Trifluoroacetylation at the 3 Position of 1-(2-Aminophenyl)-2,5-dimethylpyrrole in Trifluoroacetic Acid. Possible Remote Control of an Amino Group in Electrophilic Substitution

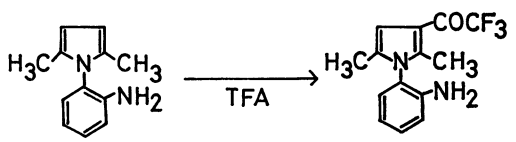
Kimie IMURO and Terukiyo HANAFUSA

Chemistry Department, Faculty of Science, Hiroshima University, Higashi-senda-cho, Hiroshima 730

(Received October 23, 1975)

Spontaneous trifluoroacetylation at the β position of the pyrrole ring in 1-(2-aminophenyl)-2,5-dimethylpyrrole (**1**) was observed in trifluoroacetic acid. The half-life of the reaction was about 3.5 h at 25 °C. This unexpected result might be explained in terms of the 1,5-participation of the amino group in the electrophilic substitution reaction.

The pyrrole ring is known as one of the most sensitive aromatics in electrophilic substitutions. Even trifluoroacetic anhydride, which dose not acylate benzene derivatives without a catalyst, reacted quite readily with a pyrrole to afford a trifluoroacetyl derivative.[1] The partial rate factor for the α position of pyrrole has been estimated up to 10^{18} compared with a single position of benzene.[2] We now wish to report the trifluoroacetylation of 1-(2-aminophenyl)-2,5-dimethylpyrrole (**1**) in trifluoroacetic acid (TFA).

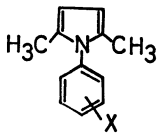


(1) (2)

Results and Discussion

It was incidentally observed during the NMR measurement that the spectrum of **1** in TFA gradually changed from its initial pattern to another spectrum. When the solution was kept at 25 °C for 48 h, a substance (mp 84—86 °C) was isolated by quenching the solution with a base. Judging from the spectral data given in Table 1, the substance thus obtained was easily identified as the 3-trifluoroacetyl derivative (**2**) of **1**. Since the NMR spectrum of **2** in TFA was almost identical with the final spectrum of **1**, the substance (**2**) was shown to be the major product under the conditions.

Despite the presumption that the *N*-trifluoroacetylation of an amino group in **1** is more feasible than *C*-acylation at the β position of the pyrrole ring, the trifluoroacetylamino derivative could not be detected. Also, there was no such significant alteration in the NMR spectrum of the other substituted derivatives, including the 2-hydroxy (**5**), 2-iodo (**7**) and 4-amino substituents (**8**), in a solution of TFA, even at higher temperatures. In these cases, the materials were recovered without any substantial change after quenching. Thus, trifluoroacetylation at the β position of **1** may be regarded as a unique example among these pyrrole derivatives.



	X
1	2'-NH_2
3	2'-$NHCOCF_3$
4	H
5	2'-OH
6	2'-CH_3
7	2'-I
8	4'-NH_2
9	4'-Cl

Table 1. Spectral data for 1-(2-aminophenyl)-2,5-dimethyl-3-(trifluoroacetyl)pyrrole (**2**)

Mass	282 (M^+)
IR	3390, 3490, 1660, 1620
PMR	7.40—6.63, 4H, m; 6.50—6.30, 1H, m; 3.69—3.36, 2H, bs; 2.33, 3H, s; 1.96, 3H, s
FMR	5.20, d, J=2 Hz[a]

a) Chemical shift is reported in ppm downfield from trifluoroacetic acid as an external standard. Coupling of the fluorine atom with a proton at position-4 in the pyrrole ring was confirmed by double resonance technique.

The following explanation might be proposed for this phenomenon. Powerful mineral acids, such as nitric or sulfuric acids, function by themselves as electrophilic reagents toward aromatics. Since TFA is almost as acidic as nitric acid, it may be anticipated that TFA would autocatalytically produce a trifluoroacetyl cation which could in turn bring about electrophilic substitution with highly reactive aromatic compounds. Also, the electrophilic substitution of five-membered hetero-aromatics generally proceeds to the transition state very close to the intermediate cation, *i.e.*, the σ complex.[3] Thus, extraordinary stabilization would have to work in the reaction intermediate of the present example.

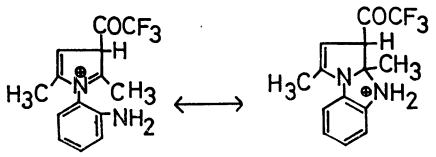
An amino group generally plays an important role in the neighbouring-group participation of various reactions in which cationic species are the intermediates. Especially, 1,5-participation by this group has been eminent in solvolytic displacement.[4] Since 1-(4-aminophenyl)-2,5-dimethylpyrrole and other derivatives did not give the trifluoroacetyl compound under the same conditions, 1,5-participation by the 2-amino group would operate in the rate-determining formation of the cationic intermediate, as is shown below.

Another possible interpretation is the rearrangement of the 2-trifluoroacetylamino derivative (**3**) into **2**. The

TABLE 2. SPECTRAL DATA FOR 1-ARYL-2,5-DIMETHYLPYRROLES

Compound	IR	Aryl-H	NMR		Others
			Pyrrole-H 2H-singlet	CH_3 6H-singlet	
1	3410, 3250, 1620, 1500	7.4—6.7 (m)	5.97	1.96	3.0—3.1 (bs, 2H)
4	1605, 1505	7.4—7.0 (m)	5.66	2.00	
5	3300, 1590, 1500	7.3—6.8 (m)	5.73	1.96	4.9—5.1 (b, 1H)
6	1500	7.3—6.9 (m)	5.70	1.83	1.93 (s, 3H)
7	1590, 1490	7.9—7.6 (m, 1H) 7.4—6.9 (m, 3H)	5.67	1.90	
8	3470, 3380, 1620, 1520	7.00 6.73 (ABq, J=9)	5.85	2.02	3.75 (bs, 2H)
9	1500	7.36 7.03 (ABq, J=9)	5.66	1.97	

reaction of **1** with trifluoroacetic anhydride gave **3** (mp 42 °C) in 40% yield, together with **2**. **3** was so labile that the sample became deeply colored and melted during storage. However, its NMR spectrum in TFA did not change remarkably at 25 °C for 48 h. Therefore, this possibility can apparently be excluded.



In conclusion, it has been shown that the 1,5-participation of an amino group is possible in the electrophilic substitution of a pyrrole derivative, even TFA acting as an electrophilic reagent in such a case.

Experimental

All the mps and bps are uncorrected. The NMR spectra were taken with a Varian T-60 instrument, and the chemical shift data are reported in ppm (δ) downfield from tetramethylsilane as an internal standard, with a coupling constant (J) in Hz. The mass spectra were run on a Hitachi RMU-7 apparatus with an ionizing potential of 70 eV. The IR spectra were recorded on a Hitachi 215 spectrophotometer, in Nujol, while the absorption maxima are reported in cm^{-1}. The spectral data for the pyrrole derivatives are summarized in Table 2.

The pyrrole derivatives were prepared by the following general method. Into an equimolar mixture of acetonylacetone and the aniline derivative dissolved in benzene, was added a drop of phosphoryl chloride. Then the solution was heated under reflux for 2 to 4 h, taking off the produced water as an azeotropic mixture. After washing, drying, and the evaporation of the solvent, the product was purified either by recrystallization or by distillation; yield, 75—90%.

1-Phenyl-2,5-dimethylpyrrole (4): mp 49—50 °C, lit,[5] 51—52 °C.

1-(2-Hydroxyphenyl)-2,5-dimethylpyrrole (5): mp 95—97 °C, lit,[6] 95 °C.

1-(2-Methylphenyl)-2,5-dimethylpyrrole (6): bp 78 °C (2 Torr), lit,[7] 105 °C (7.5 Torr).

1-(2-Iodophenyl)-2,5-dimethylpyrrole (7): mp 69—72 °C. Found: C, 48.57; H, 4.09; N, 4.70%. Calcd for $C_{12}H_{12}NI$: C, 48.48; H, 4.04; N, 4.52%.

1-(4-Aminophenyl)-2,5-dimethylpyrrole (8): mp 95—97 °C, lit,[7] 97.5—98 °C.

1-(4-Chlorophenyl)-2,5-dimethylpyrrole (9): mp 49—50 °C, lit,[5] 56—57 °C.

These six compounds were stable in TFA at 50 °C for 48 h and could be recovered intact.

1-(2-Aminophenyl)-2,5-dimethylpyrrole (1): mp 50—54 °C, *m/e* (M^+) 186. In addition to the general method, this compound was also prepared by the following procedure. An equimolar mixture of acetonylacetone and *o*-phenylenediamine was dissolved in an aqueous solution of citric acid and sodium hydrogenphosphate adjusted at pH 5.0, the mixture was then stirred at room temperature for 4 h. The precipitates were filtered, washed thoroughly with water, and recrystallized from cyclohexane to give **1** in a 90% yield.

Though the melting points (50—54 °C) of all samples obtained in several runs were different from that (77 °C) reported in the literature,[7] the product was obviously **1**, judging from the data given in Table 2.

1-(2-Aminophenyl)-2,5-dimethyl-3-trifluoroacetyl-pyrrole (2). A solution of **1** (10 g) dissolved in TFA (65 ml) was kept for 48 h in a thermostat maintained at 25 °C. During this experiment, an aliquot was subjected to NMR measurement at regular intervals in order to observe the relative ratio of the integral intensities between the signals due to the dimethyl groups of the starting **1** and that due to the product (**2**). The half-life of this reaction was 3.5 h, according to such observations. After being poured onto crushed ice, the mixture was neutralized with sodium hydrogencarbonate. The precipitates were filtered and recrystallized from light petroleum; mp 84—86 °C; purified product in a 20% yield. Found: C, 59.27; H, 4.58; N, 9.87%. Calcd for $C_{14}H_{13}N_2OF_3$ C, 59.57; H, 4.61; N, 9.93%.

Reaction of 1 with Trifluoroacetic Anhydride. A mixture of **1** (930 mg, 5 mmol) and trifluoroacetic anhydride (1.12 g, 7 mmol) dissolved in dichloroethane (10 ml) was stirred at room temperature for 1 h. After being poured into ice–water, the mixture was extracted with dichloroethane. The organic layer was washed with aqueous sodium hydrogencarbonate and then with water, after which it was dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was separated into components by column chromatography using alumina (10 g). Four compounds were eluted in the following order by a mixture of light petroleum and benzene:

(1) 1-(2-Trifluoroacetylaminophenyl)-2,5-dimethylpyrole (**3**); mp 42 °C, (370 mg). Found: C, 60.51; H, 4.75; N, 10.22%. Calcd for $C_{14}H_{13}N_2OF_3$: C, 59.57; H, 4.61; N, 9.93%. Elementary analysis was unstatisfactory because of its high unstability. IR: 3400, 1740, 1600; NMR: 8.51,

1H, d, $J=7$; 7.7—7.3, 4H, m; 5.96, 2H, s; 1.96, 6H, s. The NMR spectrum of **3** dissolved in TFA did not change substantially when it was kept at 25 °C for 48 h. The sample could be recovered from the solution after quenching, although deep coloring and some decomposition were observed.

(2) The starting material (500 mg), identified by a comparison of its spectral data with those of an authentic sample.

(3) 1-(2-Trifluoroacetylaminophenyl)-2,5-dimethyl-3-tri-, fluoroacetylpyrrole; mp 100—103 °C (26 mg) IR: 3500 3400, 1740, 1680; NMR: 8.13, 1H, d, $J=7$; 7.7—7.1, 4H, m; 6.56, 1H, m; 2.30, 3H, s; 1.96, 3H, s. Found: C, 50.81; H, 3.16; N, 7.41%. Calcd for $C_{16}H_{12}N_2O_2F_6$: C, 50.81; H, 3.17; N, 7.45%.

(4) **2** (134 mg); the identity of this compound with the sample obtained from **1** in TFA was established by a comparison of their spectral data and by a mixed-melting-point determination.

The authors are grateful to Miss Yukiko Hayashi for her skillfulness in doing part of experiments and to Mr. Yoshio Takai, The Institute for Scientific and Industrial Research, Osaka University, for his measurement of ^{19}F NMR spectrum.

References

1) S. Clementi, F. Genel, and G. Marino, *Chem. Commun.*, **1967**, 498.
2) P. Linda and G. Marino, *Chem. Commun.*, **1967**, 499.
3) G. P. Bean, *Chem. Commun.*, **1971**, 421 and references cited therein.
4) B. Capon, *Quart. Rev.*, **20**, 301 (1966).
5) R. Alan, *Aust. J. Chem.*, **19**, 289 (1966).
6) C. Paal and C. W. Th. Schneider, *Chem. Ber.*, **19**, 558 (1886).
7) W. S. Bishop, *J. Am. Chem. Soc.*, **67**, 2261 (1945).