STUDIES ON THE SYNTHESIS OF FURAN COMPOUNDS XXXI.[1]

Synthesis of 5-Nitro-2-(4-carboxystyryl)furan

Tsutomu FUJIMOTO, Hiroyasu MATSUMOTO*, Toshiharu MORITA and Ichiro HIRAO

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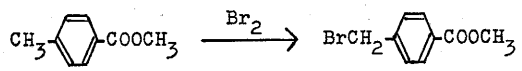
In the previous papers, the preparation of a variety of 5-nitro-2-(4-substituted styryl)furan was reported.[2,3] Among these styrylfuran derivatives, the antibacterial activity of 5-nitro-2-(4-carboxystyryl)furan (I) is superior, and one of the antibacterial characteristics of I is that it is effective against both Gram positive and negative bacteria.[4] The carboxystyrylfuran I was synthesized by the decarboxylation of 3-(5-nitro-2-furyl)-2-(4-carboxyphenyl)acrylic acid which was prepared by the Perkin type condensation reaction of 5-nitrofurfural with *p*-carboxyphenylacetic acid. Howeve, the preparation of *p*-carboxyphenylacetic acid was tedious, and a large amount of resinous substances was formed during the condensation reaction due to instability of 5-nitrofurfural. Consequently the overall yield of I was poor. Therefore, in view of the excellent antibacterial activity of I, we investigated an alternative preparation method for I, and it was found that a process by way of the Wittig reaction of 5-nitrofurfural was favorable for producing I in a good yield and conveniently. In this paper the new convenient process including the Wittig reaction of 5-nitrofurfural with *p*-methoxycarbonylbenzyltriphenylphosphonium bromide (III) is described.



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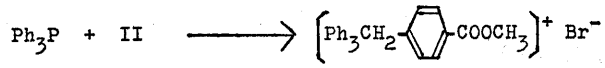

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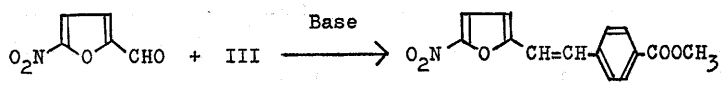

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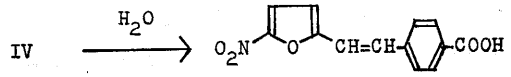

(I)

* Research Laboratory, Ueno Pharmaceutical Co., Ltd., Shimoichiba, Itami.

The phosphonium bromide III was prepared with a yield of 77 % by the reaction of triphenylphosphine with methyl *p*-bromomethylbenzoate (II) which was obtained by the bromination of methyl *p*-toluate in 77 % yield. When a solution of 5-nitrofurfural and the phosphonium salt III in methanol was treated with sodium hydride or a solution of sodium methoxide in methanol at a temperature below 30°C, the product, 5-nitro-2-(4-methoxycarbonylstyryl)furan (IV), was obtained in 64 % yield. The product IV obtained was a mixture of cis- and trans-isomers as indicated by its broad range of melting point. The hydrolysis of the methoxycarbonylstyrylfuran IV, which is a mixture of the isomers, gave only trans-isomer of the carboxystyrylfuran I in 82 % yield.

Experimental

All the melting and decomposition points are uncorrected. The elementary analyses were carried out with a Yanagimoto CHN Corder, MT-2 type. The infrared absorption spectra were recorded with a JASCO Model IR-2 grating infrared spectrophotometer.

Methyl p-bromomethylbenzoate (II) A solution of bromine (32 g, 0.2 mole) in carbon tetrachloride (50 ml) was added dropwise to a stirred, refluxed mixture of methyl *p*-toluate which was prepared by esterification of *p*-toluic acid (27.2 g, 0.2 mole) with methanol in the usual manner, benzoylperoxide (1 g) and carbon tetrachloride (100 ml). The mixture was stirred under reflux until the bromine was absorbed completely. After removal of carbon tetrachloride from the mixture by distillation, the residual oil was distilled in vacuo. II (35.3 g) was obtained in 77 % yield (bp 105-118°C/0.45 mmHg. Found : C, 46.90 : H, 3.30 %. Calcd for $C_9H_9O_2Br$: C, 47.19 ; H, 3.29 %).

p-Methoxycarbonylbenzyltriphenylphosphonium bromide (III) A solution of II (15.7 g, 0.069 mole), and triphenylphosphine (18.1 g, 0.069 mole) in anhydrous benzene (200 ml) was refluxed for 1 hr. The precipitated product obtained on cooling was collected and washed with benzene. Thus, 26.1 g (77 %) of III was obtained as colorless needles (mp 239-40°C. Found : C, 66.40 ; H, 5.01 %. Calcd for $C_{27}H_{24}O_2BrP$: C, 66.00 ; H, 4.92 %).

5-*Nitro*-2-(4-*methoxycarbonylstyryl*)*furan* (IV) A solution of sodium methoxide in methanol, prepared from sodium (1.2 g) and absolute methanol (50 ml), was added dropwise to a mixture of III (23.5 g, 0.048 mole) and 5-nitrofurfural (6.8 g, 0.048 mole) in 100 ml of absolute methanol at a temperature below 30°C with stirring. After addition, the reaction mixture was stirred for 1 hr at room temperature. The precipitated product obtained on cooling was collected. Recrystallization from dioxane-water (4 : 1) gave 8.4 g (64 %) of the mixture of cis- and trans-isomers of IV as yellow fibers which melted at 110-165°C (Found : C, 61.60 ; H, 4.12 ; N, 5.15 %. Calcd for $C_{14}H_{11}O_5N$: C, 61.54 ; H, 4.06 ; N, 5.13 %). One of

the isomers of IV which was slightly soluble in dioxane at room temperature was characterized to be the trans-form by IR (mp 189-190°C. IR : 1710 (C=0) ; 1355 (NO_2) ; 960 cm^{-1} (−CH=CH−, trans).

When sodium hydride was used as the base instead of sodium methoxide, the reaction gave essentially the same yield of IV.

5-*Nitro*-2-(4-*carboxystyryl*)*furan* (I) The hydrolysis of IV (7.0 g) was carried out by the use of 20 % sulfulic acid to give 5.5 g (82 %) of the trans-form of I as yellow needles (mp 291-2°C (decomp)). Found : C, 60.39; H, 3.55; N, 5.27 %. Calcd for $C_{13}H_9O_5N$: C, 60.24 ; H, 3.50 ; N, 5.40 %).

REFERENCES

1) Part XXX of this series; I. Hirao, Y. Kato, and S. Kozakura, *Bull. Chem. Soc. Japan*, **46**, 2498 (1973).
2) I. Hirao and Y. Kitamura, *Nippon Kagaku Zasshi*, **86**, 870 (1965).
3) Y. Kitamura and I. Hirao, *ibid*, **87**, 1063 (1966).
4) T. Matsuda and I. Hirao, *ibid*, **86**, 1195 (1965).