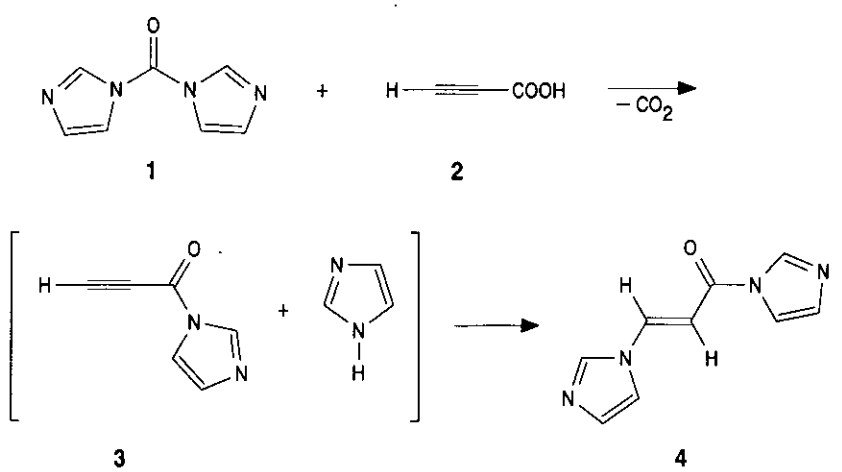
IMIDAZOLE DERIVATIVES, PART VIII.[1] STEREOSELECTIVE FORMATION OF 1-[(*E*) 3-(1-IMIDAZOLYL)-2-ALKENOYL]IMIDAZOLES

Hans-Joachim Knölker* and Abdel-Aziz El-Ahl

Institut für Organische Chemie, Universität Karlsruhe,
Richard-Willstätter-Allee, 7500 Karlsruhe 1, Germany

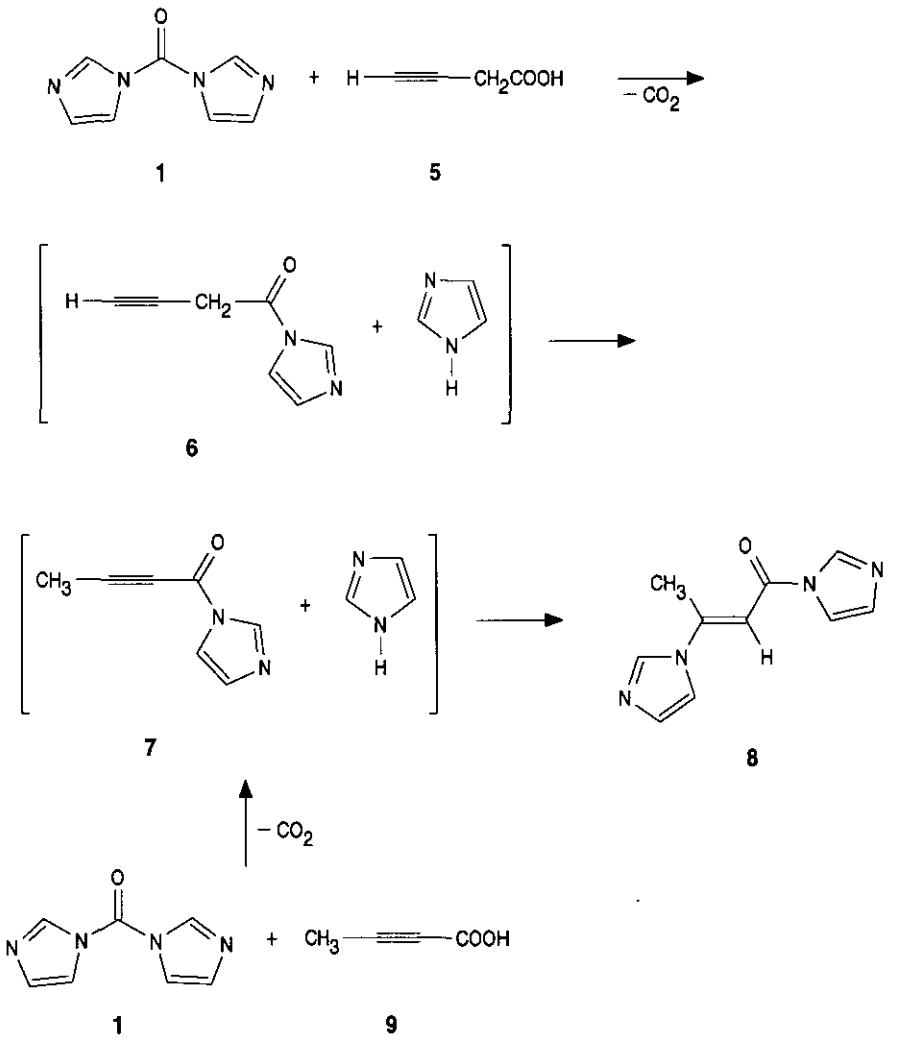
Abstract - The reaction of propynoic, 2-butynoic, and 3-butynoic acids with 1,1'-carbonyldiimidazole stereoselectively provides the corresponding 1-[(*E*) 3-(1-imidazolyl)-2-alkenoyl]imidazoles.

We have developed a method for the synthesis of 1,2-annulated imidazole derivatives by reaction of 1-acylimidazoles with electron-deficient alkynes.[1,2] The required 1-acylimidazoles are readily available by the Gerngroß procedure[3] (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-propynoylimidazole (**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).



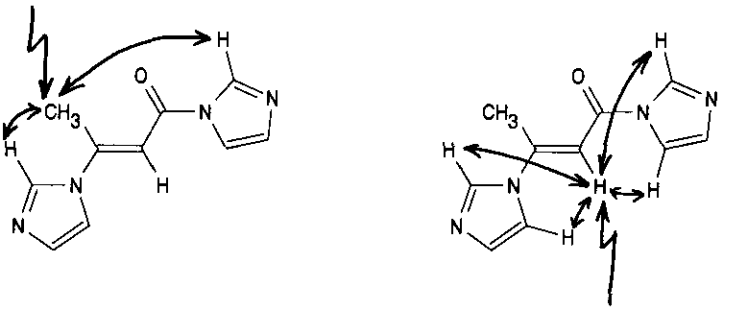
Scheme 1

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-propynoylimidazole (**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-butynoyl)imidazole (**6**) undergoes an imidazole-catalyzed isomerization of the alkyne to 1-(2-butynoyl)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-butynoic 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. Stereoequilibration 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-phenylpropynoylimidazole[12] 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; ^{1}H-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}; ^{1}H-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 $C_9H_8N_4O$: 188.0698, found: 188.0701.

1-[(*E*) 3-(1-Imidazolyl)-2-butenoyl]imidazole (8)

To a solution of 3-butynoic acid (**5**) (4.15 g, 49.4 mmol) in dry dichloromethane (80 ml) was added in small portions 1,1'-carbonyldiimidazole (**1**) (8.00 g, 49.4 mmol). After stirring for 4 h at 0°C under nitrogen the solution was washed with water and dried over magnesium sulfate. Removal of the solvent and recrystallization of the residue from ether gave **8** (5.48 g, 55%), orange-red crystals; mp 123-125°C; ir ($CHCl_3$) ν 2990, 1710, 1625, 1520, 1482, 1472, 1385, 1302, 1225, 1090, 990, 840 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.80 (d, *J* = 0.6, 3 H), 6.55 (br s, 1 H), 7.11 (s, 1 H), 7.19 (s, 1 H), 7.32 (t, *J* = 1.4, 1 H), 7.51 (t, *J* = 1.4, 1 H), 7.97 (s, 1 H), 8.20 (br s, 1 H); ^{1}H-nmr NOE experiments (300 MHz, $CDCl_3$) δ irradiation at 2.80: observed NOE's 7.97, 8.20, irradiation at 6.55: observed NOE's 7.32, 7.51, 7.97, 8.20; ^{13}C-nmr (75 MHz, $CDCl_3$) δ 17.30, 104.02, 115.99, 116.36, 130.73, 131.19, 135.28, 135.95, 152.29, 160.89; ms *m/z* (%) 202 (M^+, 9), 135 (100), 134 (11), 119 (5), 107 (15), 95 (58), 80 (24), 69 (29), 68 (52), 67 (55), 53 (24). HRms calcd for $C_{10}H_{10}N_4O$: 202.0855, found: 202.0860.

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (Kn 240/3-2), the National Institutes of Health (GM 22479) and the Fonds of Chemical Industry. A.-A. E.-A. is indepted to the Egyptian Government for a fellowship. We wish to thank Dr. G. Steiner, BASF AG, Ludwigshafen, for generous gifts of chemicals.

REFERENCES AND NOTES

1. Part VII: H.-J. Knölker, R. Boese, D. Döring, A.-A. El-Ahl, R. Hitzemann, and P. G. Jones, *Chem. Ber.*, 1992, **125**, 1939.
2. H.-J. Knölker and R. Boese, *J. Chem. Soc., Chem. Commun.*, 1988, 1151; H.-J. Knölker, R. Boese, and R. Hitzemann, *Chem. Ber.*, 1990, **123**, 327; H.-J. Knölker and R. Boese, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1821; H.-J. Knölker, R. Boese, and R. Hitzemann, *Heterocycles*, 1990, **31**, 1435; H.-J. Knölker, D. Döring, A.-A. El-Ahl, and P. G. Jones, *Synlett*, 1991, 241.
3. O. Gerngroß, *Ber.*, 1913, **46**, 1908.
4. H. A. Staab, M. Lüking, and F. H. Dürr, *Chem. Ber.*, 1962, **95**, 1275; H. A. Staab, *Angew. Chem.*, 1962, **74**, 407; *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 351.
5. J. E. Dolfini, *J. Org. Chem.*, 1965, **30**, 1298; E. Winterfeldt and H. Preuss, *Chem. Ber.*, 1966, **99**, 450; R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 1966, **99**, 2526.
6. R. C. F. Jones and M. J. Smallridge, *Tetrahedron Lett.*, 1988, **29**, 5005.
7. I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 1949, 604.
8. E. Suzuki, H. Sekizaki, and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1973, 568; E. Suzuki, H. Sekizaki, and S. Inoue, *J. Chem. Res. (S)*, 1977, 200.
9. R. Boese, H.-J. Knölker, and K. P. C. Vollhardt, *Angew. Chem.*, 1987, **99**, 1067; *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1035.
10. R. Huisgen, B. Giese, and H. Huber, *Tetrahedron Lett.*, 1967, 1883.
11. K. Herbig, R. Huisgen, and H. Huber, *Chem. Ber.*, 1966, **99**, 2546.
12. N. Latif and E. T. Kaiser, *J. Org. Chem.*, 1969, **34**, 3653.
13. C. Kashima, S. Hibi, M. Shimizu, T. Tajima, and Y. Omote, *Heterocycles*, 1986, **24**, 429.

Received, 6th January, 1993