Studies on the Nef Reaction Induced by Organic Bases

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Studies of the Nef reaction in the presence of primary, secondary and tertiary amines have been described. A convenient synthesis of *N*-substituted pyrroles and 3,6-dimethyl-4-hydrazinocarbonyl-5-(4-amino-3-nitrophenyl)-pyridazine **16** has been developed.

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Recently we have reported the synthetic utility of the Nef reaction in presence of piperidine [2-4]. Since then a number of publications concerning the Nef reaction have appeared in the literature [5-8] and this prompted us to report the details of our observations relating to Nef reactions induced by tertiary, secondary and primary amines. The results are as follows:

The reaction of 1-(4-amino-3-nitrophenyl)-2-nitropropene-1 **1** with methyl acetoacetate **3** in the presence of piperidine gave 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-

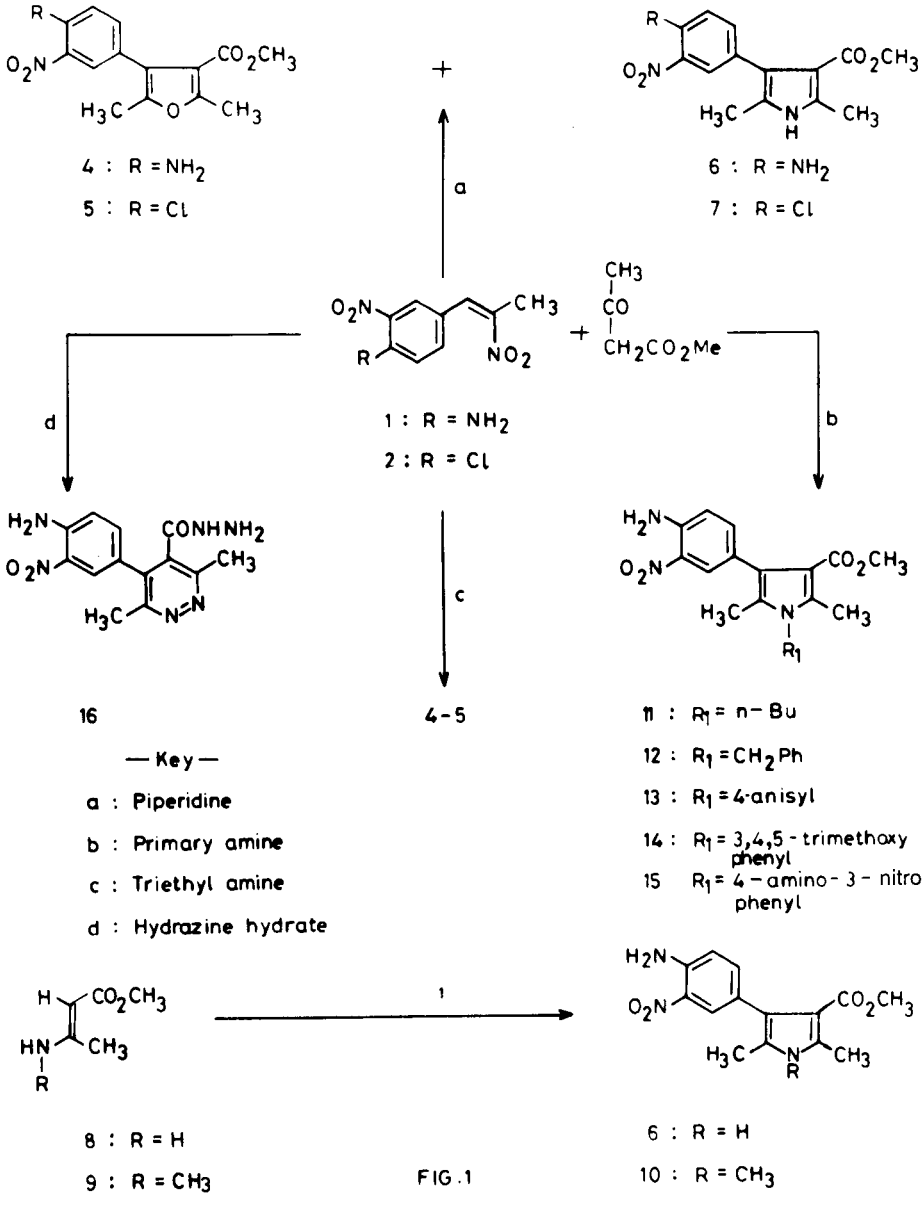

FIG. 1

3-nitrophenyl)furan **4** in moderate yields and a crystalline red compound in a very low yield. These were separated by column chromatography. The spectral data of this red compound suggested it to be 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl)pyrrole **6**. This structure was further confirmed by an unambiguous synthesis [9] which involved the reaction of methyl 3-aminocrotonate **8** with **1**. Similar observations were made in the reaction of 1-(4-chloro-3-nitrophenyl)-2-nitropropene-1 **2** with **3**. Tetrasubstituted furan **5** and pyrrole **7** were isolated by column chromatography. In view of these observations the reaction of **1** and **3** in the presence of primary, secondary and

Table 1

Physical and Analytical Data of Compounds **4-7**, **10-16**

Compound	mp °C	Yield %	Molecular formula	MS m/e (M^+)	IR (KBr) ν (Cm^{-1})	^1H NMR (deuteriochloroform) δ (ppm)	Analysis (%) Found (Calcd.) C	H	N
4	144-145	45	$C_{14}H_{14}N_2O_5$	290	1710 (COO)	2.12 (s, 3H, 5-CH_3), 2.49 (s, 3H, 2-CH_3), 3.60 (s, 3H, CO_2CH_3), 6.65-6.74 (d, 1H, 5-ArH, J_o = 9 Hz), 7.11-7.23 (dd, 1H, 6-ArH, J_o = 9 Hz, J_m = 2 Hz), 7.87-7.89 (d, 1H, 2-ArH, J_m = 2 Hz)	57.60 (57.93)	4.82 (4.82)	9.56 (9.65)
5	95-96	27	$C_{14}H_{12}ClNO_5$	309	1700 (COO)	2.15 (s, 3H, 5-CH_3), 2.41 (s, 3H, 2-CH_3), 3.61 (s, 3H, CO_2CH_3), 7.33-7.48 (m, 2H, 5 and 6-ArH), 7.70-7.72 (d, 1H, 2-ArH, J_m = 2 Hz)	53.92 (54.28)	3.84 (3.87)	4.27 (4.52)
6	223-224	20	$C_{14}H_{15}N_3O_4$	289	1700 (COO)	2.03 (s, 3H, 5-CH_3), 2.40 (s, 3H, 2-CH_3), 3.53 (s, 3H, CO_2CH_3), 6.69-6.79 (d, 1H, 5-ArH, J_o = 9 Hz), 7.12-7.24 (dd, 1H, 6-ArH, J_o = 9 Hz, J_m = 2 Hz), 7.78-7.80 (d, 1H, 2-ArH, J_m = 2 Hz) [a]	58.00 (58.13)	5.24 (5.19)	14.68 (14.53)
7	194-195	6	$C_{14}H_{13}ClN_2O_4$	308	1710 (COO)	2.06 (s, 3H, 5-CH_3), 2.45 (s, 3H, 2-CH_3), 3.57 (s, 3H, CO_2CH_3), 7.31-7.42 (m, 2H, 5 and 6-ArH), 7.68-7.70 (d, 1H, 2-ArH, J_m = 2 Hz)	54.51 (54.45)	4.21 (4.21)	8.69 (9.07)
10	162-163	70	$C_{15}H_{17}N_3O_4$	303	1700 (COO)	2.03 (s, 3H, 5-CH_3), 2.45 (s, 3H, 2-CH_3), 3.40 (s, 3H, N-CH_3), 3.50 (s, 3H, CO_2CH_3), 6.79-6.89 (d, 1H, 5-ArH, J_o = 9 Hz), 7.06-7.18 (dd, 1H, 6-ArH, J_o = 9 Hz, J_m = 2 Hz), 7.60-7.62 (d, 1H, 2-ArH, J_m = 2 Hz)	59.12 (59.40)	5.87 (5.61)	13.76 (13.86)
11	160-161	71	$C_{18}H_{23}N_3O_4$	345	1690 (COO)	0.85 (t, 3H, CH_3), 1.21-1.75 (m, 4H, 2 x CH_2), 2.04 (s, 3H, 5-CH_3), 2.48 (s, 3H, 2-CH_3), 3.53 (s, 3H, CO_2CH_3), 3.66-3.81 (t, 2H, CH_2), 5.95-6.18 (bs, 2H, NH_2), 6.62-6.72 (d, 1H, 5-ArH, J_o = 9 Hz), 7.11-7.23 (dd, 1H, 6-ArH, J_o = 9 Hz, J_m = 2 Hz), 7.83-7.85 (d, 1H, 2-ArH, J_m = 2 Hz)	62.91 (62.60)	6.83 (6.66)	11.98 (12.17)
12 [e]	132-134	60	$C_{21}H_{21}N_3O_4$	379	1680 (COO)	2.0 (s, 3H, 5-CH_3), 2.45 (s, 3H, 2-CH_3), 3.59 (s, 3H, CO_2CH_3), 5.06 (s, 2H, CH_2), 6.71-7.38 (m, 7H, ArH), 7.91-7.93 (d, 1H, 2-ArH, J_m = 2 Hz)	64.90 (64.94)	5.48 (5.67)	10.68 (10.82)
13	155-156	50	$C_{21}H_{21}N_3O_5$	395	1690 (COO)	1.80 (s, 3H, 5-CH_3), 2.20 (s, 3H, 2-CH_3), 3.55 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 6.50-7.40 (m, 6H, ArH), 7.88-7.90 (d, 1H, 2-ArH, J_m = 2 Hz)	63.71 (63.79)	5.35 (5.31)	10.27 (10.63)
14	Oil	65	$C_{23}H_{25}N_3O_7$	455	1710 [b] (COO)	1.84 (s, 3H, 5-CH_3), 2.21 (s, 3H, 2-CH_3), 3.51 (s, 3H, CO_2CH_3), 3.75 (s, 9H, 3 x OCH_3), 6.11 and 6.32 (2 bs, 2H, N-ArH), 6.59-6.69 (d, 1H, 5-ArH, J_o = 9 Hz), 7.06-7.18 (dd, 1H, 6-ArH, J_o = 9 Hz, J_m = 2 Hz), 7.78-7.80 (d, 1H, 2-ArH, J_m 2 Hz)	60.29 (60.65)	5.31 (5.49)	9.10 (9.23)

Table 1 (continued)

Compound	mp °C	Yield %	Molecular formula	MS m/e (M^+)	IR (KBr) ν (Cm^{-1})	^1H NMR (deuteriochloroform) δ (ppm)	Analysis (%) Found (Calcd.) C	H	N
15	Oil	70	$C_{20}H_{19}N_5O_6$	–	1700 [b] (COO)	1.81 (s, 3H, 5-CH_3), 2.22 (s, 3H, 2-CH_3), 3.53 (s, 3H, CO_2CH_3), 5.80 and 6.33 (2 s, 4H, 2 x NH_2), 6.50-7.03 (m, 5H, ArH), 7.90-7.92 (d, 1H, 2-ArH, J_m = 2 Hz) [c]	56.14 (56.47)	4.31 (4.47)	16.51 (16.47)
16	170-171	70	$C_{13}H_{14}N_6O_3$	302	1650 (CO)	2.18 (s, 6H, 2 x CH_3), 7.47-7.61 (m, 3H, ArH) [d]	51.45 (51.65)	4.31 (4.63)	27.96 (27.81)

[a] Deuteriochloroform + deuteriodimethylsulfoxide. [b] Neat. [c] Carbon tetrachloride. [d] Trifluoroacetic acid. [e] Analysed as the hemihydrate.

tertiary amines have been studied and the results have been monitored by hplc.

The reaction of **1** and **3** in presence of primary amines gave *N*-substituted pyrrole derivatives **11-15** and the corresponding furan derivatives could not be detected in the reaction mixture. This method has a preparative value and gives better yields of the pyrrole derivatives. The method reported in literature [9] invariabley gave poor yields of 2,5-dimethyl-3-methoxycarbonyl-4-substituted-phenylpyrroles in our hands. The reaction product of **1** and **8** was monitored by hplc and it was observed that the reaction led to the formation of around 16% of **4**. The reaction of **1** and **3** in the presence of secondary amines gave different percentage ratios of **4** and **6**. For example, in the presence of piperidine the percentage ratio of **4** and **6** was 96:4; in morpholine it was 80:20; in *N*-methylpiperazine it was 89:11; and in the presence of *N*-phenylpiperazine it was 87:13. Replacement of piperidine with triethylamine in the reaction of **1** and **3** gave only **4** and the presence of **6** in the reaction mixture was not detected. The reaction of **1** and **3** in presence of hydrazine hydrate gave 3,6- dimethyl-4-hydrazinocarbonyl-5-(4-amino-3-nitrophenyl)pyridazine **16**.

It may be concluded that a tertiary amine in the reaction of **1** and **3** gave a tetrasubstituted furan, while secondary amines furnished a mixture of tetrasubstituted pyrrole and furan and primary amines yielded only pentasubstituted pyrroles.

EXPERIMENTAL

Melting points were determined either in a sulphuric acid bath or on an electrically heated block and are uncorrected. All the compounds were routinely checked for purity by tlc and for structural assignments by ir and pmr spectroscopy. The ir spectra (ν max in cm^{-1}) were recorded on a Perkin-Elmer 157 infracord and the pmr spectra on an EM-360L or a Perkin-Elmer R32 spectrometer using TMS as internal standard (chemical shifts in δ ppm) and mass spectra on a Jeol D-300 instrument. The hplc were done on a Waters Associates HPLC model 244 using Nucleosil $7C_{18}$ column (25 Cm). Mobile phase was methanol GR (Merck). The flow rate adjusted at 2 ml/minute while recorder speed was 1 cm/minute. The detector used was an absorbance detector (Waters Model 440) at 254 nm. The physical and analytical data of compounds **4-7**, **10-16** are given in Table 1.

Reaction of 1-(4-Amino-3-nitrophenyl)-2-nitropropene-1 **1** and Methyl Acetoacetate **3** in the presence of Amines. General Procedure.

A mixture of **1** (0.002 mole), **3** (0.004 mole), and the appropriate amine (0.0022 mole) in methanol (5 ml) was stirred at room temperature for 16-24 hours. The reaction mixture was diluted with water, the separated solid filtered, washed with water, dried and recrystallized from chloroform-hexane or ethyl acetate-hexane. In cases where the solid did not separate out, the sticky mass obtained after dilution with water was extracted with ethyl acetate, the organic layer was washed with water and dried (anhydrous sodium sulphate). Removal of the solvent give a residue which was recrystallized from chloroform-hexane or purified by column chromatography over silica gel.

2,5-Dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl)pyrrole **6**.

This compound was prepared by a method similar to the one reported by Meyer [9].

2,5-Dimethyl-3-methoxycarbonyl-*N*-methyl-4-(4-amino-3-nitrophenyl)pyrrole **10**.

A solution of **1** (0.002 mole) and **9** (0.002 mole) in methanol (10 ml) was refluxed on a waterbath for 16 hours. The reaction mixture was diluted with water, the separated solid was filtered, dried and recrystallized from ethyl acetate-hexane.

3,6-Dimethyl-4-hydrazinocarbonyl-5-(4-amino-3-nitrophenyl)pyridazine **16**.

A mixture of **1** (0.002 mole), **3** (0.004 mole) and hydrazine hydrate (0.004 mole) in ethanol (10 ml) was refluxed on a waterbath for 3 hours. The reaction mixture was diluted with water, the separated solid was filtered, dried and recrystallized from ethyl acetate-hexane.

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