SYNTHESIS OF SUBSTITUTED 2-ARYL-4H-FURO[3,2-b]PYRROLES*
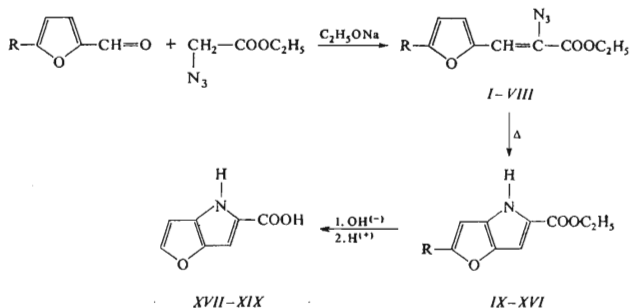
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Ethyl 3-(5-aryl-2-furyl)-2-azidoacrylates were prepared by reacting 5-aryl-2-furaldehydes with ethyl azidoacetate. Thermolysis of the prepared compounds gave 2-arylfuro[3,2-b]pyrrole-5-carboxylates.

Substituted vinylazides, which were prepared by condensation of aromatic and heterocyclic aldehydes with ethyl azidoacetate[1-3], afforded upon thermolysis condensed pyrroles. This method was further extended[4-6] to five-membered heterocycles. The substituted furo[3,2-b]pyrrole was prepared from 3-azido-2-furaldehyde[7]. Condensation of 5-aryl-2-furaldehydes with compounds containing an active methylene group was reported in our previous papers[8-10]. In the framework of this project we reacted ethyl azidoacetate with 5-aryl-2-furaldehydes to obtain ethyl 3-(5-aryl-2-furyl)-2-azidoacrylates, the thermolysis of which leads to ethyl 2-arylfuro[3,2-b]pyrrole-5-carboxylates (Scheme 1).
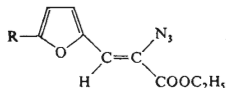

Scheme 1

The method to prepare 2-aryl-4H-5-ethoxycarbonyl derivatives of furo[3,2-b]pyrrole lies in thermal cyclization of ethyl 3-(5-aryl-2-furyl)-2-azidoacrylates. This reaction type was already utilized in the benzene series[3] for preparation of substituted indoles and can be, in terms of reaction mechanism, regarded as an insertion of the originally generated nitrene into the C—H bond. The corresponding ethyl 3-(5-aryl-2-furyl)-2-azidoacrylates were synthesized from the appropriate 5-aryl-2-furaldehydes[11] and an excess of ethyl azidoacetate in the presence of sodium ethylate. Toluene was employed as a solvent due to low solubility of 5-aryl-2-furaldehydes in ethanol. Under these conditions compounds $I-VIII$ were prepared in a 38−68% yield. The thermolysis of these compounds was carried out in boiling xylene until the liberation of nitrogen ceased; this was also seen in the infrared spectrum lacking the asymmetric N_3 absorption vibrations. This reaction is relatively rapid and affords reaction products in a 95−97% yield. Hydrolysis of some ethyl 2-aryl-4H-furo[3,2-b]pyrrole-5-carboxylates furnishes the corresponding acids.

TABLE I

Ethyl Esters 3-(5-Aryl-2-furyl)-2-azidoacrylate Acids $I-VIII$

Compound R	Formula (m.v.)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	Cl (Br) %	
I C_6H_5	$C_{15}H_{13}N_3O_3$ (283·1)	63·63 63·58	4·63 5·60	14·83 14·92	— —	65 (68·7)
II 2-$NO_2C_6H_4$	$C_{15}H_{12}N_4O_5$ (328·1)	54·90 54·78	3·69 3·60	17·06 17·09	— —	92 (61)
III 3-$NO_2C_6H_4$	$C_{15}H_{12}N_4O_5$ (328·1)	54·90 54·92	3·69 3·58	17·06 16·87	— —	169 (38·5)
IV 2-ClC_6H_4	$C_{15}H_{12}ClN_3O_3$ (317·6)	56·73 56·81	3·81 3·86	13·22 12·96	11·16 11·06	97 (62·1)
V 4-ClC_6H_4	$C_{15}H_{12}ClN_3O_3$ (317·6)	56·73 56·80	3·81 3·82	13·22 13·02	11·16 11·06	94 (57·8)
VI 4-BrC_6H_4	$C_{15}H_{12}BrN_3O_3$ (362·0)	49·76 49·90	3·34 3·40	11·60 11·46	22·07 22·11	91 (48·1)
VII 3,4-$Cl_2C_6H_3$	$C_{15}H_{11}Cl_2N_3O_3$ (352·0)	51·18 51·30	3·15 3·24	11·93 11·70	20·14 19·97	99 (53·2)
VIII 3-CF_3-4-ClC_6H_3	$C_{16}H_{11}F_3ClN_3O_3$ (373·5)	51·44 51·34	2·97 2·88	11·24 11·50	9·49 9·23	117 (39·3)

Infrared spectra of substances $I-VIII$ reveal the $\nu_{as}(N_3)$ bands in the 2126 to 2135 cm^{-1} region, $\nu(C=O)$ of the ethoxycarbonyl at 1707—1717 cm^{-1} and $\nu(C=C)$ at 1615—1618 cm^{-1}. Compounds IX and XVI show the $\nu(NH)$ band of the pyrrole skeleton at 3453—3455 cm^{-1} and $\nu(C=O)$ of the ethoxycarbonyl group at 1692 to

TABLE II

Ethyl 2-Aryl-4H-furo[3,2-b]pyrrole-5-carboxylates $IX-XVI$ and 2-Aryl-4H-furo[3,2-b]pyrrole-5-carboxylic Acids $XVII-XIX$

Compound R	Formula (m.w.)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	Cl (Br) %	
IX C_6H_5	$C_{15}H_{13}NO_3$ (255·1)	70·61 70·76	5·40 5·20	5·48 5·43	— —	169 (97)
X 2-NO$_2$C$_6$H$_4$	$C_{15}H_{12}N_2O_5$ (300·1)	60·03 60·13	4·03 4·02	9·33 9·60	— —	168 (95)
XI 3-NO$_2$C$_6$H$_4$	$C_{15}H_{12}N_2O_5$ (300·1)	60·03 60·00	4·03 4·03	9·33 9·54	— —	216 (95)
XII 2-ClC$_6$H$_4$	$C_{15}H_{12}ClNO_3$ (289·6)	62·21 62·19	4·18 4·16	4·83 5·13	12·24 12·11	160·5 (95)
$XIII$ 4-ClC$_6$H$_4$	$C_{15}H_{12}ClNO_3$ (289·6)	62·21 62·16	4·18 4·14	4·83 5·10	12·24 12·18	194 (96)
XIV 4-BrC$_6$H$_4$	$C_{15}H_{12}BrNO_3$ (334·0)	53·93 53·83	3·62 3·56	4·19 4·34	23·92 24·15	199 (96)
XV 3,4-Cl$_2$C$_6$H$_3$	$C_{15}H_{11}Cl_2NO_3$ (324·0)	55·60 55·54	3·42 3·36	4·32 4·49	21·88 21·69	182 (95)
XVI 3-CF$_3$-4-ClC$_6$H$_3$	$C_{16}H_{11}F_3ClNO_3$ (345·5)	55·61 55·49	3·21 3·18	4·05 4·21	10·25 10·43	235 (95)
$XVII$ 2-NO$_2$C$_6$H$_4$	$C_{13}H_8N_2O_5$ (272·1)	57·38 57·32	2·96 2·88	10·30 10·48	— —	197 (82)
$XVIII$ 2-ClC$_6$H$_4$	$C_{13}H_8ClNO_3$ (261·6)	59·69 59·60	3·08 3·02	5·35 5·49	13·13 13·28	180—182 (95)
XIX 4-ClC$_6$H$_4$	$C_{13}H_8ClNO_3$ (261·6)	59·69 59·60	3·08 3·03	5·35 5·55	13·13 13·41	210 (95)

1696 cm^{-1}. The electron absorption spectra of $I-VI$ display one maximum in the 357—375 nm region. The influence of a substituent attached to the benzene ring can best be seen with *ortho*-substituted compounds: thus, I (R = phenyl) $\lambda_{max} = 375$ nm, IV (R = 2-chlorophenyl) $\lambda_{max} = 363$ nm and II (R = 2-nitrophenyl) $\lambda_{max} = 359$ nm. This exemplifies once more the influence of the bulkiness of the *ortho*-substituent of the conjugated systems.

As it follows from the data of chemical shifts (δ) of H_b protons of substances $I-VIII$, the substitution on the benzene ring has no substantial impact on the value of the H_b chemical shift. Signal of the H_a-proton resonance is, due to the anizotropic effect of the azido group[12] shifted down field. Based upon this fact, one can say that compounds $I-VIII$ have the E arrangement at the double bond and that the furylethylene system is *s-cis* arranged.
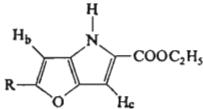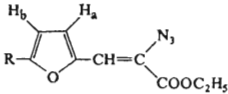
TABLE III

Infrared (v cm^{-1}) and Ultraviolet Data of Ethyl Esters of 3-(5-Aryl-2-furyl)-2-azidoacrylic Acids $I-VIII$, 2-Aryl-5-ethoxycarbonyl-4H-furo[3,2-b]pyrroles $IX-XVI$ and 2-Aryl-4H-furo[3,2-b]-pyrrole-5-carboxylic Acids $XVII-XIX$

Compound	$v(N_3)$	$v(C{=}O)$	$v(C{=}C)$	$v(N{-}H)$	λ_{max}	log ε	λ_{max}	log ε
I	2 135	1 707	1 615	—	—	—	375	(4·56)
II	2 132	1 714	1 616	—	—	—	359	(4·47)
III	2 130	1 717	1 616	—	—	—	357	(4·58)
IV	2 130	1 711	1 616	—	—	—	363	(4·00)
V	2 126	1 711	1 616	—	—	—	371	(4·59)
VI	2 131	1 714	1 618	—	—	—	367	(4·53)
VII	2 126	1 712	1 616	—	368	(4·61)	382 i	(4·45)
$VIII$	2 131	1 712	1 617	—	369	(4·48)	385	(4·40)
IX	—	1 693	—	3 455	337	(4·78)	353	(4·73)
X	—	1 695	—	3 453	—	—	327	(4·50)
XI	—	1 693	—	3 455	—	—	345	(4·64)
XII	—	1 692	—	3 455	338	(4·68)	354	(4·62)
$XIII$	—	1 696	—	3 453	342	(4·78)	358	(4·73)
XIV	—	1 693	—	3 455	347	(4·75)	362	(4·71)
XV	—	1 695	—	3 455	348	(4·70)	364	(4·68)
XVI	—	1 696	—	3 450	349	(4·51)	366	(4·50)
$XVII$	—	1 687	—	3 365	—	—	325	(4·41)
$XVIII$	—	1 645	—	3 406	338	(4·65)	353	(4·61)
XIX	—	1 683	—	3 366	344	(4·68)	359	(4·64)

The Z arrangement of the azido group towards the *ortho*-protons of the phenyl ring has already been proved[1]. A long-range interaction $J_{bc} = 0.8$ Hz between H_b and H_c protons in compounds $IX-XVI$ has been found.

TABLE IV

^{1}H-NMR Spectra of Ethyl Esters of 3-(5-Aryl-2-furyl)-2-azidoacrylic Acids $I-VIII$, Ethyl 2-Aryl--4H-furo[3,2-b]pyrrole-5-carboxylates $IX-XVI$

(Chemical shifts δ, ppm, J, Hz)

Compound[a]	H_a	H_b	$J_{a,b}$	H_c[b]	—CH=	(=CH)$_{arom}$
I	7·18 d	6·78 d	3·8	—	6·92 s	7·27—7·80
II	7·15 d	6·76 d	3·6	—	6·79 s	7·25—7·77
III	7·21 d	6·93 d	3·6	—	6·91 s	7·62—9·15
IV	7·16 d	6·74 d	3·7	—	6·88 s	7·30—8·00
V	7·17 d	6·77 d	3·7	—	6·88 s	7·28—7·66
VI	7·17 d	6·77 d	3·7	—	6·88 s	7·55 s
VII	7·13 d	6·74 d	3·7	—	6·83 s	7·43—7·72
VIII	7·16 d	6·81 d	3·6	—	6·85 s	7·26—8·06
IX	—	7·14 d	—	6·78 d	—	7·37—7·90
X	—	7·10 d	—	6·78 d	—	7·50—7·97
XI	—	7·42 d	—	6·77 d	—	7·60—7·97
XII	—	7·16 d	—	6·79 d	—	7·30—8·00
XIII	—	7·19 d	—	6·77 d	—	7·40—7·87
XIV	—	7·20 d	—	6·76 d	—	7·50—7·79
XV	—	7·32 d	—	6·77 d	—	7·59—8·05
XVI	—	7·42 d	—	6·77 d	—	7·67—8·14

[a] Compounds $I-XVI$ show in the region 1·37 ppm (t, 3 H, CH$_3$) and 4·36 ppm (q, 2 H, CH$_2$) of CH$_3$—CH—O—· group and $IX-XVI$ in the region 11·75 ppm (s, H, NH);   [b] Compounds $IX-XVI$: interaction $J_{b,c} = 0.8$ Hz.

EXPERIMENTAL

Ethyl 3-(5-Aryl-2-furyl)-2-azidoacrylates

A solution of 5-aryl-2-furaldehyde (10 mmol) and ethyl azidoacetate (10·32 g, 80 mmol) in toluene was added at 0°C during 30 min to a solution of sodium metal (1·84 g, 0·08 gat) in ethanol (60 ml). Stirring was continued for additional 60 min at a temperature not exceeding 15°C; the solution was then cooled to 0°C, ammonium chloride was added and poured in an ice-cold water. The organic layer was separated and the aqueous one extracted with ether. Combined organic solvents were dried with anhydrous sodium sulfate, the solvents removed and the crude product crystallized from ethanol.

Ethyl 2-Aryl-4H-furo[3,2-b]pyrrole-5-carboxylates

Ethyl 3-(5-aryl-2-furyl)-2-azidoacrylate (1 g) dissolved in xylene was heated under reflux and stirring for 20 min, the solvent was evaporated *in vacuo* and the product crystallized from benzene.

2-Aryl-4H-furo[3,2-b]pyrrole-5-carboxylic Acids

A 4% solution of sodium hydroxide in ethanol (10 ml) was added to ethyl 2-aryl-4H-furo[3,2-b]-pyrrole-5-carboxylate (1 g) dissolved in ethanol (25 ml). The separated salt was dissolved in ethanol, acidified with dilute (1 : 1) hydrochloric acid and the obtained product was crystallized from methanol.

Spectral Measurements

Infrared absorption spectra of compounds $I-XVI$ were measured as 10^{-2}M chloroform solutions in a 0·62 mm-NaCl cell, substances $XVII-XIX$ in KBr disc (2 mg/1 g KBr) using a UR-20 Zeiss, Jena spectrophotometer calibrated against a polystyrene foil. The electron absorption spectra were recorded with a Specord UV VIS Zeiss, Jena apparatus at a $1 . 10^{-5} - 5 . 10^{-5}$M concentration in ethanol at room temperature. The ^{1}H-NMR spectra were taken with a Tesla BS-487 instrument operating at 80 MHz in deuteriochloroform (compounds $I-VIII$), or dimethyl sulfoxide ($IX-XVI$) at 25°C, the internal reference substance being tetramethylsilane and hexamethyldisiloxane.

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