Base-Catalyzed Formation of Isoxazoles from Dialkyl Acetylenedicarboxylates and 2-Nitroacetophenones

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The reaction of dialkyl acetylenedicarboxylates with 1-aryl-2-nitroethanones in the presence of pyridine leads to dialkyl 5-aryloyl-isoxazole-3,4-dicarboxylates through a novel mechanism, which involves a [2+2] cycloaddition/ring opening/cyclization sequence.

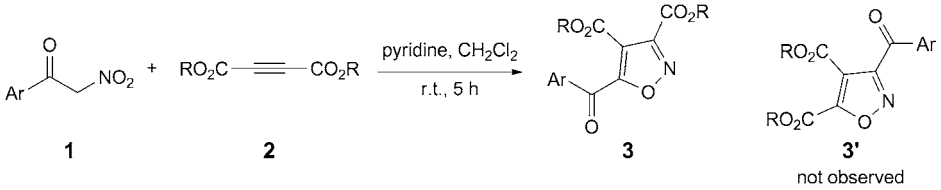
Introduction. – Isoxazoles are an important class of heterocyclic compounds and have long been targeted in synthetic investigations for their biological activities and pharmacological properties [1]. A powerful method for the construction of isoxazole ring is the [3+2] dipolar cycloaddition between alkynes and nitrile oxides [2].

As part of our studies on new routes to heterocyclic systems [3–5], we reported a synthesis of trialkyl isoxazole-3,4,5-tricarboxylates by the reaction of activated acetylenes and alkyl 2-nitroethanoates in the presence of Ph_3P under reflux condition in toluene [6]. The structures of the isoxazoles were assigned on the bases of their NMR spectroscopic data. A possible mechanism for this transformation, involving a 1,3-dipolar intermediate formed from Ph_3P and the acetylenic compound, was proposed. Now, we have found that the reaction of dialkyl acetylenedicarboxylates with 1-aryl-2-nitroethanones (2-nitroacetophenones) in the presence of pyridine proceeds by a different mechanism and does not lead to the formation of the expected product, namely dialkyl 3-aryloyl-isoxazole-4,5-dicarboxylates [6]. Single-crystal X-ray analysis for one of the products is consistent with a 5-aryloyl-isoxazole-3,4-dicarboxylate, which is formed by a [2+2] cycloaddition/ring opening/cyclization sequence.

Results and Discussion. – The reaction of 1-aryl-2-nitroethanones **1** with activated acetylenes **2** in the presence of pyridine in CH_2Cl_2 at room temperature was complete within 5 h. The ^{1}H- and ^{13}C-NMR spectra of the crude reaction mixtures cannot clearly distinguish between product **3** and **3′** (see the *Table*). Thus, we turned to X-ray diffraction. Unambiguous evidence for the proposed structure of **3a** was obtained by single-crystal X-ray-diffraction analysis. An ORTEP [7] diagram of **3a** is shown in the *Figure*. For details of the structure determination and refinement, see the *Exper. Part*.

A possible mechanism for this transformation is proposed in the *Scheme*. It is conceivable that the initial event is a [2+2] cycloaddition reaction between the conjugate base of **1** and acetylenedicarboxylates **2**, which furnishes the intermediate **5**.

Table. *Synthesis of Dialkyl 5-Aryloyl-1,2-oxazole-3,4-dicarboxylates* **3**



Entry	Ar	R	Product	Yield [%]
1	2-OH–C_6H_4	Me	**3a**	78
2	2-OH–C_6H_4	Et	**3b**	75
3	2-OH–C_6H_4	*t*-Bu	**3c**	82
4	2-OH-4,5-Me_2–C_6H_2	Me	**3d**	87
5	2-OH-4,5-Me_2–C_6H_2	Et	**3e**	83
6	2-OH-4,5-Me_2–C_6H_2	*t*-Bu	**3f**	77

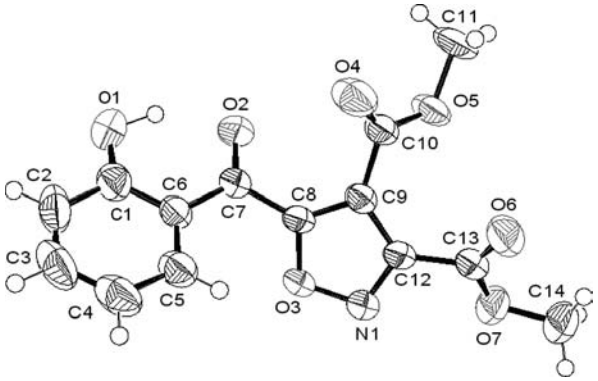
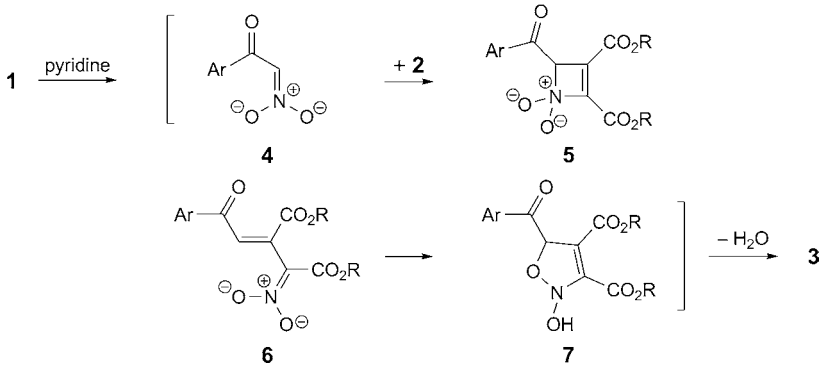


Figure. *X-Ray crystal structure of* **3a** (ORTEP-III plot [7]; arbitrary atom numbering).

Scheme



This intermediate is transformed to dihydroisoxazole derivative **7** *via* a ring opening/cyclization processes. Finally, intermediate **7** is converted to product **3** by elimination of H_2O (see *Scheme*).

In summary, we have reported that the reaction of 1-aryl-2-nitroethanones with dialkyl acetylenedicarboxylates in the presence of pyridine leads to dialkyl 5-aryloyl-isoxazole-3,4-dicarboxylates through a novel mechanism, which involves a [2 + 2] cycloaddition/ring opening/cyclization sequence.

Experimental Part

General. All chemicals were commercially available and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-300 Avance* instrument at 300 and 75 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan-MAT-8430EI-MS* mass spectrometer at 70 eV; in *m/z* (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer.

General Procedure for the Synthesis of Compounds **3**. To a stirred mixture of pyridine (0.016 g, 20 mol-%) and 1-aryl-2-nitroethanone **1** (1 mmol) in CH_2Cl_2 (5 ml) was added dialkyl acetylenedicarboxylate **2** (1 mmol). After completion of the reaction (*ca.* 5 h; TLC (AcOEt/hexane 1:3) monitoring), the precipitates were filtered and recrystallized from EtOH to give the products.

Dimethyl 5-(2-Hydroxybenzoyl)-1,2-oxazole-3,4-dicarboxylate (**3a**). Yield: 0.24 g (78%). Yellow crystals. M.p. 107–109°. IR (KBr): 1745 (C=O), 1628 (C=O), 1448, 1255, 1090, 1034. ^{1}H-NMR: 3.83 (*s*, MeO); 4.03 (*s*, MeO); 6.94 (*t*, *J* = 7.4, 1 arom. H); 7.10 (*d*, *J* = 7.4, 1 arom. H); 7.62 (*t*, *J* = 7.4, 1 arom. H); 7.71 (*d*, *J* = 7.4, 1 arom. H); 11.32 (*s*, OH). ^{13}C-NMR: 53.3 (MeO); 58.8 (MeO); 115.6 (CH); 118.3 (CH); 118.9 (CH); 120.0 (CH); 131.9 (C); 138.8 (C); 155.2 (C=N); 159.0 (C–O); 159.9 (C–O); 163.9 (C=O); 167.1 (C=O); 184.6 (C=O). MS: 305 (18, M^+), 273 (57), 246 (22), 121 (100), 93 (49). Anal. calc. for $C_{14}H_{11}NO_7$ (305.24): C 55.09, H 3.63, N 4.59; found: C 55.37, H 3.760, N 4.62.

X-Ray Crystal-Structure Determination of **3a**. Structure determination and refinement data: formula, $C_{14}H_{11}NO_7$: M_r 305.24; monoclinic, space group $P\bar{1}$, $a = 7.200(2)$, $b = 9.059(2)$, $c = 11.100(2)$ Å, $\alpha = 97.01(1)°$, $\beta = 90.83(2)°$, $\gamma = 102.91(2)°$; $Z = 2$, $V = 699.8(3)$ Å^3, $D_{calc} = 1.449$ Mg/m^3, MoK_α radiation (0.71073 Å), $T = 293(2)$ K; 3069 reflections collected on a *Bruker P4* diffractometer, 2441 unique ($R_{int} = 0.0289$), 1673 unique reflections with $I > 2\sigma(I)$. All non-H-atoms have been located by difference *Fourier* maps and refined anisotropically. All H-atoms, except that of the OH group, have been placed on calculated positions and refined isotropically by using the riding model. The H-atom of OH group has been located by difference *Fourier* maps and refined isotropically. Final indices [$I > 2\sigma(I)$]: $R_1 = 0.0620$, $wR_2 = 0.1596$, GOF = 1.007. The crystallographic data of **3a** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-1000468. Copies of the data can be obtained, free of charge, *via* the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44-1223-336033).

Diethyl 5-(2-Hydroxybenzoyl)-1,2-oxazole-3,4-dicarboxylate (**3b**). Yield: 0.25 g (75%). Yellow crystals. M.p. 120–122°. IR (KBr): 1743 (C=O), 1632 (C=O), 1450, 1245, 1087, 1032. ^{1}H-NMR: 1.23 (*t*, *J* = 7.2, Me); 1.27 (*t*, *J* = 7.2, Me); 3.87 (*q*, *J* = 7.2, CH_2); 4.06 (*q*, *J* = 7.2, CH_2); 6.92 (*t*, *J* = 7.4, 1 arom. H); 7.07 (*d*, *J* = 7.4, 1 arom. H); 7.60 (*t*, *J* = 7.4, 1 arom. H); 7.70 (*d*, *J* = 7.4, 1 arom. H); 11.31 (*s*, OH). ^{13}C-NMR: 14.7 (Me); 15.1 (Me); 63.2 (CH_2); 53.6 (CH_2); 115.3 (CH); 118.1 (CH); 118.7 (CH); 119.7 (CH); 131.8 (C); 138.6 (C); 155.1 (C=N); 159.0 (C–O); 158.9 (C–O); 163.7 (C=O); 166.9 (C=O); 184.4 (C=O). MS: 333 (14, M^+), 287 (54), 260 (21), 121 (100), 93 (46). Anal. calc. for $C_{16}H_{15}NO_7$ (333.29): C 57.66, H 4.54, N 4.20; found: C 58.87, H 4.52, N 4.23.

Di-(tert-*butyl*) *5-(2-Hydroxybenzoyl)-1,2-oxazole-3,4-dicarboxylate* (**3c**). Yield: 0.32 g (82%). Yellow crystals. M.p. 149–151°. IR (KBr): 1740 (C=O), 1631 (C=O), 1452, 1247, 1089, 1030. ^{1}H-NMR: 1.32 (*s*, Me_3C); 1.39 (*s*, Me_3C); 6.95 (*t*, *J* = 7.4, 1 arom. H); 7.08 (*d*, *J* = 7.4, 1 arom. H); 7.63 (*t*, *J* = 7.4, 1 arom. H); 7.72 (*d*, *J* = 7.4, 1 arom. H); 11.36 (*s*, OH). ^{13}C-NMR: 27.2 (Me_3C); 28.6 (Me_3C); 82.2 (Me_3C); 82.9 (Me_3C); 115.9 (CH); 118.4 (CH); 118.9 (CH); 120.6 (CH); 131.8 (C); 138.7 (C); 155.4

(C=N); 158.6 (C–O); 159.9 (C–O); 163.8 (C=O); 167.0 (C=O); 184.7 (C=O). MS: 389 (10, M^+), 313 (58), 286 (24), 121 (100), 93 (51). Anal. calc. for $C_{20}H_{23}NO_7$ (389.40): C 61.69, H 5.95, N 3.60; found: C 62.03, H 5.58, N 3.63.

Dimethyl 5-(2-Hydroxy-4,5-dimethylbenzoyl)-1,2-oxazole-3,4-dicarboxylate (**3d**). Yield: 0.29 g (87%). Yellow crystals. M.p. 121–123°. IR (KBr): 1745 (C=O), 1637 (C=O), 1455, 1250, 1092, 1033. ^{1}H-NMR: 2.12 (*s*, Me); 2.34 (*s*, Me); 3.86 (*s*, MeO); 4.05 (*s*, MeO); 7.12 (*s*, 1 arom. H); 7.62 (*s*, 1 arom. H); 11.34 (*s*, OH). ^{13}C-NMR: 22.3 (Me); 23.4 (Me); 53.2 (MeO); 53.7 (MeO); 114.8 (CH); 120.0 (CH); 127.9 (C); 131.9 (C); 134.7 (C); 138.7 (C); 154.4 (C=N); 158.7 (C–O); 159.6 (C–O); 163.8 (C=O); 166.8 (C=O); 184.9 (C=O). MS: 333 (13, M^+), 301 (56), 274 (23), 149 (100), 121 (50). Anal. calc. for $C_{16}H_{15}NO_7$ (333.29): C 57.66, H 4.54, N, 4.20; found: C 58.01, H 4.57, N 4.22.

Diethyl 5-(2-Hydroxy-4,5-dimethylbenzoyl)-1,2-oxazole-3,4-dicarboxylate (**3e**). Yield: 0.30 g (83%). Yellow crystals. M.p. 143–145°. IR (KBr): 1738 (C=O), 1629 (C=O), 1444, 1242, 1084, 1030. ^{1}H-NMR: 1.21 (*t*, *J* = 7.2, Me), 1.27 (*t*, *J* = 7.2, Me); 2.21 (*s*, Me); 2.39 (*s*, Me); 4.27 (*q*, *J* = 7.2, CH_2); 4.32 (*q*, *J* = 7.2, CH_2); 7.19 (*s*, 1 arom. H); 7.69 (*s*, 1 arom. H); 11.37 (*s*, OH). ^{13}C-NMR: 13.2 (Me); 14.6 (Me); 23.0 (Me); 42.7 (Me); 63.3 (CH_2); 63.9 (CH_2); 115.3 (CH); 120.4 (CH); 128.2 (C); 132.3 (C); 134.9 (C); 138.9 (C); 154.7 (C=N); 158.8 (C–O); 159.7 (C–O); 163.9 (C=O); 167.0 (C=O); 185.1 (C=O). MS: 361 (17, M^+), 315 (59), 288 (27), 149 (100), 121 (52). Anal. calc. for $C_{18}H_{19}NO_7$ (361.35): C 59.83, H 5.30, N 3.88; found: C 60.19, H 5.34, N 3.92.

Di-(tert-*butyl*) *5-(2-Hydroxy-4,5-dimethylbenzoyl)-1,2-oxazole-3,4-dicarboxylate* (**3f**). Yield: 0.32 g (77%). Yellow crystals. M.p. 164–166°. IR (KBr): 1742 (C=O), 1633 (C=O), 1447, 1243, 1085, 1031. ^{1}H-NMR: 1.36 (*s*, Me_3C); 1.42 (*s*, Me_3C); 2.27 (*s*, Me); 2.52 (*s*, Me); 7.21 (*s*, 1 arom. H); 7.77 (*s*, 1 arom. H); 11.34 (*s*, OH). ^{13}C-NMR: 26.3 (Me_3C); 27.7 (Me_3C); 23.2 (Me); 24.5 (Me); 83.2 (Me_3C); 82.9 (Me_3C); 115.7 (CH); 120.3 (CH); 128.7 (C); 132.4 (C); 134.5 (C); 138.7 (C); 154.3 (C–N); 158.4 (C–O); 158.9 (C–O); 164.2 (C=O); 166.8 (C=O); 184.8 (C=O). MS: 417 (11, M^+), 341 (56), 314 (23), 149 (100), 121 (52). Anal. calc. for $C_{22}H_{27}NO_7$ (417.45): C 63.30, H 6.52, N 3.36; found: C 63.09, H 6.57, N, 3.40.

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