

2-ARYLFURO[3,2-*b*]PYRROLES*

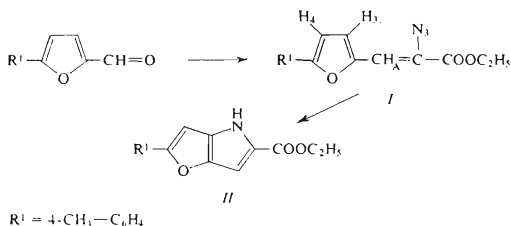
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Preparation of ethyl 2-(4-tolyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate, alkylation and hydrolysis of ethyl 2-phenyl- and 2-(tolyl)furo[3,2-*b*]pyrrole-5-carboxylate are described. Also the synthesis of 2-phenyl- and 2-(4-tolyl)-4*H*-furo[3,2-*b*]pyrroles and their *N*-methylated derivatives is presented.

As a continuation of our preceding investigation¹⁻⁴ ethyl 2-azido-3-[5-(4-tolyl)-2-furyl]acrylate (*I*) was prepared from 5-(4-tolyl)-2-furaldehyde and ethyl azido acetate in the presence of sodium ethoxide; *I* undergoes thermolysis to yield ethyl 2-(4-tolyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate, as shown in Scheme 1.



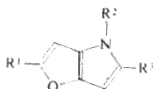
SCHEME 1

Some reactions of compound *II*, similarly as those of ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate, the preparation of which has already been published¹, were examined and derivatives of furo[3,2-*b*]pyrrole *III*–*XIV* were prepared.

Compounds *III* and *IV* were synthesized by a phase-transfer catalysis⁵⁻⁷ from *II* and ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and methyl iodide in the presence of triethylbenzylammonium bromide. Although the ethoxycarbonyl group undergoes hydrolysis during the reaction, it is still more advantageous for the shorter reaction time and more convenient reaction medium than the alkylation *via* *N*-alkali

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metal salts. 4-(2-Cyanoethyl) derivatives *V* and *VI* were obtained similarly but with the difference that the reaction does not proceed in a two-phase system; the catalyst in this particular reaction was triethylbenzylammonium hydroxide, and pyridine



	R ¹	R ²	R ³		R ¹	R ²	R ³
<i>III</i>	4-CH ₃ -C ₆ H ₄	CH ₃	COOC ₂ H ₅	<i>IX</i>	4-CH ₃ -C ₆ H ₄	CH ₃	COOH
<i>IV</i>	C ₆ H ₅	CH ₃	COOC ₂ H ₅	<i>X</i>	C ₆ H ₅	CH ₃	COOH
<i>V</i>	4-CH ₃ -C ₆ H ₄	(CH ₂) ₂ CN	COOC ₂ H ₅	<i>XI</i>	4-CH ₃ -C ₆ H ₄	H	H
<i>VI</i>	C ₆ H ₅	(CH ₂) ₂ CN	COOC ₂ H ₅	<i>XII</i>	C ₆ H ₅	H	H
<i>VII</i>	4-CH ₃ -C ₆ H ₄	H	COOH	<i>XIII</i>	4-CH ₃ -C ₆ H ₄	CH ₃	H
<i>VIII</i>	C ₆ H ₅	H	COOH	<i>XIV</i>	C ₆ H ₅	CH ₃	H

solvent. Carboxylic acids *VII*–*X* were prepared by an alkaline hydrolysis of the corresponding esters, compounds *XI*–*XIV* by decarboxylation of *VII*–*X* in quinoline in the presence of copper chromite barium promoted. This reaction affords only low yields of the desired products, what might be due to a low stability of the furo[3,2-*b*]pyrrole system. This system has been found more stable when a benzene ring was fused in positions C₍₂₎ and C₍₃₎, as backed by higher yields (c. 45%) obtained by decarboxylation of benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid. The methyl group in position 4 causes lowering of yields.

The IR spectra of *XI*–*XIV* reveal characteristic bands $\nu(\text{C}=\text{C})_{\text{arom}}$ at about 1600 cm⁻¹. These bands of acids and esters are overlapped by substantially more intense bands of the C=O group. The wave number $\gamma_{\text{as}}(\text{N}_3)$ at 2100 cm⁻¹ is indicative of compound *I*. The effect of substituents attached at positions 2 and 4 of the furo-pyrrole system is manifested on the C=O band position. Bands associated with the $\nu(\text{OH})$ of the carboxylic acids were substituted in the 3150–2640 cm⁻¹ region. Wave numbers of C—O bonds of esters are observed at 1120–1250 cm⁻¹. All esters have two bands in this region: that at higher wave number is more intense.

The UV spectra of all these systems display an intense absorption band (log ϵ 4.6) at 320–337 nm and a series of weaker ones (log ϵ = 3.7–4.1) at 200–300 nm. Spectra of carboxylic acids and esters thereof *II*–*X* have a less intense band corresponding to the $n \rightarrow \pi^*$ transition of lone electron pairs of the nonbonding *n*-orbitals of the carboxyl or ethoxycarbonyl groups of the oxygen atom. The high λ_{max} value of the most intense band (when compared with that of furan, pyrrole) is indicative of the condensed furo[3,2-*b*]pyrrole system. Compounds *XI*–*XIV* with no substitution at C₍₅₎ show the most intensive band at ~320 nm, the remaining ones, due to the coupling of C=O group into conjugation, at c. 335 nm.

The properties of the substituent at $C_{(5)}$ were reflected at the chemical shift of $C_{(6)}\text{—H}$. Due to the ethoxycarbonyl group, this signal was downfield shifted. Comparison of chemical shifts of protons in compounds *XI* and *XIII*, *XII* and *XIV* shows that methylation to position 4 changes the multiplicity of $C_{(6)}\text{—H}$ proton signal from a multiplet to a doublet-doublet and that of $C_{(5)}\text{—H}$ from the doublet-doublet to a doublet, this being the proof for structure assignment to *XII* and *XIV*. The ^1H NMR spectra of all substances have signals of aromatic protons, and those of compounds possessing an ethoxycarbonyl grouping, also signals of $\text{O—CH}_2\text{—CH}_3$ protons.

EXPERIMENTAL

Ethyl 2-Azido-3-[5-(4-tolyl)-2-furyl] Acrylate (*I*)

A solution of 5-(4-tolyl)-2-furaldehyde (3.7 g, 20 mmol) and ethyl azido acetate (10.3 g, 80 mmol) were added to sodium metal (1.84 g, 80 mmol) dissolved in ethanol (60 ml). The mixture was stirred at 10°C for 1 h, then ammonium chloride (4 g) in water (20 ml) was added and after 10 min the solution was poured into cold water (400 ml). The separated precipitate *I* was filtered off giving 3.5 g (60%) of *I*, m.p. 97°C (ethanol). For $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$ (297.3) calculated: 64.63% C, 5.08% H, 14.13% N; found: 64.58% C, 5.02% H, 14.23% N. IR spectrum (ν , CHCl_3 , cm^{-1}): 1 692 (C=O), 1 598 (C=C), 2 100 (N_3). UV spectrum (λ_{max} , nm, log ϵ): 378 (4.57), 268 (3.92). ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide, δ , ppm): 6.89 (1 H, d, $\text{C}_A\text{—H}$), 7.14 (1 H, d, $\text{C}_{(3)}\text{—H}$), 6.69 (1 H, d, $\text{C}_{(4)}\text{—H}$), 4.33 (2 H, q, —CH_2), 1.37 (3 H, t, CH_3), 2.23 (3 H, s, CH_3), 2.23 (3 H, s, CH_3), 7.57, 7.17 (4 H, d, $\text{H}_{\text{arom.}}$). $J_{3,4} = 3.2$ Hz, $J_{3,A} = 0.6$ Hz.

Ethyl 2-(4-Tolyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (*II*)

Ester *I* (1 g) in toluene (100 ml) was heated with stirring for 10 min. The solvent was distilled off under reduced pressure giving *II* (0.84 g, 93%), m.p. $170\text{—}171^\circ\text{C}$ (benzene). For $\text{C}_{16}\text{H}_{15}\text{NO}_3$ (269.3) calculated: 71.35% C, 5.61% H, 5.20% N; found: 71.25% C, 5.58% H, 5.52% N. IR spectrum (ν , KBr, cm^{-1}): 1 695 (C=O), 3 460 (N—H). UV spectrum (λ_{max} , nm, log ϵ): 342 (4.79), 233 (3.84). ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 6.80 (1 H, dd, $\text{C}_{(6)}\text{—H}$); 6.62 (1 H, d, $\text{C}_{(3)}\text{—H}$); 4.37 (2 H, q, —O—CH_2); 1.38 (3 H, t, CH_3); 2.23 (3 H, s, CH_3); 7.61—7.18 (4 H, d, $\text{H}_{\text{arom.}}$). $J_{3,6} = 0.8$, $J_{4,6} = 1.6$.

Ethyl 2-(4-Tolyl)-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate (*III*)

A solution of sodium hydroxide (50%, 30 ml), methyl iodide (1.56 g, 11 mmol) and triethylbenzylammonium chloride (0.4 g) were added to a stirred solution of ester *II* (2.69 g, 10 mmol) in benzene (100 ml). The temperature was then raised to 65°C and the mixture stirred for 4 h, cooled, diluted with water and the organic layer separated. The aqueous layer was extracted with ether and combined with the benzene solution, dried with sodium sulfate and the solvent removed. Yield 1.98 g (70%), m.p. 159°C (methanol). For $\text{C}_{17}\text{H}_{17}\text{NO}_3$ (283.3) calculated: 73.06% C, 6.04% H, 4.94% N; found: 72.10% C, 6.14% H, 5.03% N. IR spectrum (ν , KBr, cm^{-1}): 1 654 (C=O). UV spectrum (λ_{max} , nm, log ϵ): 340 (4.79), 233 (3.84). ^1H NMR spectrum (CDCl_3): 6.58 (1 H, d, $\text{C}_{(3)}\text{—H}$); 6.78 (1 H, d, $\text{C}_{(6)}\text{—H}$); 3.85 (3 H, s, CH_3); 2.37 (3 H, s, CH_3); 4.31 (2 H, q, —OCH_2); 1.37 (3 H, t, CH_3); 7.61, 7.18 (4 H, d, $\text{H}_{\text{arom.}}$). $J_{3,6} = 0.8$.

*Ethyl 2-phenyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate (IV)* was obtained in an analogous way. Yield 1.45 g (54%), m.p. 63°C (methanol). For $C_{16}H_{15}NO_3$ (269.3) calculated: 71.35% C, 5.61% H; 5.20% N; found: 71.19% C, 5.42% H, 4.97% N. IR spectrum (ν , KBr, cm^{-1}): 1654 (C=O). UV spectrum (λ_{max} , nm, log ϵ): 333 (4.74); 279 (4.24). 1H NMR spectrum ($CDCl_3$): 6.60 (1 H, d, C_{13} -H); 6.78 (1 H, d, C_{16} -H); 3.95 (3 H, s, N-CH₃); 4.31 (2 H, q, O-CH₂); 1.37 (3 H, t, CH₃); 7.20–7.80 (5 H, m, H_{arom}), $J_{3,6} = 0.8$.

*Ethyl 2-(4-Tolyl)-4-(2-cyanoethyl)furo[3,2-*b*]pyrrole-5-carboxylate (I')*

Acrylonitrile (1.5 g, 30 mmol) and triethylbenzylammonium hydroxide (0.5 mmol) were added to ester *II* (1 g, 3.7 mmol) in pyridine (10 ml) and heated to boiling temperature for 25 min. The mixture was cooled and the solvent removed *in vacuo*. Yield 0.9 g (76%), m.p. 147–148°C (ethanol). For $C_{19}H_{18}N_2O_3$ (320.4) calculated: 71.22% C, 5.66% H, 8.74% N; found: 71.24% C, 5.62% H, 8.71% N. IR spectrum (ν , KBr, cm^{-1}): 2240 (C≡N), 1649 (C=O). UV spectrum (λ_{max} , nm, log ϵ): 337 (4.58), 205 (3.78). 1H NMR spectrum ($CDCl_3$): 6.74 (1 H, d, C_{13} -H); 6.87 (1 H, d, C_{16} -H); 4.66 (2 H, t, CH₂-N); 2.9 (2 H, t, CH₂-CN); 2.37 (3 H, s, CH₃); 4.30 (2 H, q, O-CH₂); 1.36 (3 H, t, CH₃), $J_{3,6} = 0.8$ Hz.

*Ethyl 2-phenyl-4-(2-cyanoethyl)furo[3,2-*b*]pyrrole-5-carboxylate (VI)* was prepared in the same way from ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate. Yield 74%, m.p. 123°C (ethanol). For $C_{18}H_{16}N_2O_3$ (308.4) calculated: 70.09% C, 5.22% H, 9.10% N; found: 70.03% C, 5.28% H, 9.38% N. IR spectrum (ν , KBr, cm^{-1}): 2224 (C≡N), 1655 (C=O). UV spectrum (λ_{max} , nm, log ϵ): 335 (4.82); 233 (3.88). 1H NMR spectrum ($CDCl_3$): 6.76 (1 H, d, C_{13} -H); 6.86 (1 H, d, C_{16} -H); 4.65 (2 H, t, N-CH₂); 2.92 (2 H, t, CH₂-CN); 4.31 (2 H, q, O-CH₂); 1.37 (3 H, t, CH₃); 7.25–7.93 (5 H, m, H_{arom}), $J_{3,6} = 0.9$.

*2-(4-Tolyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic Acid (VII)*

Aqueous sodium hydroxide (5%, 30 ml) was added to ester *II* (2.69 g, 10 mmol) dissolved in ethanol (100 ml) and refluxed for 2 h. The separated salt of *VII* was dissolved in ethanol-water 1 : 1, simmered with charcoal, filtered and cooled. Addition of hydrochloric acid up to a weak acidic reaction makes the compound *VII* separate; it was filtered off and washed with water. Yield 1.73 g (72%), m.p. 253°C (ethanol). For $C_{14}H_{11}NO_3$ (241.3) calculated: 69.70% C, 4.59% H, 5.80% N; found: 69.64% C, 4.50% H, 5.88% N. IR spectrum (ν , KBr, cm^{-1}): 1640 (C=O), 3384 (N—H). UV spectrum (λ_{max} , nm, log ϵ): 321 (4.50); 295 (4.31). 1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 6.77 (1 H, d, C_{13} -H); 7.05 (1 H, dd, C_{16} -H); 11.57 (1 H, bs, N—H); 2.33 (3 H, s, CH₃); 7.70, 7.22 (4 H, d, H_{arom}), $J_{3,6} = 0.8$, $J_{4,6} = 1.8$.

*2-Phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid (VIII)* was obtained by saponification of its ethyl ester in the same way. Yield 78%, m.p. 225°C (methanol). For $C_{13}H_9NO_3$ (227.2) calculated: 68.72% C, 3.99% H, 6.17% N; found: 68.62% C, 3.94% H, 6.18% N. IR spectrum (ν , KBr, cm^{-1}): 1685 (C=O), 3391 (N—H). UV spectrum (λ_{max} , nm, log ϵ): 337 (4.80), 233 (3.84). 1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 6.75 (1 H, d, C_{13} -H); 7.12 (1 H, dd, C_{16} -H); 11.62 (1 H, bs, N—H); 7.25–7.93 (5 H, m, H_{arom}), $J_{3,6} = 0.8$.

*2-(4-Tolyl)-4-methylfuro[3,2-*b*]pyrrole-5-carboxylic acid (IX)* was prepared from ethyl 2-(4-tolyl)-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate. Yield 72%, m.p. 238–240°C (ethanol). For $C_{15}H_{13}NO_3$ (255.2) calculated: 69.70% C, 4.59% H, 5.48% N; found: 70.39% C, 5.16% H, 5.52% N. IR spectrum (ν , KBr, cm^{-1}): 1640 (C=O), UV spectrum (λ_{max} , nm, log ϵ): 335 (4.68), 207 (4.14). 1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 6.80 (1 H, d, C_{13} -H); 7.18 (1 H, d, C_{16} -H); 3.94 (3 H, s, N-CH₃); 2.33 (3 H, s, CH₃); 7.69 and 7.28 (4 H, d, H_{arom}), $J_{3,6} = 0.8$.

2-Phenyl-4-methylfuro[3,2-b]pyrrole-5-carboxylic acid (X) was synthesized from ethyl 2-phenyl-4-methylfuro[3,2-b]pyrrole-5-carboxylate in an analogous way. Yield 65%, m.p. 188–189°C (methanol). For $C_{14}H_{11}NO_3$ (241.2) calculated: 69.70% C, 4.59% H, 5.80% N; found: 69.59% C, 4.60% H, 5.91% N. IR spectrum (ν , KBr, cm^{-1}): 1 663 (C=O), UV spectrum (λ_{max} , nm, log ϵ): (4.68); 207 (4.14). 1H NMR (hexadeuteriodimethyl sulfoxide): 6.82 (1 H, d, $C_{(3)}-H$); 7.27 (1 H, d, $C_{(6)}-H$); 3.96 (3 H, s, N—CH₃); 7.42–7.86 (5 H, m, $H_{arom.}$), $J_{3,6} = 0.8$.

2-(4-Tolyl)-4H-furo[3,2-b]pyrrole (XI)

Compound VII (2.41 g, 10 mmol), quinoline (20 ml) and copper chromite (0.64 g) were stirred under nitrogen. The temperature was raised to 120–140°C and was kept constant until the evolution of carbon dioxide ceased (monitored with calcium hydroxide solution). The mixture was then cooled to 0°C, ether added and the ethereal solution washed both with 1M-HCl until the quinoline was removed, (consumption c. 3 000 ml) and water. The organic layer was dried with Na₂SO₄, and ether was distilled off *in vacuo*. Yield 21%, m.p. 123°C. For $C_{13}H_{11}NO$ (197.2) calculated: 79.17% C, 5.62% H, 7.10% N; found: 79.20% C, 5.60% H, 7.16% N. IR spectrum (ν , CHCl₃, cm^{-1}): 3 502 (N—H), 2 958 (CH₃). UV spectrum (λ_{max} , nm, log ϵ): 320 (4.52); 205(3.97). 1H NMR spectrum (CDCl₃): 6.22 (1 H, m, $C_{(6)}-H$); 6.63 (1 H, d, $C_{(3)}-H$); 6.75 (1 H, t, $C_{(5)}-H$); 2.37 (3 H, s, CH₃); 7.21, 7.81 (4 H, d, $H_{arom.}$), $J_{5,6} = 3.1$, $J_{4,6} = 1.6$, $J_{4,5} = 3.1$, $J_{3,6} = 0.8$.

2-Phenyl-4H-furo[3,2-b]pyrrole (XII) was prepared in the same way. Yield 24.8%, m.p. 134°C (n-hexane-ether 5 : 1). For $C_{12}H_9NO$ (183.2) calculated: 78.69% C, 4.95% H, 7.65% N; found: 78.64% C, 4.90% H, 7.75% N. IR spectrum (ν , CHCl₃, cm^{-1}): 3 480 (NH) 2 985 (C— $H_{arom.}$). UV spectrum (λ_{max} , nm, log ϵ): 324 (4.49), 246 (4.02). 1H NMR spectrum (CDCl₃): 6.22 (1 H, m, $C_{(6)}-H$); 6.67 (1 H, d, $C_{(3)}-H$); 6.76 (1 H, t, $C_{(5)}-H$); 7.2–7.78 (5 H, m, $H_{arom.}$), $J_{5,6} = 3.1$, $J_{4,6} = 1.6$, $J_{4,5} = 3.1$, $J_{3,6} = 0.8$.

2-(4-Tolyl)-4-methylfuro[3,2-b]pyrrole (XIII). Yield 18%, m.p. 101–102°C (n-hexane-ether 5 : 1). For $C_{14}H_{13}NO$ (211.3), calculated: 79.57% C, 6.20% H, 6.63% N; found: 79.60% C, 6.32% H, 6.69% N. IR spectrum (ν , CHCl₃, cm^{-1}): 2 920 (CH₃). UV spectrum (λ_{max} , nm, log ϵ): 320 (4.46), 205 (4.22). 1H NMR spectrum (CDCl₃): 6.06 (1 H, dd, $C_{(6)}-H$); 6.59 (1 H, d, $C_{(3)}-H$); 6.49 (1 H, d, $C_{(5)}-H$); 3.62 (3 H, s, N—CH₃); 2.35 (3 H, s, CH₃); $J_{5,6} = 3.1$, $J_{3,6} = 0.8$.

2-Phenyl-4-methylfuro[3,2-b]pyrrole (XIV). Yield 19%, m.p. 75–76°C (n-hexane-ether 5 : 1). For $C_{13}H_{10}NO$ (197.2): calculated 79.17% C, 5.62% H, 7.10% N; found: 79.12% C, 5.62% H, 7.14% N. IR spectrum (ν , CHCl₃, cm^{-1}): 2 920 (CH₃). UV spectrum (λ_{max} , nm, log ϵ): 312 (4.64), 240 (4.18). 1H NMR spectrum (CDCl₃): 6.08 (1 H, d, d, $C_{(6)}-H$); 6.83 (1 H, d, $C_{(5)}-H$); 7.13 (1 H, d, $C_{(3)}-H$); 3.73 (3 H, s, N—CH₃), $J_{5,6} = 3.0$, $J_{3,6} = 0.8$.

Spectral Measurements

The IR spectra were measured with a Specord 71 IR (Zeiss, Jena), the electronic spectra with a Specord UV VIS (Zeiss, Jena) spectrometers. Measuring range 200–800 nm, concentrations $2 \cdot 10^{-5}$ to $5 \cdot 10^{-5}$ mol/l in methanol. The 1H NMR spectra were recorded with a Tesla BS 487C apparatus operating at 80 MHz. Chemical shifts in hexadeuteriodimethyl sulfoxide were related to hexamethyldisiloxane as an internal reference, those in deuteriochloroform to tetramethylsilane.

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