SYNTHESIS OF 2-ETHYNYL- AND 4,5-DIETHYNYL-1-METHYLIMIDAZOLES

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The reaction for the direct replacement of halogen by acetylenic groups, catalyzed by copper, can be used to synthesize acetylenic derivatives of imidazole [1].

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In order to obtain ethynyl-N-methylimidazoles, in the present paper we used this method to insert one, two, or three moieties of the tertiary acetylenic alcohol, 2-methyl-3-butyn-2-ol, into the imidazole ring. The hydroxyl group of the starting alcohol had acetal protection [1, 2]. We used 2-iodo- (I), 4,5diiodo- (II), and 2,4,5-triiodo-1-methylimidazole (III) in the condensation



The monoiodide (I) was obtained by treating 1-methyl-2-imidazolyllithium with I_2 , while iodides (II) and (III) were obtained by the iodination of 1-methylimidazole with a mixture of I_2 and HIO₃. The position of the halogen was established on the basis of the NMR spectra of these compounds. In order to complete the reaction of imidazole (I) with 1.5 equivalents, and of imidazoles (II) and (III) with 3 equivalents of acetal (IV), under the usual conditions [1] it was necessary to respectively use 5, 35, and 70 h, while the yields of the acetylenic derivatives (V)-(VII) were 87-89%. In all cases the removal of the acetal protection went in yields exceeding 90%. The mono- and dihydric imidazolylacetylenic alcohols (VIII) and (IX) were converted to the 2-ethynyl- (XI) (70% yield) and 4,5-dicthynyl-1-methylimidazole (XII) (44% yield) in the presence of KOH, with a simultaneous removal of the formed products. 2,4,5-Triethynyl-1-methylimidazole could not be obtained by the cleavage of triol (X) under analogous conditions, apparently due to the fact that the reverse Favorskii reaction at the acetylenic grouping in the 2 position proceeds under much milder conditions than at the other side chains [1]. The intermediate substituted 2-ethynylimidazole, remaining in the reaction sphere, is polymerized on further heating. The structure of all of the synthesized compounds was confirmed by the data of the IR and NMR spectra. The method of paramagnetic additives [3] was used to assign the lines of the acetylenic protons in the NMR spectrum of diacetylenc (XII). We used NiBr, as the complexing agent here, and the measurements were made at 50°C in CHCl₃. A shift of the signals of both of the acetylenic protons upfield by 3-4 Hz was observed in the presence of the complexing agent, with a simultaneous change in their width (Fig. 1). The line of one of these protons (δ 3.19 ppm) became much broader than the lines of the other proton (δ 3.61 ppm). Since in shifts of the same order of magnitude the main contribution to the difference in the broadening of these lines is determined by dipole-dipole

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Com- pound	Yi eld,	n ²⁰ or mp, °C	Found N.	Empirical formula	C alc . N,%	v,cm ⁻¹	
						C≡C	C-O-C-O-C or OH
v	87,5	1,5020*	11,58	$C_{13}H_{20}N_2O_2$	11,86	2240	1050, 1080 1123, 1158
VI	88,5	1,5030	6,93	C22H34N2O4	7,17	2240	1055, 1083 1128, 1162
VII	87,5	1,5093	5,47	C31H48N2O6	5,14	2235	1055, 1085 1130, 1162
VIII	92,5	148,5—149 (from CH ₂ C1CH ₂ C1)	17,15	C_9 H ₁₂ N ₂ O	17,06	2240	3595
IX	93,5	136,5-137,5 (from CH ₂ ClCH ₂ Cl)	11,31	C ₁₄ H ₁₅ N ₂ O ₂	11,38	2245 †	3335 w
x	91,5	176—176,5 (from HCCl ₃)	8,79	$C_{19}H_{24}N_2O_3$	8,53	2245 †	3335 w

TABLE 1. Yields and Constants of Synthesized Compounds

* bp 113-115°C (0.5 mm).

† The spectrum was taken as a KBr pellet.



Fig. 1. NMR spectrum of compound (XII), and of (XII) containing NiBr₂ (in CHCl₃), 50° C.

cube of the distance from the proton to the paramagnetic ion in the complex, the signal with the greater width undoubtedly belongs to the proton of the ethynyl group in the 4 position of the imidazole ring.

EXPERIMENTAL

electron-nuclear interaction, which is inversely proportional to the

N-Methylimidazole was synthesized by the methylation of imidazole with CH₃I in aqueous-methanolic NaOH solution at 30-40°C [4]; yield 57.5%; bp 80-81% (11 mm); n_D^{20} 1.4975. NMR spectrum (in CCl₄)*: NCH₃ 3.56 ppm, H of ring 6.71, 6.78, and 7.15 ppm.

2-Iodo-1-methylimidazole (I). To a solution of N-methyl-2imidazolyllithium, obtained from 4 g of 1-methylimidazole and C_4H_9Li (1.5 g of Li and 14.4 g of C_4H_9Br) in 120 ml of ether at -15 to -10°C, was added 18.5 g of I₂ in 100 ml of ether. After 12 h the reaction mass was made alkaline with 1.5% NaOH solution, and the product was extracted with CHCl₃, dried over K_2CO_3 , and distilled. The yield of (I) was 8.1 g (79.5%); mp 89-90°C (from petroleum ether); bp 97-98°C (0.5 mm). Found: I 60.93%. $C_4H_5N_2I$. Calculated: I 61.02%. NMR spectrum (in CCl₄): NCH₃ 3.50 ppm, H of ring 6.80 and 6.88 ppm.

<u>4,5-Diiodo-1-methyl- (II)</u> and 2,4,5-Triiodo-1-methylimidazole (III). The iodination of 2 g of 1methylimidazole was run in the same manner as that of 1-methyl-5-chloroimidazole [1], using a mixture of 5.1 g of I₂ and 2.1 g of HIO₃ in 60 ml of glacial acetic acid at 75 °C. The obtained iodides (5.6 g) were separated by chromatographing on Al₂O₃ (V activity), using mixtures of petroleum ether, benzene, CHCl₃, and ether as eluants. The yield of (II) was 1.7 g (20.5%), mp 141.5-142.5 °C (from CCl₄). Found: I 75.65%. C₄H₄N₂I₂. Calculated: I 76.02%. NMR spectrum (in CH₂Cl₂): NCH₃ 3.58 ppm, 2-H 7.49 ppm. The yield of (III) was 3.3 g (28.8%), mp 149.5-150.5 °C (from CCl₄). Found: I 82.62%. C₄H₃N₂I₃. Calculated: I 82.80%. NMR spectrum (in CH₂Cl₂): NCH₃ 3.68 ppm.

Acetylenic Condensation. The reaction of iodides (I)-(III) was run under standard conditions, as described in [1]. In the case of (I) we used a 50% excess, while in the case of (II) and (III) we used a 200% excess of acetal (IV). The constants and yields of the obtained imidazolylacetylenic alcohol acetals (V)-(VII) are given in Table 1.

Hydrolysis of Acetals (V)-(VII). The hydrolysis of (V)-(VII) was run in acidified aqueous dioxane solution at 20° C [1, 2]. The results are given in Table 1 [compounds (VIII)-(X)].

*The NMR spectra were taken on a JNM-4-H-100 high resolution spectrometer at a frequency of 100 MHz, at 26°C, and using hexamethyldisiloxane as the internal standard.

2-Ethynyl-1-methylimidazole (XI). Two grams of (VIII) was distilled over 30 mg of powdered KOH from a Favorskii flask at 1-2 mm and a bath temperature of 145-155°C. A slight amount of (VIII) in the product was separated by chromatographing on Al₂O₃ (V activity) in CHCl₃. We obtained 0.9 g (70%) of (XI); n_D^{20} 1.5442. Found: N 26.71%. C₆H₆N₂. Calculated: N 26.41%. NMR spectrum (in CCl₄): NCH₃ 3.63 ppm, 2-C = CH 3.38 ppm, H = of ring 6.76 and 6.79 ppm. Infrared spectrum: C = C 2130, C = C - H 3320 cm⁻¹.

4.5-Diethynyl-1-methylimidazole (XII). A finely ground mixture of 300 mg of (IX) and 15 mg of KOH was charged into a sublimation apparatus and carefullyheated in vacuo at 85-110°C and a residual pressure of 1 mm. The sublimed (XII) was freed of trace impurities by chromatographing on Al₂O₃ (V activity) in CHCl₃, and then resublimed. The yield of (XII) was 70 mg (44%); mp 129-129.5°C (decompn.). Found N 26.71%. C₆H₆N₂. Calculated: N 26.41%. NMR spectrum (in CH₂Cl₂): NCH₃3.59 ppm, 4-C^Ξ CH 3.75 ppm, 5-C^Ξ CH 3.25 ppm, 2-H 7.31 ppm. Infrared spectrum: C^Ξ C 2130 (shoulder 2120), C^Ξ CH 3312 cm⁻¹.

CONCLUSIONS

1. One, two, or three 3-methyl-3-hydroxybutynyl groups were inserted into the N-methylimidazole ring by the direct replacement of iodine, catalyzed by copper.

2. 2-Ethynyl- and 4,5-diethynyl--1-methylimidazole were synthesized by the cleavage of the obtained imidazolylacetylenic alcohols.

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