Studies on Furan Derivatives. V (1). A Novel Ethoxycarbonylmethylation of the 5-Nitro-2-furan Ring in the Reaction of α-(2-Furyl)-β-(5-nitro-2-furyl)ethynyl with *N*-Ethoxycarbonylmethylpyridinium Ylide

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An unexpected product, 1-(4-ethoxycarbonylmethyl-5-nitro-2-furyl)-2-(2-furyl)-3-ethoxycarbonylindolizine was obtained by the reaction of α-(2-furyl)-β-(5-nitro-2-furyl)ethynyl with *N*-ethoxycarbonylmethylpyridinium ylide in *N,N*-dimethylformamide, together with 1-(5-nitro-2-furyl)-2-(2-furyl)-3-ethoxycarbonylindolizine.

J. Heterocyclic Chem., **16**, 1409 (1979).

In previous papers (1,2), we reported a simple preparation of α-aryl- or α-(2-furyl)-β-(5-nitro-2-furyl)ethynyls from α-aryl- or α-(2-furyl)-β-(5-nitro-2-furyl)vinylamines. These compounds are useful intermediates to prepare a number of new nitrofuran derivatives because their carbon-carbon triple bond is activated by the strong electron-withdrawing 5-nitro-2-furyl group.

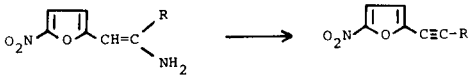

Chart 1

In the present work, the reaction of α-(2-furyl)-β-(5-nitro-2-furyl)ethynyl (I) with *N*-ethoxycarbonylmethylpyridinium ylide was investigated. It is well known that the *N*-pyridinium ylides react as 1,3-dipoles with acetylenic dipolarophiles, leading to indolizine derivatives (3). However, the reaction of I with an excess of *N*-ethoxycarbonylmethylpyridinium ylide gave an unexpected product, 1-(4-ethoxycarbonylmethyl-5-nitro-2-furyl)-2-(2-furyl)-3-ethoxycarbonylindolizine (IV) in addition to 1-(5-nitro-2-furyl)-2-(2-furyl)-3-ethoxycarbonylindolizine (III).

In the past literature on the alkylation of aromatic rings using various ylide, Traynelis and McSweeney (4) reported the methylation of aromatic nitro compounds with dimethyloxosulfonium, trimethylammonium, and triphenylphosphonium methylides. Gassman, *et. al.* (5), reported the specific *ortho*-alkylation of aromatic amines which involves an intramolecular migration of azasulfonium ylides. However, alkylation of an aromatic ring with N-pyridinium ylides has not been reported.

Compound I was allowed to react with *N*-ethoxycarbomethylpyridinium bromide (II) in the presence of sodium hydride to give III, m.p. 204-205°, in 33% yield with recovery of I (30%). In order to improve the yield of III, the reaction of I with an excess of II and sodium hydride (2-10 molar equivalents) was carried out and it afforded an unexpected compound (IV), m.p. 140-141°, together with III. These experimental results are summarized in Table 1. The yield of IV increased with increasing amount of ylide, whereas that of III showed a peak at using 3 molar equivalents of the ylide.

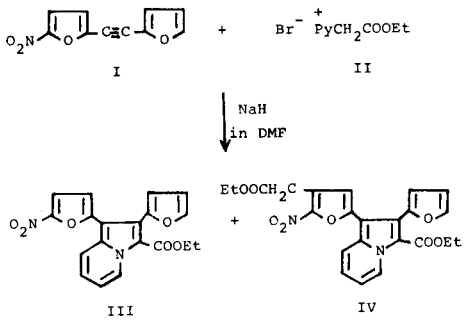

Chart 2

Table 1

Reaction of I with *N*-Ethoxycarbonylmethylpyridinium Ylide

Molar Ratio I/II/Sodium Hydride	Yield (%) of III	Yield (%) of IV	Recovery (%) of I
1/1/1	33	0	30
1/2/2	37	2	4
1/3/3	44	5	4
1/4/4	33	10	0
1/5/5	28	15	0
1/10/10	11	31	0

The structures of III and IV were confirmed from their various spectral data and elemental analyses, and from the orientation by adding amines to I (6). Comparison of the nmr spectra of III and IV shows that both chemical shifts are very much like one another with respect to the protons of their furan and indolizine rings. Concerning the protons of the nitrofuran rings, however, IV does not show any other than the 3-position proton being different than III. On the other hand, the nmr spectrum of IV shows signals which could be regarded as the methylene and ethyl protons, and it was suggested that IV has one ethoxy-

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carbonylmethyl group. Moreover, the ir spectrum of IV shows two absorption bands at 1675 and 1735 cm^{-1}, indicating a carbonyl group.

For the deduction of the alkylating stage, III was alternatively allowed to react with an excess of ylide, but only III was recovered (70%). Although it seems that the alkylation had occurred before the formation of the aromatic indolizine ring system, there is no method to ascertain this at present.

Concerning the reaction mechanism of this ethoxycarbonylmethylation, we now assume that the following contributing structure (**b**) is first attacked by the carbanion of the ylide as a nucleophile, followed by elimination of pyridine (**c** → **d**), elimination of a proton (**d** → **e**), or a 1,2-hydride shift (**d** → **f**). The subsequent aromatization occurs as shown in Chart 3. Recently, Golinski and Makosza (7) reported a similar reaction mechanism regarding the nucleophilic substitution of hydrogen in aromatic nitro compounds with nucleophiles.

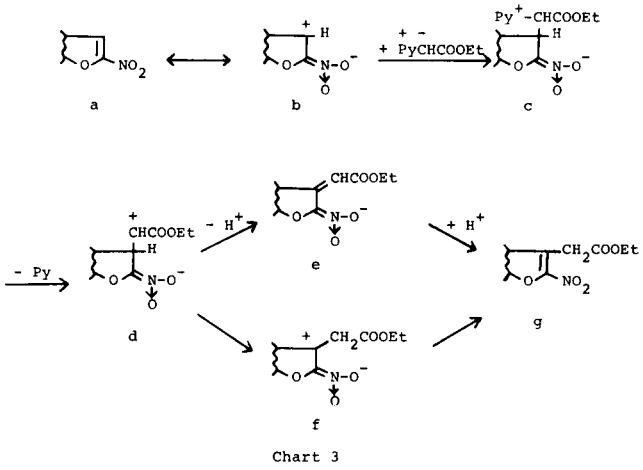

Chart 3

Since this reaction is the first example of the substitution of hydrogen on the nitrofuran ring and seems to be especially useful for nitroaromatics in which one-step synthesis of ethoxycarbonylmethylated nitroaromatics has hitherto been difficult, we plan to continue to investigate the many possible synthetic applications.

EXPERIMENTAL

All melting points are uncorrected. The following instruments were used for obtaining the physical data: nmr spectra (TMS as internal standard): JEOL JNM-60HL; ir spectra: JASCO IRI-1; mass spectra (direct solid inlet): Shimadzu LKB-9000. Column chromatography was carried out on silica gel (Wako gel C-200). Sodium hydride (50%) was purchased from Wako Chemical Industry, LTD.

Reactions of I with *N*-Ethoxycarbonylmethylpyridinium Ylide.

To a solution of I (0.5 g., 0.00246 mole) and II (0.00246-0.0246 mole) in 10 ml. of *N,N*-dimethylformamide, 50% sodium hydride (0.00246-0.0246 mole) was added under ice cooling. The stirring was continued for 4 hours at room temperature after the addition was completed. The reaction mixture was poured into ice water and extracted with benzene. The benzene extract was washed three times with water, dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was chromatographed on silica gel with benzene as eluant to give I, III, and IV. Compound III had ms: m/e 366 (M^+); ir (nujol): ν max cm^{-1}: 1675 (C=O); nmr (deuteriochloroform): δ 5.75 (1H, d, J = 4 Hz, nitrofuran H-3), 7.33 (1H, d, J = 4 Hz, nitrofuran H-4), 6.33-6.77 (2H, m, furan H-3 and H-4), 7.70 (1H, d, J = 2 Hz, furan H-5), 9.56 (1H, d-d, $J_{5,7}$ = 1 Hz, $J_{5,6}$ = 7 Hz, indolizine H-5), 6.90-7.57 (2H, m, indolizine H-6 and H-7), 8.38 (1H, d-d $J_{6,8}$ = 1.8 Hz, $J_{7,8}$ = 9 Hz, indolizine H-8), 1.15 (3H, t, J = 7 Hz, CH_2CH_3), 4.25 (2H, q, J = 7 Hz, CH_2CH_3).

Anal. Calcd. for $C_{19}H_{14}N_2O_6$: C, 62.29; H, 3.85; N, 7.65. Found: C, 62.28; H, 3.83; N, 7.62.

Compound IV had ms: m/e 452 (M^+); ir (nujol): ν max cm^{-1}: 1675, 1735 (C=O), nmr (deuteriochloroform): δ 5.85 (1H, s, nitrofuran H-3), 6.57-6.68 (2H, m, furan H-3 and H-4), 7.77 (1H, d, J = 1.8 Hz, furan H-5), 9.73 (1H, d-d, $J_{6,8}$ = 2 Hz, $J_{7,8}$ = 10 Hz, indolizine H-8), 3.94 (2H, s, CH_2), 1.17 (3H, t, J = 7 Hz, CH_2CH_3), 4.25 (4H, q, J = 7 Hz, CH_2CH_3 x 2).

Anal. Calcd. for $C_{23}H_{20}N_2O_6$: C, 61.06; H, 4.46; N, 6.19. Found: C, 61.36; H, 4.70; N, 5.95.

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REFERENCES AND NOTES

(1) Part IV: A. Tanaka, T. Usui and S. Yoshina, *J. Heterocyclic Chem.*, **16**, 493 (1979).

(2) A. Tanaka, T. Usui and S. Yoshina, *Heterocycles*, **3**, 1087 (1975).

(3) V. Boekelheide and K. Farrenholtz, *J. Am. Chem. Soc.*, **83**, 458 (1961); C. A. Hendrick, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, **20**, 2467 (1967).

(4) V. J. Traynelis and J. V. McSweeney, *J. Org. Chem.*, **31**, 243 (1966).

(5) P. G. Gassmann and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); P. G. Gassman, T. J. Bergen, D. P. Gilbert and W. C. Berkeley, *ibid*, **96**, 5495 (1974); P. G. Gassman and T. J. Bergen, *ibid.*, **96**, 5508 (1974); P. G. Gassman, G. D. Gruetzmacher and T. J. Bergen, *ibid.*, **96**, 5512 (1974).

(6) It is reasonable assumed that the initial attack by the carbanion of the ylide takes place at the same α-carbon atom of I as the addition of amines; A. Tanaka and T. Usui, "98th Annual Meeting of Pharmaceutical Society of Japan, Okayama", Abstract 3W 1-8, 1978, p. 264.

(7) J. Golinski and M. Makosza, *Tetrahedron Letters*, 3495 (1978).