Synthesis and Reactions of a Novel Furo[3,4-*d*]oxazole

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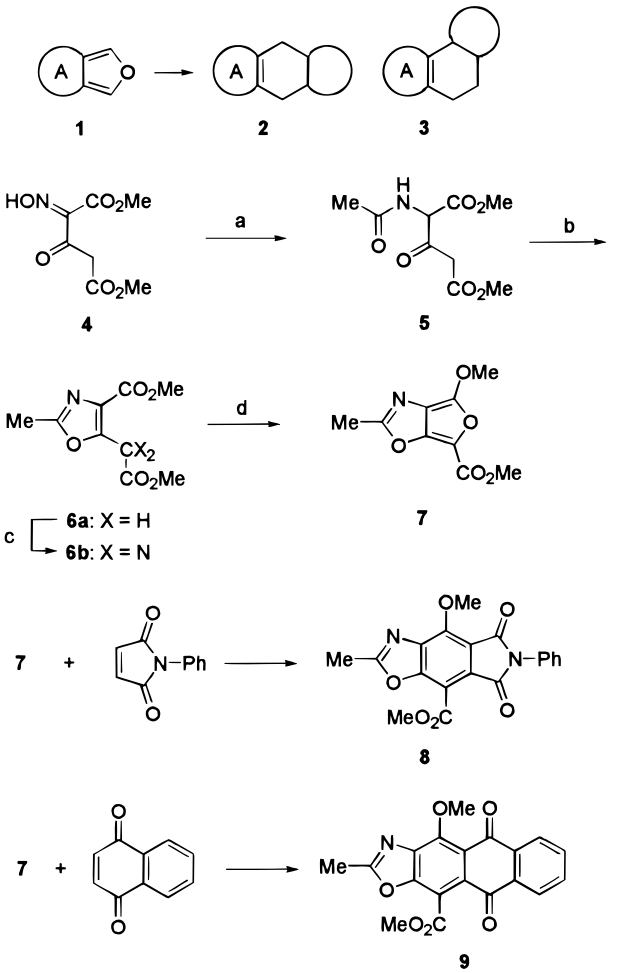
The synthesis of a novel furo[3,4-*d*]oxazole (**7**) starting from 2-hydroximino-3-oxopentanedioic acid dimethyl ester (**4**) and cycloadditions of **7** with dienophiles are reported. Density functional theoretical studies (B3LYP/6-31G*) for various *c*-annulated furans (benzo[*c*]furan, furo[3,4-*d*]-isoxazole, furo[3,4-*d*]oxazole, furo[3,4-*d*]thiazole, furo[3,4-*b*]indole) and their Diels−Alder reactions with model dienophiles (ethylene, acetylene) are in qualitative agreement with experimental data.

Introduction

Inter- and intramolecular cycloaddition reactions offer a rapid access to a wide variety of polycyclic systems.[1] Furans[2,3] and isobenzofurans (benzo[*c*]furans)[4] have been used for this purpose frequently as powerful dienes in Diels−Alder reactions.[5] Suitably substituted isobenzofurans (Scheme 1, **1**, A = benzo)−in a number of cases only prepared in situ− served as starting material for polyaromatic hydrocarbons, e.g., **2**, **3**,[4,6] inner-functionalized cavity molecules,[7] natural products (e.g., resistomycin,[8] anthracyclinones[9]), steroid analogues,[10] oxasteroid analogues,[11] azasteroid analogues,[12] polycyclic nitrogen heterocycles,[13,14] and others.[4m,15] As has been demonstrated by Padwa and co-workers, 2-aminoisobenzofurans offer an ingenious entry into the field of Erythrina alkaloids using a tandem Diels−Alder *N*-acyliminium ion cyclization sequence.[16] Progress and success in the field of isobenzofurans have prompted remarkable activities in the field of other *c*-annulated furans (**1**, Scheme 1; A

Scheme 1



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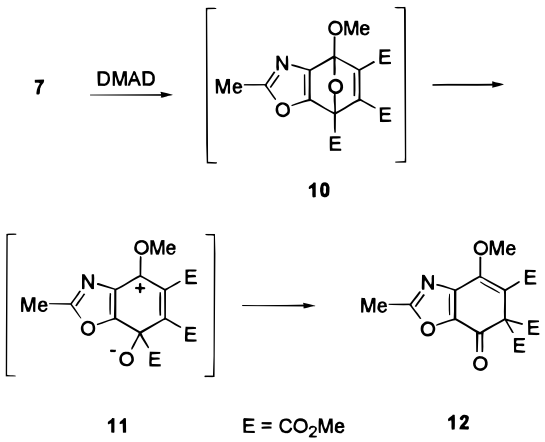
= thieno,[17,18] isoxazolo,[19] furo,[20] pyridino,[4] pyridazino,[4] benzofuro,[4,21] indolo[18,22]). In this paper we present the synthesis of furooxazole **7** and some reactions of this novel *c*-annulated furan.

Results and Discussion

As in our previous studies the synthesis of *c*-annulated furans could be accomplished by transition metal catalyzed decomposition of **6b** (Scheme 1) and subsequent intramolecular carbene reaction (Hamaguchi−Ibata reaction).[23] The starting material **6a** was prepared as follows. Compound **4** is available from dimethyl acetone dicarboxylate with ethyl nitrite/hydrogen chloride.[24] Reductive acylation[25] of **4** gives **5**[26] which, without further purification, was cyclized to oxazole[27] **6a** (19% from dimethyl acetone dicarboxylate). A diazo group transfer (Regitz reaction)[28] can be accomplished by a variety of methods. In this case 4-(azidosulfonyl)benzoic acid/DBU[29] proved to be of value, because the resulting sulfonamide can be separated from the reaction mixture quite easily. Compound **6b** was obtained as an unstable yellow oil. Transition metal catalyzed decomposition[30] of **6b** with dirhodium tetraacetate in 1,2-dichloroethane gives **7** in 39% yield (from **6a**) as stable colorless crystals. Compound **7** seems to be the first reported example of a furo[3,4-*d*]oxazole. In line with expectations (see also Theoretical Investigations) it reacts with typical dienophiles such as *N*-phenylmaleimide and 1,4-naphthoquinone to give **8** and **9**. Obviously furo[3,4-*d*]oxazoles may offer a convenient route to a variety of annulated benzoxazoles. On treatment of **7** with DMAD, compound **12** (Scheme 2) was obtained. The primary adduct (probably **10**) suffers from a ring-opening−rearrangement reaction which is well-known in the isobenzofuran,[31] furo[3,4-*b*]indole,[12,22] and furo[3,4-*d*]isoxazole series.[19,32,33] An unusual−although not unexpected−reaction occurs when **7** is treated with *p*-benzoquinone. After workup red crystals are obtained which were proved to be compound **17**. Probably in the first step the Diels−Alder adduct **14a** is formed. Whether there is a tautomeric equilibrium **14a** ⇌ **13a** is unknown, but according to density functional theoretical (DFT) calculations on the model compounds **13b** and **14b** (Scheme 3; see Theoretical Investigations, Table 4), **14b** is more favored than **13b** (ΔE (**14b** − **13b**) = 6.9−8.2 kcal/mol). Ring opening (to **15**) with subsequent rearrangement may give **16** which tautomerizes to **17**. It is not unreasonable that these last two steps occur in reversed order (**15** → **18** → **17**). To explore the synthetic utility of furo[3,4-*d*]oxazoles in *intra*molecular cycloadditions with *unactivated* olefins, the tethered precursors **20a**,**b** were prepared. Selective saponification of **6a** with KOH gives **19** (Scheme 4) in 67% yield.[34] Esterification with allyl alcohol and buten-1-ol-4 using the Neises−Steglich procedure (DCC/DMAP/$CHCl_3$)[35] gives **20a** and **20b**, respectively, which can be transformed to the diazoesters **21a**,**b**. These latter compounds were obtained as unstable yellow oils. Sub-

Scheme 2



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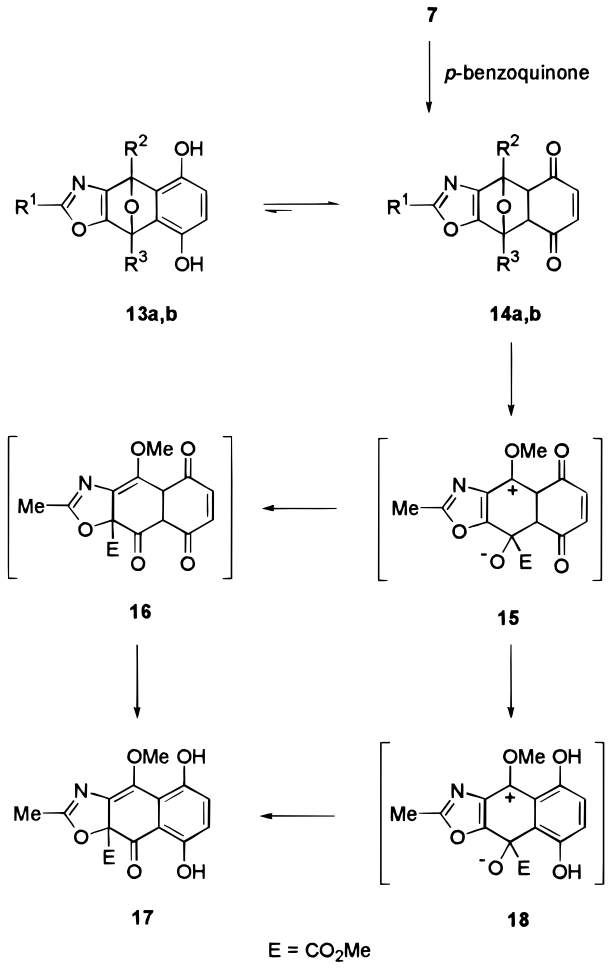
Scheme 3



jection of these precursors to metal-catalyzed decomposition conditions failed to provide any cycloadduct derived from a furo[3,4-*d*]oxazole. Instead, cyclopropane derivatives **22a**,**b** were formed, albeit in low yields (27% and 25%, respectively). It is unclear whether furo[3,4-*d*]-oxazoles of type **23** (Scheme 5) are formed in small amounts and whether compounds of this type are not sufficiently reactive to participate in an intramolecular cycloaddition reaction with an unactivated olefin. From a *purely thermodynamic* point of view one can expect that compounds of type **25** (Scheme 5) are formed with preference (see Theoretical Investigations, Table 4).

Theoretical Investigations. The *detailed* structure of furo[3,4-*d*]oxazoles is unknown. Quantum chemical calculations in the furo[3,4-*d*]isoxazole series revealed that for the prediction of geometric data (bond distances, etc.) DFT methods[36−40] seem to be most reliable especially when Becke's three parameters[41] DFT exchange functional in combination with the Lee, Yang, and Parr correlation functional[42] (B3LYP)[43] together with a 6-31G* basis[44] is used. It has been demonstrated that this hybrid functional gives optimized geometries for a wide range of molecules.[45] Therefore, it can safely be expected that the bond distances[46] given in Table 1 for **7** and the parent system **32** can be met with trust. Semiempirical methods (AM1, PM3)[47,48] seem to fail, as were also observed in the furo[3,4-*d*]isoxazole series. The *reactivity* of furo[3,4-*d*]-oxazoles in Diels−Alder reactions has not been investigated *quantitatively*, but *qualitative* observations reveal that furo[3,4-*d*]oxazoles are less reactive than benzo[*c*]-furans. Recent results obtained by other authors[49,50] have shown that transition states of Diels−Alder reactions can be calculated with some confidence by DFT methods. To get insight into the reactivity of *c*-annulated furans, both the thermochemistry as well as the transition states of the following two series of model reactions 1−5, 6−10, Scheme 6, Tables 2−4) have been investigated with different quantum chemical methods.

The following results were obtained (Table 2):

(a) Benzofuran (**26**) is most reactive in both series (lowest transition state energies). The transition state for reaction 1 is−in line with expectations−symmetric with $r(7-11) = r(8-9) = 2.26$ Å (the new formed bonds, see Figure 1). The reaction centers (C(7), C(8), C(9), C(11), Figure 1) are slightly pyramidalized. Furo[3,4-*d*]-isoxazole (**29**)[19] is of intermediate reactivity in both series (reactions 2, 7). Furo[3,4-*d*]oxazole (**32**), furo[3,4-*d*]-thiazole (**35**),[51] and furo[3,4-*b*]indole (**38**)[22] are least reactive in both series (reactions 3, 8, 4, 9, and 5, 10, respectively). The transition state for reaction 3 is asymmetric with $r(5-7) = 2.19$ Å and $r(9-10) = 2.23$ Å (see Figure 2) again with a sligthly pyramidalized ethene. In both series there is a strong linearity between the heats of reaction and the corresponding transition state energies: Highly exothermic reactions point to low transition state energies (and *vice versa*), but this linearity holds only for DFT calculations (Table 2). These results offer the opportunity to take heats of reaction

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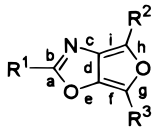
Table 1. Calculated Bond Distances (Å) for 7 and 32



7: R^1 = Me, R^2 = OMe, R^3 = CO_2Me

32: $R^1 = R^2 = R^3$ = H

method	a	b	c	d	e	f	g	h	i	ΔH,[a] E[b]
AM1 (**32**)	1.435	1.320	1.408	1.494	1.384	1.362	1.407	1.398	1.373	+27.86
PM3 (**32**)	1.404	1.319	1.426	1.456	1.385	1.364	1.392	1.385	1.367	+5.72
RHF/6-31G* (**32**)	1.360	1.262	1.400	1.411	1.357	1.334	1.358	1.350	1.341	−395.18103
RHF/6−311yG** (**32**)	1.359	1.260	1.400	1.411	1.353	1.333	1.356	1.348	1.340	−395.27196
B3LYP/6-31G* (**32**)	1.389	1.288	1.401	1.419	1.372	1.357	1.377	1.369	1.366	−397.46203
B3LYP/6-31G* (**7**)	1.408	1.291	1.395	1.408	1.356	1.372	1.409	1.352	1.377	−779.19525

[a] In kcal/mol (AM1, PM3).[47,48] [b] In au (*ab initio* and DFT methods).[37]

Table 2. Transition State Energies ΔE(ts) and Reaction Energies (ΔE) and Enthalpies ($\Delta\Delta H_f$) for Reactions 1−10 (values in kcal/mol)

		ΔE[b] ($\Delta\Delta H_f$)[c]			
reaction	ΔE(ts − tg)[a]	AM1	PM3	RHF/6-31G*	B3LYP/6-31G*
1	+15.39	−34.84	−32.47	−36.91	−29.76
2	+17.78	−22.86	−21.09	−27.95	−23.40
3	+19.63	−23.39	−20.92	−20.02	−19.04
4	+19.68	−25.71	−19.50	−23.08	−19.60
5	+19.60	−22.15	−22.00	−22.36	−19.02
6	+17.77	−28.92	−28.27	−37.23	−34.44
7	+20.20	−15.93	−16.39	−25.01	−25.17
8	+21.76	−16.49	−16.22	−18.36	−20.24
9	+21.90	−19.39	−15.06	−20.22	−21.59
10	+21.94	−15.69	−17.57	−19.13	−20.65

[a] Energy difference between the ground state and the transition state. [b] Reaction energy (*ab initio*, DFT). [c] Reaction enthalpy (AM1, PM3).

Table 3. Reaction Energies (ΔE)[a] and Enthalpies (ΔH_f)[b] for the Formation of 41−44, 46, and 47 (in kcal/mol)

	ΔE, $\Delta\Delta H_f$			
	AM1	PM3	6-31G*	B3LYP/6-31G*
41	−17.44	−16.63	−14.18	−10.19
42	−20.94	−17.76	−17.26	−11.27
43	−10.76	−13.34	−12.15	−12.75
44	−14.27	−13.58	−14.89	−13.84
46	−29.69	−30.01		−16.42
47	−22.57	−25.40		−25.98

[a] Reaction energies (*ab initio*, DFT). [b] Reaction enthalpies (AM1, PM3).

calculated for two or more strongly related reactions with DFT methods mentioned above as a *qualitive* tool for Diels−Alder reactions of *c*-annulated furans (and other compounds). In line with this reasoning are the results of the reactions which lead to **41**−**44**, and **46**, and **47** (Scheme 7, Table 3): (1) 1-Alkoxy-3-alkoxycarbonyl substituted *c*-annulated furans are *less reactive* than their unsubstituted counterparts; (2) Furo[3,4-*d*]oxazoles and -thiazoles are *less reactive* than the corresponding benzo[*c*]furan.

Conclusion

The Hamaguchi−Ibata reaction proved to be of value for the synthesis of furo[3,4-*d*]oxazoles and other *c*-annulated furans (benzo[*c*]furans, furo[3,4-*d*]isoxazoles, furo[3,4-*b*]indoles, furo[3,4-*d*]thiazoles[51]) and complements other methods for the preparation of these compounds[4m] (e.g., Pummerer-induced cyclization of sulfoxides). Generally speaking heteroannulated furans are less reactive than benzo[*c*]furans but may nevertheless serve as an entry to heteroannulated polycyclic ring systems. DFT methods are valuable quantum chemical tools for exploring the Diels−Alder reactivity of these compounds.

Experimental Section

General. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Acetonitrile was distilled from CaH_2, cyclohexane and 1,2-dichloroethane were distilled from P_2O_5, and chloroform and EtOAc were distilled from $CaCl_2/K_2CO_3$.

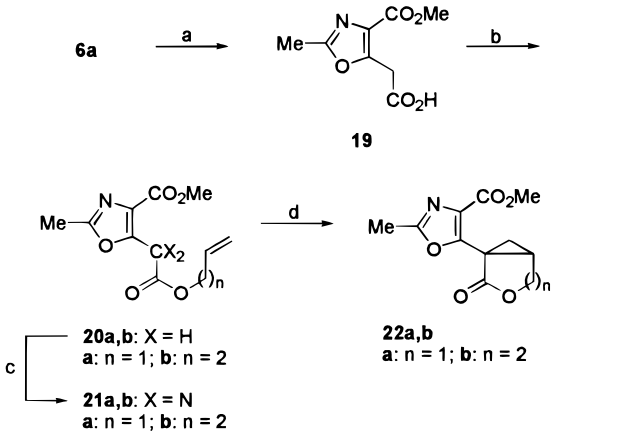
5-(Methoxycarbonyl)-2-methyloxazole-4-carboxylic acid methyl ester (6a): 2-Hydroximino-3-oxopentanedioic acid dimethyl ester was prepared starting from 45.0 g (0.26 mol) of acetone dicarboxylic acid dimethyl ester following the reported method.[24] The obtained green-yellow oil was dissolved in acetic acid (150 mL) and acetic anhydride (75 mL). Zinc dust (56 g, 0.86 mol) was added portionwise so that the temperature stayed below 40 °C (cooling with ice/salt bath). After stirring for 10 min, 150 mL of water was added dropwise at such a rate that the temperature again stayed below 40 °C. After additional stirring for 2 h at room temperature, the reaction mixture was filtered, the filter cake was washed with water (2 × 60 mL), and the combined filtrates were extracted with chloroform (5 × 100 mL). The collected organic layers were washed with water (2 × 75 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 2-(acetylamino)-3-oxopentanedioic acid dimethyl ester as crude orange oil (42.3 g, 71%). This oil was dissolved in 150 mL of chloroform, and after cooling to 5 °C ,20 mL (0.27 mol) of thionyl chloride was added. The ice bath was removed, and the mixture was slowly heated to reflux. After gas evolution ceased, the solution was allowed to come to room temperature and then concentrated *in vacuo*. The residue was dissolved in ether and washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and purified by column chromatography (silica gel, cyclohexane/EtOAc (1:1)) to give, after recrystallization, oxazole **6a** as colorless needles (11.3 g, 19% overall yield): mp 69−70 °C; IR (KBr) ν 1741, 1716, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H), 3.75 (s, 3H), 3.90 (s,

Table 4. DFT Energies[a,b] for Compounds 7, 13, 14, 23, 25−47 and the Transition States of Reactions 1−10[c] (in au)

compound		compound		compound		reaction	
7	−779.19425	**30**	476.04814	**40**	−592.57673	1	−462.21329
13b	−778.91373	**31**	−474.78915	**41**	−857.79795	2	−475.98251
14b; *endo*	−778.92473	**32**	−397.46203	**42**	−1180.78580	3	−476.01820
14b; *exo*	−778.92673	**33**	−476.07983	**43**	−856.54022	4	−799.00691
23	−817.24495	**34**	−474.81992	**44**	−1179.52807	5	−593.77440
25	−817.31796	**35**	−720.45081	**45**	−726.06082	6	−460.94769
26	−383.65037	**36**	−799.06951	**46**	−804.67445	7	−474.71685
27	−462.28524	**37**	−797.81086	**47**	−803.42787	8	−474.75299
28	−461.03090	**38**	−515.21817			9	−797.74156
29	−397.42339	**39**	−593.83594			10	−592.50885

[a] B3LYP/6-31G*. [b] Ethene: −78.587457 au; acetylene: −77.325645 au. [c] The Hesse matrix of the transition states showed one negative eigenvalue.

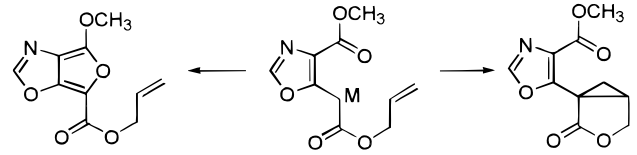
Scheme 4



a: KOH, MeOH; b: DCC, DMAP, $CH_2=CHCH_2OH$ or $CH_2=CH(CH_2)_2OH$;

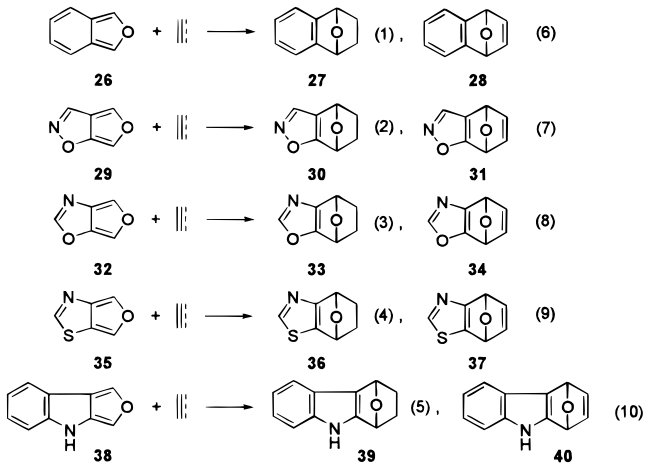
c: $HO_2CC_6H_4SO_2N_3$, DBU, MeCN; d: $Rh_2(OAc)_4$, 1,2-dichloroethane.

Scheme 5



M: Rh_2Ln_4

Scheme 6



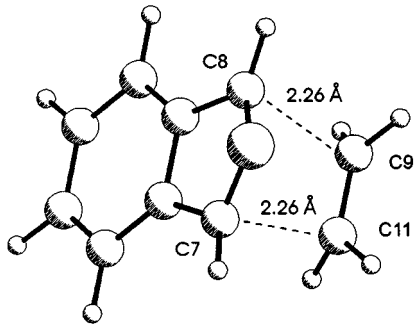


Figure 1. Transition state of reaction 1 (Scheme 6; B3LYP/6-31G*).

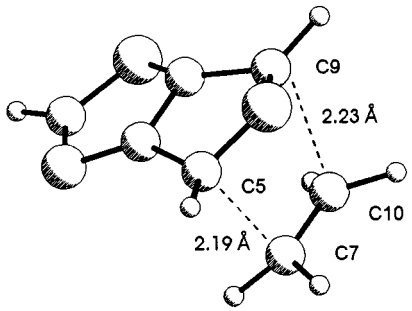
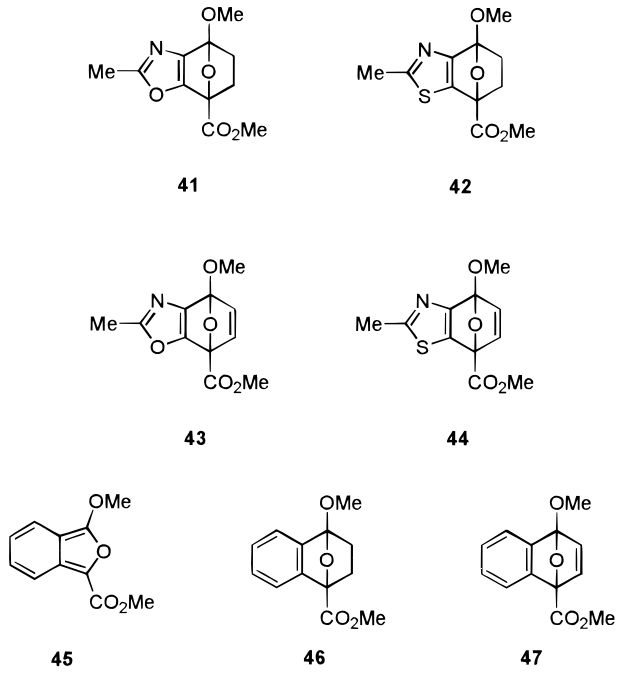


Figure 2. Transtion state of reaction 3 (Scheme 6; B3LYP/6-31G*).

3H), 4.10 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 31.4 (t), 51.6 (q), 52.1 (q), 128.9 (s), 151.1 (s), 160.3 (s), 161.8 (s), 167.7 (s); MS (EI, 70 eV) *m*/*z* 213 (21, M^+), 181 (100), 154 (73), 150 (21); HRMS calcd for $C_9H_{11}NO_5$ 213.0637, found 213.0635. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.95; H, 5.19; N, 6.65.

4-Methoxy-2-methylfuro[3,4-*d*]oxazole-6-carboxylic Acid Methyl Ester (7). A suspension of 4-(azidosulfonyl)benzoic acid (1.76 g, 7.5 mmol) in a solution of oxazole **6a** (1.5 g, 7.0 mmol) in 70 mL of acetonitrile was cooled under nitrogen to 0 °C. To this mixture 2.43 mL (16.3 mmol) of DBU was added. The acid dissolved immediately, the solution became dark red, and, after a short period, the DBU salt of 4-sulfamoylbenzoic acid precipitated. After stirring for 1 h at room temperature, the precipitate was filtered off, and the filtrate was purified by chromatography over silica gel eluting with EtOAc. The yellow solution of 5-(diazo(methoxycarbonyl)methyl)-2-methyloxazole-4-carboxylic acid methyl ester **6b** was concentrated carefully *in vacuo* (bath temperature below 30 °C) to obtain **6b** as a yellow oil, which shows slow decomposition. IR (film) ν 2955, 2125, 1717, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.2 (q), 51.4 (q), 51.9 (q), 126.9 (s), 142.5 (s), 160.6 (s), 161.8 (s), 162.4 (s) (signal for CN_2 not observed); MS (EI, 70 eV) *m*/*z* 239 (4, M^+), 211 (70), 180 (9), 168 (15), 140 (100), 112 (22). The diazoester **6b** was dissolved immediately after isolation in 75 mL of 1,2-dichloroethane. This solution was dropped under nitrogen in 1 h to a suspension of $Rh_2(OAc)_4$ (1.5 mg) in 1,2-dichloroethane (100 mL) heated to reflux. After refluxing for additional 30 min, the reaction mixture was cooled to room temperature, concentrated *in vacuo*, filtered over silica gel, and purified by

Scheme 7



radial chromatography (silica gel, cyclohexane/EtOAc 2:1). After recrystallization from ether/pentane, furan **7** is obtained as fine colorless needles (580 mg, 39%): mp 133−134 °C; IR (KBr) ν 1720, 1670, 1633, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 3.89 (s, 3H), 4.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.7 (q), 51.5 (q), 59.0 (q), 110.9 (s), 115.2 (s), 146.5 (s), 152.3 (s), 157.2 (s), 168.0 (s); UV (MeCN) λ (log ϵ) 215 (4.266), 287 (4.430); MS (EI, 70 eV) *m*/*z* 211 (70, M$^+$), 180 (16), 168 (11), 140 (100); HRMS calcd for $C_9H_9NO_5$, 211.0481, found 211.0478. Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.19; H, 4.27; N, 6.53.

4-Methoxy-2-methyl-5,7-dioxo-6-phenyl-6,7-dihydro-5*H*-oxazolo[4,5-*f*]isoindole-8-carboxylic Acid Methyl Ester (8). A solution of furooxazole **7** (600 mg, 2.8 mmol) and *N*-phenylmaleimide (1.48 g, 8.5 mmol) in chloroform (50 mL) was heated to reflux for 2 h. Removal of the solvent and chromatographic workup yield compound **8** as colorless crystals (239 mg, 23%): mp 217−218 °C; IR (KBr) ν 1764, 1718, 1710, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3H), 4.04 (s, 3H), 4.62 (s, 3H), 7.36−7.40 (m, 1H), 7.42−7.44 (m, 2H), 7.47−7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7 (q), 53.3 (q), 61.9 (q), 107.9 (s), 109.6 (s), 113.6 (s), 126.7 (d), 127.4 (s), 128.1 (d), 129.0 (d), 131.5 (s), 135.6 (s), 150.6 (s), 153.9 (s), 163.0 (s), 164.6 (s), 165.2 (s); UV (MeCN) λ (log ϵ) 247 (4.972), 370 (3.914); MS (EI, 70 eV): *m*/*z* 366 (91, M$^+$), 335 (21), 306 (100). HRMS calcd for $C_{19}H_{14}N_2O_6$, 366.08517, found 366.08500. Anal. Calcd for $C_{19}H_{14}N_2O_6$: C, 62.30; H, 3.85; N, 7.65. Found: C, 62.85; H, 3.90; N, 7.51.

4-Methoxy-2-methyl-5,10-dioxoanthra[2,3-*d*]oxazole-11-carboxylic Acid Methyl Ester (9). 1,4-Naphthoquinone (1.62 g, 10.2 mmol) was added to a solution of 720 mg (3.4 mmol) of furooxazole **7** in chloroform (50 mL) and the solution heated under nitrogen for 3 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica gel, cyclohexane/EtOAc 2:1). Recrystallization from dichloromethane/pentane gives **9** as yellow crystals (240 mg, 24%): mp 224−225 °C; IR (KBr) ν 1728, 1668, 1602, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3H), 4.10 (s, 3H), 4.59 (s, 3H), 7.70−7.82 (m, 2H), 8.16−8.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 53.4 (q), 62.1 (q), 112.0 (s), 119.5 (s), 126.8 (d), 127.3 (d), 129.9 (s), 132.1 (s), 133.3 (d), 134.6 (d), 135.0 (s), 135.8 (s), 152.1 (s), 153.7 (s), 165.2 (s), 166.3 (s), 181.7 (s), 182.4 (s); UV (MeCN) λ (log ϵ) 245 (4.869), 265 (4.466), 325 (3.653), 375 (3.728); MS (EI, 70 eV) *m*/*z* 351 (80, M$^+$), 322 (100), 290 (13); HRMS calcd for $C_{19}H_{13}NO_6$, 351.07428, found 351.074028. Anal. Calcd for $C_{19}H_{13}NO_6$: C, 64.96; H, 3.73; N, 3.99. Found: C, 64.55; H, 3.76; N, 3.91.

4-Methoxy-2-methyl-7-oxo-7*H*-benzoxazole-5,6,6-tricarboxylic Acid Trimethyl Ester (12). A solution of furooxazole **7** (520 mg, 2.5 mmol) and DMAD (874 mg, 6.2 mmol) in chloroform (40 mL) was heated to reflux for 1.5 h. After cooling to room temperature and evaporation of the solvent, the residual oil was filtered over silica gel and purified by radial chromatography (silica gel, cyclohexane/EtOAc 5:1). Crystallization from ether/pentane yields **12** as nearly colorless crystals (269 mg, 31%): mp 163−164 °C; IR (KBr) ν 1785, 1745, 1715, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H), 3.79 (s, 6 H), 3.83 (s, 3H), 4.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.8 (q), 52.6 (q), 54.0 (q), 61.6 (q), 72.2 (s), 117.5 (s), 143.6 (s), 148.7 (s), 152.3 (s), 164.1 (s), 164.3 (s), 168.9 (s), 173.8 (s); UV (MeCN) λ (log ϵ) 240 (4.304), 333 (3.439); MS (EI, 70 eV) *m*/*z* 353 (21, M$^+$), 322 (13), 309 (64), 294 (100); HRMS calcd for $C_{15}H_{15}NO_9$; 353.07468, found 353.07440. Anal. Calcd for $C_{15}H_{15}NO_9$: C, 51.00; H, 4.28; N, 3.96. Found: C, 50.90; H, 4.33; N, 3.87.

5,8-Dihydroxy-4-methoxy-2-methyl-9-oxo-9*H*-naphtho-[2,3-*d*]oxazole-9a-carboxylic Acid Methyl Ester (17). A solution of furooxazole **7** (500 mg, 2.3 mmol) and *p*-benzoquinone (761 mg, 7.0 mmol) in chloroform (30 mL) was heated under nitrogen for 6 h to reflux. After chromatographic workup compound **17** was obtained from ether/*n*-pentane as red crystals (68 mg, 9%): mp 169 °C (decomp); IR (KBr) ν 3422, 2964, 1737, 1719, 1633, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.71 (s, 3H), 4.28 (s, 3H), 6.85 (d, 1H, J = 9.2 Hz), 7.11 (d, 1H, J = 9.2 Hz), 8.43 (s, 1H), 11.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7 (q), 54.3 (q), 61.3 (q), 88.6 (s), 110.0 (s), 116.2 (s), 120.9 (d), 127.0 (s), 130.4 (d), 137.7 (s), 148.5 (s), 157.1 (s), 165.8 (s), 168.6 (s), 195.6; UV (MeCN) λ (log ϵ) 235 (4.188), 261 (4.247), 293 (3.905, sh), 380 (3.428), 454 (3.661); MS (EI, 70 eV) *m*/*z* 319 (15, M$^+$), 304 (19), 260 (100), 245 (20); HRMS calcd for $C_{15}H_{13}NO_7$; 319.06921, found 319.06910. Anal. Calcd for $C_{15}H_{13}NO_7$: C, 56.43; H, 4.10. Found: C, 56.29; H, 4.19.

5-Carboxymethyl-2-methyl-oxazole-4-carboxylic Acid Methyl Ester (19). A solution of oxazole **6a** (3.00 g, 14.1 mmol) in 80 mL of methanol was treated with KOH (946 mg, 16.9 mmol), heated to reflux for 4 h, cooled to room temperature, and neutralized with 1.9 mL (16.9 mmol) of 60% perchloric acid. The precipitate of $KClO_4$ was filtered off and the filtrate concentrated *in vacuo*. Recrystallization from methanol/ether gives **19** as a colorless solid (1.87 g, 67%): mp 144−145 °C; IR (KBr) ν 3422, 1737, 1719, 1633, 1594 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 3.77 (s, 3H), 4.01 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 13.4 (q), 32.3 (t), 51.8 (q), 128.2 (ss), 153.1 (st), 160.2 (sq), 162.0 (sq), 169.4 (st) MS (EI, 70 eV) *m*/*z* 189 (1, M$^+$), 168 (7) 155 (37), 123 (100). Anal. Calcd for $C_8H_9NO_5$: C, 48.25; H, 4.55; N, 7.03. Found: C, 48.20; H, 4.51; N, 7.01.

5-[(Allyloxycarbonyl)methyl]-2-methyloxazole-4-carboxylic Acid Methyl Ester (20a). To a solution of oxazole **19** (1.50 g, 7.5 mmol), allylic alcohol (569 mg, 9.8 mmol), and (dimethylamino)pyridine (DMAP) (60 mg, 0.5 mmol) in 75 mL of chloroform 2.02 g (9.8 mmol) of dicyclohexyl carbodiimide (DCC) were added. After stirring for 2 days, the mixture was filtered and the solvent was removed *in vacuo*. Chromatographic workup (silica gel, cyclohexane/EtOAc 1:1) gives **20a** as a colorless oil (667 mg, 37%): IR (film) ν 1743, 1714, 1627, 1595, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 3.90 (s, 3H), 4.13 (s, 2H), 4.65 (dt, 2H, J = 5.72, J = 1.40 Hz), 5.26 (dq, 1H, J = 10.42, J = 1.27 Hz), 5.32 (dq, 1H, J = 17.21, J = 1.50 Hz), 5.91 (ddt, 1H, J = 17.20, J = 10.41, J = 5.73 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5 (q), 31.7 (t), 51.8 (q), 65.8 (t), 118.4 (t), 129.0 (s), 131.3 (d), 151.1 (s), 160.5 (s), 162.0 (s), 167.1 (s); UV (MeCN) λ (log ϵ) 214 (3.905), 230 (3.949); MS (EI, 70 eV) *m*/*z* 239 (12, M$^+$), 183 (8), 154 (100); HRMS calcd for $C_{11}H_{13}NO_5$; 239.07938, found 239.07930.

5-[(But-3-enyloxycarbonyl)methyl]-2-methyloxazole-4-carboxylic acid methyl ester (20b) was prepared from oxazole **19** (1.80 g, 9.1 mmol), 3-buten-1-ol (846 mg, 11.8 mmol), DMAP (71 mg, 0.6 mmol), and DCC (2.42 g, 11.8 mmol) in 80 mL of chloroform following the method for **20a**. Compound **20b** was obtained as a colorless oil (579 mg, 25%): IR

(film) ν 1742, 1714, 1627, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (tq, 2H, $J = 6.71$, $J = 1.36$ Hz), 2.48 (s, 3H), 3.90 (s, 3H), 4.09 (s, 2H), 4.20 (t, 2H, $J = 6.70$ Hz), 5.07 (ddt, 1H, $J = 10.37$, $J = 1.80$, $J = 1.18$ Hz), 5.10 (ddd, 1H, $J = 17.15$, $J = 3.29$, $J = 1.55$ Hz), 5.75 (ddt, 1H, $J = 17.01$, $J = 10.30$, $J = 6.76$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.4 (q), 31.6 (t), 32.6 (t), 51.6 (q), 64.2 (t), 117.1 (t), 128.8 (s), 133.4 (d), 151.3 (s), 160.3 (s), 161.8 (s), 167.3 (s); UV (MeCN) λ (log ϵ) 214 (3.901), 228 (3.929); MS (EI, 70 eV) *m*/*z* 253 (19, M^+), 238 (22), 194 (10), 181 (12), 154 (100); HRMS calcd for $C_{12}H_{15}NO_5$: 253.09502, found 253.09500.

2-Methyl-5-(2-oxo-3-oxabicyclo[3.1.0]hex-1-yl)oxazole-4-carboxylic Acid Methyl Ester (22a). A suspension of 4-(azidosulfonyl)benzoic acid (697 mg, 3.1 mmol) in a solution of oxazole **20a** (667 mg, 3.1 mmol) in acetonitrile (50 mL) was cooled to 0 °C under nitrogen. To this mixture was added 0.96 mL (6.5 mmol) of DBU. The acid dissolved immediately, and, after a short period, the DBU salt of 4-sulfamoyl-benzoic acid precipitated. After stirring for 1 h at room temperature, the precipitate was filtered off, and the filtrate was purified by chromatography over silica gel eluting with EtOAc. The yellow solution of **21a** was concentrated carefully *in vacuo* (bath temperature below 30 °C) and dissolved immediately in 1,2-dichloroethane (50 mL). This solution was dropped over 1 h under nitrogen to a suspension of 1.5 mg of $Rh_2(OAc)_4$ in 1,2-dichloroethane (75 mL) heated to reflux. After refluxing for an additional 30 min, the reaction mixture was cooled to room temperature, concentrated *in vacuo*, filtered over silica gel, and purified by chromatography (silica gel, cyclohexane/EtOAc 1:1). Recrystallization from ether/pentane gives **22a** as colorless crystals (183 mg, 27%): mp 135−136 °C; IR (KBr) ν 1758, 1740, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (t, 1H, $J = 5.4$ Hz), 1.98 (ddt, 1H, $J = 8.0$, $J = 5.5$, $J = 0.5$ Hz), 2.49 (s, 3H), 2.57 (dddd, 1H, $J = 8.0$, $J = 5.3$, $J = 4.6$, $J = 0.7$ Hz), 3.91 (s, 3H), 4.34 (dt, 1H, $J = 9.3$, $J = 0.6$ Hz), 4.64 (ddt, 1H, $J = 9.3$, $J = 4.7$, $J = 0.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 17.2 (t), 24.6 (s), 26.6 (d), 51.9 (q), 68.2 (t), 130.8 (s), 151.1 (s), 160.8 (s), 161.5 (s), 172.6 (s); UV (MeCN) λ (log ϵ) 206 (3.862), 238 (3.924); MS (EI, 70 eV) *m*/*z* 237 (59, M^+), 222 (11), 205 (100), 176 (18); HRMS calcd for $C_{11}H_{11}NO_5$: 237.06372, found 237.06370. Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 56.28; H, 4.69; N, 5.85.

2-Methyl-5-(2-oxo-3-oxabicyclo[4.1.0]hept-1-yl)oxazole-4-carboxylic acid methyl ester (22b) was prepared from oxazole **20b** (733 mg, 2.9 mmol), 4-(azidosulfonyl)benzoic acid (723 mg, 3.2 mmol), and DBU (1.0 mL, 6.7 mmol) following the procedure for **22a**. Colorless crystals (179 mg, 25%): mp 165−166 °C (from ether/*n*-pentane); IR (KBr) ν 1712, 1625, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77−1.82 (m, 1H), 2.00−2.14 (m, 3H), 2.48 (s, 3H), 2.53−2.62 (m, 1H), 3.90 (s, 3H), 4.24 (ddd, 1H, $J = 12.9$, $J = 11.9$, $J = 3.4$ Hz), 4.44 (dddd, 1H, $J = 11.9$, $J = 5.9$, $J = 1.80$, $J = 1.48$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 15.2 (t), 20.6 (t), 22.0 (s), 24.9 (d), 52.0 (q), 65.2 (t), 129.6 (s), 155.4 (s), 160.3 (s), 161.8 (s), 168.5 (s); UV (MeCN) λ (log ϵ) 206 (3.839), 234 (3.877); MS (EI, 70 eV) *m*/*z* 251 (34, M^+), 223 (26), 219 (100), 191 (24), 189 (29); HRMS calcd for $C_{12}H_{13}NO_5$: 251.07938, found 251.07940. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.42; H, 5.27; N, 5.53.

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