A NEW METHOD OF PREPARATION OF α-AMINO DERIVATIVES OF FURAN*

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The reaction of 5-nitro-2-furfuryl nitrate with sodium azide and malonodinitrile or methyl cyanoacetate was studied. Products of this treatment are 5-amino-2-furfurylidenemalonodinitrile and methyl 3-(5-amino-2-furyl)-2-cyanoacrylate.

Two methods of preparation of α-amino derivatives of furan have so far been described, the principle of the first being a reduction of α-nitrofuran compounds with aluminium[1,2], or sodium[3] amalgams, or with hydrogen under catalysis of Pt (ref.[4]). The second method[5] is based upon cyclization of suitable aliphatic compounds to furnish derivatives of α-aminofuran.

Investigation of the reaction of 5-nitro-2-furyl nitrate (*I*) with nucleophilic reagents resulted in discovery of a new preparation method of α-amino derivatives of furan from the corresponding α-azido derivatives. The aim of nucleophilic displacement of the nitrate group of *I* by an azide anion was to obtain 5-nitro-2-furylazide (*II*). Nevertheless, *I* gave with sodium azide and malonodinitrile in dimethyl sulfoxide *IIIa*; its identity with the product synthesized from 5-nitro-2-furylidenemalonodinitrile (*VIa*) by reduction with aluminium amalgam was corroborated by spectral means.

Since *IIIa* could be formed in several ways, the most probable course of this reaction was investigated. It was found that the highest yields of *IIIa* were achieved when using 2 mol of malonodinitrile. Concurrently, a brisk evolution of 2 mol of a gas (determined volumetrically) took place. The gas consisted of nitrogen and nitrous oxide. If malonodinitrile was replaced by methyl cyanoacetate, methyl 3-(5-amino-2-furyl)cyanoacrylate (*IIIb*) was isolated; both *IIIa* and *IIIb* exchanged hydrogens of amino group for deuterium in hexadeuteriodimethyl sulfoxide in the presence of deuteriotrifluoroacetic acid. The isotopic exchange also occured at furan ring in position 4, as observed by gradual disappearance of the doublet associated with $C_{(4)}$—H and a collapse of the doublet of $C_{(3)}$—H to a singlet; the amino form

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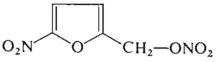
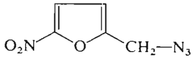
of amines *IIIa,b* was evidenced by IR and ^{1}H-NMR spectra. An alternative preparation of *IIIa* started from sodium azide, malonodinitrile and either 5-nitro-2-furaldehyde (*V*), or 5-bromo- or 5-nitro-2-furylidenemalonodinitrile (*VIa*).



I



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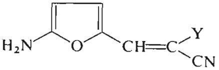
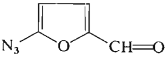
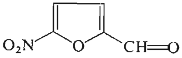


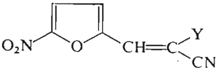
IIIa, Y = CN
IIIb, Y = $COOCH_3$



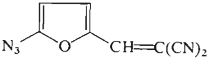
IV



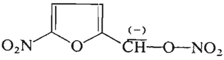
V



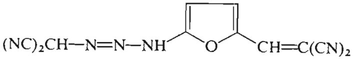
VIa, Y = CN
VIb, Y = $COOCH_3$



VIIa



VIII



IXa

Compound *I* reacted with sodium azide in dimethyl sulfoxide to afford a mixture of *II* and 5-azido-2-furaldehyde (*IV*), the ratio of which depends on the solvent and pH of the medium. Thus, in dimethyl sulfoxide *I* afforded with azoimide (trichloroacetic acid and sodium azide) exclusively *II* in a high yield; in dimethyl sulfoxide or in pure dimethylformamide *I* gave with sodium azide a mixture of *II* and *IV* in a various ratio depending on the reaction time. On the other hand, *IV* was found to be the main reaction product if the reaction was carried out in dimethylformamide (particularly if it contained free dimethylamine). As evident, the formation of *IV* involves an attack of the active methylene group of *I*. Base $\bar{B}$ attacks its hydrogen and the carbanion being originated *VIII* (Scheme 1) was stabilized by the decay of O—N bond under formation of compound *V* similarly, as already observed[6]. Sodium azide present in the reaction mixture reacts with nitrous acid being formed[8]; consequently, the equilibrium was shifted towards the final products (Scheme 1).

$$I \underset{BH^+}{\overset{-BH^+}{\rightleftharpoons}} VIII \xrightarrow{-NO_2^-} V$$

$$BH^+NO_2^- \rightleftarrows \bar{B} + HNO_2$$

$$2\,HNO_2 + NaN_3 \rightarrow N_2O + N_2 + NaNO_2 + H_2O$$

SCHEME 1

Moreover, nitrous oxide, nitrogen, water, sodium nitrite, the regenerated base $\bar{B}$ and 5-nitro-2-furaldehyde (*V*) were generated; the latter undergoes a nucleophilic displacement to furnish *IV*, ref.[7].

Compounds *IV* and *V* can react with malonodinitrile; treatment of *V* with malonodinitrile afforded 5-nitro-2-furylidenemalonodinitrile (*VIa*, ref.[9]). We found that *IV* reacts in an analogous way with one mole of malonodinitrile to yield 5-azido-2-furylidenemalonodinitrile (*VIIa*) at 15–20°C; with two moles, at room temperature and in the presence of a base, *IIIa* was formed in a high yield.

To bring this potential synthetic way into effect, the relative reactivities of aldehydes *IV* and *V* had to be verified. It has been shown that *IV* and *V* reveal various reactivities upon condensation with malonodinitrile. The equimolar mixture of *IV*, *V* and malonodinitrile afforded almost quantitatively *VIa* within 5 min, whereas *IV* did not react at all. Likewise, it was necessary to estimate the relative reactivities of both nucleophilic reagents, namely of the azide anion and of the carbanion of malonodinitrile. Both are suitable to react with *V*, but at different rate: the condensation with malonodinitrile is finished within some minutes, the nucleophilic replacement of NO_2 group by an azide anion proceeds 4 h with a 60% conversion. As evident, the conversion of *I* to *IIIa* proceeds mainly through *VIa*.

Compound *VIa* afforded *VIIa* with sodium azide in dimethyl sulfoxide. This nucleophilic displacement continues in the presence of malonodinitrile to give *IIIa* in a high yield. Substance *VIIa* was isolated in a 30% yield upon reaction of sodium azide with 5-bromo-2-furylidenemalonodinitrile in dimethyl sulfoxide or sulfolane. Displacement of *VIIa* into *IIIa* is subject to the presence of a methylene group either of malonodinitrile or of methyl cyanoacetate and a base (Triton B, sodium azide, sodium nitrite or sodium acetate). The best catalyst was shown to be sodium nitrite, which did not give rise to by-products. An analogous type of conversion of azido group to an amine was also reported[10,11]. The nucleophilic attack of a carbanion of compounds with an active methylene group on an azide proceeds *via* a substituted triazene *IXa*, which undergoes a decomposition to give the amine and diazo compound. The conversion of azides *VIIa,b* to *IIIa,b* may proceed in this way (Scheme 2). A concurrent reaction through a nitrene is unlikely, since nitrenes resulting from the decomposition of azides under investigation are unstable and are stabilized by opening the furan ring[12] excluding thus the possibility to form an amine by a mechanism involving the abstraction of hydrogen by nitrene.

$$\mathit{VIIa} \xrightarrow[\text{B}]{CH_2(CN)_2} \mathit{IXa} \xrightarrow{-N_2C(CN)_2} \mathit{IIIa}$$

SCHEME 2

These results let us conclude that the transformation of *I* to *IIIa,b* proceeds in four main stages. The first step involves an attack of the base to hydrogen of the active methylene group of *I*. The intermediate carbanion is stabilized under formation of *V*, which reacts with malonodinitrile or methyl cyanoacetate to afford *VIa,b*. A nucleophilic displacement of the nitro group of *VIa,b* by an azide anion yielded unstable triazenes *IXa,b*; these decompose to amines *IIIa,b*.

The above-mentioned synthesis of α-amino derivatives of furan is of general use for all compounds with furan ring having a functionality in α-position capable to give the corresponding α-azido derivatives by nucleophilic displacement. A subsequent reduction or another transformation of the azido group to amino group makes it possible to prepare the hitherto little known primary α-amino derivatives of furan.

EXPERIMENTAL

The IR spectra were recorded with a UR 20 (Zeiss) spectrophotometer, the UV spectra with a UV-VIS Specord apparatus, the ^{1}H-NMR spectra (δ, ppm) with a Tesla BS 487 C (80 MHz), and mass spectra with AEI MS 902 S instruments. Melting points were measured on a Kofler block. The starting material was synthesized according to[7,9,13,14]. Deuterio compounds were prepared by labelling with deuteriotrifluoroacetic acid (99·5%). Gaseous nitrogen and nitrous oxide were determined with an apparatus for volumetric estimation of nitrogen. Nitrous oxide was qualitatively estimated with triphenylphosphine.

5-Amino-2-furfurylidenemalonodinitrile (*IIIa*)

A) A mixture of 5-nitro-2-furfuryl nitrate (3·76 g, 20 mmol), or 5-nitro-2-furaldehyde (2·8 g, 20 mmol), sodium azide (2·4 g, 40 mmol) and malonodinitrile (2·6 g, 40 mmol) in dimethyl sulfoxide or dimethylformamide (10 ml) was cooled to 5°C and stirred; the temperature rose spontaneously to 30°C within a short time. This temperature was kept for 20 min and at 40—45°C for additional 15 min. The mixture was poured into ice-cold water and the brown needles, which separated, were suction-filtered and crystallized from ethanol. Yield 2·4 g (54%), m.p. 198 to 200°C. For $C_8H_5N_3O$ (159·1; *m/e* 159 (M^+)) calculated: 60·40% C, 3·17% H, 20·40% N; found: 60·47% C, 3·12% H, 20·48% N. IR spectrum (KBr, cm^{-1}): 3400—3200 (NH_2 cluster), 2220, 2205 (C≡N). UV spectrum (methanol, nm, (log ε)): 447 (4·82), 230 (4·20). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): 5·66 (d, J = 4·0 Hz, 1 H, $C_{(4)}$—H_{fur}), 7·06 (s, 1 H, C—$H_{ethylenic}$), 7·38 (d, J = 4·0 Hz, 1 H, $C_{(3)}$—H_{fur}), 8·33 (s, broad, 2 H, NH_2).

B) A mixture of 5-nitro-2-furylidenemalonodinitrile (4 g, 20 mmol), aluminium turnings (activated with 10% NaOH and 0·5% $HgCl_2$ solutions) and ethanol (300 ml) was stirred at room temperature for 3 h. The insoluble residue was filtered off and the filtrate concentrated *in vacuo* to dryness was chromatographed (silica-gel-packed column, chloroform–acetone 1 : 1). Yield 1 g (32%), m.p. 198—200°C.

C) A mixture of 5-bromo or 5-nitro-2-furylidenemalonodinitrile (20 mmol), sodium azide (1·2 g, 20 mmol) and malonodinitrile (1·3 g, 20 mmol) in dimethyl sulfoxide (15 ml) was stirred till the evolution of gases ceased. The work-up analogous to *A* afforded 2·3 g (73%) of *IIIa*, m.p. 198—200°C.

D) A mixture of 5-azido-2-furaldehyde (1·37 g, 10 mmol), malonodinitrile (1·3 g, 20 mmol) and ethanol (50 ml) was stirred in the presence of sodium nitrite at room temperature. The ethanolic solution was concentrated after no more gases were evolved and the precipitated crystals were suction-filtered. Yield 2·7 g (87%), m.p. 198—202°C.

E) A mixture of 5-azido-2-furylidenemalonodinitrile (1·8 g, 10 mmol) and malonodinitrile (0·65 g, 10 mmol) in ethanol (20 ml) was stirred at room temperature for 15 min and worked up as in procedure *D*. Yield 1·5 g (96%) m.p. 198—200°C.

Methyl 3-(5-Amino-2-furyl)-2-cyanoacrylate (*IIIb*)

A mixture of 5-nitro-2-furfuryl nitrate (3·76 g, 20 mmol), sodium azide (2·4 g, 40 mmol) and methyl cyanoacetate (4 g, 40 mmol) in dimethyl sulfoxide (20 ml) was cooled to 5°C. The temperature of the solidified mixture rose to 25—30°C within some minutes; the mixture was stirred at this temperature for 20 min and at 40°C for 15 min, then it was poured into cold water (300 ml) and extracted with ethyl acetate–ether 1 : 1. The extract was three times washed with water, the solvent removed and the residue crystallized from benzene. Yield 1·4 g (36%) m.p. 194—195°C. For $C_9H_8N_2O_3$ (192·1 *m/e* 192 (M^+) calculated: 56·25% C, 14·19% H, 14·58% N; found: 56·31% C, 4·20% H, 14·70% N. IR spectrum (KBr, cm^{-1}): 3350—3180 (NH_2 cluster), 2215 (C≡N), 1682 ($COOCH_3$); UV spectrum (ethanol, nm (log ε)): 447 (4·64), 227 (4·08). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·64 (s, 3 H, OCH_3), 5·56 (d, J = 4·0 Hz, 1 H, $C_{(4)}$—H_{fur}), 7·35 (s, 1 H, C—$H_{ethylenic}$), 7·48 (d, J = 4·0 Hz, 1 H, $C_{(3)}$—H_{fur}).

Reaction of 5-Nitro-2-furfuryl Nitrate with Sodium Azide

A) A mixture of 5-nitro-2-furfuryl nitrate (18·8 g, 0·1 mol), sodium azide (10·8 g, 0·15 mol) and dimethylformamide (technical grade) was stirred at 3—5°C and after 4 h poured into ice-cold water (500 ml). The ethereal extract (4 . 300 ml) was washed with water, dried and concentrated to dryness under reduced pressure. The residue crystallized from tetrachloromethane and gave 6·8 g (41%) of 5-nitro-2-furfurylazide and 5-azido-2-furaldehyde in a 1 : 7 ratio. Several crystallizations afforded 5-azido-2-furaldehyde (0·5 g), m.p. 56—57°C (ref.[7] 56°C). IR spectrum (KBr, cm^{-1}): 2145 (N_3), 1685 (CH=O); UV spectrum (methanol, nm, (log ε)): 313 (4·91), 216 (4·12). ^{1}H-NMR spectrum (CCl_4): 5·92 (d, J = 3·7 Hz, 1 H, $C_{(4)}$—H_{fur}), 7·24 (d, J = 3·7 Hz, 1 H, $C_{(3)}$—H_{fur}), 9·30 (s, 1 H, CH=O).

B) A mixture of 5-nitro-2-furfuryl nitrate (18·8 g, 0·1 mol), sodium azide (13 g, 0·2 mol), trichloroacetic acid (8·17 g, 50 mmol) in dimethyl sulfoxide (150 ml) was stirred at 13—15°C (caution, danger of explosion). After 4 h the mixture was poured into ice-cold water (500 ml) and extracted with ether (200 ml). Work-up according to procedure *A* furnished a liquid, which was dissolved in tetrachloromethane, washed with KOBr solution, water, dried with sodium sulfate and vacuum concentrated to give 5-nitro-2-furfurylazide (8·5 g, 54%). An attempt to distil the substance *in vacuo* resulted in an explosion. For $C_5H_4N_4O_3$ (168·1) calculated: 35·72% C, 2·40% H, 33·33% N; calculated: 35·91% C, 2·48% H, 33·20% N. IR spectrum (CCl_4, cm^{-1}): 2110 (N_3), 1521, 1358 (NO_2). ^{1}H-NMR spectrum (CCl_4): 4·45 (s, 2 H, CH_2), 6·64 (d, J = 3·7 Hz, 1 H, $C_{(3)}$—H_{fur}), 7·26 (d, J = 3·7 Hz, 1 H, $C_{(4)}$—H_{fur}).

5-Azido-2-furylidenemalonodinitrile (*VIIa*)

A) A mixture consisting of 5-azido-2-furaldehyde (1·37 g, 10 mmol), malonodinitrile (0·65 g, 10 mmol) and ethanol (10 ml) was stirred at a temperature not exceeding 10°C for 30 min; the title compound, which precipitated at —10°C was crystallized from ether. Yieldd 0·9 g (47%), m.p. over 36°C (decomp.). For $C_8H_3N_5O$ (185·1) calculated: 51·90% C, 1·63% H, 37·85% N; found: 51·89% C, 1·61% H, 37·97% N. IR spectrum ($CHCl_3$, cm^{-1}): 2231 (C≡N), 2155 (N_3); UV spectrum (methanol, nm, (log ε)): 395 (4·18), 242 (4·10), 207 (3·80). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): 6·50 (d, J = 4·0 Hz, 1 H, $C_{(4)}$—H_{fur}), 7·47 (d, J = 4·0 Hz, 1 H, $C_{(3)}$—H_{fur}), 8·03 (s, C—$H_{ethylenic}$).

B) A mixture of 5-bromo- or 5-nitro-2-furylidenemalonodinitrile (20 mmol) and sodium azide (1·2 g, 20 mmol) in dimethyl sulfoxide (15 ml) was stirred with exclusion of light for 2 h, poured into ice-cold water and extracted with ether. The extract was three times washed with water, dried with Na_2SO_4 and concentrated under reduced pressure. The precipitated azidonitrile was crystallized from ether. Yield 1 g (30%) of *VIIa*, which undergoes a rapid decomposition.

Reaction of 5-Nitro-2-furaldehyde and 5-Azido-2-furaldehyde with Malonodinitrile

5-Nitro-2-furaldehyde (1·4 g, 10 mmol), 5-azido-2-furaldehyde (1·37 g, 10 mmol), malonodinitrile (0·65 g, 10 mmol) and ethanol (20 ml) were stirred at 10°C for 5 min. The precipitated substance was suction-filtered, washed with ethanol and dried. Yield 1·2 g (85%) of 5-nitro-2-furfurylidenemalonodinitrile, m.p. 174—176°C, ref.[9] 179°C. Chromatography of the filtrate on silica gel (eluent CCl_4) afforded 5-azido-2-furaldehyde (1 g, 71%), m.p. 56—57°C. ^{1}H-NMR spectrum of the filtrate revealed signals diagnostic of 5-azido-2-furaldehyde and 5-nitro-2-furylidenemalonodinitrile.

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