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# Stereoselective *C*(2)-Vinylation of 1-Substituted Imidazoles with 3-Phenyl-2-propynenitrile

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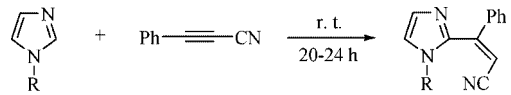


**1a-e** **2** **3a-e**

R = Me (**a**), Et (**b**), Am (**c**), Ph (**d**), Allyl (**e**)

First examples of direct vinylation of 1-substituted imidazoles at the 2-position of the imidazole nucleus are described. 1-Substituted imidazoles **1a**−**e** are *C*(2)-vinylated with 3-phenyl-2-propynenitrile (**2**) at room temperature without catalyst and solvent to afford 3-(1-organyl-1*H*-imidazol-2-yl)-3-phenyl-2-propenenitriles **3a**−**e**, mainly (*c.a.* 95%) as (*Z*)-isomers, in 56−88% yield. The reaction is likely to involve the zwitterionic intermediates, which prototropically isomerizes to imidazole carbene and eventually undergoes the selective 3,2-shift of the functionalized vinyl substituent.

The imidazole nucleus is a common structural unit of important biomolecules such as biotin, essential amino acids (histidine, histamine), and the pilocarpin alkaloids.[1a,b] Other imidazole alkaloids exhibit antimicrobial, anticryptococcal, and cytotoxic activities.[1b,2] Imidazole derivatives include nitric oxide synthase[3] and 5-lipoxygenase inhibitors,[2,4] substances with $CB_1$[1b,5] and VEGF receptors I and II,[1b,6] and neuropeptide Y antagonistic activities.[1b,7] Variously functionalized imidazoles are antibiotics,[8] fungicides,[9] antiulceretics,[10] antidiabetics, antihypertensive, and anti-inflammatory agents.[1b,11] Imidazole-based drugs such as cimetidine, etomidate, and ketoconazole are currently in clinical use.[1b,12] Recent advances in the imidazole-tailored ionic liquids (e.g., refs 1b, 13), stable nucleophilic carbenes (e.g., refs 14a−d), and organic catalysts[11,15] are other applications of imidazole derivatives.

Consequently, efforts are focused on the development of methodologies for the synthesis and functionalization of imidazoles. 2-Vinylimidazoles are of interest as potent building blocks for synthesis of novel imidazole derivatives. 2-Vinylimidazoles were obtained by vapor-phase (300−1000 °C) catalytic dehydrogenation of 2-ethylimidazoles, the crude product being a mixture of target and starting compounds.[16] 2-Vinylimidazole and 1-methyl-2-vinylimidazole were also prepared by the dehydration of the corresponding 2-hydroxyethylimidazoles in 12% yield.[17] 1-Methyl-2-(1-phenylethenyl)-1*H*-imidazole was obtained by dehydration of the 2-(1-hydroxy-1-phenylethyl) derivatives (in 73−80% yield).[18] 2-Vinylimidazoles having ester and cyano functions in the vinyl group were synthesized from 1*H*-imidazole-2-carbaldehyde and active methylene compounds.[19] The Wittig reaction with 2-chloromethylbenzimidazoles led to 2-vinylbenzimidazoles.[20] From 1-alkylimidazole-2-carbaldehydes and tribenzylphosphine oxide (Wittig−Horner reaction) 2-(2-phenylethenyl)imidazoles were synthesized in

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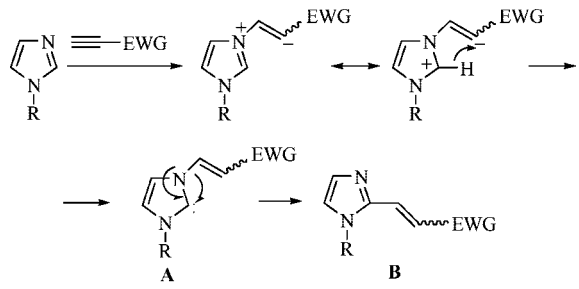
**SCHEME 1**




42−52% yield.[21] 2-Vinylimidazoles were also assembled from 2,4-dicarbonyl compounds and allylamine in 40−65% yield.[22] Despite the above achievements in the synthesis of 2-vinylimidazoles, no straightforward *C*(2)-vinylation of the imidazole nucleus with acetylenes was known until this work, though nucleophilic addition of imidazoles by their *N*(1)-position to acetylene[23] and propyne[24] was documented. It was also mentioned, that 1-methylimidazole with dimethylacetylenedicarboxylate gave polymer, while 1-acyl imidazole with the same acetylene afforded a mixture of 1- and 2-imidazolyl maleates and -fumarates in low yield.[25]

Recently we found that zwitterionic adducts were common for the reactions of α,β-acetylenic γ-hydroxy nitriles with pyridines,[26] quinoline and quinoxaline,[27] phenanthridines,[28] natural alkaloid (anabasine),[29] and 1-substituted imidazoles.[15b] In the case of the reaction of 1-substituted benzimidazoles with α,β-acetylenic γ-hydroxy nitriles, a multiposition rearrangement of the zwitterionic adducts occurred to end up with the formation of *N*-(2-{[5-amino-2,2-dialkyl-3(2*H*)-furanylidene]amino}phenyl)-*N*-substituted formamides.[30]

Therefore, one might expect that 1-substituted imidazoles would form, with electron-deficient acetylenes having no proton-donor function, the zwitterions, which further could be converted to 2-vinyl derivatives according to Scheme 1.

The proton is transferred from the 2-position of the imidazole ring toward the carbanionic center in the vinyl substituent to afford the carbene **A**, in which the 3,2-shift of the functionalized vinyl group should lead to 2-vinylimidazole **B**. Recently, nucleophilic carbenes similar to species **A** have been efficiently pioneered in three component syntheses of several heterocycles.[14b]

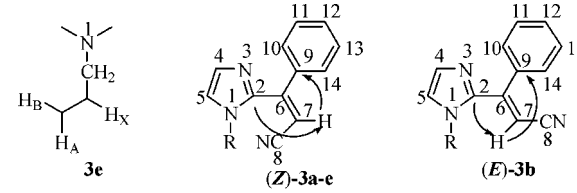



**FIGURE 1.** Assignment of *H* and C nuclei in vinylimidazoles **3a**−**e**.

This paper is to check the validity of the above general methodology for the synthesis of the *C*(2)-vinylated imidazoles on the example of 1-subsituted imidazoles **1a**−**e** and 3-phenyl-2-propynenitrile (acetylene **2**), a typical representative of electron-deficient acetylenes.

Noteworthy, as mentioned above, until this work no clear-cut precedent of the direct *C*(2)-vinylation of imidazoles with acetylenes was published.

Our experiments have shown that the reaction of 1-substituted imidazoles **1a**−**e** with acetylene **2** (in 2:1 mol ratio) proceeds smoothly under mild conditions (20−25 °C, no catalyst and solvent) to deliver mainly (*Z*)-3-(1-organyl-1*H*-imidazol-2-yl)-3-phenyl-2-propenenitriles **3a**−**e** in 56−88% yield, thus corresponding to the mechanism suggested in Scheme 1, that is, through the carbene intermediate **A**.

Alternatively, the 3,2-migration of the carbanionic moiety accompanied by a 1,5-sigmatropic shift on the imidazole, finally followed by the 2-proton transferee to the carbanionic center, may be considered. But in this case, the highly reactive carbon ion should survive the above transformation, that seems less probable.

The reaction is stereoselective: the content of the minor (*E*)-isomer usually does not exceed 5% ($^1$H NMR). The reaction was monitored by TLC (until the acetylene had disappeared). Noteworthy, that no the expected regioisomers of **3a**−**e** resulted from the alternative 1,2-shift of substituents R are detectable in the reaction mixture. The driving force of 3,2-shift of the vinyl moiety is likely the energy gain (due to the conjugation of vinyl substituents with the imidazole ring) released upon such a conversion.

For the structure determination of vinylimidazoles **3a**−**e**, $^1$H, $^{13}$C, $^{15}$N NMR and $^1$H−$^1$H homonuclear and $^1$H−$^{13}$C heteronuclear 2D (COSY, NOESY, HMBC, HSQC) techniques have been employed. In $^1$H NMR spectra of the vinylimidazoles (*Z*)-**3a**−**e**, singlets of the vinyl protons (7-H) are observed at 5.78−5.98 ppm. The signal of the same proton of (*E*)-**3b** is shifted downfield to 6.10 ppm. The vinyl moiety of vinylimidazoles **3a**−**e** is manifested itself in the $^{13}$C NMR spectrum by the signals in the region of 151.29−151.62 ppm (C-6) and 99.51−99.90 ppm (C-7). The nitrile C-atom resonates at 116.52−116.86 ppm (C-8). The large difference between chemical shifts of the olefinic carbon atoms C-6 and C-7 (∼50 ppm) is explained by the high polarization of the double bond under the electron-withdrawing effect of the cyano group (Figure 1).

The configurational assignment and substituent location for the compounds **3a**−**e** were based on the values of vicinal coupling constant $^3J_{CH}$ between olefinic proton 7-H and the imidazole carbon C-2 ($^3J_{C\text{-}2,\ H\text{-}7}$ = 10.8−11.0 Hz) as well as

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carbon C-9 of the phenyl substituents ($^3J_{C\text{-}9,\ H\text{-}7} = 5.2-5.4$ Hz). Since the *trans*-vicinal $^3J_{CH}$ value is always larger than the corresponding *cis*-$^3J_{CH}$ value, the 7-H atom is located in the *trans*-position relative to the imidazole ring and hence in the *cis*-position with respect to the phenyl substituent. Therefore, vinylimidazoles **3a**−**e** are (*Z*)-izomers. For (*E*)-isomers **3b** (which are discernible as weak signals in some $^1$H NMR spectra of (*Z*)-isomers) the corresponding $^3J_{CH}$ values are inverted: $^3J_{C\text{-}2,\ H\text{-}7} = 5.3$ Hz and $^3J_{C\text{-}9,\ H\text{-}7} = 8.5$ Hz, thus indicating the *cis*-orientation of the 7-H atom toward the imidazole ring (Figure 1). In $^1$H, $^{13}$C and $^{15}$N NMR spectra of vinylimidazoles **3a**−**e**, the following signals of the imidazole ring are present: 4-H, 5-H; C-2, C-4, C-5 and N-1, N-3. The C-2 atom lacks protons thus confirming the location of the vinyl substituent at the 2-position of the imidazole ring. In the $^{13}$C NMR spectra of compounds **3a**−**e**, the signals of C-4 and C-5 have the similar values as in starting imidazoles, while the C-2 signal is shifted downfield (from 136−137 to 142−143 ppm) by the carbon $\sigma$-effect of the functionalized vinyl substituents. As expected, in the $^{15}$N NMR spectra of the compounds **3a**−**e**, the N-1 and N-3 nuclei resonate at the different regions from −195 to −220 and from −109 to −111 ppm, respectively.

Thus, the stereoselective facile (room temperature) *C*(2)-vinylation of 1-substituted imidazoles **1** with electron-deficient acetylenes represented by 3-phenyl-2-propynenitrile (**2**) to give 3-(1-organyl-1*H*-imidazol-2-yl)-3-phenyl-2-propenenitriles **3** in 56−88% yield has been discovered. The reaction is stereoselective: mainly (*Z*)-isomers of **3a**−**e** are formed. Thus, for the first time the direct one-pot introduction of the functionalized vinyl group to the 2-position of the imidazole ring under unusually mild (close to physiological) conditions has been realized. The reaction found may be considered as a basic contribution to both the imidazole and acetylene chemistry as well as to synthetic application of zwitterions and their isomeric carbenes generated from imidazoles and electron-deficient acetylenes.

## Experimental Section

**(*Z*)-3-(1-Methyl-1H-imidazol-2-yl)-3-phenyl-2-propenenitrile (3a).** A mixture of 1-methylimidazole (**1a**) (164 mg, 2 mmol) and acetylene **2** (127 mg, 1 mmol) was stirred at 20−25 °C for 24 h. The reaction mixture was passed through a column (neutral $Al_2O_3$ with chloroform/benzene/ethanol (20:4:1) mixture as eluent), and the fraction containing the reaction product and initial imidazole **1a** was collected. Then the fraction was passed through the column again to obtain 2-propenenitrile **3a** (153 mg, 73%, brown oil) and initial imidazole **1a** (79 mg, 0.96 mmol).

**(*Z* and *E*)-3-(1-Ethyl-1H-imidazol-2-yl)-3-phenyl-2-propenenitrile (3b).** Analogously, from 1-ethylimidazole (**1b**) (192 mg, 2 mmol) and acetylene **2** (127 mg, 1 mmol) (20 h) were prepared (*E*, *Z*)-2-propenenitrile (0.3:9.7, respectively) **3b** (124 mg, 56%, brown oil) and initial imidazole **1b** (90 mg, 0.94 mmol).

**(*Z*)-3-(1-Amyl-1H-imidazol-2-yl)-3-phenyl-2-propenenitrile (3c).** Analogously, from 1-amylimidazole (**1c**) (276 mg, 2 mmol) and acetylene **2** (127 mg, 1 mmol) (24 h) were prepared 2-propenenitrile **3c** (234 mg, 88%, brown oil) and initial imidazole **1c** (130 mg, 0.94 mmol).

**(*Z*)-3-(1-Phenyl-1H-imidazol-2-yl)-3-phenyl-2-propenenitrile (3d).** Analogously, from 1-phenylimidazole (**1d**) (288 mg, 2 mmol) and acetylene **2** (127 mg, 1 mmol) (24 h) were prepared 2-propenenitrile **3d** (160 mg, 59%, brown oil) and initial imidazole **1d** (137 mg, 0.95 mmol).

**(*Z*)-3-(1-Allyl-1H-imidazol-2-yl)-3-phenyl-2-propenenitrile (3e).** Analogously, from 1-allylimidazole (**1e**) (216 mg, 2 mmol) and acetylene **2** (127 mg, 1 mmol) (24 h) were prepared 2-propenenitrile **3e** (136 mg, 58%, brown oil) and initial imidazole **1e** (100 mg, 0.93 mmol).

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**Supporting Information Available:** Spectral data and $^1$H and $^{13}$C NMR spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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