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SYNTHESIS OF 3-SUBSTITUTED FURYLETHYLAMINES

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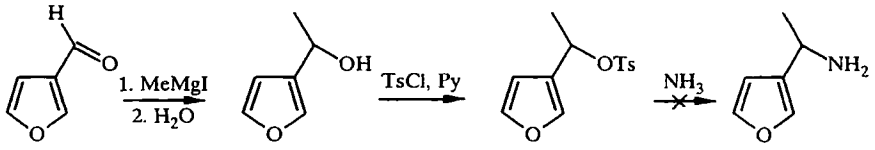
A method for the synthesis of the previously unknown 1-(3-furyl)ethylamine and [1-(3-furyl)ethyl]-N-methylamine was developed. The 3-furylcarbaldehyde was converted sequentially to 3-cyanofuran and then 3-acetylfuran. Reduction of the oxime or methylimine of 3-acetylfuran leads to the corresponding 3-substituted furylethylamines.

Derivatives of furan are compounds which have been studied in ample detail; many of them are contained in natural substances and exhibit varied biological activity. Different 2-substituted furans were investigated in the greatest detail, and can be obtained on the basis of the available furfurol [1]. In particular, a series of works were dedicated to the isolation and study of the biological activity of amines of the 2-substituted furan series containing the amino group in the side chain [2-4]. However, the analogous amines — derivatives of 3-substituted furan — have not been described in the literature up to the present time, and the development of preparative methods for their synthesis utilizing accessible initial compounds presents interest in connection with the possible isolation of biologically active compounds from them.

We developed a convenient method for the synthesis of 1-(3-furyl)ethylamines starting from the available 3-furylcarbaldehyde (I). The direct synthetic path which we undertook using the addition of methylmagnesium iodide to the aldehyde (I) and the subsequent conversion of the resulting 1-(3-furyl)ethanol (II) to the tosylate (III) and its ammonolysis did not facilitate the isolation of the compound sought due to the inadequate stability of the tosylate (III).



I II, 97% III

Although there was previous communication on the possible synthesis of amines by the ammonolysis of the more stable acetates containing the electron-rich aromatic nucleus in the α-position [5], we did not manage to perform nucleophilic substitution of the acetoxy group by the amine group in view of the insufficient activity of the acetate of 1-(3-furyl)ethanol.

A more preferable synthesis of 1-(3-furyl)ethylamines proved to be the reduction of the corresponding Schiff bases, synthesized from 3-acetylfuran (V), which may be obtained from the alcohol (II). However, its oxidation with acceptable yield is unsuccessful. Thus, the utilization of pyridinium dichromate, which is widely employed for the oxidation of natural alcohols [6], led to resinification of the reaction mixture. The Dess-Martin reagent, which is probably the mildest of the oxidizing agents known at present [7], allows the isolation of the ketone (V) with the yield of about 20%. The best results were achieved in the synthesis of compound (V) via the corresponding nitrile (IV).

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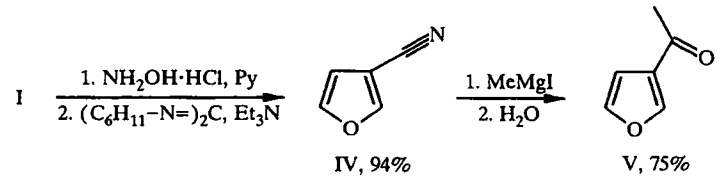
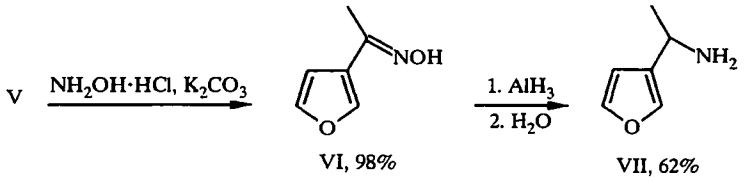
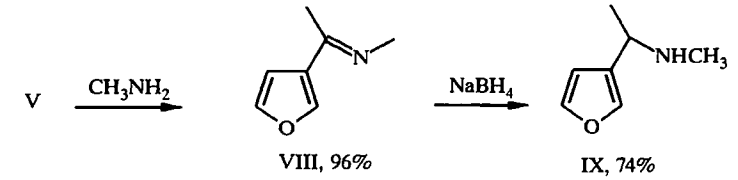


Reduction of the oxime of 3-acetylfuran (VI) leads to the requisite 1-(3-furyl)ethylamine (VII). Among the reducing agents employed for this purpose, we investigated lithium aluminum hydride, sodium borohydride in the presence of nickel chloride, as well as aluminum hydride. The best result was obtained by utilizing aluminum hydride, which was synthesized by the action of the equimolar amount of 100% sulfuric acid on the solution of lithium aluminum hydride in THF [8].



The 1-(3-furyl)ethyl-N-methylamine (IX) was obtained by the reduction of 3-acetylfuran methylimine (VIII) with sodium borohydride [9].



The amines (VIII) and (IX) obtained are colorless, readily mobile, liquids. Their structure was shown using ^{1}H and ^{13}C NMR spectroscopy and confirmed by the data of elemental analysis.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on Bruker AMX 400 spectrometers, with the working frequency 100 MHz on the ^{13}C nuclei, using $CDCl_3$; TMS was used as the internal standard.

3-Cyanofuran (IV). This compound is obtained from 3-furylcarbaldehyde by the method of [10]. It is purified by distillation. The yield is 94%. It has bp 150°C, mp 37-38°C, and the n_D^{20} 1.4780. According to the data of [10], it has bp 151°C and n_D^{20} 1.4790.

3-Acetylfuran (V). This compound is obtained by the method of [11]. The yield is 75%. It has bp 74-75°C (10 torr) and mp 53-54°C. According to the data of [11], it has bp 78°C (12 torr) and mp 54°C.

The corresponding 3-acetylfuran methylimine (VIII) and 3-acetylfuran oxime (VI) are obtained by the method of [12], and are utilized further without preliminary purification.

1-(3-Furyl)ethylamine (VII). To the well-stirred solution of 16.7 g (0.43 mol) of lithium aluminum hydride in 500 ml of THF in argon atmosphere with the cooling to -10°C are added, dropwise, 11.7 ml of 100% sulfuric acid in the course of 30 min. At the end of the addition, the temperature is increased to room temperature, and the stirring is continued for 1 h more. Solution of 27.5 g (0.22 mol) of the oxime (VI) in 100 ml of THF is then added slowly. The strong exothermic reaction causes the boiling of the solution, which is continued for 1 h more after the completion of addition of the oxime. The reaction mixture is decomposed using the standard procedure by the sequential addition of 17 ml of water, then 17 ml of 15% aqueous NaOH, and again 35 ml of water. The thick residue is filtered off. The solvent is evaporated, and the residue is distilled *in vacuo*. The yield is 15.2 g (62%),

and bp is 54-55°C (20 torr). The ^{1}H NMR spectrum ($CDCl_3$): 7.26 (1H, t, ^3J = 3.4 Hz, 5-H); 7.22 (1H, m, 4-H); 6.29 (1H, br. s, 2-H); 3.93 (1H, t, ^3J = 6.6 Hz, CH); 1.71 (2H, br. s, NH_2); 1.26 ppm (3H, d, ^3J = 6.6 Hz, CH_3). The ^{13}C NMR spectrum ($CDCl_3$): 142.89 ($C_{(5)}$ or $C_{(2)}$); 137.62 ($C_{(5)}$ or $C_{(2)}$); 131.72 ($C_{(3)}$); 108.56 ($C_{(4)}$); 43.01 (CH); 24.59 ppm (CH_3). Found, %: C 64.79; H 8.32. C_6H_9NO. Calculated, %: C 64.84; H 8.16.

[1-(3-Furyl)ethyl]-N-methylamine (IX). This compound is obtained by reduction of 3-acetylfuran methylimine utilizing the literature method [9]. The yield is 74%, and bp is 57-58°C (12 torr). The ^{1}H NMR spectrum ($CDCl_3$): 7.25 (1H, m, 5-H); 7.21 (1H, m, 4-H); 6.26 (1H, br. s, 2-H); 3.52 (1H, t, ^3J = 6.6 Hz, CH); 2.33 (3H, s, N-CH_3); 2.16 (1H, br. s, NH); 1.22 ppm (3H, d, ^3J = 6.6 Hz, CH_3). The ^{13}C NMR spectrum ($CDCl_3$): 142.68 ($C_{(5)}$ or $C_{(2)}$); 138.55 ($C_{(5)}$ or $C_{(2)}$); 128.64 ($C_{(3)}$); 108.33 ($C_{(4)}$); 50.62 ($CH_3\underline{C}H$); 33.51 ($\underline{C}H_3NH$); 24.59 ppm ($\underline{C}H_3CH$). Found, %: C 66.67; H 8.75; N 11.14. $C_7H_{11}NO$. Calculated, %: C 67.17; H 8.86; N 11.19.

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