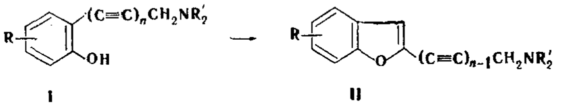
ALKYNYL DERIVATIVES OF BENZOFURAN

M. I. Bardamova, R. N. Myasnikova,
and I. L. Kotlyarevskii

UDC 547.728.1:543.422.25.4

A general method for the preparation of alkynyl derivatives of benzofuran, including α-ethynylbenzofuran, consists in the cyclization of o-mono- and dialkynylphenols under the conditions of the Mannich and Cadiot–Chodkiewicz reactions.

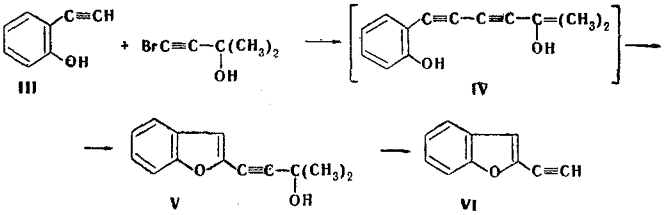
It has been shown [1] that the introduction of o-ethynylphenols into the Mannich and Cadiot–Chodkiewicz reactions is accompanied by intramolecular cyclization of the condensation products (I) to benzofuran derivatives (II):



A similar cyclization to benzofurans under such mild conditions has been observed for the first time and can be used as a general method for the synthesis of α-alkynylbenzofurans. Closure to a benzofuran ring under more severe conditions has been reported [2,3].

The aim of the present study was to ascertain the possibility of using the indicated cyclization as a general method for the synthesis of ethynylbenzofuran derivatives, including α-ethynylbenzofuran, which has a free acetylenic hydrogen.

α-Ethynylbenzofuran was synthesized via the following scheme:



The reaction of o-ethynylphenol with bromoethynyldimethylcarbinol [4] under the conditions of the Cadiot–Chodkiewicz reaction gives carbinol V in 86% yield. The course of the reaction was followed by means of thin-layer chromatography (TLC) on Al_2O_3 (elution by ether); the formation of intermediate IV could not be recorded under these conditions.

Carbinol V was subjected to decomposition via the reverse Favorskii reaction over 2 moles of potassium hydroxide by gentle heating in vacuo or by heating in ether; 2-ethynylbenzofuran (VI) was isolated in 30% yield as a liquid that darkened rapidly in light and air. The IR spectrum of VI did not contain the absorption band of an OH bond at 3600 cm^{-1} that is present in starting V; the spectrum does contain a band at 3330 cm^{-1}, corresponding to a ≡C–H band, and at 2200 cm^{-1}, corresponding to a –C≡C– group. The PMR spectrum also corresponds to structure VI and is presented in Fig. 1.

Institute of Chemical Kinetics and Combustion, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1457-1460, November, 1972. Original article submitted October 12, 1971.

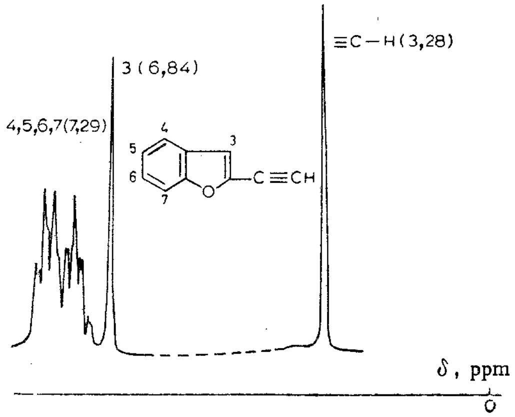
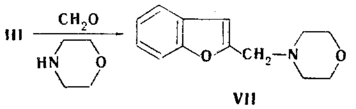


Fig. 1. PMR spectrum of 2-ethynylbenzofuran (VI).

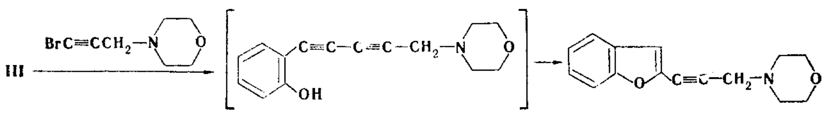
2-Morpholinomethylbenzofuran (VII) was obtained under the conditions of the Mannich reaction in 60% yield from o-ethynylphenol, paraformaldehyde, and morpholine in the presence of CuCl (40-60° for 3 h):



VII

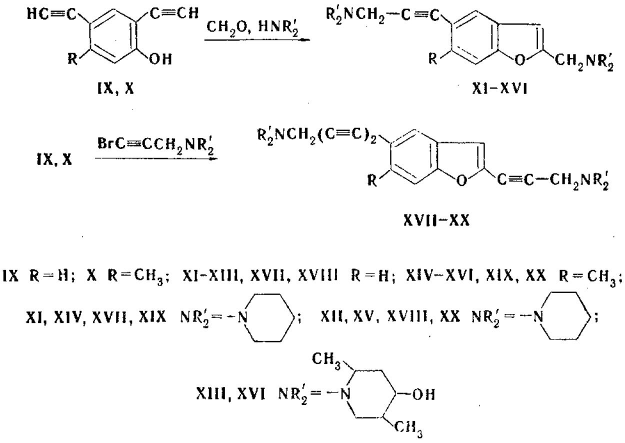
The physical constants of VII are in agreement with the literature values [5].

o-Ethynylphenol reacts with 1-bromomorpholinopropyne [6] when it is introduced into the Cadiot–Chodkiewicz condensation to give 2-morpholinopropynylbenzofuran (VIII) in 67% yield:



VIII

A similar cyclization occurs when the Mannich and Cadiot–Chodkiewicz reactions are carried out with diethynylphenols IX and X and gives mono- and triynamino derivatives of benzofuran:



IX R=H; X R=CH$_3$; XI-XIII, XVII, XVIII R=H; XIV-XVI, XIX, XX R=CH$_3$;

XI, XIV, XVII, XIX NR'$_2$=; XII, XV, XVIII, XX NR'$_2$=;

XIII, XVI NR'$_2$=

The IR spectra of bases VII-XX contain the absorption bands of a disubstituted acetylene bond at 2200-2300 cm^{-1}, of an ether oxygen at 1100-1300 cm^{-1}, and of a C–N bond at 1000-1110 cm^{-1}; the spectra do not contain the absorption band of an OH group. The PMR spectrum of a CCl$_4$ solution of XVIII contains a multiplet with a maximum at 1.48 ppm, which corresponds to the protons of the 3,4,5-CH$_2$ groups of the piperidine ring, a multiplet at 2.43 ppm, which corresponds to the protons of the 2- and 6-CH$_2$ groups of the piperidine ring, a singlet at 2.46 ppm, which corresponds to the CH$_3$ group in the 6 position of the benzofuran ring, and two singlets at 3.41 and 3.49 ppm, which correspond to the CH$_2$ groups of the substituents in the 2 and 5 positions of the benzofuran ring, respectively. The PMR spectra of the other amines are similar.

EXPERIMENTAL

The starting ethynylphenols were synthesized via the method in [7].

1-(2-Benzofuranyl)-3-methylbut-1-yn-3-ol (V). A 5-g (0.03 mole) sample of 1-bromo-3-methylbut-1-yn-3-ol was added dropwise under nitrogen to a cooled (–10°) mixture of 3.3 g (0.028 mole) of o-ethynylphenol (III), 0.1 g (0.014 mole) of NH$_2$OH · HCl, 6 ml of ethylamine, and 0.1 g of Cu$_2$Cl$_2$ in 100 ml of methanol. The course of the reaction was followed by TLC on activity II Al$_2$O$_3$. The reaction was completed at 5° 30 min from the start of the addition of the bromo compound, and the mixture was then stirred for

TABLE 1. Characteristics of the Compounds Obtained

Comp.	mp, °C	Empirical formula	N, %		Yield, %	Hydrochlorides			
			found	calc.		mp, °C	empirical formula	Cl, % found	Cl, % calc.
XI	89	$C_{20}H_{24}N_2O_3$	8,2	8,2	85,9	230—232	$C_{20}H_{26}N_2O_3Cl_2$	17,1	17,2
XII	43,5—44	$C_{22}H_{28}N_2O$	8,2	8,3	63	240—241	$C_{22}H_{30}N_2OCl_2$	17,3	17,3
XIII	191—192	$C_{26}H_{36}N_2O_3$	6,6	6,6	30	211—213	$C_{26}H_{37}N_2O_3Cl$	7,7	7,7
XIV	78,5—79	$C_{21}H_{26}N_2O_3$	8,2	7,9	75	144—145	$C_{21}H_{28}N_2O_3Cl_2$	16,4	16,6
XV	70,5—71	$C_{23}H_{30}N_2O$	7,9	8,0	65	254—254,5	$C_{23}H_{32}N_2OCl_2$	16,7	16,7
XVI	214—215	$C_{27}H_{38}N_2O_3$	6,5	6,4	33,4	260	$C_{27}H_{40}N_2O_3Cl_2$	13,7	13,8
XVII	139—140	$C_{24}H_{24}N_2O_3$	7,0	7,2	47	198—200	$C_{24}H_{26}N_2O_3Cl_2$	15,6	15,4
XVIII	91—92	$C_{26}H_{28}N_2O$	7,3	7,3	44	229	$C_{26}H_{30}N_2OCl_2$	15,8	15,8
XIX	141—141,5	$C_{25}H_{26}N_2O_3$	7,1	7,0	62	146—148	$C_{25}H_{28}N_2O_3Cl_2$	14,7	14,9
XX	113—113,5	$C_{27}H_{30}N_2O$	6,8	7,0	70	148—150	$C_{27}H_{32}N_2OCl_2$	14,8	15,0

another hour. The methanol was removed by distillation, the precipitated crystals were removed by filtration, and the residual oil was dissolved in ether and filtered through Al_2O_3. Removal of the ether gave 3.8 g (86%) of V with mp 52-53° (sublimed). Found: C 78.2; H 6.0%. $C_{13}H_{12}O_2$. Calculated: C 78.0; H 6.0%.

2-Ethynylbenzofuran (VI). A. A 0.4-g (0.034 mole) sample of V was heated with 0.28 g (0.005 mole) of powdered calcined potassium hydroxide in vacuo, and the reaction products were removed by distillation. Two sublimations gave 0.1 g of VI as a colorless liquid that darkened rapidly in light and air.

B. A 0.5-g (0.042 mole) sample of V was dissolved in 50 ml of absolute ether, and the solution was refluxed for 2 h over 0.28 g (0.005 mole) of KOH. The ether was decanted, and VI was isolated by means of preparative chromatography on Al_2O_3 with elution with benzene–petroleum ether (low-boiling) (1 : 1). The solvents were removed, and the residue was sublimed in vacuo to give 0.07 g of VI. Found: C 84.5; H 4.3%. $C_{10}H_6O$. Calculated: C 84.5; H 4.3%.

2-(N-Morpholinomethyl)benzofuran (VII). A mixture of 0.6 g (0.02 mole) of paraformaldehyde and 1.74 g (0.02 mole) of morpholine in 30 ml of anhydrous dioxane was heated to 40° for 1 h. It was then cooled, and 2.2 g (0.018 mole) of o-ethynylphenol (III) in 20 ml of dioxane and 0.05 g (0.0005 mole) of Cu_2Cl_2 were added. The reaction was carried out under nitrogen at 40-60°. The course of the reaction was followed by TLC on activity II Al_2O_3 with elution with ether–benzene (1 : 1). After 3 h, the reaction mixture was cooled, washed with water, and treated with ether to isolate the product through the hydrochloride. Chromatography on activity II Al_2O_3 and removal of the solvent gave 2 g (60.6%) of white crystals of VII with mp 51-52° and bp 154-156° (3 mm) (bp 152-154° (1 mm) [5]). The hydrochloride was obtained in quantitative yield by bubbling dry HCl through an ether solution of VII and had mp 226° (mp 223° [5]).

The amino alkynyl derivatives of benzofuran (XI-XVI), data on which are presented in Table 1, were similarly obtained.

2-(3-N-Morpholino-1-propynyl)benzofuran (VIII). A 6.4-g (0.03 mole) sample of 1-bromo-3-N-morpholino-1-propyne was added dropwise under nitrogen to a cooled (–10°) mixture of 3.2 g (0.027 mole) of o-ethynylphenol (III), 0.1 g (0.0014 mole) of $NH_2OH \cdot HCl$, 6 ml of ethylamine, and 0.1 g (0.0001 mole) of Cu_2Cl_2 in 100 ml of methanol. The temperature was raised to 20° for 1 h, and the reaction was carried out at this temperature for 2 h and then at 30° for 1 h. The mixture was washed with water and extracted with ether. The product was isolated as the hydrochloride and was chromatographed on activity II Al_2O_3 to give 3.8 g (67%) of VIII with mp 39-40°. Found: N 6.0%. $C_{15}H_{15}NO_2$. Calculated: N 5.8%. The hydrochloride had mp 212-213°. Found: Cl 12.7%. $C_{15}H_{15}NO_2 \cdot HCl$. Calculated: Cl 12.8%.

Amines XVII-XX, data on which are presented in Table 1, were similarly obtained.

LITERATURE CITED

1. I. L. Kotlyarevskii, R. N. Myasnikova, and M. I. Bardamova, Izv. Akad. Nauk SSSR, Ser. Khim., 202 (1971).
2. C. E. Castro, R. Halvin, V. K. Honwad, A. Malte, and S. Moje, J. Am. Chem. Soc., 91, 6464 (1969).
3. F. Toda and M. Nakagawa, Bull. Chem. Soc. Japan, 32, 514 (1959).
4. F. Strauss, L. Kollek, and W. Heyn, Ber., 63, 1868 (1930).
5. A. L. Mndzhoyan and M. A. Kaldrikyan, Izv. Akad. Nauk Arm. SSR, 13, 55 (1960).

6. É. K. Andrievskaya, I. L. Kotlyarevskii, and S. I. Dondo, Izv. Akad. Nauk SSSR, Ser. Khim., 1639 (1968).
7. R. N. Myasnikova, M. I. Bardamova, I. L. Kotlyarevskii, and Z. P. Trotsenko, Izv. Akad. Nauk SSSR, Ser. Khim., 2637 (1970).