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The Pseudo-Gomberg Reaction of Benzene Derivatives with 1-Substituted Pyrroles

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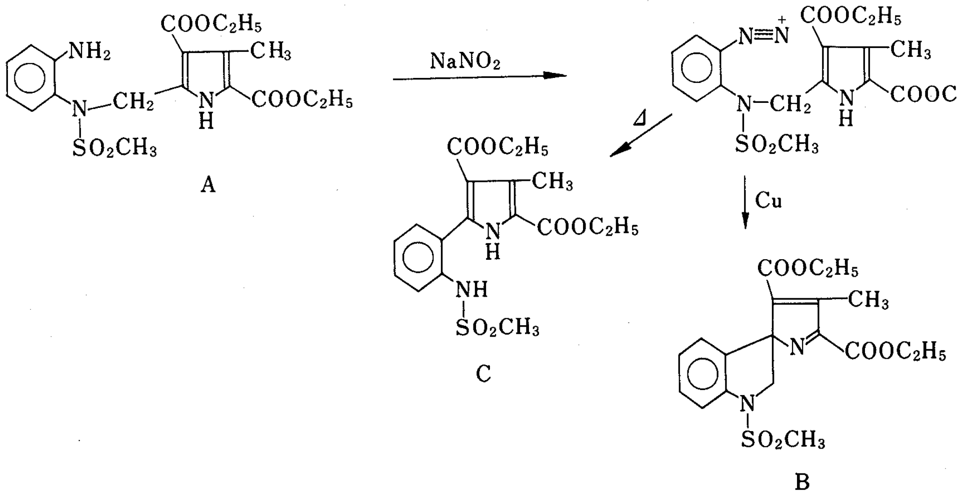
The pseudo-Gomberg reaction of 1-substituted pyrrole derivatives with substituted anilines was examined. Pyrrole derivatives with electron-attracting groups at the 1-position, *i.e.*, ethoxycarbonyl, methanesulfonyl, and benzoyl groups, were found to react smoothly with nitroaniline, chloroaniline and aniline. In each case, 2-arylated pyrrole derivatives were obtained in good or moderate yields.

Keywords——nitrobenzene substituted; pyrrole 1-substituted; amyl nitrite; pyrrole 2-arylated; pseudo-Gomberg reaction; coupling reaction

In the previous paper, we showed that 4-amino- and 2-aminopyridine *N*-oxides smoothly underwent pseudo-Gomberg reaction to afford the arylated products in fairly good yields.[1] There has been only one other report on the arylation of the pyrrole ring by means of the Gomberg reaction. Berveridge[2] reported that upon treatment of compound A with sodium nitrite and subsequent heating with or without copper, intramolecular coupling took place to give B or C, respectively.



In this paper, we describe the pseudo-Gomberg reaction of a variety of aromatic amines with 1-substituted pyrroles in the presence of amyl nitrite.

First, the attempted reaction of *o*-nitroaniline (**1a**) with a large excess of pyrrole (**2d**) in the presence of amyl nitrite was unsuccessful, and an undesired reaction of amyl nitrite with pyrrole (**2d**) took place to form only resinous substances. Next, we tried the similar reaction of *o*-nitroaniline (**1a**) with 1-methylpyrrole (**2e**), but **2e** was also found to give resinous substances without any formation of the arylated product.

As a change of the substituent at the nitrogen of the pyrrole ring might alter the reaction course, the reaction of 1-ethoxycarbonylpyrrole (**2a**) was examined. Amyl nitrite (1.3 mmol) was added to a mixture of *o*-nitroaniline (**1a**) (2 mmol) and 1-ethoxycarbonylpyrrole (**2a**) (20 mmol) in acetic acid, and the whole was heated at 75 °C for 1 h. Chromatographic separation on silica gel afforded 1-ethoxycarbonyl-2-(2-nitrophenyl)pyrrole (**3a**) in 83.8% yield, with some recovery (54.4%) of **2a**.

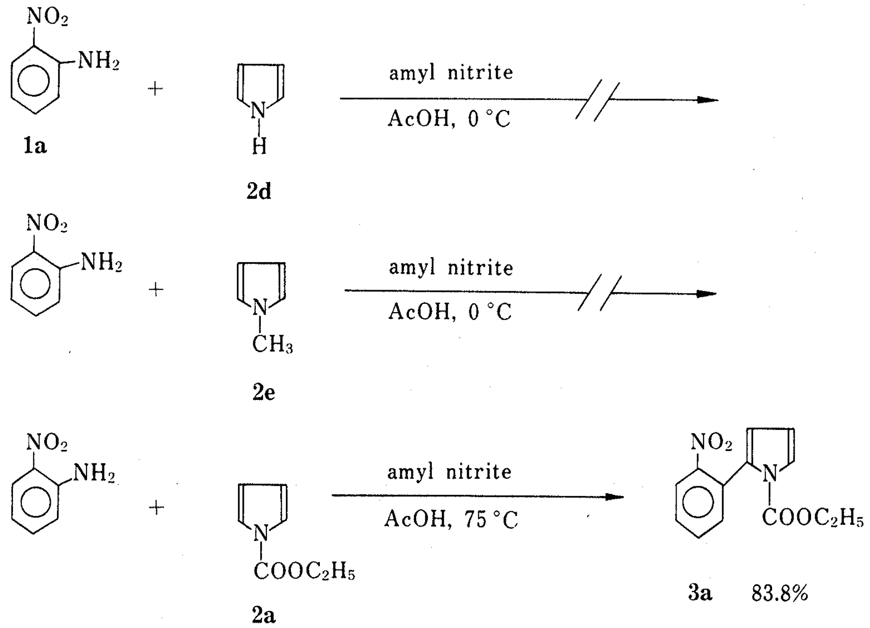
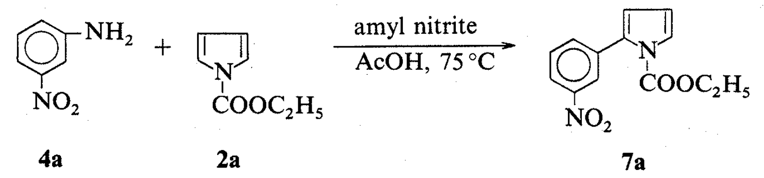


Chart 1

TABLE I. The Reaction of **4a** and **2a** at Various Molar Ratios and Yields of **7a**



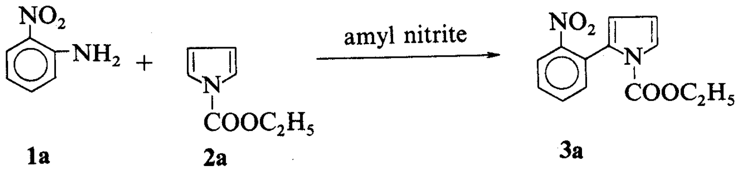
2a	**4a**	Product yield (%)[a]
1 (eq)	2 (eq)	25.1
1	1	29.1
2	1	40.8
10	1	74.6

a) Based on the amine **4a**.

Next, the reaction was studied at various molar ratios of *m*-nitroaniline (**4a**) to 1-ethoxycarbonylpyrrole (**2a**), and the results are summarized in Table I. Usually, a large excess of the aromatic hydrocarbons to be coupled is used in the pseudo-Gomberg reaction. As illustrated in Table I, the yield of the product increased with increase in the ratio of pyrrole derivative to the aromatic amine and the best yield (74.6%) was obtained when a 10-fold excess (by weight) of 1-ethoxycarbonylpyrrole (**2a**) was used.

Next, we examined the effects of solvents and the temperature in the reaction of 1-ethoxycarbonylpyrrole (**2a**) with *o*-nitroaniline (**1a**). The results are shown in Table II. In acetic acid, the yield of the product was not much affected by change of the temperature, but a

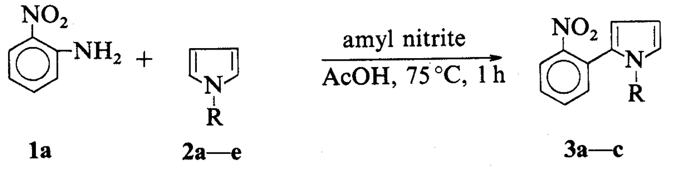
TABLE II. Reactions in Various Solvents



Solvent	Temp. (°C)	Duration (h)	Yield (%)
AcOH	r.t.	Overnight	81.9
AcOH	75	1	83.8
CH_3CN	50	1	82.3
DMF	75	1	32.3
CH_2Cl_2	Reflux	3	68.5

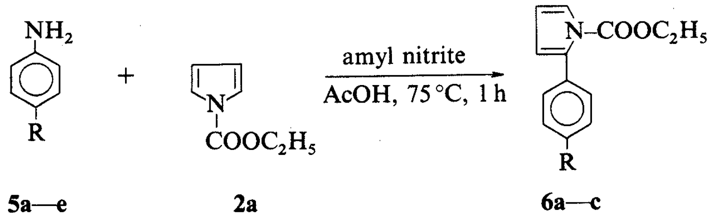
r.t.: room temperature.

TABLE III. The Reaction of **1a** with 1-Substituted Pyrroles (**2a**—**e**)



Compound	R	Product yield (%)
2a	$COOC_2H_5$	83.8
2b	SO_2CH_3	79.3
2c	COPh	75.7
2d	H	—
2e	CH_3	—

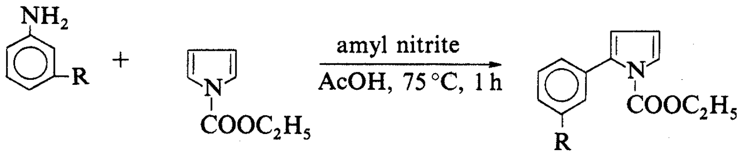
TABLE IV. The Reaction of *p*-Substituted Anilines (**5a**—**e**) with **2a**



Compound	R	Product yield (%)
5a	NO_2	80.0
5b	Cl	51.7
5c	H	28.8
5d	CH_3	—
5e	OCH_3	—

slight increase of the yield was observed at 75 °C. When acetonitrile was used as a solvent, the reaction was found to give the product in a good yield of 82.3%. In the cases of DMF and CH_2Cl_2, yields were rather low.

Table V. The Reaction of *m*-Substituted Anilines with **2a**



4a, b, d, e; 5c **2a** **7a, b, 6c**

Compound	R	Product yield (%)
4a	NO_2	74.6
4b	Cl	48.1
5c	H	28.8
4d	CH_3	—
4e	OCH_3	—

Table VI. Spectral Data

Compounds	MS (M^+)	IR (cm^{-1}, Nujol)	NMR (δ, $CDCl_3$)
3a	260	1740 (C=O) 1614, 1590, 1570 (C=C) 1530 (NO_2)	8.20 (1H, dd, $J_{3,4}=7.0$ Hz, $J_{3,5}=2.2$ Hz, Ph-H_3) 7.42—7.65 (3H, m, Ph-H_4, H_5, H_6) 7.40 (1H, dd, $J_{4,5}=3.2$ Hz, $J_{3,5}=1.9$ Hz, pyrr-H_5) 6.30 (1H, t, $J_{3,4}=3.2$ Hz, $J_{4,5}=3.2$ Hz, pyrr-H_4) 6.22 (1H, dd, $J_{3,5}=1.9$ Hz, $J_{3,4}=3.2$ Hz, pyrr-H_3)
7a	260	1750 (C=O) 1580, 1560 (C=C) 1520 (NO_2)	8.10—8.28 (2H, m, Ph-H_2, H_4) 7.52—7.66 (2H, m, Ph-H_5, H_6) 7.42 (1H, dd, $J_{3,5}=2.0$ Hz, $J_{4,5}=3.0$ Hz, pyrr-H_5) 6.32 (1H, dd, $J_{3,4}=3.2$ Hz, $J_{3,5}=2.0$ Hz, pyrr-H_3) 6.28 (1H, t, $J_{3,4}=3.2$ Hz, $J_{4,5}=3.0$ Hz, pyrr-H_4)
3b	266	1610, 1570 (C=C) 1520 (NO_2) 1346 (NO_2 or SO_2)	7.92—8.0 (1H, m, Ph-H_3) 7.50—7.64 (3H, m, Ph-H_4, H_5, H_6) 7.28 (1H, dd, $J_{3,5}=1.9$ Hz, $J_{4,5}=3.1$ Hz, pyrr-H_5) 6.40 (1H, t, $J_{4,5}=3.1$ Hz, $J_{3,4}=3.2$ Hz, pyrr-H_4) 6.24 (1H, dd, $J_{3,4}=3.2$ Hz, $J_{3,5}=1.9$ Hz, pyrr-H_3)
3c	292	1692 (C=O) 1610, 1570 (C=C) 1520 (NO_2)	7.32—8.18 (9H, m, Ar-H) 7.00 (1H, dd, $J_{3,5}=1.8$ Hz, $J_{4,5}=3.2$ Hz, pyrr-H_5) 6.40 (1H, dd, $J_{3,4}=3.2$ Hz, $J_{3,5}=1.8$ Hz, pyrr-H_3) 6.31 (1H, t, $J_{3,4}=3.2$ Hz, $J_{4,5}=3.2$ Hz, pyrr-H_4)
6a	260	1740 (C=O) 1595 (C=C) 1518, 1340 (NO_2)	8.19 (2H, d, $J=9.0$ Hz, Ph-H_3, H_5) 7.51 (2H, d, $J=9.0$ Hz, Ph-H_2, H_6) 7.42 (1H, dd, $J_{3,5}=1.9$ Hz, $J_{4,5}=3.2$ Hz, pyrr-H_5) 6.36 (1H, dd, $J_{3,4}=3.2$ Hz, $J_{3,5}=1.9$ Hz, pyrr-H_3) 6.28 (1H, t, $J_{3,4}=3.2$ Hz, $J_{4,5}=3.2$ Hz, pyrr-H_4)
6b	249 251	1750 (C=O) 1600, 1570 (C=C)	7.36 (1H, dd, $J_{3,5}=2.0$ Hz, $J_{4,5}=3.0$ Hz, pyrr-H_5) 7.28 (4H, s, Ph-H) 6.24 (1H, t, $J_{3,4}=3.0$ Hz, $J_{4,5}=3.0$ Hz, pyrr-H_4) 6.20 (1H, dd, $J_{3,4}=3.0$ Hz, $J_{3,5}=2.0$ Hz, pyrr-H_3)
6c	215	1760, 1750 (C=O) 1592 (C=C)	7.32 (5H, s, Ph-H) 7.24 (1H, m, pyrr-H_5) 6.20 (2H, m, pyrr-H_3, H_4)

Various 1-substituents on the pyrrole ring were used in the reaction with *o*-nitroaniline (**1a**). When the nitrogen of the pyrrole ring carried an electron-withdrawing group, such as ethoxycarbonyl, methanesulfonyl or benzoyl, the reaction proceeded well to afford the

TABLE VII. Physical Properties and Elemental Analysis

Compounds	mp (°C)	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3a	65.5—67	Yellow needles (Isopropyl ether–hexane)	$C_{13}H_{12}N_2O_4$	59.99 (59.99	4.65 4.68	10.77 10.82)
7a	60—61	Pale yellow needles (Isopropyl ether–hexane)	$C_{13}H_{12}N_2O_4$	59.99 (60.08	4.65 4.64	10.77 10.80)
3b	83—83.5	Yellow pillars (Isopropyl ether)	$C_{11}H_{10}N_2O_4S$	49.63 (49.59	3.79 3.81	10.52 10.51)
3c	98—99	Yellow plates (Ether–hexane)	$C_{17}H_{12}N_2O_3$	69.85 (69.71	4.14 4.17	9.59 9.75)
6b	bp 135/0.8 mmHg (bath temp.)	Orange oil	$C_{13}H_{12}ClNO_2$	62.52 (62.19	4.80 4.97	5.61 5.67)
6a	93—95	Yellow needles (Isopropyl ether–hexane)	$C_{13}H_{12}N_2O_4$	59.99 (60.01	4.65 4.65	10.77 10.65)
6c	bp 72/0.6 mmHg (bath temp.)	Yellow oil	$C_{13}H_{13}NO_2$	72.54 (72.48	6.09 6.18	6.51 6.36)
7b	bp 125/0.7 mmHg (bath temp.)	Orange oil	$C_{13}H_{12}ClNO_2$	62.52 (62.37	4.80 4.85	5.61 5.80)

products in good yields from 75.7 to 83.8%. However, as described before, it was found that pyrrole (**2d**) itself or 1-methylpyrrole (**2e**) reacted with amyl nitrite and the coupling reaction did not take place.

Examination of the effect of various substituents on the aryl radicals in this reaction showed that in the cases of *p*-nitroaniline (**5a**), *p*-chloroaniline (**5b**) and aniline (**5c**), the reaction products were obtained in moderate yields, 80.0, 51.7 and 28.8%, respectively, whereas in the cases of aromatic amines bearing an electron-donating group, such as *p*-toluidine (**5d**) and *p*-anisidine (**5e**), the product could not be isolated. The *meta*-substituted anilines behaved similarly to the *para*-substituted ones, as shown in Table V.

Pyrroles **2a**—**c** bearing an electron-withdrawing group at the 1-position may still be π-rich systems. If this is so, the electrophilic phenyl radicals generated from anilines bearing an electron-withdrawing group would be expected to react smoothly with the pyrrole derivatives.

The infrared (IR), nuclear magnetic resonance (NMR) and mass spectral data for the products described in this paper were consistent with the proposed structures. Elemental analytical values were also satisfactory (Tables VI and VII).

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were obtained on a JMS 01SG spectrometer. Column chromatography was performed on Merck silica gel PF_{254}.

General Procedure for Pseudo-Gomberg Reaction of Substituted Anilines with 1-Substituted Pyrroles——A substituted aniline (2 mmol) was dissolved in 30 ml of acetic acid and a 1-substituted pyrrole (20 mmol) was added. The reaction mixture was stirred under heating at 75 °C, amyl nitrite (1.2 mmol) was added, and stirring was continued for 1 h. The solvent was distilled off, 10% Na_2CO_3 solution was added and the product was extracted with CH_2Cl_2. Chromatographic separation on silica gel gave the product.

Reaction of 1a with 2a——Chromatography on silica gel gave 1.36 g of **2a** from the fraction eluted with hexane–

benzene (10 : 1) and 436 mg (83.8%) of 1-ethoxycarbonyl-2-(2-nitrophenyl)pyrrole (**3a**) from the fraction eluted with hexane–benzene (6 : 1).

Reaction of 4a with 2a——Chromatography on silica gel gave 1.46 g of **2a** from the fraction eluted with hexane–benzene (10 : 1) and 388 mg (74.6%) of 1-ethoxycarbonyl-2-(3-nitrophenyl)pyrrole (**7a**) from the fraction eluted with hexane–benzene (3 : 2).

Reaction in the Various Solvents——The reaction of **1a** with **2a** was conducted as above. Reaction conditions were as shown in Table II. The volume of each solvent used was 10 ml except in the case of acetic acid. The recoveries of **2a** were 67.4, 88.7 and 44.9% in CH_2Cl_2, DMF and CH_3CN, respectively.

Reaction of 1a with 1-Methanesulfonylpyrrole (2b)——On chromatography, **2b** (1.66 g) was recovered from the fraction eluted with hexane–benzene (3 : 2) and 422 mg (79.3%) of 1-methanesulfonyl-2-(2-nitrophenyl)pyrrole (**3b**) was obtained from the fraction eluted with hexane–benzene (1 : 5).

Reaction of 1a with 1-Benzoylpyrrole (2c)——After chromatographic separation, 2.66 g of **2c** was recovered from the fraction eluted with hexane–benzene (3 : 2) and 1-benzoyl-2-(2-nitrophenyl)pyrrole (**3c**) (442 mg) was obtained from the fraction eluted with hexane–benzene (1 : 2).

Reaction of 5a with 1-Ethoxycarbonylpyrrole (2a)——Chromatography gave 1.4 g of **2a** from the fraction eluted with hexane–benzene (10 : 1) and 410 mg (80%) of 1-ethoxycarbonyl-2-(4-nitrophenyl)pyrrole (**6a**) from the fraction eluted with hexane–benzene (3 : 2).

Reaction of 5b with 2a——Chromatography gave 1.48 g of **2a** from the fraction eluted with hexane–benzene (10 : 1) and 258 mg (51.7%) of 1-ethoxycarbonyl-2-(4-chlorophenyl)pyrrole (**6b**).

Reaction of 5c with 2a——Chromatography gave 1.51 g of **2a** from the fraction eluted with hexane–benzene (10 : 1) and 124 mg (28.8%) of 1-ethoxycarbonyl-2-phenylpyrrole (**6c**) from the fraction eluted with hexane–benzene (2 : 1).

Reaction of 4b with 2a——Chromatography gave 1.23 g of **2a** from the fraction eluted with hexane–benzene (10 : 1) and 240 mg of 1-ethoxycarbonyl-2-(3-chlorophenyl)pyrrole (**7b**).

References and Notes

1) S. Saeki, S. Kondo, T. Hayashi and M. Hamana, *Chem. Pharm. Bull.*, **32**, 1780 (1984).
2) S. Berveridge and J. L. Hupatz, *Aust. J. Chem.*, **23**, 781 (1970).