

IMIDAZOLE DERIVATIVES, PART VIII.¹

STEREOSELECTIVE FORMATION OF

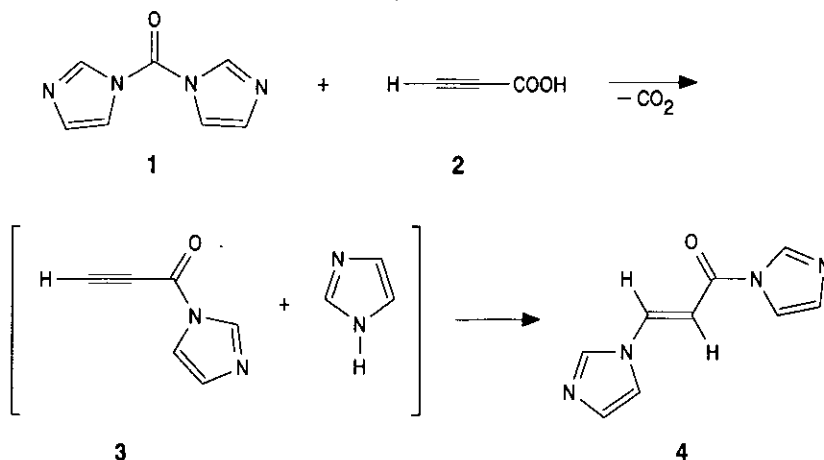
1-[(*E*) 3-(1-IMIDAZOLYL)-2-ALKENOYL]IMIDAZOLES

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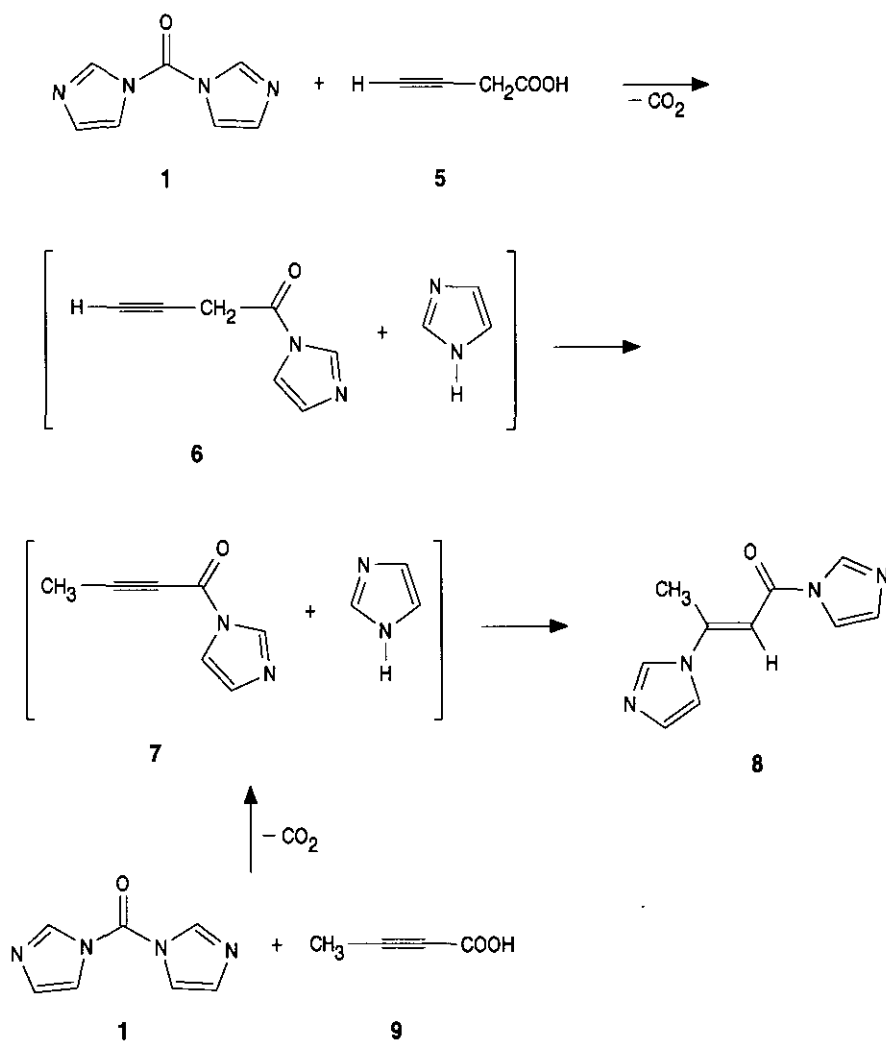
Abstract - The reaction of propynoic, 2-butynoic, and 3-butynoic acids with 1,1'-carbonyldiimidazole stereoselectively provides the corresponding 1-[(*E*) 3-(1-imidazolyl)-2-alkenoyl]imidazoles.

We have developed a method for the synthesis of 1,2-annulated imidazole derivatives by reaction of 1-acyl-imidazoles with electron-deficient alkynes.^{1,2} The required 1-acylimidazoles are readily available by the Gerngroß procedure³ (reaction of 2 equiv. of imidazole with 1 equiv. of the acyl chloride in an inert solvent) or even more conveniently by reaction of 1,1'-carbonyldiimidazole (CDI)⁴ with the corresponding acid. In an attempt to prepare 1-propynyylimidazole (**3**) by reaction of CDI (**1**) with propynoic acid (**2**), we obtained the *cis*-adduct of imidazole to the C-C triple bond of **3** (Scheme 1).



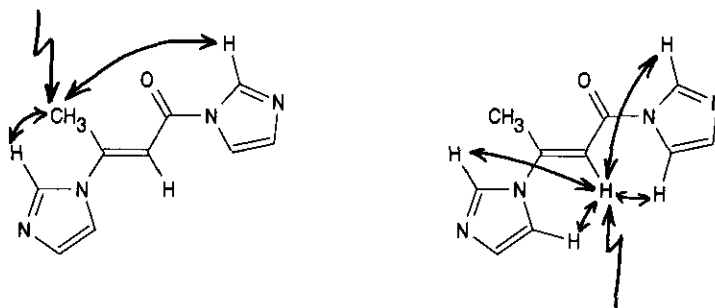
Scheme 1

After aqueous workup and crystallization, compound (4) was isolated as a single stereoisomer. The stereochemistry of the double bond is assigned on the basis of the 13.6 Hz coupling of the two olefinic protons, which is characteristic of an *E* configuration for this type of system.⁵ The reaction of CDI with propynoic acid generates in the first step 1-propynylimidazole (3),⁶ carbon dioxide and imidazole. Subsequent addition of the imidazole to the electron deficient alkyne moiety stereoselectively provides compound (4). The reaction of 3-butynoic acid (5)⁷ with CDI (1) gives a similar result (Scheme 2).



Scheme 2

It is most likely that the initially formed 1-(3-butyryl)imidazole (**6**) undergoes an imidazole-catalyzed isomerization of the alkyne to 1-(2-butyryl)imidazole (**7**)⁸. This is subsequently followed by addition of the imidazole to the activated alkyne which stereoselectively affords compound (**8**). The proposed sequence is supported by the reaction of 2-butyric acid (tetrolic acid) (**9**) with CDI (**1**) in which compound **8** was also obtained (Scheme 2). In contrast, 1-(4-pentynoyl)imidazole was the only product isolated from the reaction of CDI with 4-pentynoic acid.⁹



Representation of NOE experiments

The configuration of the double bond of **8** was determined by NOE experiments (see Experimental). Irradiation at the olefinic methyl group leads to an enhancement of the signals of the protons at C-2 of both imidazole rings while irradiation at the olefinic proton gives a signal enhancement for the protons at C-2 and C-5 of both imidazole rings.

The addition of imidazole to methyl propynoate affords under kinetic conditions the stereoisomeric adducts in an *E/Z* ratio ranging from 1:2 (reaction in dioxane) to 1:4 (reaction in methanol), depending on the solvent used.¹⁰ This stereochemical outcome is explained by a disfavored internal proton shift for steric reasons. Stereoequilibrium under the present reaction conditions is assumed to be responsible for the exclusive formation of the thermodynamically favored *E* stereoisomer.¹¹ The reaction of phenylpropynoic acid with CDI leads to 1-phenylpropynoylimidazole¹² and no further addition of the imidazole to the alkyne is observed in this case.

In conclusion, the present method provides a simple and stereoselective access to 1-[(*E*)-3-(1-imidazolyl)-2-alkenoyl]imidazoles which possibly can be exploited for the regio- and stereoselective construction of α,β -unsaturated carbonyl systems.¹³

EXPERIMENTAL

Melting points: Thomas-Hoover Unimelt apparatus; ir spectra: Perkin-Elmer 681 infrared spectrophotometer; ^1H -nmr and ^{13}C -nmr spectra: superconducting FT spectrometer equipped with a Nicolet 1280 computer system at 300 and 75 MHz respectively, internal standard: chloroform, coupling constants in Hz; mass spectra (electron impact): Kratos MS 50, Hewlett-Packard 5970A, ionization potential: 70 eV.

1-[(*E*) 3-(1-Imidazolyl)propenoyl]imidazole (4)

To a solution of propynoic acid (**2**) (2.10 g, 30.0 mmol) in dry dichloromethane (60 ml) was added in small portions 1,1'-carbonyldiimidazole (**1**) (4.86 g, 30.0 mmol). The solution was stirred for 4 h at 0°C under nitrogen, then washed with water and dried over magnesium sulfate. Removal of the solvent and recrystallization of the residue from ether provided **4** (3.25 g, 58%), bright yellow crystals; mp 180°C; ir (CHCl_3) ν 2990, 1712, 1635, 1525, 1495, 1475, 1385, 1280, 1230, 1085, 985 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 6.62 (d, $J = 13.6$, 1 H), 7.16 (m, 1 H), 7.24 (m, 1 H), 7.34 (t, $J = 1.4$, 1 H), 7.56 (t, $J = 1.4$, 1 H), 7.87 (br s, 1 H), 8.23 (d, $J = 13.6$, 1 H), 8.24 (br s, 1 H); ^{13}C -nmr (75 MHz, CDCl_3) δ 103.52, 116.20, 116.29, 131.50, 132.68, 136.08, 138.61, 140.35, 160.99; ms m/z (%) 188 (M^+ , 20), 121 (100), 97 (23), 95 (35), 94 (22), 93 (43), 83 (24), 81 (26), 71 (30), 69 (51), 68 (33). HRms calcd for $\text{C}_9\text{H}_8\text{N}_4\text{O}$: 188.0698, found: 188.0701.

ACKNOWLEDGEMENTS

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