SUBSTITUTED VINYL AZIDES IN SYNTHESIS OF FURO[3,2-*b*:4,5-*b*']-DIPYRROLES AND PYRROLO[2',3':4,5]FURO[3,2-*c*]PYRIDINES

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(Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday)

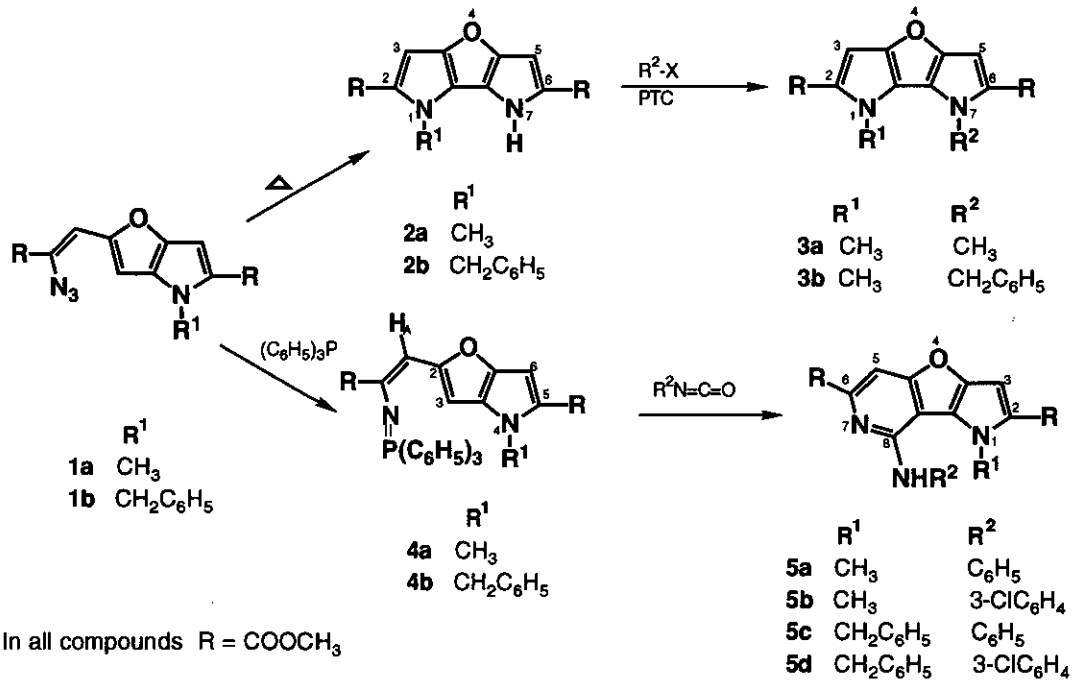
Abstract - A number of pyrrolo[2',3':4,5]furo[3,2-*c*]pyridines (**5a-5d**) were prepared by the reaction of corresponding iminophosphoranes (**4a, 4b**), available from substituted vinylazides (**1a, 1b**) and triphenylphosphine, with phenyl or 3-chlorophenyl isocyanates. The appropriate vinylazides (**1a, 1b**) were used for the preparation of substituted furo[3,2-*b*:4,5-*b*']-dipyrroles (**2a, 2b**). Compounds (**3a, 3b**) were prepared in phase transfer catalysis conditions.

The several reaction centres of substituted furo[3,2-*b*]pyrroles were studied[1] and utilized in the synthesis of new heterocyclic systems. The paper[1] presents the formylation, nitration, Mannich reaction and copulation of variously substituted furo[3,2-*b*]pyrroles or their benzo[b]derivatives. The studies[1] of addition and cycloaddition reactions of furo[3,2-*b*]pyrroles and their condensed derivatives showed that their reaction course is influenced by the substituents attached to this system.

Several methods have been described[2] for the synthesis of furo[3,2-*c*]pyridine system, starting either from pyridines or furans.[3-6] Electrophilic[7] and nucleophilic[8] reactions and biological properties[9] of the substituted furo[3,2-*c*]pyridines were studied.

In continuation of our previous efforts[1,11] towards the preparation of condensed *O*-,*N*-heterocycles we here report efficient syntheses of some representatives of the title ring systems (Scheme 1).

Reaction of methyl 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate with methyl azidoacetate in the presence of a sodium ethoxide was found[11] to proceed smoothly to give **1a**, the thermolysis of which was carried out in boiling toluene and lent to dimethyl 1-methyl-7*H*-furo[3,2-*b*:4,5-*b*']dipyrrole-2,6-carboxylate (**2a**). Analogously (**2b**) was prepared. This reaction was relatively rapid and afforded the product in good yield.



	R¹
2a	CH_3
2b	$CH_2C_6H_5$

	R¹	R²
3a	CH_3	CH_3
3b	CH_3	$CH_2C_6H_5$

	R¹
1a	CH_3
1b	$CH_2C_6H_5$

	R¹
4a	CH_3
4b	$CH_2C_6H_5$

	R¹	R²
5a	CH_3	C_6H_5
5b	CH_3	3-ClC_6H_4
5c	$CH_2C_6H_5$	C_6H_5
5d	$CH_2C_6H_5$	3-ClC_6H_4

Scheme 1

The phase transfer catalysis was found to be successful for methylation and benzylation of compound (**2a**) or (**2b**) to give **3a** or **3b** .

Further the compounds (**1a**) and (**1b**) reacted with triphenylphosphine in dry dichloromethane to give iminophosphoranes (**4a**) and (**4b**) in very good yield. Compounds (**4a**) and (**4b**) reacted with phenyl or 3-chlorophenyl isocyanate in dry toluene under reflux to give triphenylphosphine oxide and corresponding substituted pyrrolo[2'3':4,5]furo[3,2-*c*]pyridines (**5a-5d**) *via* appropriate carbodiimides which were not isolated.

EXPERIMENTAL

Melting points were determined on a Kofler hot apparatus and are uncorrected. ^1H Nmr (300 MHz) and ^{13}C nmr (75.43 MHz) spectra were recorded on a Bruker AM-300 FT nmr spectrometer at 298 K. Chemical shifts are expressed in ppm relative to TMS as internal standard. The *uv* spectra

were measured on a M-40 (Carl Zeiss Jena) spectrophotometer in methanol, concentration 10^{-4} mol.dm^{-3} or saturated solution of (**5a**, **5b**, **5d**) (λ_{max}/log ε; λ_{max} in nm, ε in m^{2}mol^{-1}). The *ir* spectra were recorded on a FTIR PU 9802/25 (Philips) spectrophotometer using KBr technique (0.5 mg / 300 mg KBr, ν in cm^{-1}). The starting compounds (**1a**) and (**1b**) were prepared according to ref.[11]

Dimethyl 1-Methyl-7H-furo[3,2-b:4,5-b']dipyrrole-2,6-dicarboxylate (**2a**)

Methyl 2-azido-3-[(5-methoxycarbonyl-4-methyl)furo[3,2-*b*]-2-pyrrolyl]propenoate (**1a**) (1g, 3.29 mmol) was dissolved in toluene (100 ml). The mixture was refluxed under stirring for 1 h, the solvent was evaporated in *vacuo* and the product was crystallized. Yield 66 %; mp 291-293°C (methanol). *Anal.* Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14 %. Found: C, 56.79; H, 4.46; N, 10.02 %. *uv* : 358 (3.83), 345sh (3.74), 273 (2.84), 227 (2.99); *ir* : 1695, 1666 (C=O), 3290 (NH); *^{1}H nmr (DMSO-d_6)*: 6.75 (s, 1H, H-3), 6.78 (d, 1H, H-5, $J_{5,7}$ = 2.0 Hz), 12.43 (br s, 1H, NH), 4.06 (s, 3H, N-CH_3), 3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); *^{13}C nmr (DMSO-d_6)*: 121.90 (C-2), 99.02 (C-3) 150.07 (C-3a), 152.65 (C-4a), 97.29 (C-5), 121.90 (C-6), 117.27 (C-7a), 121.10 (C-7b), 161.30 and 161.25 (CO), 52.35 and 51.07 (OCH_3), 35.86 (N-CH_3).

Starting from **1b** analogously was prepared *methyl 1-benzyl-7H-furo[3,2-b:4,5-b']dipyrrole-2,6-carboxylate* (**2b**).Yield 74 %; mp 226-227°C (methanol). *Anal.* Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95 %. Found: C, 64.99; H, 4.66; N, 7.84 %. *uv* : 359 (3.77), 346sh (3.68), 274 (2.81), 227 (2.94); *ir* : 1699, 1664 (C=O), 3294 (NH); *^{1}H nmr (DMSO-d_6)*: 6.98 (br s, 1H, H-3), 6.91 (s, 1H, H-5), 12.42 (br s, 1H, NH), 7.00-7.37 (m, 5H, H_{arom}), 5.82 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3); *^{13}C nmr (DMSO-d_6)*: 122.21 (C-2), 100.37 (C-3), 150.42 (C-3a), 152.96 (C-4a), 97.45 (C-5), 121.90 (C-6), 117.20 (C-7a), 120.55 (C-7b), 161.32 and 161.02 (CO), 51.43 and 51.15 (OCH_3), R^1: 50.50 (CH_2), 138.6 (C-1'), 128.45 (C-3', 5'), 127.16 (C-4'), 126.36 (C-2', 6').

Dimethyl 1,7-Dimethylfuro[3,2-b:4,5-b']dipyrrole-2,6-dicarboxylate (**3a**)

A solution of sodium hydroxide (50%, 30 ml), methyl iodide (1.56 g, 11 mmol) and triethylbenzylammonium chloride (0.4 g, 1.76 mmol) were added to a stirred solution of **2a** (2.76, 10 mmol) in toluene (100 ml). The temperature was then raised to 65°C and the mixture was stirred for 4 h, diluted with water and the organic layer was separated. The aqueous layer was extracted with ether and combined with toluene solution, dried over sodium sulfate and the solvent was removed. The residue was crystallized. Yield 86 %; mp 240-241°C (dimethylformamide). *Anal.* Calcd for $C_{14}H_{14}N_2O_5$:

C, 57.93; H, 4.86; N, 9.65 %. Found: C, 57.79; H, 4.76; N, 9.82 %. *uv*: 359 (3.66), 345sh (3.61), 275 (2.65) 229 (2.78); *ir*: 1709, 1691 (C=O); *^{1}H nmr* (DMSO-d_6): 6.82 (s, 2H, H-3,5), 4.15 (s, 6H, 2x N-CH_3) 3.72 (s, 6H, 2x OCH_3); *^{13}C nmr (DMSO-d_6)*: 121.30 (C-2,6), 99.03 (C-3,5), 150.31 (C-3a,4a), 121.30 (C-7a,7b), 161.30 (CO), 51.24 (OCH_3), 35.69 (N-CH_3).

Starting from **2b** was made *dimethyl 1-benzyl-7-methylfuro[3,2-b:4,5-b']dipyrrole-2,6-dicarboxylate* (**3b**). Yield 84 %; mp 197-200°C (methanol). *Anal.* Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65 %. Found: C, 65.79 ; H, 4.86; N, 7.72 %. *uv*: 359 (3.73), 345sh (3.64), 274 (2.74), 229 (2.77); *ir*: 1691 (C=O); *^{1}H mmr (DMSO-d_6)*: 7.40-6.90 (m, 5H, H_{arom}), 6.98 (s, 1H, H-3), 6.82 (s, 1H, H-5), 5.94 (s, 2H, CH_2), 3.80 (s, 3H, N-CH_3), 3.68 (s, 6H, 3x OCH_3); *^{13}C nmr (DMSO-d_6)*: 100.01 (C-3), 150.74 (C-3a), 150.60 (C-4a), 99.12 (C-5), 121.70, 121.65, 121.50, 121.40 (C-2, 6, 7a, 7b), 161.15 (CO), 51.28 (OCH_3), 35.07 (N-CH_3). R^2: 35.07 (CH_2), 137.86 (C-1'), 128.79 (C-3', 5'), 127.25 (C-4'), 125.40 (C-2',6').

Methyl 2-Triphenylphosphoimino-3-[(4-methyl-5-methoxycarbonyl)furo[3,2-b]pyrrol-2-yl]propenoate (**4a**). A solution of triphenylphosphine (1.31 g, 5 mmol) in dry dichloromethane (20 ml) was added dropwise under nitrogen to a stirred solution of **1a** (1.52 g, 5 mmol) in the same solvent (10 ml) at 0°C. The reaction mixture was allowed to warm to the room temperature and stirring was continued for 20 h. The solvent was removed under reduced pressure and the residual solid was recrystallized to give **4a**. Yield 2.42 g, 90%; mp 215-217°C (dichloromethane / isohexane 1:1). *Anal.* Calcd for $C_{31}H_{27}N_2O_5P$: C, 69.14; H, 5.05; N, 5.20 %. Found: C, 69.29; H, 4.96 ; N, 5.32%. *uv*: 411 (3.60), 289 (2.91); *ir*: 1690 (C=O); *^{1}H nmr (CDCl$_3$)*: 6.71 (d, 1H, H-6, $J_{3,6}$ = 0.8 Hz), 6.80 (d, 1H, H_A, $J_{A,P}$ = 7.2 Hz), 7.25-7.87 (m, 16H, H_{arom} and H-3), 3.83 (s, 3H, N-CH_3), 3.81 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3).

Starting from **1b** analogously was prepared methyl *2-triphenylphosphoimino-3-[(4-benzyl-5-methoxycarbonyl)furo[3,2-b]pyrrol-2-yl]propenoate* (**4b**). Yield 76 %; mp 217-220 °C (dichloromethane / isohexane 1:1). *Anal.* Calcd for $C_{37}H_{31}N_2O_5P$: C, 72.30; H, 5.08; N, 4.56 %. Found: C, 72.29; H, 5.16; N, 4.32 %. *uv*: 412 (3.60), 290 (2.91); *ir*: 1693 (C=O); *^{1}H nmr (CDCl$_3$)*: 6.77(d, 1H, H-6, $J_{3,6}$ = 0.8 Hz), 6.81 (d, 1H, H_A, $J_{A,P}$=7.0 Hz), 7.00-7.87 (m, 21H, H_{arom} and H-3), 5.49 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3).

Dimethyl 1-Methyl-8-phenylaminopyrrolo[2',3':4,5]furo[3,2-c]pyridine-2,6-dicarboxylate (**5a**)

A solution of the phenyl isocyanate (0.60 g, 5 mmol) in dry toluene (50 ml) was added dropwise under nitrogen to stirred solution of **4a** (2.69 g, 5 mmol). The reaction mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the solid residue was crystallized. Yield 1.02 g, 66%; mp 215-217°C (methanol). *Anal.* Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08 %. Found: C, 63.29; H, 4.58; N, 11.18 %. *uv* : 368, 318, 270; *ir* : 1738, 1734, 1703 (C=O), 3290 (NH); *^{1}H nmr (DMSO-d_6)*: 6.99 (s, 1H, H-3), 7.84 (s, 1H, H-5), 8.90 (br s, 1H, NH), 6.75-7.60 (m, 5H, H_{arom}), 4.11 (s, 3H, N-CH_3), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3); *^{13}C nmr (DMSO-d_6)*: 125.82 (C-2), 97.89 (C-3), 104.62 (C-5), 141.17 (C-6), 147.47 (C-8), 147.20 (C-3a), 160.90 (C-4a), 125.82 (C-8b), 107.58 (C-8a), 165.25 and 164.90 (CO), 52.42 and 51.57 (OCH_3), 35.52 (N-CH_3), R^2: 141.65 (C-1'), 128.72 (C-3', 5'), 121.14 (C-4'), 117.94 (C-2', 6').

Starting from **4a** analogously was prepared *dimethyl 1-methyl-8-(3-chlorophenylamino)pyrrolo-[2',3':4,5]furo[3,2-c]pyridine-2,6-dicarboxylate* (**5b**). Yield 67 %; mp 214-217 °C (methanol). *Anal.* Calcd for $C_{20}H_{16}ClN_3O_5$: C, 58.05; H, 3.89; N, 10.15 %. Found: C, 58.19; H, 3.88; N, 10.18 %. *uv*: 367, 319, 270; *ir*: 1738, 1709 (C=O), 3462 (NH); *^{1}H nmr* (DMSO-d_6): 6.99 (s, 1H, H-3), 7.86 (s, 1H, H-5), 9.02 (br s, 1H, NH), 7.81 (t, 1H, H-2', $J_{2',4'} = J_{2',6'} = 2.0$ Hz), 6.70-7.50 (m, 3H, H-4',5',6'), 4.19 (s, 3H, N-CH_3), 3.84 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); *^{13}C nmr (DMSO-d_6)*: 125.98 (C-2), 97.90 (C-3), 104.97 (C-5), 140.88 (C-6), 147.62 (C-8), 146.42 (C-3a), 160.90 (C-4a), 107.58 (8a), 125.18 (8b), 165.22 and 164.74 CO), 52.47 and 51.60 ($0CH_3$), 35.68 (N-CH_3), R^2: 142.88, 116.45, 133.20, 120.63, 130.20, 117.53 (C-1', 2', 3', 4', 5', 6').

Starting from **4b** analogously were prepared: *Dimethyl 1-Benzyl-8-phenylaminopyrrolo[2',3':4,5]-furo[3,2-c]pyridine-2,6-dicarboxylate* (**5c**). Yield 69 %; mp 206-209 °C (methanol). *Anal.* Calcd for $C_{26}H_{21}N_3O_5$: C, 68.56; H, 4.65, N, 9.23 %. Found: C, 68.49; H, 4.69; N, 9.33 %. *uv*: 372 (3.28), 317 (3.30), 270 (3.41); *ir*: 1738, 1705 (C=O), 3408, 3381 (NH); *^{1}H nmr (DMSO-d_6)*: 7.16 (s, 1H, H-3), 7.85 (s, 1H, H-5), 8.61 (br s, 1H, NH), 6.02 (s, 2H, CH_2), 6.75-7.50 (m, 5H, H_{arom}), 3.81 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3); *^{13}C nmr (DMSO-d_6)*: 125.40 (C-2), 99.60 (C-3), 104.58 (C-5), 141.20 (C-6), 148.02 (C-8), 147.07 (C-3a), 160.92 (C-4a), 125.24 (C-8b), 107.21 (C-8a), 165.50 and 164.84 (CO), 52.47 and 51.74 (OCH_3), 50.15 (CH_2), R^1 : 138.02 (C-1''), 128.65 (C-3'', 5''), 127.40 (C-4''), 125.74 (C-2'', 6''), R^2: 141.40 (C-1'), 128.65 (C-3',5'), 121.37 (C-4'), 116.19 (C-2', 6').

Dimethyl 1-Benzyl-8-(3-chlorophenylamino)pyrrolo[2',3':4,5]furo[3,2-c]pyridine-2,6-dicarboxylate (**5d**). Yield 79 %; mp 225-226°C (methanol). *Anal.* Calcd. for $C_{26}H_{20}ClN_3O_5$: C, 63.74; H, 4.11; N, 8.58 %. Found: C, 63.49; H, 4.19; N, 8.43 %; *uv*: 367, 319, 270; *ir*: 1711 (C=O), 3372 (NH); *^{1}H nmr* (DMSO-d_6): 7.18 (s, 1H, H-3), 7.90 (s, 1H, H-5), 8.84 (br s, 1H, NH), 7.65 (t, 1H, H-2' in R^2, $J_{2',4'} = J_{2',6'} = 2.0$ Hz), 6.75-7.50 (m, 8H, H_{arom}), 6.10 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3,75 (s, 3H, OCH_3); *^{13}C nmr (DMSO-d_6)*: 125.91 (C-2), 99.63 (C-3), 105.06 (C-5), 141.20 (C-6), 148.20 (C-8), 146.30 (C-3a), 160.90 (C-4a), 107.51 (C-8a), 125.10 (C-8b), 165.50 and 164.70 (CO), 52.53 and 51. 80 (OCH_3), 50.28 (CH_2), R^1: 137.96 (C-1"), 128.58 (C-3", 5"), 125.64 (C-2", 6"), 127.35 (C-4"), R^2: 142.67 , 116.53, 133.10, 120.78, 130.14, 117.59 (C-1', 2', 3', 4', 5', 6').

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