THE SYNTHESIS AND REACTIVITY OF 5-NITRO-2-FURYLACETYLENE

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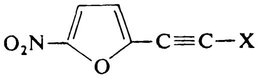
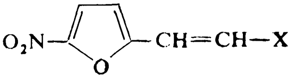
This paper describes the preparation of 5-nitro-2-furylacetylene (*I*), the starting material for the synthesis of 1-iodo-2-(5-nitro-2-furyl)ethylene (*II*), 3-(5-nitro-2-furyl)propinoic acid (*III*) and 1,2-bis-(5-nitro-2-furyl)-acetylene (*IX*), substances possessing antibacterial properties.

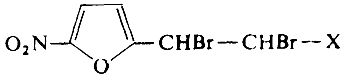
The 5-nitro-2-furyl derivatives having a C≡C grouping at $C_{(2)}$ of the furan ring have been studied only rarely[1–8], when contrasted with those with a C=C grouping, which displayed an antibacterial activity. 5-Nitro-2-furylacetylene (*I*) was synthesized from the commercially available 3-(5-nitro-2-furyl)propenoic acid (*V*) *via* 2,3-dibromo-3-(5-nitro-2-furyl)propanoic acid[9] (*VII*) and the corresponding propinoic-acid *III* in a 40–60% yield; steam distillation of *III* gave *I* in a 17% yield. Thus the over-all yield varied within 5–7% and therefore, this procedure cannot be exploited for a large-scale preparation as uneconomic and time-consuming.



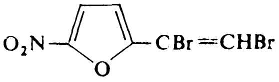
I, X = H
II, X = I
III, X = COOH



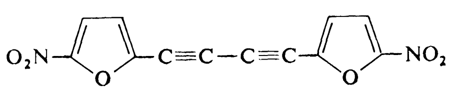
IV, X = Br
V, X = COOH



VI, X = H
VII, X = COOH



VIII



IX

The aim of this paper was to investigate the conversion of some available 5-nitrofuran synthons as *IV*(ref.[10]), *V*(ref.[12,13]), *VI* (ref.[11]), and *VII* (ref.[9]) to *I*.

Starting from 3-(5-nitro-2-furyl)propenoic acid (*V*) analogously as in[3] *via* the product of bromination *VII* 1-bromo-2-(5-nitro-2-furyl)ethene ((Z)−*IV*) was obtained in a 80% yield using sodium carbonate in acetone. The reactivity of *IV* is close to that of 1-bromo-2-(4-nitrophenyl)ethene[14,15] and further vinylic substrates as *e. g.* β-ketovinyl halide[16], β-sulfovinyl halide[17], already converted to the corresponding acetylenes. Conversion of the (Z)-isomer *IV* to 5-nitro-2-furylacetylene (*I*) proceeded smoothly in a 65−84% yield with basic reagents as *e.g.* sodium or potassium hydroxide in ethanol, or with sodium or potassium alkoxides as ethoxide or tert-butoxide[18]. The weakly polarizable and strongly basic alkoxide anion eliminates the hydrogen halide of the (Z) isomer *IV*, this being due to a favourable steric arrangement of the molecule. The (Z)−*IV* isomer was within 10 min quantitatively converted (according to thin-layer chromatography) into 5-nitro-2-furylacetylene *I* (isolated yield 84%) and compounds without furan ring in a 10-fold molar excess of 2M-NaOH in 95% ethanol at 10°C. The yield of the isolated compound *I* dramatically decreases at 40 to 50° due to a high sensitivity of 5-nitrofuran backbone towards basic reagents to give mainly oily products without furan ring. A longer reaction time 1−2 h at room temperature also causes a decrease of the yield of *I* to 65% and the appearance of a little amount of addition products of *I* with one or two molecules of ethanol. The conversion of (Z)−*IV* to *I* by means of tertiary potassium butoxide proceeds in a 70−73% yield. Compound *I* was obtained in a 49−53% yield from 1,2-dibromo-1-(5-nitro-2-furyl)ethane (*VI*) synthesized from furfuryl alcohol *via* 5-nitro-2-vinylfuran[11].

5-Nitro-2-furylacetylene (*I*) is a yellow crystalline compound, which, when purified by chromatography on silica gel, is sufficiently stable in an inert atmosphere in the dark at −10°C. At an ambient temperature in the air compound *I* turns dark and becomes oily. The high reactivity of the activated triple bond and the hydrogen at the triple bond offers broad possibilities to make use of this compound both for preparation of practically not accessible ethylene and acetylene derivatives of 5-nitrofuran, and also polymers and copolymers containing a 5-nitro-2-furyl substituent.

Compound *I* reacts with bromine in chloroform furnishing a mixture of stereomeric substances *VIII* in a 94% yield and in a 4 : 1 ratio. With the Ilosvay reagent[19] (the ammonium hydroxide solution of cuprous chloride) *I* undergoes a characteristic quantitative reaction to give 5-nitro-2-furylcopper acetylide, which reacts with iodine to furnish 1-(5-nitro-2-furyl)-2-iodoacetylene(II) in a 70% yield and a little amount of 1,4-bis-(5-nitro-2-furyl)-1,3-butadiine (*IX*). Oxygen introduced into the suspension of this copper acetylide afforded *IX* in a 37−42% yield as a result of an analogous oxidation condensation. The presence of an acetylene bond was corroborated by a highly sensitive reaction with methanolic $AgNO_3$ under formation of a yellow precipitate of silver acetylide, which gaves iodoacetylene with iodine in a 80–90% yield.

Derivatives *I*, *II*, *III* and *IX* displayed a high biologic activity against Gram-positive and Gram-negative bacteria as *e.g. Bacillus subtillis*, *Staphylococcus aureus* (both Gram$^+$), *Escherichia coli* and *Pseudomonas aeruginosa* (both Gram –) in a 1–10 ppm concentration.

EXPERIMENTAL

Melting points were determined with a Kofler micro hot-stage, IR spectra of chloroform solutions were measured with a UR-20 (Zeiss, Jena) spectrophotometer, the ^{1}H NMR spectra of deuteriochloroform solutions containing tetramethylsilane were recorded with Tesla BS 487 C apparatus operating at 80 MHz; mass spectra were run with an MS 902 S (AEI-Manchester) instrument.

3-(5-Nitro-2-furyl)propionoic acid (*III*), m.p. 129–130°C was prepared according to[1], (*Z*)-1-bromo-2-(5-nitro-2-furyl)-ethene (*IV*), m.p. 39–41°C according to[10], 3-(5-nitro-2-furyl)-propenoic acid (*V*), m.p. 230–233°C (decomp.) according to[13], 1,2-dibromo-1-(5-nitro-2-furyl)-ethane (*VI*), m.p. 55–57°C according to[11], and 2,3-dibromo-3-(5-nitro-2-furyl)propanoic acid (*VII*), m.p. 146–147°C according to[9].

5-Nitro-2-furylacetylene *I*

a) A solution of (*Z*)-*IV* (21·8 g, 0·1 mol) in 95%-ethanol (200 ml) was added to a stirred solution of sodium hydroxide (40 g, 1 mol) in 95%-ethanol (600 ml) at 0–5°C during 10 min. After 10 to 20 min (monitored by thin-layer chromatography) glacial acetic acid (50 ml) was added in one instalment and ethanol was distilled off. Water (100 ml) was added to the residue and the product was taken into ether, dried with $MgSO_4$, the solvent was removed and the residue was chromatographed over a silica gel column (10^{-2}–2 . 10^{-2} cm, eluent benzene, chloroform). Yield 11·5 g (84%), m.p. 51–53°C, (ref.[3] 52–53°C). IR spectrum, cm^{-1}: 2 130 (C≡C), 1 537 $\nu_{as}(NO_2)$, 1 357$\nu_s(NO_2)$. ^{1}H NMR spectrum, ppm: 7·24 (d, J = 4·0 Hz, 1 H, $C_{(4)}$—H_{fur}), 6·74 (d, J = 4 Hz, 1 H, $C_{(3)}$—H_{fur}), 3·51 (s, 1 H, ≡C—H).

b) A solution of (*Z*)-*IV* (21·8 g, 0·1 mol) in tert-butanol (300 ml) was dropwise added to a solution of potassium metal (10 g) in tert-butanol at 10°C with stirring. After 3 h-stirring at room temperature the solvent was distilled off under reduced pressure (t_{max} 40°C) and the residue was worked up after neutralization with glacial acetic acid (11 ml) as *ad a*). Yield 10 g (73%), m.p. 50–53°C.

c) A solution of 1,2-dibromo-1-(5-nitro-2-furyl)ethane (*VI*, 3 g, 10 mmol) in 95% ethanol (50 ml) was added to NaOH (4 g in 95% ethanol (100 ml)) at 5–10°C, and after 10–30 min (checked by thin-layer chromatography) acetic acid (5 ml) was poured in, the solvent was distilled off *in vacuo* and the residue was worked up as with procedure *a*). Yield 0·73 g (53%), m.p. 50–53°C.

Copper 5-nitro-2-furylacetylide: Powdered cuprous chloride (2 g) was dissolved in ammonium hydroxide (25%) with an addition of hydroxylamine hydrochloride (0·1 g) and then an equal amount methanol was added. Compound *I* (1·4 g, 10 mmol) dissolved in methanol (20 ml) was added to the stirred copper solution; the precipitate formed was filtered off, washed with an aqueous 0·1%-solution of NH_2OH. HCl, methanol, and ether, and finally it was protected by a layer of ether for further reaction.

Silver 5-nitro-2-furylacetylide: Compound *I* (1·4 g, 10 mmol) in methanol (20 ml) was added to a solution of $AgNO_3$ 1·8 g in water (10 ml) and methanol (50 ml). The precipitate was filtered off, washed with water, methanol and ether, and protected by a layer of ether; it was used for further reaction.

1-(5-Nitro-2-furyl)-2-iodoacetylene (*II*)

a) Iodine (2·3 to 2·6 g) was successively added to a suspension of copper 5-nitro-2-furylacetylide in ether. The next portion of iodine was added after a preceding decolouration of the solution. The ethereal solution was separated, the solvent removed and the residue was chromatographed on a silica gel column (10^{-1} mm, eluent benzene, ethyl acetate). Yield 1·8 g (70%), m.p. 125—128°C. For $C_6H_2INO_3$ (263·0) calculated: 27·40% 0·74% H, 5·32% N; found: 27·11% C, 0·81% H, 5·44% N. IR spectrum, cm^{-1}: 1 535$\nu_{as}(NO_2)$, 1 355$\nu_s(NO)_2$, 2 177 (C≡w). ^1H NMR spectrum: 7·20 (d, $J = 4·0$ Hz, 1 H, $C_{(4)}$—H_{fur}), 6·80 (d, $J = 4·0$ Hz, 1 H, $C_{(3)}$—H_{fur}). Mass spectrum, *m/z*: 263 (M^+), 233, 205, 189 (100%), 151, 137, 127, 107, 94, 80 and 62.

b) Starting from silver 5-nitro-2-furylacetylide 2·1 to 2·3 g of *II*, m.p. 125—128°C, (80—90%) was obtained by the same procedure as with *a*).

1,4-Bis-(5-nitro-2-furyl)-1,3-butadiine (*IX*)

Oxygen was introduced into a suspension of copper 5-nitro-2-furylacetylide (prepared from 1·4 g of *I* in ether (25 ml)) in 1,2-dimethoxyethane (50 ml) at room temperature for 1 h and at reflux for 2 h. The residue after evaporating the solvent was sorbed at silica gel (10 g) and purified on a silica gel column (10^{-2}—2 . 10^{-2} cm, eluent benzene, ether, acetone). Yield 0·5 to 0·55 g (37—42%), m.p. 155—157°C; (ref.[3]) 154—155°C.

(*Z*) and (*E*)-1-(5-Nitro-2-furyl)-1,2-dibromoethene (*VIII*)

Bromine (0·6 ml) in chloroform (10 ml) was poured into a solution of 5-nitro-2-furylacetylene (1·4 g) in chloroform (25 ml) at 10°C and after 10 to 20 min the solvent was distilled off under reduced pressure (the addition was monitored by thin-layer chromatography). The residue was crystallized from methanol. Yield 2·8 g (94%), m.p. 87—92°C. The (*E*) to (*Z*) ratio was found to be 3 : 1 according to ^1H NMR. For $C_6H_3Br_2NO_3$ (296·9) calculated: 24·27% C, 1·02% H, 4·72% N, 53·83% Br; found: 24·06% C, 1·11% H, 4·77% N, 53·55% Br. ^1H NMR spectrum for the (*Z*) isomer: 7·31 (d, $J = 3·9$ Hz, 1 H, $C_{(4)}$—H_{fur}), 6·81 (d, $J = 3·9$ Hz, 1 H, $C_{(3)}$—H_{fur}), 7·80 (s, 1 H, CH=); for the (*E*) isomer: 7·27 (d, $J = 3·9$ Hz, 1 H, $C_{(4)}$—H_{fur}), 7·10 (d, $J = 3·9$ Hz, 1 H, $C_{(3)}$—H_{fur}), and 6·53 (s, 1 H, CH=).

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