2. A method for the quantitative determination of piperidyloxy-p-benzoquinones in the reaction mixture was developed, based on the chromatographic separation of these compounds and the determination of benzoquinones in the extracts of the chromatographic zones by EPR.

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SYNTHESIS AND ACETYLENIC CONDENSATION OF IODINE DERIVATIVES OF N-METHYLIMIDAZOLE

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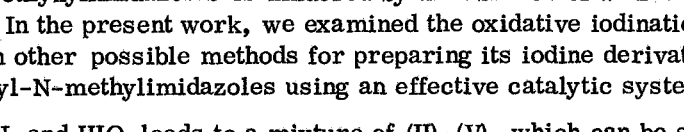
To clarify the chemical properties of the acetylenic derivatives of imidazole, compounds are needed containing unsubstituted ethynyl groups in different positions of the heterocyclic ring. The most general method for synthesizing imidazolylacetylenes is the catalyzed nucleophilic substitution of halogen, usually iodine, in the aromatic ring by the action of terminal acetylenes [1-3]. The alkaline cleavage of the tertiary acetylenic alcohols thus obtained represents a preparative path to mono- and diethynylimidazoles [1, 2]. However, in many cases this synthesis of ethynylimidazoles is hindered by the absence of well-developed methods for preparing the initial iodides. In the present work, we examined the oxidative iodination of 1-methylimidazole (I) by I_2 and HIO_3, and certain other possible methods for preparing its iodine derivatives. From the results, we synthesized several ethynyl-N-methylimidazoles using an effective catalytic system.

The iodination of (I) by I_2 and HIO_3 leads to a mixture of (II)-(V), which can be separated by chromatography on Al_2O_3.



The properties of neither of the two monoiodides formed correspond to those of 2-iodo-1-methylimidazole [2]. In the PMR spectra of the two isomers there is a signal corresponding to the proton in the 2 position (7.23 and 7.51 ppm), and in a stronger field [4], to the 4-H or 5-H proton (6.90 and 7.00 ppm). Hence the iodides obtained

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are 4-iodo-1-methyl- (II) and 5-iodo-1-methylimidazoles (III). It was found after converting the iodides into ethynylimidazoles (see below) that the lower-melting (mp 53-54°C), high-boiling isomer [bp 113-115°C (2 mm)] is the iodide (II). The 5-iodide (III) differs appreciably from (II): mp 106-107°C; in the PMR spectrum the 2-H signal is shifted into the weaker field by ~0.3 ppm than that of (II). Proofs for the structure of (IV) and (V) are given in [2].

During iodination with 1-3 equivalents of the iodinating mixture at 20-75°C, imidazole (I) preferentially forms polyiodides (IV) and (V). The total yield of (II) and (III) invariably remains low; pure (V) is not formed even in the reaction with 3 equivalents of the iodinating agents at 75°C. Continuous control of the reaction products during the course of iodination showed that their enrichment with triiodide (V) occurs at the initial period of the reaction only. With the passage of time, the absolute content of (V) in the reaction mixture begins to decrease, and after fairly prolonged heating, it is completely converted into the 4,5-diiodide (IV), which then becomes practically the only reaction product. The deiodination process intensifies with the increase in temperature: in special experiments, after heating with MeCOOH for 16-18 h at 100°C, or 65-70 h at 75°C, compound (V) completely lost iodine from position 2. Sulfuric acid and CCl_4 present in the reaction mixture do not influence the rate of reduction. During deiodination, the formation of free iodine is observed. It is clear that under the conditions of oxidative iodination of (IV), two competing reactions take place: the direct one in which I_2 and HIO_3 are consumed, and the "reverse" one in which the total iodine which initially entered position 2, separates out in the form of I_2. After HIO_3 has been consumed, the iodination of (IV) ceases, and the deiodination of (V) proceeds to completion. The role of the reducing agent is probably played by the solvent MeCOOH

$$5\,(IV) + 2I_2 + HIO_3 \rightarrow 5\,(V) + 3H_2O$$

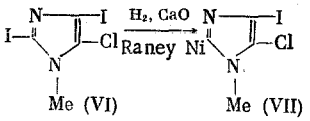
$$(V) + [H] \xrightarrow[MeCOOH]{} (IV) + \frac{1}{2} I_2$$

Thus, by the action of a large (threefold) excess of I_2 and HIO_3 at 100°C for 1.5-2 h, compound (IV) is almost completely converted into (V). If the reaction mixture is heated for another 20 h, product (V) is completely reduced to the initial (IV). Under these conditions, 4,5-diiodide (IV) can also be deiodinated to (II) and (III), but much more slowly than triiodide (V). At 100°C and after 80 h, the reaction proceeds to less than 50%. By understanding the nature of the secondary process during the oxidative iodination of (I), we can easily determine the conditions for the directed preparation of polyiodides (IV) and (V).

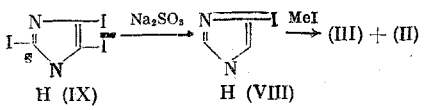
The extremely slow reduction of (IV) on heating in MeCOOH, similarly as the direct iodination of (I), is unsuitable as a method for synthesizing monoiodoimidazoles (II) and (III). However, it was found that (V) is gradually reduced to (IV), and then into the 4-iodide (II) by a calculated amount of H_2 at atmospheric pressure and at 20°C over a Raney nickel catalyst in the presence of CaO. The 5-iodide (III) is not formed.

$$(V) \xrightarrow[\text{Raney Ni}]{H_2,\ CaO} (IV) \xrightarrow[\text{Raney Ni}]{H_2,\ CaO} (II)$$

Hydrogenation can be used as a method for the selective 2-deiodination of other haloimidazoles also, for example, 5-chloro-2,4-diiodoimidazole (VI)

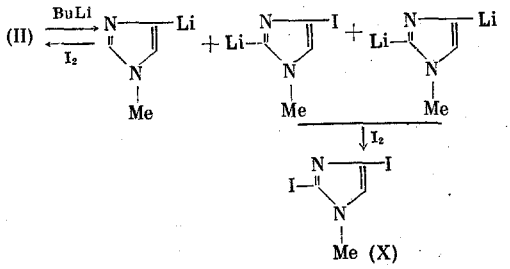


It is known that iodoimidazoles unsubstituted at the nitrogen atom are reduced by Na_2SO_3 in an aqueous-alcoholic solution [4, 5]. Compounds (IV) and (V) can be similarly reduced, but because of the sparing solubility in H_2O, a very prolonged boiling in a diluted solution of the iodide with a large excess of Na_2SO_3 is necessary. Moreover, as in hydrogenation, the 4-iodide (II) is the only reaction product. There is another possible method for the preparation of the 5-iodide, namely, the methylation of 4(5)-iodoimidazole (VIII), followed by the separation of isomers (III) and (II)



Compounds (IX) and (VIII) are readily available, since the NH-imidazole, in contrast to its N-substituted derivatives, can be readily exhaustively C-iodinated by I_2 in an alkali or neutral medium [6]. Methylation of (VIII) by MeI in an aqueous methanol solution of NaOH at 25-35°C leads to a 90% yield of a mixture of (III) and (II) (1.4 : 1). Pure (III) and (II) were isolated by column chromatography on Al_2O_3.

As methods are available for the introduction of iodine into any position of the 1-substituted imidazole ring, the preparation of 2,4- and 2,5-diiodo derivatives remains the most complex problem. One of various solutions of this problem can be demonstrated by the synthesis of 2,4-diiodo-1-methylimidazole (X). During the reaction of (II) with BuLi, at least two competing reactions can be expected: metallation in position 2, and substitution of iodine by lithium in position 4. The possible formation of 2,4-dilithium derivative and alkylation at position 4, must also be considered. The iodination of the above organolithium compounds should lead to the formation of the iodide (X) with regeneration of (II)



In fact, as the result of the reaction of (II) successively with BuLi and I_2, a mixture of products with a predominant content of (X) has been obtained. The maximum yield of (X) was 40% at a BuLi : (II) ratio of 3 : 1.

Thus, by the oxidative iodination of 1-methylimidazole and iodination of the imidazole unsubstituted at the nitrogen atom combined with reduction, metallation and N-alkylation reactions, any mono- and polyiodo-1-methylimidazoles can be synthesized. All these compounds can be condensed with acetalized 2-methylbut-3-yn-2-ol (XI), and after removal of acetal protection (acid hydrolysis) and alkaline splitting of the alcohol obtained, can be converted into ethynyl derivatives as follows [7]

$$HetI_n \xrightarrow{HC\equiv CC(Me_2)OCH(Me)OEt} Het[C\equiv C(Me_2)OCH(Me)OEt]_n \xrightarrow{H_3O^+} Het[C\equiv CC(Me_2)OH]_n \xrightarrow[KOH]{} Het(C\equiv CH)_n$$

In [1, 2] we describe the condensation of acetal (XI) with several iodoimidazoles in the presence of powdered copper and K_2CO_3 in boiling pyridine. This method was also successfully used for the condensation of (XI) with iodides (II) and (X) (Table 1, method A). Its main drawback is the long duration of the reaction, especially in the case of slightly reactive halides, including 4- and 5-iodo derivatives of imidazole (not less than 75 h). In recent years, new catalysts have been proposed which considerably intensify the process [8-11]. We used one of the most effective catalyst systems: $(PH_3P)_2PdCl_2-CuI$ in Et_2NH [11] for the preparation of imidazolylacetylenic alcohols (XIV)-(XVI) and (XII) (see Table 1). In this system, the substitution of iodine in the imidazole ring by the acetylenic group takes place much more rapidly than in the presence of metallic copper: the 4- (VII) and 5-iodide (III) reacted completely with (XI) at 45°C (method B) in the course of 6-10 h. It is known that with active catalysts it is possible to introduce 2-methylbut-3-yn-2-ol (XVII) into the reaction with aromatic halides without any protection of the hydroxyl group [8]. To compare this one-stage synthesis with a two-stage one, the 4-iodide (II) and the much more reactive 2-iodo-1-methylimidazole (XVIII) [2] were condensed directly with (XVII) (method C). The reaction proceeded much more slowly than with acetal (XI), and after 25-30 h of heating at 45°C, the reaction mixture still contained a noticeable amount of the initial iodide.

All the synthesized imidazolylacetylenic alcohols were cleaved by heating in vacuo at 120°C with powdered KOH (10-15% by weight) under conditions ensuring a rapid removal of the products formed, i.e., ethynylimidazole and acetone, from the reaction sphere (Table 2). To avoid local overheating leading to a reduction in yield, the cleavage was usually carried out in a high-boiling inert diluent [12]. Because of differences in the rates of splitting of the alkynol groupings at positions 2 and 4 [2], the yield of 2,4-diethynyl-1-methylimidazole (XX) was lower than that of the other acetylenes, and reached only 25%.

We have already noted that in the PMR spectra of ethynylpyrazoles, ethynylimidazoles and ethynyl-1,2,4-triazoles, the proton signal of the acetylenic group vicinal to the methylated ring nitrogen atom, is shifted into the weaker field relative to the proton of this group in other positions [13]. It is therefrom clear that ethynylimidazole with $\delta_{HC\equiv}$ = 3.08 ppm, synthesized from monoiodide with mp 53-54°C, is 4-ethynyl-1-methylimidazole (XIX), while its isomer with $\delta_{HC\equiv}$ = 3.52 ppm, obtained from the iodide melting at 106-107°C is 5-ethynyl-1-methylimidazole (XXI). Hence, the initial iodides and all the compounds synthesized from them have a corresponding structure.

TABLE 1. Imidazolylacetylenic Alcohols Het[C ≡ CC(Me$_2$)OH]$_n$

Compound	n	Initial iodide	Condensation method	Condensation time, h	Yield, %	mp, °C	Empirical formula	N, % found / calculated*
(XII)	1	(II)	A C	76 24	36.0 57,6	126,5–127 ($ClCH_2CH_2Cl$)	$C_9H_{12}N_2O$	17,14 17,06
(XIII)	2	(X)	A	75	49,4	143–143.5 ($ClCH_2CH_2Cl$)	$C_{14}H_{18}N_2O_2$	11,32 11,37
(XIV)	1	(VII)	B	6	72,3	125–126 [1]	–	–
(XV)	1	(III)	B	10	95,0	105–105.5 (CCl_4)	$C_9H_{12}N_2O$	16,97 17,06
(XVI)	1	(XVIII)	C	27	65,0	148.5–149 [2]	–	–

*IR spectra of (XII)–(XVI) ($CHCl_3$, ν cm^{-1}): 2235–2247 (C≡C), 3595–3608, 3260–3350 sh(OH).

TABLE 2. Ethynylimidazoles Het(C ≡ CH)$_n$

Compound	n	Yield, %	mp, °C	Empirical formula	N, % found / calculated	IR spectrum (CCl_4, ν, cm^{-1}) C≡C	IR spectrum (CCl_4, ν, cm^{-1}) ≡CH	PMR spectrum (CH_2Cl_2, δ, ppm)
(XIX)	1	70,0	82–82,5 (CCl_4)	$C_6H_6N_2$	26,45 26,40	2130	3320	3,57 (MeN), 3,08 (4-C≡CH), 7,05 (5-H), 7,26 (2-H)
(XX)	2	24.8*	111,5–112	$C_8H_6N_2$	21,69 21,53	(in $CHCl_3$) 2125	3305	3,63 (MeN), 3,36 (2-C≡CH), 3,01 (4-C≡CH), 7,08 (5-H)
(XXI)	1	66,0	n_D^{20} 1,5295	$C_6H_6N_2$	26,19 26,40	2120	3324	(in $CDCl_3$): 3,70 (MeN), 3,52 (5-C≡CH), 7,30 (4-H), 7,42 (2-H)
(XXII)	1	84,4	92–92,5 [1]	–	–	–	–	–

*Diol (XIII) was cleaved in the absence of solvent.

EXPERIMENTAL

Iodination of 1-Methylimidazole (I). A 10-g portion of (I), 39 g of I_2, and 13 g of HIO_3 in a mixture with 300 ml of MeCOOH, 55 ml of 30% H_2SO_4, and 30 ml of CCl_4 were heated for 40 h at 90-92°C (bath temperature 110-120°C). After cooling, the reaction mixture was neutralized by ~450 ml of 50% KOH, and extracted with $CHCl_3$, and the extract was dried over K_2CO_3. After distillation of the solvent, 25 g of a partially crystallized mixture of iodides and the initial (I) was obtained. The crystals, consisting mainly of 4,5-diiodo-1-methylimidazole (IV), were filtered (12.6 g) and recrystallized from CCl_4 to give 10.2 g of pure (IV). The recrystallization mother liquors were evaporated, and the residue was combined with the liquid part of the products. Further separation was carried out by chromatography on Al_2O_3 (activity grade V), with elution with petroleum ether–benzene, and $CHCl_3$–ether mixtures. Thus, 1 g (1.8%) of (V), mp 149.5-150.5°C [2]; 3.3 g of (IV) (total yield of (IV) being 33.1%, mp 141.5-142.5°C [2]); 3.5 g (13.8%) of a mixture of 4-iodo-1-methyl- (II) and 5-iodo-1-methylimidazole (III) (4 : 1 according to GLC); and 1.5 g (15%) of (I) were isolated. The mixture of (II) and (III) were separated by distillation into fractions bp 100-112°C (2 mm) and 113-115°C (2 mm), enriched with (III) and (II), respectively, followed by chromatography and recrystallization. Compound (II), mp 53-54°C (from CCl_4–petroleum ether). Found: C 23.22; H 2.42; I 60.75%. $C_4H_5IN_2$. Calculated: C 23.10; H 2.43; I 61.02%. PMR spectrum (CH_2Cl_2, δ, ppm): 3.60 (MeN), 7.23 (2-H), 6.90 (5-H). Compound (III), mp 106-107°C (from CCl_4). Found: C 22.91; H 2.30; I 60.76%. $C_4H_5IN_2$. Calculated: C 23.10; H 2.43; I 61.02%. PMR spectrum (CH_2Cl_2, δ, ppm): 3.51 (MeN), 7.51 (2-H), 7.00 (4-H).

When the iodination temperature was decreased to 75°C, and the time reduced to 3 h, the yield of (V) increased to 17.7%, and that of (IV) decreased to 13.7%.

Deiodination of 2,4,5-Triiodo-1-methylimidazole (V). A 0.5-g portion of (V) in 25 ml of MeCOOH was heated for 18 h at 100°C, and I_2 vapors were evolved. When the reduction was complete (TLC), the reaction mixture was made alkaline with ~40 ml of 50% KOH to pH 10, extracted with $CHCl_3$ and dried over K_2CO_3. Yield, 0.3 g (82.7%) of (IV). At 75°C, the reaction was prolonged to 67 h.

Deiodination of 4,5-Diiodo-1-methylimidazole (IV). A 0.5-g portion of (IV) in 25 ml of MeCOOH was heated at 100°C. After 20 h, the formation of (II) and (III) was distinctly noted by TLC. After 82 h of heating, the reaction mixture was treated in conventional manner, and the products were separated by chromatography. Yield 0.1 g (32.3%) of a mixture of (II) and (III), and 0.2 g (40%) of (IV) were recovered.

2,4,5-Triiodo-1-methylimidazole (V). a) A 1-g portion of (IV) was iodinated for 5.5 h at 75°C with 0.9 g of I_2 and 0.3 g of HIO_3 in 10 ml of MeCOOH, 1.8 ml of 30% H_2SO_4, and 2 ml of CCl_4. After alkalization of the reaction mixture, the chloroform extract was filtered through Al_2O_3 (activity grade V), and then through basic Al_2O_3. Yield of (V) 1.3 g (94%).

At 100°C, the reaction was complete after 1.5-2 h. Further heating for 20 h led to complete conversion of (V) formed into the initial (IV).

b) A 1-g portion of (I) was iodinated with 5.2 g of I_2 and 3.9 g of HIO_3 (70-75°C, 3 h). Yield of (V), 3.6 g (64%).

4-Iodo-1-methylimidazole (II). a) A 30.5-g portion of (V) in 900 ml of MeOH was hydrogenated at atmospheric pressure and at 20°C in the presence of 18.5 g of CaO and Raney nickel catalyst to the absorption of the calculated amount of H_2 (3.25 liters). The precipitate was then separated, MeOH distilled, and the residue in $CHCl_3$ passed through Al_2O_3 (activity grade V). The product, consisting of (II) with a small admixture of (IV) and (I), was distilled. The fraction boiling at 108-112°C (1 mm) is practically pure (II) (9.6 g); after recrystallization from a CCl_4–petroleum ether mixture, the yield of (II) was 8.7 g (63.2%).

Similarly, by the reduction of (IV), 69% of (II) were obtained.

b) A 2-g portion of (V) and 19.2 g of Na_2SO_3 in a mixture of 200 ml of alcohol and 160 ml of water was heated for 50 h at 100°C, and then evaporated in vacuo. The residue was extracted with $CHCl_3$. The product (0.9 g), consisting of (II) and (IV), was chromatographed on Al_2O_3 (activity grade V) in a mixture of benzene and ether (3 : 1). Yield, 0.6 g (61%) of (II).

An 8.6-g portion of (IV) was similarly reduced in the course of 80 h with 40 g of Na_2SO_3 in 170 ml of alcohol and 200 ml of water. Yield, 3 g (56%) of (II).

5-Chloro-4-iodo-1-methylimidazole (VII). A 39.4-g portion of (VI) [1] in 2 liters of MeOH was hydrogenated in the presence of 30 g of CaO and Raney nickel catalyst at atmospheric pressure and 20°C with a calculated amount of H_2 (2.6 liters). After separation of the residue and distillation of MeOH, the residue was dissolved in 800 ml of $CHCl_3$, washed with aqueous NH_3 and water, and dried over K_2CO_3. Chromatography on anhydrous Al_2O_3 in an ether–petroleum ether mixture (1 : 1) gave 17.8 g (68.7%) of VII, mp 75.5-76°C [1].

Methylation of 4(5)-Iodoimidazole (VIII). A 9.6-g portion of MeI was added in the course of 1 h at 25°C to 12.4 g of (VIII) [4] in 5 ml of MeOH and 7 ml of 40% aqueous NaOH. The mixture was stirred for 1 h at 30-35°C, and water and MeOH were distilled. After chromatography on anhydrous Al_2O_3 in an ether–petroleum ether mixture (2 : 1), 5.1 g (38.3%) of (II) and 6.9 g (51.9%) of (III) were obtained.

2,4-Diiodo-1-methylimidazole (X). A 2.1-g portion of (II) in 20 ml of ether was added at −5 to −10°C in the course of 15 min to a solution of BuLi (prepared from 0.5 g of Li and 4.1 g of BuBr) in 50 ml of ether. The mixture was stirred for 45 min without cooling. After cooling to −5°C, 7.6 g of I_2 in 50 ml of ether were gradually added. After 2 h, the reaction mixture was diluted with $CHCl_3$, and alkalized with 50 ml of 40% NaOH to the disappearance of the iodine color. From the chloroform solution, 2.8 g of a mixture of iodides was obtained. After chromatography on Al_2O_3 (activity grade IV), followed by elution with petroleum ether–benzene and ether–$CHCl_3$ mixtures, the yield was 1.3 g (38.9%) of (X), mp 122.5-123.5°C (from CCl_4). Found: C 14.35; H 1.05; I 75.88%. $C_4H_4I_2N_2$. Calculated: C 14.39; H 1.21; I 76.01%. PMR spectrum (CH_2Cl_2, δ, ppm): 3.50 (MeN), 7.05 (5-H).

Imidazolylacetylenic Alcohols (XII)-(XVI). Method A. The reaction of 4.2 g of (II) with 4.7 g of (XI) was carried out under the conditions described in [1]. Ethyl-[4-(1'-methylimidazolyl-4')-2-methylbut-3-yn-2-yl]-acetoacetal was isolated by chromatography on anhydrous Al_2O_3, and eluted successively with benzene, a benzene–ether mixture (3 : 1) and $CHCl_3$. Yield, 2.4 g (50%); n_D^{20} 1.5050. Found: N 12.00%. $C_{13}H_{20}N_2O_2$. Calculated: N 11.86%. IR spectrum (CCl_4, ν, cm^{-1}): 2248 (C≡C), 1165, 1145, 1080, and 1060 (COCOC).

Similarly, 3.9 g of (X) were condensed with 10.9 g of (XI). Yield, 3.2 g (68.1%) of acetalized (XIII); n_D^{20} 1.5052. Found: N 7.15%. $C_{22}H_{33}N_2O_2$. Calculated: N 7.17%. IR spectrum (CCl_4, ν, cm^{-1}): 2235 (C=C), 1160, 1125, 1080, 1056 (COCOC).

The acetal derivatives obtained were hydrolyzed in an acidified aqueous dioxane solution at 20°C [1].

Method B. A 7.3-g portion of (VII), 5.2 g of (XI), 105 mg of $(Ph_3P)_2PdCl_2$, and 50 mg of CuI in 90 ml of Et_2NH were heated for 6 h at 45°C in a N_2 atmosphere. The mixture was diluted with ether, filtered, and the solvent was distilled. The residue was dissolved in 10 ml of dioxane, and then 5 ml of water and 2 ml of concentrated HCl were added. The mixture was stirred for 3 h, and alkalized; compound (XIV) was extracted with $CHCl_3$.

Compound (XV) was obtained in a similar manner.

Method C. A 7.2-g portion of (XVIII) and 3.1 g of (XVII) were condensed under the conditions given in method B. Compound (XVI) was isolated by chromatography on anhydrous Al_2O_3 in a mixture of ether–petroleum ether (1:1).

Similarly, compound (XII) was synthesized from (II) and (XVII). The properties and yields of compounds (XII)-(XVI) are listed in Table 1.

4-Ethynyl-5-chloro-1-methylimidazole (XXII). A 150-mg portion of (XIV) and 25 mg of powdered KOH in 1-2 ml of m-pentaphenyl ether was heated in a sublimator in vacuo (1 mm) at 120°C. The sublimed (XXII) was separated from the small admixture of the initial (XIV) by chromatography and sublimation.

Ethynylimidazoles (XIX)-(XXI) were obtained similarly (see Table 2).

CONCLUSIONS

1. Methods for the preparation of iodine derivatives of 1-methylimidazole have been developed.

2. When heated in acetic acid, iodo-1-methylimidazoles are deiodinated, and in this reaction the iodine atom in the 2 position is substituted by hydrogen much more readily than in other cases. The reduction of triiodo-1-methylimidazole with Na_2SO_3 or hydrogen in the presence of Raney nickel catalyst and a base proceeds gradually. Depending on its position in the ring, the reactivity of the halogen atom decreases along the series: 2 > 5 > 4.

3. A catalytic condensation of the iodoimidazoles obtained with 2-methylbut-3-yn-2-ol was carried out with both preliminary protection of the hydroxyl groups in the latter, and without it. By cleavage of the imidazolylacetylenic alcohols, 4-ethynyl-, 5-ethynyl-, and 2,4-diethynyl-1-methylimidazoles were synthesized.

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