11.2 mL) and potassium hydroxide (3.5 g), affording 60 mg (14%) of white needles (from dichloromethane/hexane): mp 143–144 °C; NMR δ 9.89 (1 H, br s, NH), 9.63 (1 H, s, CHO), 7.00 (1 H, m, 5-H), 2.32 (3 H, s, Me). The substituent orientation in this compound was established in a preliminary X-ray study.

2,4-Diformyl-3-methylpyrrole (14). In an analogous manner, benzyl 4-formyl-3-methylpyrrole-2-carboxlyate (**13**) (510 mg) in ethanol (10.0 mL) containing chloroform (0.84 mL) and potassium hydroxide (1.76 g) was transformed into the title compound (35 mg, 13%) obtained as white needles: mp 155–156 °C (dichloromethane/hexane); NMR δ 10.19 (1 H, br s, NH), 9.94 (1 H, s, 4-CHO), 9.76 (1 H, s, 2-CHO), 7.60 (1 H, d, 5-H), 2.65 (3 H, s, Me). The orientation of the groups in this pyrrole were established in a NOE study.

Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.07; H, 5.36; N, 10.03.

Acknowledgment. This work was supported by grants from the National Science Foundation (CHE-81-20891) and the National Institutes of Health (HL-22252).

Registry No. **1**, 3284-46-6; **2**, 94781-43-8; **3**, 94781-44-9; **5**, 24014-18-4; **6**, 51089-83-9; **7**, 19711-71-8; **8**, 94781-45-0; **9**, 94781-46-1; **10**, 94781-47-2; **11**, 89909-42-2; **12**, 94781-48-3; **14**, 94781-49-4; **15**, 75488-16-3.

Supplementary Material Available: Thermal ellipsoid drawings of X-ray structures for compounds **5**, **7**, and **10**, tables of X-ray crystallographic data for pyrroles **5**, **7**, and **10**, and NOE difference spectra for pyrroles **7**, **10**, and **14**. (14 pages). Ordering information is given on any current masthead page.

(6) Terry, W. G., Jackson, A. H.; Kenner, G. W.; Kornis, G. *J. Chem. Soc.* **1965**, 4389–4393.

(7) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Akademische Verlag: Leipzig, 1934; Vol. I, p 154.

(8) Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4980–4982.