

Oxazoles in Diels-Alder Reactions. Novel Transformation of the Adducts to 6-Substituted Pyridines

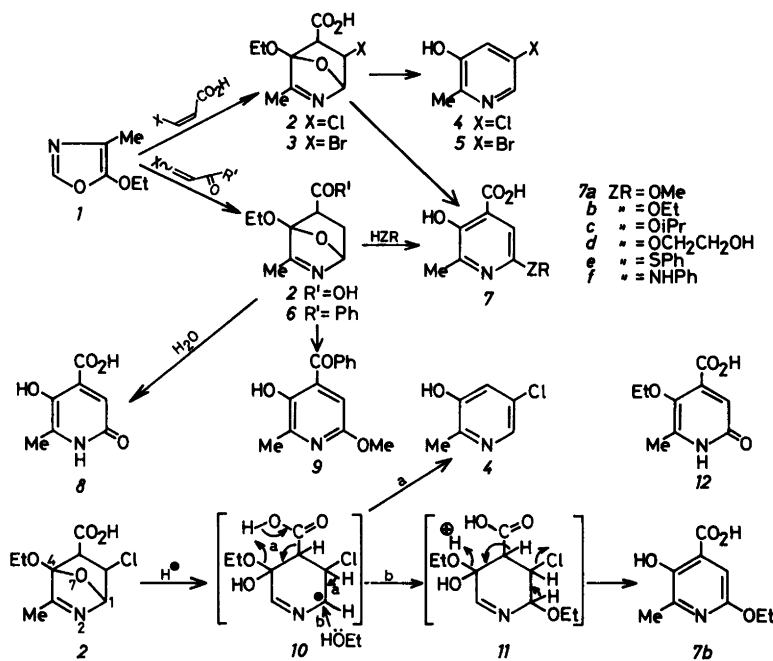
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The cycloadducts from (*Z*)- β -halopropenoic acids and 4-methyl-5-ethoxyoxazole in the presence of hydroxy, mercapto or amino derivatives are converted as formed to 6-substituted 3-hydroxypyridines with concurrent elimination of hydrogen halide. In the absence of added nucleophile, a 3-hydroxy-5-halopyridine is formed in a competitive breakdown of the adduct involving decarboxylation.

A preparatively important route to substituted β -hydroxypyridines consists of an initial Diels-Alder reaction between an ethylenic dienophile

and a 5-ethoxyoxazole which is followed by an acid catalyzed rearrangement.¹ For α,β -unsaturated carbonyl dienophiles the regioselectivity in the adduct formation is such that the carbonyl function becomes a 4-substituent in the pyridine.² Recently we have reported adduct formations from an α,β -unsaturated acid, ester, nitrile and ketones.³ We herein report on the behaviour of (*Z*)- β -halo- α,β -unsaturated carbonyl dienophiles towards 4-methyl-5-ethoxyoxazole. Our new reaction leads to a novel introduction of a 6-heterosubstituent into the pyridine ring.



Scheme 1.

The Diels-Alder adduct which is slowly formed from a mixture of 4-methyl-5-ethoxyoxazole and (*Z*)-3-bromo- or 3-chloropropenoic acid without a solvent, is unstable under the acid conditions of the reaction and is transformed as formed to a mixture of two β -hydroxypyridines. The 3-hydroxy-5-halopyridine 4 (5) has the expected substitution pattern,³ except for the 4-carboxy group which has been lost. The other product has been identified as the 6-ethoxy derivative 7b, which involves the loss of HCl (or HBr) from the intermediate adduct 2 (3). As shown in the formation of the 4-benzoyl derivative 9, the latter type of reaction can also be effected from a β -chlorovinyl ketone.

The formation of the two types of products can be rationalized by a common cationic intermediate 10 which is formed by acid catalyzed cleavage of the C(1)-O(7) bond in the Diels-Alder adduct 2. The cleavage may initially be catalyzed by the acidity of the carboxy function in the adduct, or more likely by the acidity of the 3-halopropenoic acid (pK_a 3.32 for 3-chloropropenoic acid).⁴ Decarboxylation of the intermediate 10 leads to the 3-hydroxy-5-chloropyridine 4. In a competitive reaction, however, the ethanol liberated can add to the cationic carbon giving the adduct 11; the latter on HCl and ethanol elimination yields the 4-carboxypyridine 7b. In the presence of added ethanol 7b was obtained, which supports the postulated reaction paths. In the presence of methanol or 2-propanol the corresponding 6-methoxy 7a and 6-propyloxy 7c derivatives were formed. This novel way of introducing 6-substituents was further explored in the reaction of 2 with ethane-1,2-diol which gave the monosubstituted diol 7d. In thiophenol the corresponding 6-thioether 7e, and in aniline the corresponding 6-amine 7f, were formed. By analogy, the reaction in aqueous ethanol led to the introduction of a hydroxy group and hence to the formation of the 2-pyridinone 8.

The assignment of structure 7b, rather than the isomeric 3-alkoxy-2-pyridinone structure 12 to the degradation product from the adduct 2, is based on spectroscopy and chemical properties; 12 could be visualized as formed by initial cleavage of the C(4)-O(7) bond in 2. Thus the product was not decarboxylated on heating in anisole, it was sublimed unchanged on heating at 200 °C at reduced pressure, and it was not decarboxylated when its vapour was passed

through a small quartz tube (length 20 cm) kept in an oven at 400 °C. The resistance towards decarboxylation is best rationalized by intramolecular hydrogen bonding between vicinal hydroxy and carboxy groups as in 7b, but not in 12.

Potentiometric titration⁵ gave pK_a 3.9 for 7b, which is *ca.* 1 unit lower than the value (pK_a 4.86) reported⁶ for 4-picolinic acid. The pK_a 4.20 for benzoic acid is reduced by *ca.* 1.3 units in 2-hydroxybenzoic acid; a 2- or 3-ethoxy group has little effect on the pK_a of benzoic acid.⁷ The pK_a values therefore support the assignment of structure 7b, which is further supported by the pK_a 3.8 for 4-carboxy-5-hydroxy-6-methyl-2-pyridinone 8, which was determined by the same technique.

In ¹³C NMR the chemical shifts for the pyridine carbons in 3-hydroxy- and 3-ethoxypyridine pairs are very similar; the shifts in 2-hydroxy and 2-ethoxy pairs, however, differ significantly.⁸ The ¹³C NMR shifts for 7b were: δ 144.4 (C-2), 144.7 (C-3), 122.2 (C-4), 105.3 (C-5) and 154.9 (C-6), which are to be compared with the corresponding shifts for 8: δ 147.7 (C-2), 140.9 (C-3), 126.1 (C-4), 107.3 (C-5) and 155.7 (C-6). The significant differences in the chemical shifts for the same positions in the two molecules are again interpreted in favour of the assigned structure 7b.

EXPERIMENTAL

Mass spectra are presented as [70 eV; *m/z* (% rel.int.)].

2-Methyl-3-hydroxy-5-chloropyridine 4 and 2-methyl-3-hydroxy-4-carboxy-6-ethoxypyridine 7b. 4-Methyl-5-ethoxyoxazole³ (1.27 g, 0.01 mol) and (*Z*)-3-chloropropenoic acid⁴ (1.06 g; 0.01 mol) were stirred together at room temperature for 1 week. The reaction mixture was then dissolved in acetone and dry HCl was bubbled through the solution. The precipitated salt was dissolved in water and the solution neutralized with NaOH when the title compound 4 was precipitated; yield 0.11 g (8%), m.p. 174 °C (H₂O). Anal. C₆H₆ClNO: C, H. ¹H NMR (NaOD/D₂O): δ 2.30 (2-Me), 6.90 (H-4, *J* 2 Hz), 7.50 (H-6). MS: 145/143 (33/100, *M*), 116 (7), 114 (18), 108 (9), 80 (18).

The acetone filtrate above was evaporated and the residue triturated with dichloromethane and recrystallized from water; yield of 7b (13%),

m.p. 212 °C. Analytical data are given below.

2-Methyl-3-hydroxy-5-bromopyridine 5 was prepared as above from (*Z*)-3-bromopropenoic acid⁹ in 12 % yield, m.p. 221 °C (decomp.). Anal. C₆H₆BrNO: C, H. ¹H NMR (NaOD/D₂O): δ 2.27 (2-Me), 7.07 (H-4, J 2 Hz), 7.62 (H-6). MS: 189 (98, M), 187 (100, M), 160 (21), 158 (21), 119 (10), 117 (11), 108 (14), 81 (20), 80 (32).

2-Methyl-3-hydroxy-4-carboxy-6-ethoxypyridine 7b was isolated from the acetone filtrate as above in 12 % yield.

2-Methyl-3-hydroxy-4-carboxy-6-methoxypyridine 7a. 4-Methyl-5-ethoxyoxazole³ (1.27 g, 0.01 mol) and (*Z*)-3-chloropropenoic acid (1.06 g, 0.01 mol) were added to methanol (1 ml) and the solution left at room temperature for 1 week. The solvent was then distilled off, the residue triturated with dichloromethane and recrystallized from water; yield 0.61 g (33 %), m.p. 228 °C. Anal. C₈H₉NO₄: ¹H NMR (NaOD/D₂O): δ 2.29 (2-Me), 3.77 (6-OMe), 6.52 (H-5). IR (KBr): 2550 and 1660 cm⁻¹ (CO₂H). MS: 183 (37, M), 165 (100), 137 (20), 136 (28), 109 (16), 94 (27).

When (*Z*)-3-bromopropenoic acid was used instead of the chloro analogue, the yield of **6a** was about the same.

2-Methyl-3-hydroxy-4-carboxy-6-ethoxypyridine 7b was prepared as above in ethanol solution: yield 29 %, m.p. 212 °C (H₂O). Anal. C₉H₁₁NO₄: C, H. ¹H NMR (NaOD/D₂O): δ 1.30 and 4.10 (OEt), 2.32 (2-Me), 6.63 (H-5). IR (KBr): 2500 and 1665 cm⁻¹ (CO₂H). MS: 197 (63, M) 182 (17), 179 (100), 164 (22), 151 (74), 123 (58), 95 (30).

2-Methyl-3-hydroxy-4-carboxy-6-(2-propyloxy)pyridine 7c was prepared as above in 2-propanol solution; yield 24 %, m.p. 198–200 °C (H₂O); MS molecular ion: *m/z* 211.0839; calc. for C₁₀H₁₃NO₄: 211.0845. ¹H NMR (NaOD/D₂O): δ 1.30 and 4.12 (O-2-Pr), 2.27 (2-Me), 6.59 (H-5). IR (KBr): 2600 and 1665 cm⁻¹ (CO₂H). MS: 211 (42, M), 193 (100), 165 (33), 137 (23), 95 (14), 67 (19).

2-Methyl-3-hydroxy-4-carboxy-6-(2-hydroxyethyloxy)pyridine 7d was prepared from 4-methyl-5-ethoxyoxazole (1.56 g, 0.012 mol), (*Z*)-3-chloropropenoic acid (1.32 g, 0.012 mol) and ethane-1,2-diol (1.5 g, 0.025 mol); the mixture was stirred for 2 weeks at room temperature when it was almost solidified. This mixture was triturated with chloroform and the residual material recrystallized from water; yield 0.58 g (25 %), m.p. 218 °C. Anal. C₉H₁₁NO₅: C, H. ¹H NMR (NaOD/D₂O): δ 2.25 (2-Me), 6.47 (5-H), 3.95 (CH₂CH₂). IR (KBr): 3470 (OH), 2500 and 1670 cm⁻¹ (CO₂H). MS: 213 (22, M), 195 (25), 169 (28), 151 (100), 123 (58), 95 (21).

2-Methyl-3-hydroxy-4-carboxy-6-phenylthiopyridine 7e. 4-Methyl-5-ethoxyoxazole (0.63 g, 0.005 mol), (*Z*)-3-chloropropenoic acid (0.53 g, 0.005 mol) and thiophenol (1 g, 0.01 mol) were mixed and stirred together for 1 week at room temperature. The semisolid reaction mixture was then triturated with chloroform and the residue recrystallized from water; yield 0.32 g (25 %), m.p. >340 °C. Anal. C₁₃H₁₁NO₃S: C, H. ¹H NMR (NaOD/D₂O): δ 2.33 (2-Me), 7.27 (Ph), 7.30 (H-5). IR (KBr): 2500 and 1685 cm⁻¹ (CO₂H). MS: 261 (61, M), 244 (19), 243 (100), 215 (14), 214 (49), 186 (26), 146 (13), 145 (13).

2-Methyl-3-hydroxy-4-carboxy-6-phenylaminopyridine 7f. 4-Methyl-5-ethoxyoxazole (0.63 g, 0.005 mol), (*Z*)-3-chloropropenoic acid (0.53 g, 0.005 mol) and anilin (0.92 g, 0.01 mol) were mixed and stirred together for 2 weeks at room temperature. The precipitate formed was collected by filtration and washed with chloroform and crystallized from water; yield 0.13 g (11 %), m.p. >340 °C. MS: molecular ion *m/z* 244.0848; calc. for C₁₃H₁₂N₂O: 244.0846. ¹H NMR (NaOD/D₂O): δ 2.28 (2-Me), 6.06 (H-5), 6.8–7.4 (Ph). IR (KBr): 3140 (NH), 2800 and 1670 cm⁻¹ (CO₂H). MS: 244 (86, M), 227 (13), 226 (100), 198 (20), 170 (61), 169 (17), 129 (53).

4-Carboxy-5-hydroxy-6-methylpyridin-2-one 8. 4-Methyl-5-ethoxyoxazole³ (1.27 g, 0.01 mol) and (*Z*)-3-chloropropenoic acid⁴ (1.06 g, 0.01 mol) were dissolved in ethanol (4 ml) and water (1 ml) and the solution left at room temperature for 1 week. Evaporation of the solution left a solid which was triturated with dichloromethane and recrystallized from water; yield 0.22 g (13 %), m.p. 300 °C (decomp.). Anal. C₇H₇NO₄: C, H. ¹H NMR (NaOD/D₂O): δ 2.17 (6-Me), 6.12 (H-3). IR (KBr): 2550 and 1685 cm⁻¹ (CO₂H). MS: 169 (44, M) 151 (100), 123 (67), 95 (43), 82 (11), 67 (44).

2-Methyl-3-hydroxy-4-benzoyl-6-methoxypyridine 9. (*E*)-1-Phenyl-3-chloro-2-propen-1-one¹⁰ (1.66 g, 0.01 mol) and 4-methyl-5-ethoxyoxazole (1.27 g, 0.01 mol) were dissolved in methanol (15 ml) and the solution left at room temperature for 3 d before the solvent was distilled off. The residue was subjected to preparative TLC on silica gel (Merck PF 254) using dichloromethane as developer. The appropriate chromatographic band was scraped off from the plates and the title compound extracted into dichloromethane and recovered by evaporation of the solvent; yield 0.14 g (6 %), m.p. 106–107 °C. Anal. C₁₄H₁₃NO₃: C, H. ¹H NMR (CDCl₃): 2.49 (2-Me), 3.85 (OMe), 6.63 (H-5), 7.7 (Ph). IR (KBr): 1670 cm⁻¹ (CO). MS: 243 (20, M), 242 (11), 148 (8), 147 (8), 105 (100), 77 (59).

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