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Regio-Control of Formal [3 + 2] Cycloadditions of 5-Alkoxyoxazoles with Diethyl Oxomalonate

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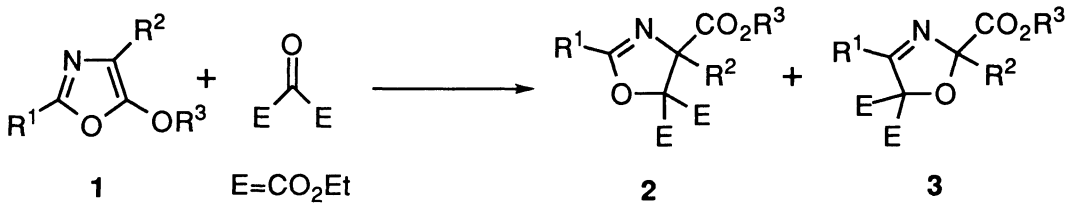
Tin(IV) chloride-catalyzed formal [3 + 2] cycloadditions of 5-alkoxy-2-(*p*-methoxyphenyl)- or 2-phenyloxazoles with diethyl oxomalonate gave 2-oxazoline-4,5,5-tricarboxylates in high regioselectivity. 4-Substituted 5-alkoxy-2-methyloxazoles showed a trend to shift the regioselectivity to offer more 3-oxazoline-2,5,5-tricarboxylates in terms of regioselectivity than 2-oxazolines.

Recently, we have reported stereo-[1a] and diastereoselective[1b] syntheses of 2-oxazoline-4-carboxylates by Lewis acid-catalyzed formal [3 + 2] cycloadditions of 4-unsubstituted 5-alkoxyoxazoles with aldehydes. In the Lewis acid-catalyzed reactions of 5-methoxy-2-(*p*-methoxypheny)oxazole (**1a**) with aldehydes, 2-oxazolines were regioselectively produced without formation of 3-oxazolines. Hassner reported thermal reactions of alkoxyoxazoles with diethyl oxomalonate.[2] For example, 5-ethoxy-2-phenyloxazole (**1b**) undergoes a cycloaddition with diethyl oxomalonate under reflux in xylene to give a mixture of 2-oxazoline and 3-oxazoline in a 1.2:1 ratio. The primary factors to control the regioselectivity of the formal [3 + 2] cycloadditions have not been understood.[3] Here, we wish to report the regio-control of the reactions of various 4-unsubstituted and 4-substituted 5-alkoxyoxazoles with diethyl oxomalonate.

The tin(IV) chloride-catalyzed reaction of oxazoles **1a** and **1b** with diethyl oxomalonate (1 equiv) at rt in MeCN gave 2-oxazolines **2a** and **2b** in complete regioselectivity and high yields (entries 1 and 3) in contrast to the results of Hassner's low regioselectivity (entry 4). 4-Phenyl-, 4-(*p*-nitrophenyl)-, and 4-methyl-substituted 5-methoxy-2-(*p*-methoxypheny)oxazoles **1c–1e** also underwent the [3 + 2] cycloadditions with diethyl oxomalonate in high regioselectivity under similar conditions to give the corresponding 2-oxazolines **2c–2e** as a sole product in high yields (entries 5, 7, and 8). In the case of 4-(isopropyl)oxazole **1f**, a small degree of 3-oxazoline **3f**[4] was produced probably due to the steric interaction of a 4-isopropyl group with ethoxycarbonylgroup (entry 9). Thus, 4-unsubstituted and 4-substituted 2-aryl-5-alkoxyoxazoles **1a–1e** were

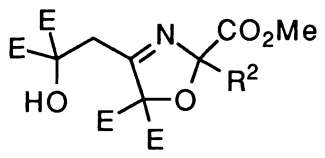


1 E=CO_2Et **2** **3**

Table 1. Reactions of Oxazole **1** with Diethyl Oxomalonate

Entry	1	R^1	R^2	R^3	Conditions (Time /h)[a]	Yield/%	2-ox:3-ox[b]	Recov.[c]
1	**1a**	*p*-$MeOC_6H_4$	H	Me	A (19)	79	100:0	5%
2	**1a**	*p*-$MeOC_6H_4$	H	Me	B (44)[n]	12[d,e]	100:0	47%
3	**1b**	Ph	H	Et	A (19)	79	100:0	4%
4[f]	**1b**	Ph	H	Et	D (46)	96	55:45	–
5	**1c**	*p*-$MeOC_6H_4$	Ph	Me	A (20)	95	100:0	–
6	**1c**	*p*-$MeOC_6H_4$	Ph	Me	D (69)	23	ca. 1:99[o]	–
7	**1d**	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	Me	A (72)	60	100:0	–
8	**1e**	*p*-$MeOC_6H_4$	Me	Me	A (2)	97	100:0	–
9	**1f**	*p*-$MeOC_6H_4$	*i*-Pr	Me	A (120)	40	78:22	–
10	**1g**	Me	H	Et	A (72)	16[d]	100:0	–
11	**1g**	Me	H	Et	C (68.5)	73[d]	96:4	–
12[f]	**1g**	Me	H	Et	D (24)	10	0:100[g]	–
13	**1h**	Me	*p*-$NO_2C_6H_4$	Me	A (33)	56	94:6	21%
14	**1h**	Me	*p*-$NO_2C_6H_4$	Me	A (62)[h]	40	30:70	19%
15	**1h**	Me	*p*-$NO_2C_6H_4$	Me	B (120)[i]	47[j]	0:100	47%
16	**1h**	Me	*p*-$NO_2C_6H_4$	Me	B (120)[k]	45[l]	0:100	trace
17	**1i**	Me	Me	Me	A (46)	89	34:66	–
18	**1i**	Me	Me	Me	B (74)[m]	68[l]	0:100	–
19	**1j**	Me	*i*-Pr	Me	A (96)	78	0:100	–

a) Condition A: In the presence of $SnCl_4$ (1 equiv) at rt in MeCN unless otherwise noted. Condition B: Under high pressure (0.85 GPa) at 40 °C in MeCN unless otherwise noted. Condition C: Under high pressure (0.85 GPa) in the presence of $ZnCl_2$ (1 equiv) at 40 °C. Condition D: Under reflux in xylene. b) 2-oxazoline:3-oxazoline. c) Recovered **1**. d) A hydrolysis product **5** was obtained (entry 2: 13%, entry 10: 31%, entry 11: 9%). e) Product **6a** was also obtained in 5% yield. f) Results of Ref. 2. g) See Ref. 5. h) In the presence of catalyst B ($AlMe_3$ + 2,4,6-tribromophenol (2 equiv.))[1a] at rt in CH_2Cl_2. i) One equiv of diethyl oxomalonate was used. j) **3h**:**4h** = 21:26. k) Two equiv of diethyl oxomalonate was used. l) Yield of **4**. m) Three equiv of diethyl oxomalonate was used. n) At 60 °C. o) A trace amount of 2-oxazoline **2c** was detected by ^1H NMR.



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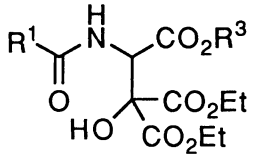

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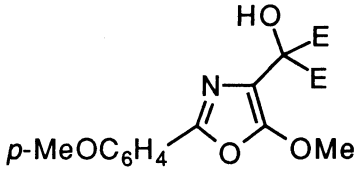

6a

shown to produce 2-oxazolines regioselectively under tin(IV) chloride-catalyzed conditions independent of electronic factor of 4-substituents.

2-Methyl substituted oxazoles showed different trend in terms of regioselectivity (entries 10–19). The tin(IV) chloride-catalyzed reactions of oxazoles **1g** (R^2=H) and **1h** (R^2=*p*-$NO_2C_6H_4$) gave 2-oxazolines **2g** and **2h** with high regioselectivity (entries 10 and 13) as in the case of 2-(*p*-methoxyphenyl)oxazoles. In the case of 4-methyloxazole **1i**, the regioselectivity turn out to the direction to give 3-oxazoline **3i** as a major product (entry 17). And 4-isopropyloxazole **1j** completely changed the regioselectivity to yield only 3-oxazoline **3j** (entry 19). The use of methylaluminum bis(2,4,6-tribromophenoxide)[1a] in the reaction of 4-(*p*-nitrophenyl)oxazole **1h** changed the regioselectivity to give 3-oxazoline in comparison with the tin(IV) chloride-catalyzed reaction (entries 14 and 13).

It is also interesting to note that 3-oxazolines were regioselectively formed under high pressure conditions in the reactions of oxazole **1h** and **1i** (entries 15, 16 , and 18). In these cases, initially produced 3-oxazolines **3h** and **3i** reacted further with diethyl oxomalonate to give 1:2 products **4h** and **4i** as major products. For 4-unsubstituted oxazole **1a**, the high pressure was not so effective to promote [3 + 2] cycloaddition but 2-oxazolines were regioselectively obtained in low yields with forming hydrolysis product **5a** (entry 2). Addition of $ZnCl_2$ was effective under high pressure conditions to produce 2-oxazoline **2g** in good yield in the reaction of oxazole **1g** (entry 11), although the reaction was not proceeded without $ZnCl_2$. 5-Methoxy-4-(*p*-nitrophenyl)-2-phenyloxazole did not undergo [3 + 2] cycloaddition with diethyl oxomalonate under high pressure (0.85 GPa, 60 °C, 64 h, recovered oxazole: 92%).

In addition, thermal reaction of **1c** (reflux in xylene for 69 h) with diethyl oxomalonate gave 3-oxazoline **3c** regioselectively in low yield (entry 6), and thermal reaction of **1h** (reflux in MeCN for 30 h) gave no [3 + 2] cycloadducts because decomposition of **1h** occurred under the reaction conditions.

In conclusion, the above-described methodology involving the tin(IV) chloride-catalyzed formal [3 + 2] cycloaddition of 5-alkoxy-2-aryloxazoles with diethyl oxomalonate has the advantage of high regioselectivity and generality over thermal reactions from the viewpoint of 2-oxazoline syntheses. 3-Oxazoline-2,5,5-tricarboxylates could be also regioselectively synthesized by use of 5-alkoxy-2-methyloxazoles under above-described appropriate conditions except 4-unsubstituted cases.

References

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2) A. Hassner and B. Fisher, *Tetrahedron*, **45**, 3535 (1989).

3) Reactions of 5-alkoxyoxazoles with thioaldehydes and nitrosobenzene gave 3-thiazolines and 1,2,4-oxadiazoline, respectively, with complete regioselectivity. Thioaldehyde: E. Vedejs and S. Fields, *J. Org. Chem.*, **53**, 4663 (1988); Nitrosobenzene: H. Suga and T. Ibata, *Chem. Lett.*, **1991**, 1221.

4) Structures of 2-oxazoline **2f** and 3-oxazoline **3f** was determined by following spectroscopic data especially by ^{13}C NMR spectra (chemical shifts of oxazoline ring-carbons).

2f: Colorless oil; IR (Neat) 1750 (C=O) and 1663 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ = 0.79 (3H, d, J = 6.6 Hz, Me of *i*-Pr), 1.04 (3H, d, J = 6.6 Hz, Me of *i*-Pr), 1.23 (3H, t, J = 7.3 Hz, Me of OEt), 1.38 (3H, t, J = 7.3 Hz, Me of OEt), 2.68 (1H, sept. J = 6.6 Hz, CH of *i*-Pr), 3.78(3H, s, OMe), 3.85 (3H, s, OMe), 4.19 (2H, m, CH_2 of OEt), 4.40 (2H, q, J = 7.3 Hz, CH_2 of OEt), 6.93 (2H, m, Arom), and 8.02

(2H, m, Arom); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ = 13.78 (q, Me of OEt), 13.94 (q, Me of OEt), 16.52 (q, Me of *i*-Pr), 18.73 (q, Me of *i*-Pr), 34.11 (d, CH of *i*-Pr), 52.33 (q, OMe), 55.43 (q, OMe), 62.48 (t, CH_2 of OEt), 62.87 (t, CH_2 of OEt), 88.33 (dq, $^2J_{C-H}$=8.5 Hz, $^3J_{C-H}$=4.3 Hz, 4-C), 90.64 (s, 5-C), 113.76 (d, Arom), 118.66 (s, Arom), 130.76 (d, Arom), 161.95 (s, C=N), 162.80 (s, Arom), 165.34 (s, C=O), 166.54 (s, C=O), and 171.66 (s, C=O).

3f: Colorless oil; IR (Neat) 1749 (C=O) and 1605 (C=N) cm^{-1}, ^1H NMR ($CDCl_3$, 270 MHz) δ =1.01 (3H, d, *J* = 6.9 Hz, Me of *i*-Pr), 1.03 (3H, d, *J* = 6.9 Hz, Me of *i*-Pr), 1.23 (3H, t, *J* = 7.3 Hz, Me of OEt), 1.27 (3H, t, *J* = 7.3 Hz, Me of OEt), 2.68 (1H, sept. *J* = 6.9 Hz, CH of *i*-Pr), 3.76 (3H, s, OMe), 3.84 (3H, s, OMe), 4.21 – 4.33 (4H, m, CH_2 of OEt), 6.90 (2H, m, Arom), and 7.99 (m, Arom); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ = 13.79 (q, Me of OEt), 13.85 (q, Me of OEt), 16.28 (q, Me of *i*-Pr), 16.36 (q, Me of *i*-Pr), 34.61 (d, CH of *i*-Pr), 52.45 (q, OMe), 55.34 (q, OMe), 62.53 (t, CH_2 of OEt), 62.61 (t, CH_2 of OEt), 93.78 (s, 5-C), 113.48 (d, Arom), 114.80 (s, 2-C), 122.28 (s, Arom), 131.85 (d, Arom), 162.38 (s, Arom), 163.82 (s, C=N), 165.93 (s, C=O), 166.29 (s, C=O), and 169.28 (s, C=O).

5) The structure of the adduct assigned to 2-oxazoline by Hassner should be corrected to 3-oxazoline on the basis of its ^{13}C NMR spectrum.[2)]

3g: ^{13}C NMR ($CDCl_3$,75.5 MHz) δ = 13.89 (q, Me), 16.41 (q, Me), 62.02 (t, CH_2), 62.60 (t, CH_2), 62.90 (t, CH_2), 90.00 (s, C-5), 102.82 (d, C-2), 164.99 (s, C=N), 164.86 (s, C=O), and 167.55 (s, C=O).[2)]

The ^{13}C NMR spectrum of **2g** obtained under condition A (entry 10) and condition C (entry 11) was shown below.

2g: ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 13.82 (q, Me), 13.86 (q, Me), 13.91 (q, Me), 14.02 (q, Me), 61.98 (t, CH_2), 62.78 (t, CH_2), 63.27 (t, CH_2), 75.11 (d, 4-C), 87.93 (d, $^2J_{C-H}$=2.3 Hz, 5-C), 165.39 (dq, $^3J_{C-H}$=6.0 Hz, $^2J_{C-H}$=7.4 Hz, C=N), 165.90 (s, C=O), 166.05 (s, C=O), and 168.45 (s, C=O).

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