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COMBINATORIAL CHEMICAL SYNTHESIS OF 4-HETEROARYL-3-SUBSTITUTED PYRROLES FROM NITROALKENES‡

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Abstract – A small library of 4-(2-furyl)- or 4-(2-thienyl)-3-substituted pyrroles has been prepared by reaction of 2-(2-furyl or 2-thienyl)-1-nitro-1-alkenes **(1)** with secondary enamines **(2)**. The reaction gives pyrrole derivatives by means of a Michael-type addition intermediate. Cyclization is influenced by the nature of the solvent and the substituent in the enamine β position, and by enamine-nitrogen nucleophilicity.

INTRODUCTION

The synthesis of pyrroles remains extremely interesting in heterocyclic chemistry because of the biological and pharmacological activities of these products. Many substituted pyrroles are incorporated as the core unit of many natural products,[1] especially in the family of alkaloids and natural marine products,[2] particularly those that are 3,4-diaryl substituted.[3]

In continuing our studies of heterocyclic synthesis (particularly the synthesis of pyrrole compounds),[4] we were interested in preparing 4-heteroaryl substituted pyrroles, such as 2-furyl or 2-thienyl (isosters of the phenyl group), in order to evaluate their potential activity as antibacterial products. Among the various methods of synthesis of the pyrrole ring,[5] we decided to use the reaction between 2-nitroalkenes and enamines reported by Grob in 1953.[6] This method makes use of easily prepared reagents and is particularly suitable for a combinatorial approach[7] to the synthesis of a small library of 4-heteroaryl-substituted pyrroles. In accordance with the proposed mechanism,[8] the Michael intermediate adduct **A** undergoes intramolecular displacement of the nitro group by the amino group, thus affording pyrrole **B** as a result of the elimination of water and hyponitrous acid (Scheme 1).

‡ On the occasion of the 70th birthday of Dr. Pierre Potier
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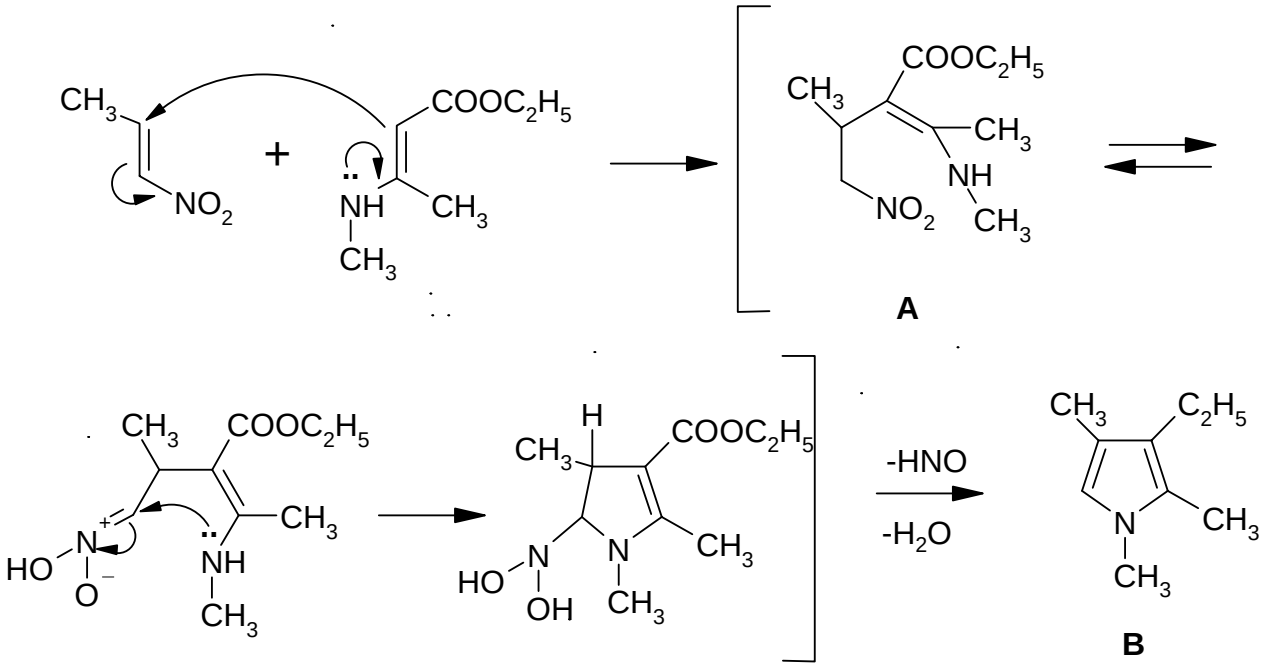
Scheme 1

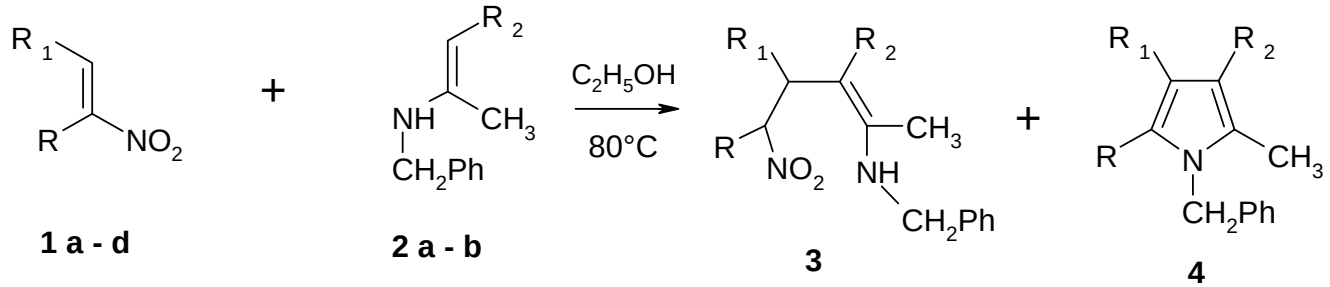


This scheme makes it possible to obtain variously substituted pyrroles starting from the suitable 2-nitroalkenes and enamines.

RESULTS AND DISCUSSION

Experiments with different substituents on both 2-heteroaryl-1-nitroalkenes **(1a-d)** and enamines **(2a-b)** were performed in a Carousel Reaction Station by heating equimolecular quantities of the two reagents in boiling ethanol and monitoring the progress of the reaction by TLC. A standard work-up afforded compounds **(3)** and/or **(4)** which were separated by chromatography. All of the products were identified by means of analytical and spettroscopic data.

Scheme 2



1 a - d **2 a - b** **3** **4**

1a : R = H; R_1 = 2-furyl
1b : R = CH_3; R_1 = 2-furyl
1c : R = H; R_1 = 2-thienyl
1d : R = CH_3; R_1 = 2-thienyl

2a : R_2 = $COOCH_3$
2b : R_2 = CN

As shown in Scheme 2 and Table 1, the reactions afforded pyrroles **(4)** only when the β-carbometoxy-substituted enamine **(2a)** was reacted (Entries 1-4); when β-cyanoenamine **(2b)** was used, the Michael adducts **(3)** were mainly obtained (Entries 5-8).

Table 1

Entry	**Reagents**	**Products**	**Yield** (%)	**Time** (hs)
1	**1a + 2a**	**4aa**	35	48
2	**1b + 2a**	**4ba**	80	48
3	**1c + 2a**	**4ca**	49	48
4	**1d + 2a**	**4da**	81	48
5	**1a + 2b**	**3ab**	45	72
6	**1b + 2b**	**3bb**	50	72
		4bb	18	
7	**1c + 2b**	**3cb**	70	72
8	**1d + 2b**	**3db**	55	72
		4db	14	

The results summarised in Table 1 are slightly different from those previously reported. It has been generally supposed[6,8,9] that the reaction between 2-nitroalkenes and secondary enamines would afford pyrrole compounds when performed in refluxing ethanol or Michael intermediate adducts when performed in acetonitrile at room temperature. It was suggested that the aprotic solvent favors a stabilising intramolecular hydrogen bond between the carbomethoxy group and the enamine-hydrogen in the *Z* isomer **A**, thus preventing the further cyclization to pyrrole **B**. None of the reported examples deals with β-cyano-substituted enamines. This group, which is unable to give rise to an intramolecular hydrogen bond, should favour the *E* isomer **A** and consequent ring closure. In order to explain the reasons for this behaviour, we studied the reaction between **1b** and **2a,b** under different experimental conditions (Table 2).

Table 2

Entry	**Reagents**	**Solvent**	**T** (°C)	**t** (hs)	**Products**	**Yield** (%)
1	**1b + 2a**	C_2H_5OH	80	48	**4ba**	80
2	**1b + 2a**	C_2H_5OH	40	36	**4ba**	89
3	**1b + 2a**	C_2H_5OH	20	36	**4ba**	79
4	**1b + 2a**	Acetonitrile	20	120	**4ba**	70
5	**1b + 2b**	C_2H_5OH	80	72	**3bb**	50
					4bb	18
6	**1b + 2b**	*n*-C_3H_7OH	100	48	**3bb**	47
					4bb	13
7	**1b + 2b**	*n*-C_4H_9OH	120	40	**3bb**	40
					4bb	10
8	**1b + 2b**	Acetonitrile	20	96	=	=
9	**1b + 2b**	Acetonitrile	80	72	**3bb**	70

As shown in Table 2, the reaction of enamine **(2a)** always gives the pyrrole **(4ba)** in ethanol and in acetonitrile at room temperature (Entries 1-4); no traces of the adduct **(3ba)** were detected. On the contrary, adduct **(3bb)** was the predominant product obtained using enamine **(2b)** in all cases (Entries 5-9). The reaction of **1** with **2** does not depend on solvent polarity or temperature, but on the substituents on both reagents. One possible explanation is a greater capacity in delocalising the electron pair of enamine nitrogen atom onto the cyano group in compound **(3bb)** than in **3ba** (which bears a methoxycarbonyl substituent). This delocalisation may prevent nucleophilic intramolecular attack and ring closure.

In conclusion, using the technique of Combinatorial Chemical Synthesis, this method leads to 4-heteroaryl-3-substituted pyrroles **(4)**, a relatively unknown class of compounds of potential biological interest.[10]

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Elemental analysis was performed by the Microanalytical Laboratory of the Department. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC 300 MHz spectrometer, and chemical shifts are given in ppm relative to TMS. IR spectroscopy was performed using a Perkin-Elmer 1725X FT-IR spectrophotometer.

2-(2-Nitrovinyl)furan (1a);[11] **2-(2-nitropropenyl)furan (1b)**;[12] **2-(2-nitrovinyl)thiophene (1c)**;[13] **2-(2-nitropropenyl)thiophene (1d)**;[13] **3-Benzylamino-but-2-enoic acid methyl ester (2a)**,[14] **3-benzylamino-2-butenenitrile (2b)**,[15] were prepared according to the reported methods.

Synthesis of products 3 and 4 : General Procedure

A solution of **1a-d** (5 mmol) and **2a,b** (5 mmol) in ethanol (20 mL) was stirred and heated at reflux temperature under nitrogen in a Radleys Carousel Reaction Station for the time reported in Table 1. After evaporation of the solvent, the crude mixture was separated using column chromatography (silica gel, toluene:100- toluene/ethyl acetate:95/5). The solid products were recrystallised and identified by means of analytical and spectroscopic data. The relative yields are reported in Table 1.

3-Benzylamino-2-[1-(2-furyl)-2-nitroethyl]-2-butenenitrile (3ab). Oil, (thermal unstable). ^{1}H-NMR (mixture 63:37 of *E* and *Z* isomers) δ: 2.04, 2.20 (s, 3H, CH_3), 4.44, 4.46 (d, *J*=5.95 Hz, 2H, NH-CH_2), 4.50-4.85 (m, 3H, CH-CH_2NO_2), 5.29, 5.48 (br t, 1H, NH), 6.27 (dd, *J*=12.18 Hz, *J*=3.32 Hz, 1H, H3-Furan), 6.35 (m, 1H, H4-Furan), 7.23-7.45 (m, 6H, Ph and H5-Furan). IR (nujol) cm^{-1} 3432 (NH), 2185 (CN), 1602 (C=C), 1553 (NO_2). *Anal.* Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.28; H, 5.22; N, 13.25.

2-(1-Benzylaminoethylidene)-3-(2-furyl)-4-nitropentanenitrile (3bb). Oil, (thermal unstable). ^{1}H-NMR (mixture 54:46 of *E* and *Z* isomers) δ: 1.50, 1.65 (d, *J*=6.69 Hz, 3H, O_2N-C-CH_3), 2.00, 2.15 (s, 3H, CH_3-C=), 4.19, 4.24 (d, *J*=10.04 Hz, 1H, C*H*-Furan), 4.41,4.45 (d, *J*=6.03 Hz, 2H, NH-CH_2), 5.14 (m, 1H, $CHNO_2$), 5.33, 5.39 (br t, 1H, NH), 6.25-6.38 (m, 2H, H3, H4-Furan), 7.16-7.43 (m, 6H, Ph and H5-Furan). IR (nujol) cm^{-1} 3433 (NH), 2188 (CN), 1604 (C=C), 1554 (NO_2). *Anal.* Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.38; H, 5.72; N, 12.85.

3-Benzylamino-2-[2-nitro-1-(2-thienyl)ethyl]-2-butenenitrile (3cb). Oil, (thermal unstable). ^{1}H-NMR (mixture 67:33 of *E* and *Z* isomers) δ: 2.04, 2.20 (s, 3H, CH_3), 4.38, 4.45 (d, *J*=6.01 Hz, 2H, NH-CH_2), 4.61-4.96 (m, 3H, CH-CH_2NO_2), 5.15, 5.48 (br t, 1H, NH), 6.95-7.12 (m, 3H, H3, H4, H5-Thiophene), 7.27-7.48 (m, 5H, Ph). IR (nujol) cm^{-1} 3342 (NH), 2173 (CN), 1598 (C=C), 1545 (NO_2). *Anal.* Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.20; H, 5.12; N, 12.76.

2-(1-Benzylaminoethylidene)-4-nitro-3-(2-thienyl)pentanenitrile (3db). Solid, mp 120-122°C (*i*-PrOH / *i*-Pr_2O). ^{1}H-NMR (mixture 60:40 of *E* and *Z* isomers) δ: 1.49, 1.51 (d, *J*=6.65 Hz, 3H, O_2N-C-CH_3), 2.01, 2.15 (s, 3H, CH_3-C=), 4.31 (t, *J*=11.20 Hz, 1H, CH-Thiophene), 4.42 (d, *J*=5.37 Hz, 2H, NH-CH_2), 5.15 (m, 1H, $CHNO_2$), 5.01, 5.31 (br t, 1H, NH), 7.01-7.35 (m, 8H, Ph and Thiophene). IR (nujol) cm^{-1} 3344 (NH), 2170 (CN), 1594 (C=C), 1548 (NO_2). *Anal.* Calcd for $C_{18}H_{19}N_3O_2S$: C, 63.34; H, 5.57; N, 12.32. Found: C, 63.33; H, 5.32; N, 12.04.

Methyl 1-benzyl-4-(2-furyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4aa). Solid, mp 77-78°C (MeOH). ^{1}H-NMR δ: 2.45 (s, 3H, 2-CH_3), 3.82 (s, 3H, $COOCH_3$), 5.04 (s, 2H, N-CH_2), 6.42 (dd, *J*=3.34 Hz, *J*=1.84 Hz, 1H, H4-Furan), 6.75 (d, *J*=3.30 Hz, 1H, H3-Furan), 6.94 (s, 1H, H5-Pyrrole), 7.06 (d, *J*=6.38 Hz, 2H, H_{ortho} Ph), 7.23-7.37 (m, 4H, Ph and H5-Furan). ^{13}C-NMR δ: 11.6 (q, 2-CH_3), 50.6 (t, N-CH_2), 50.6 (q, OCH_3), 107-140.2 (C_{arom}), 165.7 (s, CO). IR (nujol) cm^{-1} 1696 (CO), 1461, 1377 (CH_3). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.98; H, 5.62; N, 4.54.

Methyl 1-benzyl-4-(2-furyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (4ba). Solid, mp 84-85°C (*i*-Pr_2O). ^{1}H-NMR δ: 2.16 (s, 3H, 5-CH_3), 2.47 (s, 3H, 2-CH_3), 3.73 (s, 3H, $COOCH_3$), 5.12 (s, 2H, N-CH_2), 6.31 (d, *J*=3.17 Hz, 1H, H3-Furan), 6.45 (dd, *J*=3.17 Hz, *J*=1.91 Hz, 1H, H4-Furan), 6.96 (d, *J*=6.95 Hz, 2H, H_{ortho} Ph), 7.31-7.40 (m, 3H, Ph), 7.45 (d, *J*=1.88 Hz, 1H, H5-Furan). ^{13}C-NMR δ: 10.7 (q, 5-CH_3), 11.5 (q, 2-CH_3), 47.1 (t, N-CH_2), 50.7 (q, OCH_3), 108-149.5 (C_{arom}), 165.9 (s, CO). IR (nujol) cm^{-1} 1698 (CO), 1461, 1378 (CH_3). *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.72; H, 6.20; N, 4.44.

Methyl 1-benzyl-2-methyl-4-(2-thienyl)-1*H*-pyrrole-3-carboxylate (4ca). Solid, mp 67-70°C (*i*-PrOH). ^{1}H-NMR δ: 2.47 (s, 3H, 2-CH_3), 3.75 (s, 3H, $COOCH_3$), 5.07 (s, 2H, N-CH_2), 7.02 (dd, *J*=5.16 Hz, *J*=3.56 Hz, 1H, H4-Thiophene), 7.09 (d, *J*=6.41 Hz, 2H, H_{ortho} Ph), 7.17 (dd, *J*=3.56 Hz, *J*=1.17 Hz, 1H, H3-Thiophene), 7.21 (dd, *J*=5.16 Hz, *J*=1.17 Hz, 1H, H5-Thiophene), 7.30-7.40 (m, 3H, Ph). ^{13}C-NMR δ: 11.6 (q, 2-CH_3), 50.5 (t, N-CH_2), 50.5 (q, OCH_3), 119.4-130.8 (C_{arom}), 165.9 (s, CO). IR (nujol) cm^{-1} 1701 (CO), 1438, 1377 (CH_3). *Anal.* Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.33; H, 5.42; N, 4.22.

Methyl 1-benzyl-2,5-dimethyl-4-(2-thienyl)-1*H*-pyrrole-3-carboxylate (4da). Solid, mp 78-79°C (*i*-Pr_2O). ^{1}H-NMR δ: 2.07 (s, 3H, 5-CH_3), 2.47 (s, 3H, 2-CH_3), 3.65 (s, 3H, $COOCH_3$), 5.11 (s, 2H, N-CH_2), 6.88 (dd, *J*=3.50 Hz, *J*=1.01 Hz, 1H, H3-Thiophene), 6.94 (d, *J*=7.05 Hz, 2H, H_{ortho} Ph), 7.02 (dd, *J*=5.2 Hz, *J*=3.5 Hz, 1H, H4-Thiophene), 7.27 (dd, *J*=5.2 Hz, *J*=1.01 Hz, 1H, H5-Thiophene), 7.30-7.35 (m, 3H, Ph). ^{13}C-NMR δ: 10.5 (q, 5-CH_3), 11.5 (q, 2-CH_3), 47.2 (t, N-CH_2), 50.5 (q, OCH_3), 124.7-136.6 (C_{arom}), 166 (s, CO). IR (nujol) cm^{-1} 1697 (CO), 1456, 1378 (CH_3). *Anal.* Calcd for $C_{19}H_{19}NO_2S$: C, 70.15; H, 5.85; N, 4.31. Found: C, 69.98; H, 5.72; N, 4.23.

1-Benzyl-4-(2-furyl)-2,5-dimethyl-1*H*-pyrrole-3-carbonitrile (4bb). Solid, mp 68-70°C (*i*-Pr_2O). ^{1}H-NMR δ: 2.36 (s, 3H, 5-CH_3), 2.37 (s, 3H, 2-CH_3), 5.10 (s, 2H, N-CH_2), 6.47 (dd, *J*=3.36 Hz, *J*=1.90 Hz, 1H, H4-Furan), 6.65 (d, *J*=3.35 Hz, 1H, H3-Furan), 6.92 (d, *J*=6.98 Hz, 2H, H_{ortho} Ph), 7.30-7.42 (m, 3H, Ph), 7.44 (d, *J*=1.90 Hz, 1H, H5-Furan). ^{13}C-NMR δ: 11.6 (q, 5-CH_3), 12 (q, 2-CH_3), 48.1 (t, N-CH_2), 108-140.5 (C_{arom}), 178 (s, CN). IR (nujol) cm^{-1} 2213 (CN), 1454, 1356 (CH_3). *Anal.* Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.14; H, 5.65; N, 10.24.

1-Benzyl-2,5-dimethyl-4-(2-thienyl)-1*H*-pyrrole-3-carbonitrile (4db). Solid, mp 72-74°C (*i*-Pr_2O). ^{1}H-NMR δ: 2.27 (s, 3H, 5-CH_3), 2.36 (s, 3H, 2-CH_3), 5.08 (s, 2H, N-CH_2), 6.92 (d, *J*=7.5 Hz, 2H, H_{ortho} Ph), 7.09 (t, *J*=4.15 Hz, 1H, H4-Thiophene), 7.21 (d, *J*=3.46 Hz, 1H, H3-Thiophene), 7.30-7.40 (m, 4H, Ph and H5-Thiophene). ^{13}C-NMR δ: 11.4 (q, 5-CH_3), 12 (q, 2-CH_3), 48.2 (t, N-CH_2), 116.3-138.3 (C_{arom}), 177.9 (s, CN). IR (nujol) cm^{-1} 2214 (CN), 1453, 1355 (CH_3). *Anal.* Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58. Found: C, 73.68; H, 5.42; N, 9.43.

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