1,3-DIPOLAR CYCLOADDITIONS OF YLIDE OF 5-NITRO-2-FURFURYLPYRIDINIUM BROMIDE IN INDOLIZINE SYNTHESIS*

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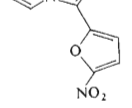
Substituted 3-(5-nitro-2-furyl)indolizines *III*—*X* were synthesized by 1,3-dipolar cycloaddition reaction of the ylide *II*, generated from 5-nitro-2-furfurylpyridinium bromide (*I*), with acrylonitrile, ethyl acrylate, diethyl maleate, benzalacetophenone, ethyl 3-(5-nitro-2-furyl)acrylate, (5-nitro-2-furfurylidene)acetophenone, β-nitrostyrene and dimethyl acetylenedicarboxylate. The structure of these products is discussed on the basis of their ^{1}H NMR and mass spectra.

Cycloadditions and cyclizations of various N-onium ylides represent general methods for synthesis of heterocycles with bridgehead nitrogen atoms, such as indolizines, quinolizines, imidazopyridines *etc.*[1]. Also the facile deprotonization of the methylene group in 5-nitro-2-furfurylpyridinium bromide[2] (*I*) can be, in addition to other reactions[3], used for this purpose.

This paper concerns the preparation of substituted 3-(5-nitro-2-furyl)indolizines *III*—*X* by 1,3-dipolar cycloaddition of pyridinium-5-nitro-2-furylmethylide (*II*) to compounds, containing an activated multiple bond.



III—*X*

The dipole *II*, generated from 5-nitro-2-furfurylpyridinium bromide (*I*) reacted with 1,3-dipolarophiles such as acrylonitrile, ethyl acrylate, diethyl maleate[4], benzal-

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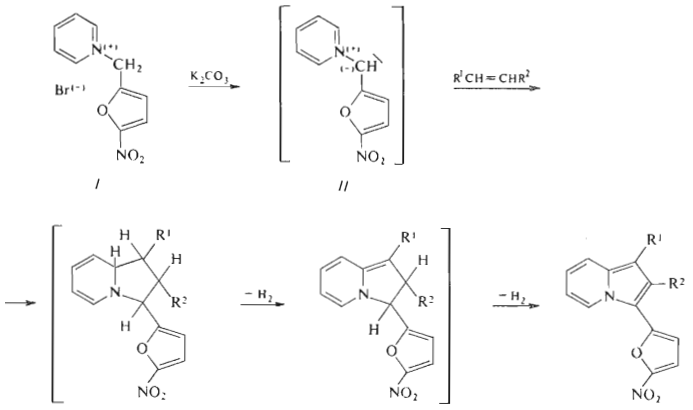
acetophenone[5], ethyl 3-(5-nitro-2-furyl)acrylate[6-8], (5-nitro-2-furfurylidene)acetophenone[9], β-nitrostyrene[10] or dimethyl acetylenedicarboxylate, with subsequent aromatization of the whole system (Scheme 1). The 5-nitrofuryl group of the N-onium salt plays a double role: on the one hand it increases the acidity of the methylene hydrogens, on the other hand it stabilizes – at least partially – the arising ylide *II*.



I *II* *III–IX*

SCHEME 1

The primary products of cycloaddition of the mentioned olefins to the ylide *II*, *i.e.* tetrahydroindolizines or dihydroindolizines, could not be isolated because they were oxidized spontaneously with air oxygen during the reaction and isolation. However, it is known that Fröhlich and coworkers[11] obtained by 1,3-dipolar cycloaddition of acrylonitrile to various N-ylides the corresponding tetrahydroindolizines which were partially dehydrogenated to indolizines. The formation of stable 2,3-dihydroindolizines is reported also by other authors[12]. Cyclization of the compound with an activated triple bond gave the expected[9,13-15] aromatic indolizine derivative *X*, although in some cases formation of a stable cycloadduct was proved[16].

The dipole *II*, arising *in situ* from the salt *I* by action of anhydrous potassium carbonate in chloroform–ethanol, chloroform–2-methoxyethanol or benzene–ethanol–water, reacted for 2–4 days at room temperature with the above-mentioned dipolarophiles. The extraordinary sensitivity of 5-nitro-2-furan derivatives towards alkaline reagents, as well as the low stability of the generated ylide, affected the yields

of these reactions (9·0–23·7%). Great amount of unidentified polymeric products was separated from the desired indolizines by chromatography on a column of silica gel (more than 100 fold excess) using benzene–acetone (40 : 1) or n-heptane–benzene (1 : 1) mixtures as eluants. The synthesized indolizines *III*–*X* are listed in Table I and their IR and UV spectral parameters in Table II. In order to suppress polymerization and enhance the yield of cycloaddition products, we conducted several reactions under nitrogen, however, with no substantial increase in the yields. No improvement of yields was observed also when working in dichloromethane with triethylamine as catalyst according to Fröhlich and Kröhnke[11], in boiling chloroform in the presence of triethylamine according to Abramovitch[14] or Curtze and coworkers[17], in dimethylformamide with sodium methoxide as catalyst. The solvent plays an important

TABLE I

Substituted 3-(5-nitro-2-furyl)indolizines *III*–*X*

Compound	R^1	R^2	Formula (mol.wt.)	M.p., °C (yield, %)	Calculated/Found		
					% C	% H	% N
III	CN	H	$C_{13}H_7N_3O_3$ (253·2)	262–263[a] (23·7)[f]	61·66 60·95	2·78 2·93	16·59 16·14
IV	$COOC_2H_5$	H	$C_{15}H_{12}N_2O_5$ (300·3)	213–214[b] (20·0)[f]	60·00 59·87	4·03 4·00	9·33 8·99
V	$COOC_2H_5$	$COOC_2H_5$	$C_{18}H_{16}N_2O_7$ (372·3)	144–145[c] (21·5)[f]	58·06 58·07	4·33 4·39	7·53 7·50
VI	C_6H_5CO	C_6H_5	$C_{25}H_{16}N_2O_4$ (408·4)	206–207[d] (12·2)[f]	74·07 73·86	3·95 3·96	6·86 6·72
VII	$COOC_2H_5$	5-NO_2-2-furyl	$C_{19}H_{13}N_3O_8$ (411·3)	207–208[c] (13·9)[g]	55·48 56·00	3·18 3·64	10·22 9·54
VIII	C_6H_5CO	5-NO_2-2-furyl	$C_{23}H_{13}N_3O_7$ (443·4)	137–138[d] (9·0)[f]	62·31 59·76	2·95 3·56	9·48 7·81
IX	NO_2	C_6H_5	$C_{18}H_{11}N_3O_5$ (349·3)	255·5–257[d] (17·2)[f]	61·89 60·87	3·18 3·15	12·03 11·63
X	$COOCH_3$	$COOCH_3$	$C_{16}H_{12}N_2O_7$ (344·3)	156–158[e] (23·2)[h]	55·81 55·54	3·51 3·67	8·14 7·53

[a] Crystallized from chloroform–ligroin; [b] acetone; [c] ethanol; [d] methanol; [e] ether–benzene–ligroin; [f] reaction in the system chloroform–ethanol; [g] chloroform–2-methoxyethanol; [h] benzene–ethanol–water.

role: thus, for example, 1-cyano-3-(5-nitro-2-furyl)indolizine (*III*) is formed in chloroform–ethanol in 24% yield whereas in benzene–water–ethanol only in 8% yield.

Analytical data, as well as IR spectra and, particularly, ^{1}H NMR and mass spectra, confirm the suggested structure of the synthesized derivatives. The interpretation of ^{1}H NMR spectra of compounds *III*–*X* (Table III) is based on previous studies[9,11,12,14,18]. Spectrum of the compound *X* ($R^1 = R^2 = COOCH_3$) exhibited signals at δ 8·78, 7·01, 7·30 and 8·30, ascribed to the four protons of the six-membered ring, the H_5 proton signal being shifted downfield because of the neighbouring nitrogen atom. The upfield shift of the H_8 signal relative to the H_6 and H_7 signals is due to anisotropy of the methoxycarbonyl group in the position 1. The H_6 and H_7 signals were assigned by decoupling experiments. The presence of the 5-nitro-2-furan grouping in the molecule manifested itself by two doublets at δ 6·80 and 7·44 ($J_{A,B}$ = = 3·9 Hz), the CH_3 signals at δ 3·99 and 3·91. Spectra of the other derivatives have similar features. The substituents R^1 and R^2 have the largest effect on the chemical

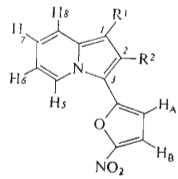
TABLE II
Infrared (cm^{-1}) and ultraviolet spectra of substituted 3-(5-nitro-2-furyl)indolizines *III*–*X*

Compound	ν(C=O)	$\nu_{as}(NO_2)$ $\nu_s(NO_2)$	δ_{br} [a]	Other bands	λ_{max}, nm (log ε)
III	—	1 550 1 350	1 033	2 217ν(C≡N)	435 (4·22)
IV	1 703	1 535 1 350	1 039	1 435$\delta_{as}(CH_3)$ 1 378$\delta_s(CH_3)$	446 (4·13)
V	1 739 1 706	1 540 1 350	1 033	1 448$\delta_{as}(CH_3)$ 1 379$\delta_s(CH_3)$	426 (4·19)
VI	1 635	1 542 1 353	1 025	—	444 (3·85)
VII	1 718	1 541 1 354	1 031	1 448$\delta_{as}(CH_3)$ 1 380$\delta_s(CH_3)$	455 (4·30)
VIII	1 665	1 540 1 352	1 030	—	472 (3·93)
IX	—	1 555 1 340	1 032	—	407 (4·26)
X	1 740 1 702	1 538 1 356	1 034	1 450$\delta_{as}(CH_3)$ 1 380$\delta_s(CH_3)$	426 (4·08)

[a] Ring breathing vibrations.

TABLE III

^{1}H NMR data (δ, ppm; J, Hz) for substituted 3-(5-nitro-2-furyl)indolizines *III*—*X*



Compound	H_A ($J_{A,B}$)	H_B	H_5 ($J_{5,6}$; $J_{5,7}$)	H_6 ($J_{5,8}$)	H_7 ($J_{6,7}$)	H_8 ($J_{7,8}$; $J_{6,8}$)	Other signals
III[a]	7·00 (4·1)	7·53	8·81 (7·1; 1·2)	7·07 (1·1)	7·30 (7·1)	7·70 (8·7; 1·5)	7·62 (H_2)
IV[a]	7·31 (4·2)	7·76	8·80 (6·8; 1·0)	7·17 (1·0)	7·40 (6·8)	8·23 (8·8; 1·5)	4·30 (CH_2); 1·31 (CH_3); 7·83 (H_2)
V[b]	6·80 (3·9)	7·44	8·78 (6·9; 1·1)	7·01 (1·1)	7·30 (6·9)	8·31 (9·0; 1·6)	4·50 (CH_2); 1·39 (CH_3); 4·41 (CH_2); 1·39 (CH_3)
VI[b]	5·81 (3·9)	7·22	9·03 (6·8; 1·1)	[c] (1·1)	[c]	8·10 (8·7; 1·4)	(7·00—7·62)[c]
VII[a]	7·03 7·23	7·70 7·79	8·62 (6·9; 1·1)	7·10 (1·1)	7·38 (7·0)	8·09 (9·0; 1·6)	4·32 (CH_2); 1·17 (CH_3)
VIII[b]	6·31 6·56	7·23 7·27	8·88 (6·9; 1·1)	[c]	[c]	8·34 (9·0; 1·5)	(7·01—8·12)[c]
IX[b]	5·74 (3·9)	7·20	9·07 (6·9; 1·1)	[c]	[c]	8·64 (9·0; 1·6)	(7·10—7·75)[c]
X[b]	6·80 (3·9)	7·44	8·78 (6·9; 1·1)	7·01 (1·1)	7·30 (6·9)	8·30 (9·0; 1·6)	3·99 (CH_3); 3·91 (CH_3)

[a] In hexadeuteriodimethyl sulfoxide; [b] in deuteriochloroform; [c] multiplet of aromatic protons.

shift of H_8 and H_A and to a smaller extent also on the H_5 and H_B shifts. In compound *IX* ($R^1 = NO_2$, $R^2 = C_6H_5$) the H_8 signal was shifted downfield in comparison with the compound *X* as the result of a larger anisotropic effect of the nitro group relative to the methoxycarbonyl group. The presence of phenyl in the position 2 of indolizine (compounds *VI* and *IX*) caused a downfield shift of the furan H_A proton due to the shielding effect of the benzene ring currents. On the basis of this fact, together with the literature data on stereochemistry of furylethylene derivatives[19,20], we can assume the *s-cis* relation of the furan ring and the $C_{(2)}=C_{(3)}$ bond of indolizine.

The mass spectroscopic study of fragmentation of indolizine and some of its derivatives has been described elsewhere[21-23]. We have measured mass spectra of compounds *III*–*VII* and *IX*–*X* (Table IV) and limited their interpretation only to structural proof. The spectra exhibit abundant molecular ion peaks which for *IV*–*V*, *VII*, *IX* and *X* represent the base peaks. The main fragmentation pathways depend first of all on the kind of substituents.

EXPERIMENTAL

Melting points were determined on a Boetius hot stage and are uncorrected. IR spectra were taken on a double-beam UR-20 spectrophotometer (Zeiss, Jena) in KBr pellets (1 mg of compound

TABLE IV
Mass spectra[a] of compounds *III*–*VII*, *IX* and *X*

Compound	*m/z*, %[a]
III	254 (12), 253, $M^{+\cdot}$ (58), 207 (28), 180 (17), 179 (100), 178 (16), 152 (9), 78 (14), 76 (9), 51 (11)
IV	301 (18), 300, $M^{+\cdot}$ (100), 268 (18), 255 (24), 254 (46), 226 (75), 198 (51), 153 (18), 152 (19), 78 (14)
V	373 (23), 372, $M^{+\cdot}$ (100), 340 (23), 327 (23), 326 (22), 298 (41), 252 (61), 224 (20), 152 (26), 78 (23)
VI	409 (19), 408, $M^{+\cdot}$ (67), 376 (25), 362 (30), 334 (15), 257 (13), 228 (28), 166·5 (21), 105 (100), 77 (38)
VII	412 (23), 411, $M^{+\cdot}$(100), 379 (14), 338 (19), 337 (80), 309 (27), 234 (21), 206 (16), 178 (17), 78 (16)
IX	350 (23), 349, $M^{+\cdot}$ (100), 287 (18), 286 (62), 275 (17), 256 (25), 229 (21), 228 (72), 227 (24), 78 (34)
X	345 (21), 344, $M^{+\cdot}$ (100), 313 (27), 298 (30), 271 (15), 270 (94), 266 (26), 153 (20), 152 (17), 78 (19)

[a] For each compound 10 most abundant peaks are given.

in 300 mg of KBr), electronic absorption spectra were recorded in methanol at room temperature on a UV VIS spectrophotometer (Zeiss, Jena). ^{1}H NMR spectra were measured on a Tesla BS 487 80 MHz instrument in deuteriochloroform and hexadeuteriodimethyl sulfoxide at 25 to 60°C with tetramethylsilane and hexamethyldisiloxane, respectively, as internal standard. Because of their low solubility, derivatives *III* and *IV* were measured on a Jeol FX-100 instrument at 99·6 MHz. Mass spectra were taken on an MS 902 spectrometer (AEI Manchester; direct inlet, ionization energy 70 eV, electron current 100 μA, source temperature 150°C).

5-Nitro-2-furfurylpyridinium bromide[2] (*I*) was prepared from furfuryl alcohol *via* 5-nitro-2-furfuryl nitrate and 5-nitro-2-furfuryl bromide. Diethyl maleate was synthesized by azeotropic esterification of maleic acid with ethanol in the presence of sulfuric acid and benzene[4]. Benzalacetophenone was obtained by condensation of benzaldehyde with acetophenone in an alkaline medium[5]. Ethyl 3-(5-nitro-2-furyl)acrylate was prepared by azeotropic esterification[8] of the corresponding acid[7] which in turn was obtained by nitration of 3-(2-furyl)acrylic acid, synthesized by Perkin reaction from fural and acetic anhydride in the presence of potassium acetate[6]. (5-Nitro-2-furfurylidene)acetophenone was prepared by condensation of 5-nitro-2-furaldehyde with acetophenone in glacial acetic acid in the presence of concentrated sulfuric acid[9]. β-Nitrostyrene[10] was obtained by condensation of benzaldehyde with nitromethane in an alkaline medium. The three remaining dipolarophiles, used in this work, were commercial products.

Substituted 3-(5-Nitro-2-furyl)indolizines *III*—*IX*

Potassium carbonate (4 g; 0·029 mol) was added to a stirred and cooled (ice) suspension of 5-nitro-2-furfurylpyridinium bromide (1·4 g; 0·005 mol) and dipolarophile (0·005 mol) in a mixture of chloroform (50 ml) and ethanol (5 ml) (in the preparation of *VII*, 50 ml of chloroform and and 6 ml of 2-methoxyethanol were used). After stirring for 3 days at room temperature the inorganic material was removed by filtration, the filtrate taken down and the residue separated on a silica gel column, using benzene–acetone (40 : 1) mixture as eluant (in the case of *IX*, benzene–n-heptane (1 : 1) was employed). Further work-up procedure afforded compounds *III*—*IX* as red or orange crystalline compounds which were crystallized from a suitable solvent (Table I).

1,2-Dimethoxycarbonyl-3-(5-nitro-2-furyl)indolizine (*X*)

Potassium carbonate (0·5 g; 0·0036 mol) was added to a stirred and cooled solution of 5-nitro-2-furfurylpyridinium bromide (1·02 g; 0·0036 mol) and dimethyl acetylenedicarboxylate (0·36 g; 0·0025 mol) in a mixture of benzene (30 ml), water (10 ml) and ethanol (10 ml). After stirring at room temperature for 2 days, water (20 ml) was added and the mixture extracted 3—5times with benzene (30 ml). The extract was dried over anhydrous sodium sulfate and taken down under diminished pressure. The above-mentioned work-up procedure afforded 0·2 g (23·7%) of a red compound, m.p. 156—158°C (ether–benzene–ligroin).

REFERENCES

1. Katritzky A. R., Boulton A. J. (ed.): *Advances in Heterocyclic Chemistry*, Vol. 23. Academic Press, New York 1978.
2. Štetinová J., Dandárová M., Knoppová V., Kováč J.: This Journal *43*, 2041 (1978).
3. Oleinik A. F., Novitskii K. Iu., Voziakova T. I., Modnikova G. A., Padeiskaia E. N., Polukhina L. N., Guskova T. A., Berliand E. A., Pershin G. N., Kováč J., Štetinová J.: U.S.S.R. 782 344 (1980).
4. Becker H.: *Organikum*, p. 500. Deutscher Verlag der Wissenschaften, Berlin 1976.

5. Kohler E. P., Chadwell H. M. in the book: *Organic Syntheses* (A. H. Blatt, Ed.), Collective Volume I, p. 78. Wiley, New York 1948.
6. Scipioni A., Borsetto V.: Ann. Chim. (Rome) *42*, 185 (1952).
7. Venter K. K., Giller S. A., Cirule V. W.: Izv. Akad. Nauk Latv. SSR, Ser. Khim. *1962*, 131.
8. Kováč J., Štetinová J., Surá J., Špaček F., Brežný R.: This Journal *42*, 1871 (1977).
9. Sasaki T., Yoshioka T.: Bull. Chem. Soc. Jap. *44*, 803 (1971).
10. Woirall D. E. in ref.5, p. 413.
11. Fröhlich J., Kröhnke F.: Chem. Ber. *104*, 1621 (1971).
12. Kakehi A., Ito S.: Bull. Chem. Soc. Jap. *47*, 938 (1974).
13. Sasaki T., Kanematsu K., Yukimoto Y., Ochiai S.: J. Org. Chem. *36*, 813 (1971).
14. Abramovitch R. A., Alexanian V.: J. Org. Chem. *41*, 2144 (1976).
15. Tanaka A., Toshinao U.: Chem. Pharm. Bull. *27*, 3078 (1979).
16. Basketter N. S., Plunkett A. O.: Chem. Commun. *1971*, 1578.
17. Curtze J., Dach R., Duchardt K. H., Kröhnke F.: Chem. Ber. *112*, 2197 (1979).
18. Paudler W. W., Kuder J. E.: J. Heterocycl. Chem. *3*, 33 (1966).
19. Fisichella S., Mineri G., Scarlata G., Sciotto D.: Tetrahedron *31*, 2445 (1975).
20. Považanec F., Kováč J., Dandárová M.: Chem. Zvesti *32*, 397 (1978).
21. Ricard M., Corval M., Dizabo P., Fakhri S. A. in the book: *Advances in Mass Spectrometry* (N. R., Daly, Ed.), Vol. 7B, p. 1211. Heyden, London 1978.
22. Jones G., Stanyer J.: Org. Mass Spectrom. *3*, 1489 (1970).
23. Terentiev P. B., Vinogradova S. M., Kost A. N.: Khim. Geterotsikl. Soedin. *1975*, 509.

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