5-NITRO-2-FURYLVINYLATION OF SECONDARY AND TERTIARY AMINES*

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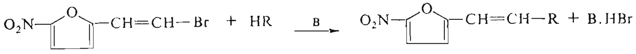
Reaction of 12 secondary amines and trimethylamine with (*Z*) and (*E*)-5-nitro-2-furylvinyl bromide (*I*) was studied. Whereas the enamines *II*, obtained from secondary amines, have the *E* configuration, the quaternisation of trimethylamine affords stereospecifically the corresponding (*Z*) or (*E*) vinylammonium salts *III*.

Our studies on reactions of 5-nitro-2-furylvinyl bromide[1,2] (*I*) with various nucleophiles resulted in finding general conditions for 5-nitro-2-furylvinylation (introduction of the biologically essential 5-nitro-2-furylethylene group). In our previous paper[3] we described the preparation of several biologically active 5-nitro-2-furylethylene enamines *II* by 5-nitro-2-furylvinylation of cyclic secondary and tertiary amines with the compound *I*. These derivatives represent important starting compounds for further syntheses[4]. General applicability of this reaction is now confirmed by synthesis of 12 new aliphatic (*IIa*–*IIh*), alicyclic (*IIj*, *IIk*), aliphatic-alicyclic (*IIl*) and aliphatic-aromatic (*IIm*) enamines.



Ia' (*Z*)
Ib' (*E*)

II

R ≡ *a* $N(CH_3)_2$
b $N(C_3H_7)_2$
c $N(i-C_3H_7)_2$
d $N(C_4H_9)_2$
e $N(C_5H_{11})_2$
f $N(i-C_5H_{11})_2$
g $N(C_8H_{17})_2$
h $N(CH_2—CH=CH_2)_2$
j $N(CH_2)_6$
k $N(cyclo-C_6H_{11})_2$
l $NCH_3(cyclo-C_6H_{11})$
m $N(CH_2-C_6H_5)C_6H_5$

B = RH; NaH, $NaCO_3$

SCHEME 1

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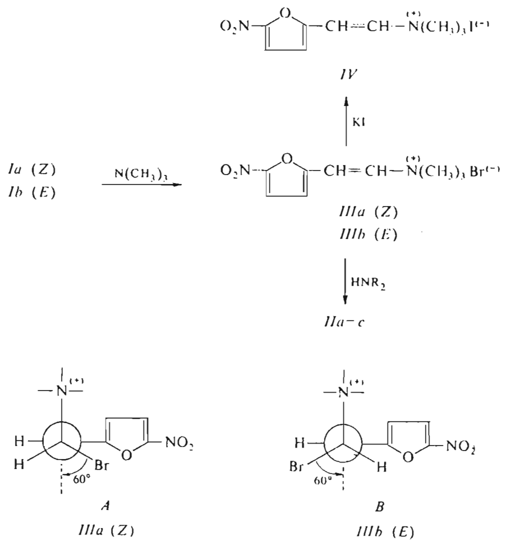
* Part CXLII in the series Furan Derivatives; Part CXLI: This Journal *45*, 150 (1980).

The reaction (Scheme 1) takes place in organic solvents, such as benzene, ether, tetrahydrofuran, or dimethoxyethane already at room temperature and affords the deeply coloured enamines *II*. Deeply coloured reaction mixtures (even in high dilution) and the presence of a UV maximum in the region 490 – 520 nm are characteristic indications of this reaction. As the base we used a twofold excess of the secondary amine or an alkali metal hydride or carbonate. Best results were achieved with amines and carbonates. Whereas the isolation of lower dialkyl enamines *IIa*, *IIb*, *IIh*, *IIj*, *IIl* was relatively simple, it was difficult to obtain pure higher alkyl derivatives owing to their low solubility, intense colour and low thermal stability. The lower homologues *IIa*, *IIb*, *IIh*, *IIj* and *IIl* were isolated by precipitation from benzene–diethyl ether or benzene–tetrahydrofuran, the higher homologues *IIc*–*IIg*, *IIk* and *IIm* were purified by column chromatography on silica gel.

Kinetic measurements of the reaction of 5-nitro-2-furylvinyl bromide with secondary amines[5] show that the reaction proceeds by an addition-elimination mechanism. The isolated product *II* has *E* configuration, irrespective of the original configuration of *I*. The strong UV maximum in the region 490 – 520 nm indicates the presence of a highly conjugated system in the enamines *II*. Its considerable bathochromic shift (140 – 170 nm; for the parent compound[1] *I* λ_{max} 344 nm) proves that compounds *II* exist in planar conjugated form which can isomerise into the more advantageous *E* form. Planarity of this system was proved also by X-ray studies of selected enamines[6].

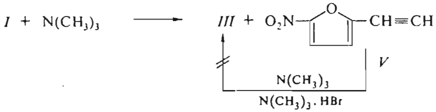
Quaternary salts, arising from 5-nitro-2-furylvinyl bromide and the tertiary amines *III*, play a specific role in the chemistry of 5-nitro-2-furylethylenes because they represent highly reactive 5-nitro-2-furylvinylation agents. The strongly electron-accepting ammonium group in position 2 of the ethylenic system (–I effect) enhances the electrophilicity of the terminal carbon atom of the vinyl group in comparison with the vinyl halide.

The quaternisation of trimethylamine with (*Z*) or (*E*)-5-nitro-2-furylvinyl bromide (*Ia* or *Ib*) in ether, chlorobenzene, nitrobenzene and other solvents, is sufficiently fast already at room temperature (Scheme 2). The obtained vinylammonium salts retain configuration of the starting vinyl halide *I*. As proved by high sensitivity to the reaction medium, the quaternisation proceeds *via* a highly polar transition state *A*, *B* (ref.[5]). Thus, *e.g.*, on transition from chlorobenzene to nitrobenzene, the reaction rate increases about ten times[5]. On the basis of kinetic data (second order reactions) we assume that the reaction proceeds by an addition-elimination mechanism[5] and that the arising carbanion is stabilised by rotation for 60° and subsequent elimination.



SCHEME 2

This fact supports the conclusions of the theory of nucleophilic vinylic substitution *via* carbanions[7,8] according to which the activated vinyl halides afford products with retained configuration (*A*, *B* in Scheme 2). As shown in Scheme 2 (formula *A*), the rotation for 60° prior the elimination of bromine is more advantageous than the rotation of bromine atom (*A*) or trimethylammonium group (*B*) over the 5-nitro-2-furan nucleus (120°). Vinylammonium salts of Z-configuration have not been hitherto mentioned in the literature[9,10]. Substitution reactions of (*Z*)-vinyl halides were investigated; it was found, however, that on treatment with bases they undergo elimination and afford acetylene derivatives. In our case, identification of 5-nitro-2-furylacetylene (*V*) as the reaction product (Scheme 3) does not prove unequivocally that the reaction proceeds *via* an elimination-addition mechanism.



SCHEME 3

TABLE I

Physical Constants of Compounds *II*, *III* and *IV*

Compound	Formula (mol. w.)	M.p. °C	Yield, % time, h	Calculated/Found % C	% H	% N	λ_{max} (log ε)	ν_s (NO$_2$) ν_{as} (NO$_2$)	ν(C=CH)
IIa	$C_8H_{10}N_2O_3$ (182·2)	63—65	74^a, 85^b 5	52·73 52·44	5·53 5·45	15·37 15·49	276 (4·15) 504 (4·31)	1 358 1 512	1 645
IIb	$C_{12}H_{18}N_2O_3$ (238·3)	45—47	82^a, 85^b 5	60·47 60·23	7·61 7·55	11·75 11·68	280 (3·95) 514 (4·16)	1 359 1 509	1 634
IIc	$C_{12}H_{18}N_2O_3$ (238·3)	53—57	75^a, 90^b 5	60·47 60·35	7·61 7·50	11·75 11·65	280 (3·97) 516 (4·09)	1 398 1 510	1 634
IId	$C_{14}H_{22}N_2O_3$ (266·3)	^{c}	53^a 24	63·14 62·95	8·33 8·25	10·51 10·40	280 (4·11) 520 (4·32)	1 356 1·356	1 632 1 631
IIe	$C_{16}H_{26}N_2O_3$ (294·4)	^{c}	48^a, 51^b 24	65·27 65·11	8·90 8·77	9·51 9·39	280 (3·98) 516 (4·14)	1 354 1 510	1 631
IIf	$C_{16}H_{26}N_2O_3$ (294·4)	^{c}	29^a, 48^b 24	65·27 65·08	8·90 8·80	9·51 9·39	280 (3·98) 520 (4·07)	1 354 1 510	1 631
IIg	$C_{22}H_{38}N_2O_3$ (378·5)	^{c}	34^a 24	69·80 69·50	10·11 10·01	7·40 7·35	282 (3·90) 523 (4·00)	1 356 1 510	1 631
IIh	$C_{12}H_{14}N_2O_3$ (234·2)	51—53	57^a 24	61·53 61·50	6·02 5·95	11·95 12·03	280 (4·19) 526 (4·28)	1 354 1 509	1 633
IIj	$C_{12}H_{16}N_2O_3$ (236·2)	49—50	87^a 24	61·02 60·91	6·83 6·75	11·85 11·72	280 (3·94) 514 (4·17)	1 353 1 511	1 632

IIk	$C_{18}H_{26}N_2O_3$	50—52	55^a	67·89	8·23	8·79	280 (3·96)	1 354	1 633
	(318·4)		24	67·71	8·17	8·66	522 (4·07)	1 510	
IIl	$C_{13}H_{18}N_2O_3$	53—55	64^a	62·37	7·24	11·19	276 (4·13)	1 355	1 632
	(250·3)		24	62·15	7·18	11·09	504 (4·20)	1 510	
IIm	$C_{19}H_{16}N_2O_3$	67—69	28^a	71·24	5·04	8·74	250 (4·23)	1 351	1 628
	320·3		40	71·11	5·12	8·73	492 (3·92)	1 504	
IIIa	$C_9H_{13}BrN_2O_3$	193—198	87	39·00	4·72	10·11	225 (4·11)	1 358	1 645
	(277·1)		24	38·88	4·66	10·15	257 (3·65)	1 532	
							337 (4·10)		
IIIb	$C_9H_{13}BrN_2O_3$	189—192	90	39·00	4·72	10·11	225 (4·09)	1 356	1 649
	(277·1)		1	39·11	4·80	10·01	258 (3·70)	1 535	
							340 (4·15)		
IVa	$C_9H_{13}IN_2O_3$	169—171	90	33·64	4·04	8·64	255 (3·80)	1 355	1 642
	(324·1)		1	33·45	3·97	8·52	340 (4·15)	1 529	
IVb	$C_9H_{13}IN_2O_3$	180—185	90	33·64	4·04	8·64	257 (3·85)	1 355	1 643
	(324·1)		1	33·74	4·14	8·82	342 (4·10)	1 530	

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[a] Prepared by procedure A; [b] prepared by procedure B; [c] violet oil.

According to the existing experience, acetylenes generally do not react with tertiary amines. The only preparation of a quaternary vinylammonium salt from acetylene is reported by Cavallito[11]. In order to check the possibility that the reaction proceeds via an elimination-addition mechanism (Scheme 3) we treated 5-nitro-2-furylacetylene (*V*) with a tertiary amine under conditions of the quaternisation. The negative result proved that, under the experimental conditions used, the transformation of *I* to *III* cannot proceed by an elimination-addition mechanism.

Thanks to high solubility of vinylammonium salts *IIIa*, *IIIb* in water and to the relatively high stability of these solutions it was possible to use them for the synthesis of other hardly accessible 5-nitro-2-furylethylene derivatives in very good yields. The use of quaternary ammonium salts is advantageous, since the products are obtained in the state of analytical purity. Their reaction with iodide ion is instantaneous and the iodides *IV* precipitate from the mixture. Aqueous solution of *III* reacts with secondary amines to give enamines identical with those obtained directly from 5--nitro-2-furylvinyl bromide. The yields are practically identical but the reaction starting from *III* affords the pure products *II* whereas the reaction starting from *I* requires an unpleasant separation of *II* from *I* which is a vesicant.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. The IR spectra were taken in chloroform on a UR-20 (Zeiss, Jena) spectrophotometer, UV spectra in methanol on a UV VIS (Zeiss, Jena) spectrophotometer. The ^{1}H-NMR spectra were measured on an 80 MHz Tesla BS 487C instrument in deuteriochloroform or trifluoroacetic acid at 25° C with tetramethylsilane as internal standard. 5-Nitro-2-furylvinyl bromide, (*Z*), m.p. 39—40°C, or a mixture of (*Z*) and (*E*) isomers, was prepared according to ref.[1], (*E*)—*I* (m.p. 62—64°C) was synthesized by bromination of sodium 3-(5-nitro-2-furyl)acrylate or by isomerisation of (*Z*) — *I* with aluminium chloride.

Synthesis of the Enamines *II*

A) A solution of the corresponding secondary amine (0·01 mol) in benzene (10 ml) was added dropwise to a solution of 5-nitro-2-furylvinyl bromide (1·09 g; 0·005 mol) in benzene (10 ml) and the mixture was stirred for 5—40 h at room temperature (Table I). Isolation procedure: *IIa*, *IIb*, *IIh*, *IIj* and *IIl*: after filtration of the hydrobromide the filtrate was mixed with equal amount of ether and the violet product was collected on filter; *IIc*—*IIg*, *IIk* and *IIm*: isolated by chromatography on a column of silica gel (150—250 mesh, eluant benzene, chloroform, ether). For physical constants of the products see Table I.

B) A solution of 5-nitro-2-furylvinyl bromide (2·18 g; 0·01 mol) in tetrahydrofuran (25 ml) was added to a mixture of the amine (0·01 mol) and sodium hydride (0·25 g) in tetrahydrofuran (25 ml). After stirring for 4—5 h at room temperature, the final products were purified chromatographically as described in the procedure *A*. For yields see Table I.

5-Nitro-2-furylvinyltrimethylammonium Bromide (*IIIa* or *IIIb*)

IIIa: Dry trimethylamine (0·06—0·08 mol) was introduced at 5—10°C into a solution of (*Z*)-5-nitro-2-furylvinyl bromide (*Ia*; 11 g; 0·05 mol) in benzene (75 ml) and the mixture was set aside at room temperature overnight. The separated crystals of 5-nitro-2-furylvinylmethylammonium bromide were collected and washed with ether; yield 12 g (87%) of the yellow product, m.p. 193—198°C (dec.) (methanol-ether). For physical constants see Tables I and II.

IIIb: A solution of trimethylamine (0·9 g) in benzene (20 ml) was added dropwise at −5°C to a stirred solution of (*E*)-5-nitro-2-furylvinyl bromide (*Ib*; 2·18 g; 0·01 mol) in benzene (30 ml). The mixture was allowed to stand at −5°C for 30 min and at room temperature for 1 h. The yellow-brown product was filtered, washed with ether and crystallized from methanol–ether; m.p. 189—192°C, yield 1·45 g (90%). For physical constants see Tables I and II.

5-Nitro-2-furylvinyltrimethylammonium Iodide (*IVa* and *IVb*)

A solution of potassium iodide (0·012 mol) in methanol (25 ml) and water (5 ml) was added dropwise to a solution of *IIIa* or *IIIb* (2·77 g; 0·01 mol) in methanol (50 ml) at room temperature. After 1 h the precipitated orange-yellow product was filtered, washed with ether and crystallized from a methanol–ether mixture, affording 2·85 g (90%) of *IVa* or *IVb*. For physical constants see Table I.

TABLE II

^{1}H-NMR Data (σ, ppm; J, Hz) for Compounds *II* and *III*

Compound[a]	H_A	H_B	J_{AB}	H_3	H_4	J_{34}
IIa	7·28	4·98	13·2	6·02	7·36	4·0
IIb	7·30	5·03	13·3	5·96	7·38	4·0
IIc	7·30	5·05	13·4	5·97	7·36	4·0
IId	7·28	5·02	13·4	5·97	7·37	4·0
IIe	7·27	5·00	13·4	5·93	7·38	4·1
IIf	7·26	5·00	13·1	5·94	7·37	4·1
IIg	7·31	5·08	13·2	5·96	7·34	3·9
IIh	7·30	5·08	13·2	5·96	7·35	4·0
IIj	7·30	4·97	13·4	5·89	7·29	4·0
IIk	7·33	5·00	13·4	5·97	7·33	4·0
IIl	7·33	5·07	13·5	6·07	7·39	4·0
IIm	7·30	5·00	13·2	6·00	7·35	4·0
IIIa	6·10	6·29	10·5	6·69	7·13	4·0
IIIb	6·82		—	6·55	7·07	4·0

[a] *IIa*—*IIm* in deuteriochloroform, *IIIa*, *IIIb* in trifluoroacetic acid.

Preparation of *IIa—IIc*

The corresponding secondary amine (0·02—0·025 mol) was added to a solution of *III* (2·77 g; 0·01 mol) in water (50 ml). A red coloration of the solution indicated the course of the reaction. After 2 h the solution was extracted three times with benzene (50 ml each), the solvent evaporated or the product precipitated by addition of an equal amount of ether to the benzene solution. Yield 75%.

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