Studies on Furan Derivatives IV. (1)
A Simple Preparation of α-Substituted β-(5-Nitro-2-furyl)ethynyls from α-Substituted β-(5-Nitro-2-furyl)vinylamines

Akira Tanaka and Toshinao Usui

Faculty of Pharmaceutical Sciences, Josai University, Sakado-shi, Saitama, Japan

Shigetaka Yoshina (the late)

Faculty of Pharmacy, Meijo University, Tenpaku-ku, Nagoya, Japan

Received September 1, 1978

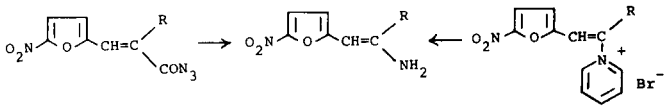
α-Substituted β-(5-nitro-2-furyl)ethynyls were conveniently prepared by the deamination of α-substituted β-(5-nitro-2-furyl)vinylamines. Also the application of this reaction toward α,β-bis(*p*-nitrophenyl)vinylamine was examined and afforded α,β-bis(*p*-nitrophenyl)ethynyl as the main product.

J. Heterocyclic Chem., **16**, 493 (1979).

A number of 5-nitro-2-furyl derivatives having marked antibacterial activities have been reported (2). These derivatives, however, do not include β-(5-nitro-2-furyl)-ethynyls, due to the difficulty of their systematic syntheses.

Recently, we reported that certain interesting primary vinylamines, namely, α-substituted β-(5-nitro-2-furyl)vinyl-amines, were easily obtained from α-substituted β-(5-nitro-2-furyl)acryloyl azides and *N*-[α-substituted β-(5-nitro-2-furyl)vinyl]pyridinium bromides as shown in Scheme I (3).

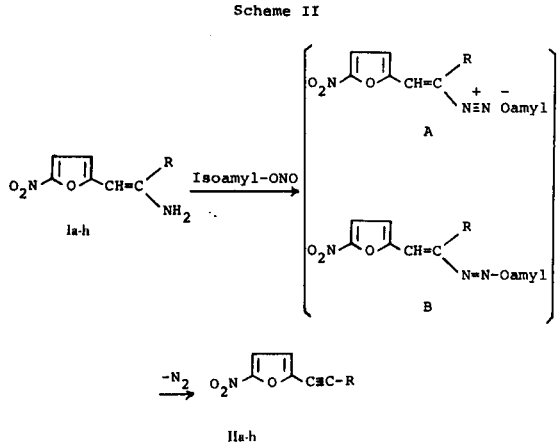
Scheme I



These compounds are very useful as intermediates for preparing various nitrofuran derivatives, especially 5-nitro-2-furyl heterocyclic compounds. However, only a few examples of β-(5-nitro-2-furyl)ethynyls have been synthesized, because general synthetic methods for obtaining them have not been developed. In the present work, a simple one-step synthesis of α-substituted β-(5-nitro-2-furyl)ethynyls from α-substituted β-(5-nitro-2-furyl)vinyl-amines was studied in order to investigate the chemical reactions of primary vinylamines and to prepare new nitrofuran derivatives.

Concerning the preparation of ethynyls from α,β-disubstituted vinylamines, the elimination of quaternized enamines has only been reported in the literature by Kröhnke, *et al.* (4), Hauser, *et al.* (5), and Hendrickson, *et al.* (6). Curtin, *et al.* (7), and Cariou (8) reported that α,β-disubstituted ethynyls were obtained by the deamination of α,α-disubstituted vinylamines. The conventional preparations of β-(5-nitro-2-furyl)ethynyls can be divided into two methods: (a) dehydrohalogenation of 5-nitro-2-furylhaloalkanes or -haloalkenes in base (9); and (b) the coupling of metal acetylides with 2-iodo-5-nitrofuran (10). However, each of these methods is undesirable, since the nitrofuran ring is usually unstable under basic conditions and since metal acetylides are dangerous to handle. Therefore, we attempted the deamination of α-substituted β-(5-nitro-2-furyl)vinylamines (Ia-h) with isoamyl nitrite. When an excess of isoamyl nitrite was added in small portions to a solution of Ia-h in dry dioxane at 80°, α-substituted β-δ-5-nitro-2-furyl)ethynyls (IIa-h) were formed. The end of the reaction could be recognized by a cessation of nitrogen gas evolution.

Scheme II

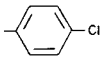
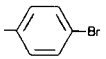
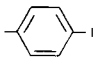
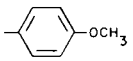
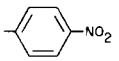
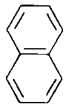


Compound IIa was identified as α-(2-furyl)-β-(5-nitro-2-furyl)ethynyl, which has been previously reported in the literature, by its mixed melting point and ir spectrum (11). The structures of IIb-h were confirmed by their spectral data and elemental analyses. The ir spectra of IIb-f,h showed an absorption band for the acetylenic stretching vibration at around 2200 cm^{-1}. However, IIg did not show this absorption band, forbidden by the nearly equivalent electrophilicity of both the 5-nitro-2-furyl and

0022-152X/79/030493-04$02.25

Table I

α-Substituted β-(5-Nitro-2-furyl)ethynyls

Compound No.	R	Appearance	M.p. (°C)	Yield (%)	Recrystallization	Formula	Analyses Calcd. (Found) C	H	N
IIa		Yellow needles	135-136.5	38	benzene	$C_{10}H_5NO_4$	59.12 (59.41)	2.48 (2.55)	6.90 (7.05)
IIb		Yellow prisms	131-132	40	petroleum benzine	$C_{12}H_7NO_3$	67.60 (67.35)	3.31 (3.24)	6.57 (6.46)
IIc		Yellow needles	154-156	86	benzene	$C_{12}H_6ClNO_3$	58.20 (58.12)	2.44 (2.56)	5.66 (5.30)
IId		Yellow needles	168-169	90	methanol	$C_{12}H_6BrNO_3$	49.34 (49.57)	2.07 (2.28)	4.80 (4.67)
IIe		Yellow plates	175-176	84	methanol	$C_{12}H_6INO_3$	42.50 (42.67)	1.78 (1.55)	4.13 (4.03)
IIf		Yellow prisms	138-139	25	petroleum benzine	$C_{13}H_9NO_4$	64.20 (64.18)	3.73 (3.59)	5.76 (6.01)
IIg		Yellow needles	170-172	58	methanol	$C_{12}H_6N_2O_5$	55.82 (55.65)	2.34 (2.27)	10.85 (11.02)
IIh		Yellow needles	117-118	50	petroleum benzine	$C_{16}H_9NO_3$	73.00 (72.78)	3.45 (3.62)	5.32 (5.62)

Nmr (a) δ (Acetone-d_6) of α-Substituted β-(5-Nitro-2-furyl)ethynyls

Compound No.	NF-3H (b)	NF-4H (b)	Aromatic-H	-CH_3
IIb	7.12 (1H, d, J = 4)		7.30-7.80 (6H, m)	---
IIc	7.27 (1H, d, J = 4)		7.50-8.00 (5H, m)	---
IId	7.27 (1H, d, J = 4)	7.74 (1H, d, J = 4)	7.80 (4H, s)	---
IIe	7.28 (1H, d, J = 4)	7.73 (1H, d, J = 4)	7.60 (2H, d, J = 8) 8.06 (2H, d, J = 8)	---
IIf	7.02 (1H, d, J = 4)	7.55 (1H, d, J = 4)	7.05 (2H, d, J = 9) 7.58 (2H, d, J = 9)	3.86 (3H, s)
IIg	7.37 (1H, d, J = 4)	7.77 (1H, d, J = 4)	8.18 (2H, d, J = 9) 8.53 (2H, d, J = 9)	---
IIh	7.27 (1H, d, J = 4)		7.50-8.50 (8H, m)	---

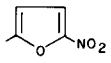
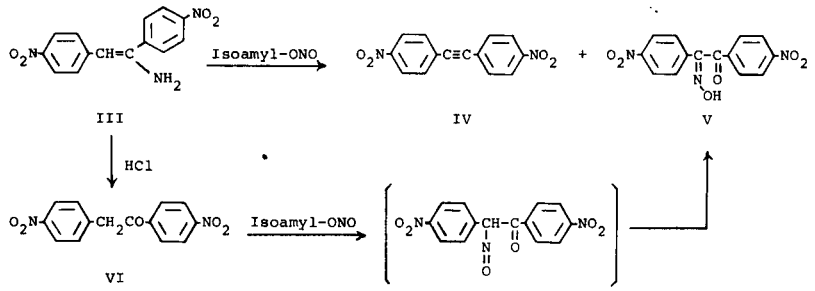
(a) s = singlet, d = doublet, m = multiplet. (b) NF = 

Table III

Spectral Data of α-Substituted β-(5-Nitro-2-furyl)ethynyls

Compound No.	Ir ν Max (nujol) Cm^{-1} for C≡C	Uv λ Max (ethanol) nm	Ms m/e (M^+)
IIb	2200	267, 355	213
IIc	2200	277, 353	247
IId	2200	278, 354	291
IIe	2210	280, 358	339
IIf	2200	275, 372	243
IIg	-----	220, 353	258
IIh	2200	300, 373	263

Scheme III



p-nitrophenyl groups. Uv spectral maxima of IIa-h shifted to shorter wavelength regions in comparison with those of the corresponding β-(5-nitro-2-furyl)vinyls (about 30 nm) (12). Compounds IIb-h also showed results consistent with their structures in their nmr and mass spectra as summarized in Tables II and III.

It is assumed that the mechanism of this reaction would be formulated in terms of a diazonium ion pair (A) or the related covalently bonded diazoate (B), followed by elimination of nitrogen gas to give IIa-h.

In addition, the reaction of α,β-bis(*p*-nitrophenyl)-vinylamine (III) (13) with isoamyl nitrite was carried out in order to investigate behavior of the benzene ring system in this reaction. Thus, α,β-bis(*p*-nitrophenyl)-ethynyl (IV) and α,β-bis(*p*-nitrophenyl)ethanedione α-oxime (V) were obtained in 46% and 14% yield,

respectively. The structures of IV and V were assigned on the basis of spectral data and elemental analyses.

The unexpected product (V) could be formed by nitrososation of the ketone (VI), produced from the reaction with a little water by diazotization, followed by the migration of a proton. The ketone (VI), which was easily obtained by the hydrolysis of III, reacted with isoamyl nitrite to quantitatively give V.

Thus, it was established that α,β-disubstituted ethynyls were easily obtained *via* the deamination of primary α,β-disubstituted vinylamines. By applying this method, β-(5-nitro-2-furyl)ethynyls, which were hitherto difficult to prepare, can now be easily obtained so long as the corresponding primary vinylamines can be prepared. The antibacterial and anticancer activity tests of IIa-i are in progress.

Acknowledgement.

The authors are greatly indebted to all the staff of the central analytical center of this university for elemental analyses and spectral measurements.

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 and PS-100; ir spectra: JASCO IRI-1; uv spectra: JASCO UVIDEC-1; mass spectra (direct solid inlet): Shimadzu LKB-9000. Column chromatography was carried out on silica gel (Wako gel C-200). Isoamyl nitrite was purchased from Wako Chemical Industries, LTD.

α-Substituted β-(5-Nitro-2-furyl)ethynyls (IIa-h).

A.

A solution of 2.3 g. (0.02 mole) of isoamyl nitrite in 10 ml. of dry dioxane was added in small portions to a stirred solution of Ia,b,f,g,h (0.004 mole) in 50 ml. of dry dioxane at 80°. The heating was continued for 2-3 hours after the addition was complete and the solvent was then removed *in vacuo*. The residue was chromatographed on silica gel with benzene as eluent and recrystallized from suitable solvents to give IIa,b,f,g,h.

B.

A solution of 2.3 g. (0.02 mole) of isoamyl nitrite in 10 ml. of dry dioxane was added in small portions to a stirred solution of Ic,d,e (0.004 mole) in 50 ml. of dry dioxane. The heating was continued for 2-3 hours after the addition was complete; then the solvent was removed *in vacuo*. The residue was recrystallized from suitable solvents to give IIc,d,e.

Reaction of α,β-*Bis*(*p*-nitrophenyl)vinylamine (III) wiht Isoamyl Nitrite.

A solution of 2 g. (0.0175 mole) of isoamyl nitrite was added in small portions to a stirred solution of 1 g. (0.0035 mole) of III in 50 ml. of dry dioxane. The mixture was heated at 80° for 2 hours after the addition was complete; then the solvent was removed *in vacuo*. The residue was washed with benzene and filtered to give 0.25 g. of yellow crystals (IV). The filtrate was chromatographed on silica gel with benzene as eluent to give 0.2 g. of yellow prisms (IV) and 0.18 g. of yellow needles (V).

Compound IV was recrystallized from ethanol to give 0.4 g. (43%) of pale yellow needles, m.p. 221-221.5°. Compound V was recrystallized from benzene to give 0.15 g. (14%) of yellow needles, m.p. 215°. Compound IV had ir (nujol): ν max cm^{-1}: 1350, 1510 (NO_2); nmr (deuteriochloroform): δ 7.63 (4H, d, J = 9 Hz, *ortho* protons of the nitrophenyl ring), 8.27 (4H, d, J = 9 Hz, *meta* protons of the nitrophenyl ring); ms: m/e 268 (M^+).

Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3,01; N, 10.45. Found: C, 62.53; H, 3,15; N, 10.40.

Compound V had ir (nujol): ν max cm^{-1} 1600 (C=O); nmr (acetone-d_6): 7.30-8.60 (8H, m, nitrophenyl ring protons); ms: m/e 315 (M^+).

Anal. Calcd. for $C_{14}H_9N_3O_6$: C, 53.34; H, 2.88; N, 13.33. Found: C, 53.20; H, 2.80; N, 13.18.

α,β-Bis(*p*-nitrophenyl)ethanedione α-Oxime (V).

A mixture of 0.3 g. (0.001 mole) of VI, 0.6 g. (0.005 mole) of isoamyl nitrite and 20 ml. of dry dioxane was refluxed for 6 hours and the solvent was removed *in vacuo*. The crystals thus obtained were recrystallized from benzene to give 0.3 g. (91%) of yellow needles (V), m.p. 215°. This structure was identified with the compound obtained above by the mixed melting point and ir spectrum.

REFERENCES AND NOTES

(1) Part III of this series: A. Tanaka and T. Usui, *Chem. Pharm. Bull.*, **26**, 3576 (1978).

(2) M. C. Dodd and W. B. Stilman, *J. Pharmacol. Exp. Ther.*, **82**, 11 (1944); W. R. Shermann, *J. Med. Chem.*, **8**, 25 (1965); K. Miura and H. K. Reckendorf, *Prog. Med. Chem.*, **5**, 320 (1967); H. Saikachi and A. Tanaka, *J. Pharm. Soc. Japan*, **80**, 1586 (1960).

(3) A. Tanaka, T. Usui and S. Yoshina, *J. Heterocyclic Chem.*, 15, 555 (1978).

(4) R. F. Kröhnke and M. M. Delius, *Chem. Ber.*, **84**, 940 (1951).

(5) C. R. Hauser, H. M. Taylor and T. G. Ledford, *J. Am. Chem. Soc.*, **82**, 1786 (1960).

(6) J. B. Hendrickson and J. R. Sufrin, *Tetrahedron Letters*, 1513 (1973).

(7) D. Y. Curtin, J. A. Kampmeier and Brian R. O'Connor, *J. Am. Chem. Soc.*, **87**, 863 (1965).

(8) M. Cariou, *Bull. Soc. Chim. France*, 210 (1969).

(9) F. Kai and H. Ogawa, *Chem. Pharm. Bull.*, 11, 1025 (1963); I. Saikawa, S. Takano and T. Maeda, *J. Pharm. Soc. Japan*, **87**, 1514 (1967); S. Yoshina, I. Maeba and K. Asai, *ibid.*, **88**, 984 (1968); T. Sasaki and K. Shoji, *J. Syn. Org. Chem. Japan*, **26**, 264 (1968).

(10) L. I. Vereshchagin, R. I. Katkevich, S. Hillers, S. L. Venters, L. N. Alekseeva, L. Kruzmetras, A. Zile and N. P. Glazunova, *Khim.-Farm. Zh.*, **2**, 31 (1968); *Chem. Abstr.*, **70**, 47190x (1969); L. Vereshchagin, S. P. Korshunov, Ya A. Eidus, K. K. Venter and S. A. Giller, *Zh. Org. Khim.*, **3**, 184 (1967); *Chem. Abstr.*, **66**, 94565a (1967).

(11) S. Yoshina, A. Tanaka and T. Usui, *J. Pharm. Soc. Japan*, **97**, 1007 (1977); *Idem., ibid.*, **98**, 286 (1978).

(12) S. Yoshina and A. Tanaka, *ibid.*, **88**, 410 (1968).

(13) This compound was prepared from *N*-[α,β-bis(*p*-nitrophenyl)vinyl]pyridinium bromide; see H. Ahlbrecht and R. F. Kröhnke, *Ann. Chem.*, **701**, 126 (1967).