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Reactions of 5-Alkoxyoxazoles with Aldehydes in the Presence of Lewis Acid: Regio- and Stereoselective Formation of 4-Alkoxycarbonyl-2-oxazolines

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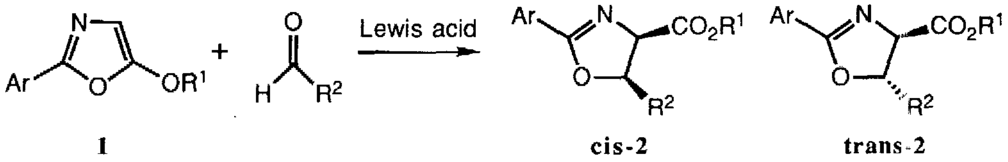
Summary: The [3 + 2] cycloaddition of 5-alkoxyoxazoles with aldehydes in the presence of the organoaluminum reagent, which was prepared from (±)-2,2'-dihydroxy-1,1'-dinaphthyl and $AlMe_3$, gave *cis*-4-alkoxycarbonyl-2-oxazolines in high regio- and stereoselective manner.

4-Alkoxycarbonyl-2-oxazolines have been a versatile building block in organic synthesis as a masked form of β-hydroxyamino acids or 2-amino-1,3-diols.[3] In general, trans isomers of 5-substituted 4-alkoxycarbonyl-2-oxazolines are selectively synthesized in the aldol reaction of isocyanoacetates with aldehyde under thermodynamic control.[1-3] We recently reported that oxazoles undergo formal [3 + 2] cycloaddition with some dienophiles having strong electron-deficient character, and the mechanism through the stepwise pathway involving a zwitterionic intermediate was proposed.[4] Carbonyl compounds are usually unreactive in this [3 + 2] cycloaddition,[5] but could be activated by Lewis acid according to the proposed mechanism.[4] In this paper we report the first example of regio- and cis-selective synthesis of 5-substituted 4-alkoxycarbonyl-2-oxazolines by the formal [3 + 2] cycloaddition of 5-alkoxyoxazoles with aldehydes.

The reaction of oxazole **1a** with benzaldehyde was carried out in the presence of several kinds of Lewis acids. As expected, 4-methoxycarbonyl-2-(*p*-methoxyphenyl)-5-phenyl-2-oxazoline (**2a**) was formed in an exclusively regioselective manner[6] in high yield (Table 1, Run a – e). Organoaluminum reagents[7] or tin(IV) chloride was found to be effective, and high cis selectivity (cis:trans = 98:2) was observed by using catalyst A



1a: Ar=*p*-$MeOC_6H_4$, R^1=Me;
1b: Ar=Ph, R^1=Et;

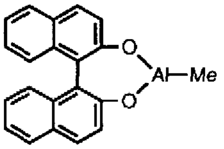
2a: Ar=*p*-$MeOC_6H_4$, R^1=Me, R^2=Ph;
2b: Ar=*p*-$MeOC_6H_4$, R^1=Me, R^2=*p*-$NO_2C_6H_4$;
2c: Ar=*p*-$MeOC_6H_4$, R^1=Me, R^2=*p*-ClC_6H_4;
2d: Ar=*p*-$MeOC_6H_4$, R^1=Me, R^2=*p*-$MeOC_6H_4$;
2e: Ar=*p*-$MeOC_6H_4$, R^1=Me, R^2=PhCH=CH(*E*);
2f: Ar=*p*-$MeOC_6H_4$, R^1=Me, R^2=Et;
2g: Ar=Ph, R^1=Et, R^2=EtO_2C;

Table 1. Reactions of Oxazoles **1a** and **1b** with Aldehydes[a]

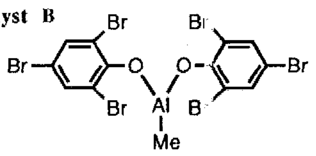
Run	1	Aldehyde	Conditions		2	Yield(%)[b]		
			Lewis acid	Solvent, Temp., Time		**cis-2**	**trans-2**[i]	cis/trans
a	**1a**	PhCHO	Catalyst A[c]	CH_2Cl_2 + CH_3CN[d], 0 °C, 93 h	**2a**	76[g]	1.7[g]	98/2
b	**1a**	PhCHO	Catalyst A[c,e]	CH_3CN, r.t., 94 h	**2a**	85[g]	1.8[g]	98/2
c	**1a**	PhCHO	Catalyst B[f]	CH_2Cl_2, 0 °C, 112 h	**2a**	33[g]	54[g]	38/62
d	**1a**	PhCHO	$SnCl_4$	CH_3CN, 0 °C, 120 h	**2a**	10[g]	58[g]	15/85
e	**1a**	PhCHO	$SnCl_4$	CH_2Cl_2, r.t., 21 h	**2a**	30[g]	54[g]	36/64
f	**1a**	*p*-NO_2-C_6H_4CHO	Catalyst A[c]	CH_2Cl_2 + CH_3CN[d], 0 °C, 45 h	**2b**	84	5.9	93/7
g	**1a**	*p*-Cl-C_6H_4CHO	Catalyst A[c]	CH_2Cl_2 + CH_3CN[d], 0 °C, 66.5 h	**2c**	81	1.4	98/2
h	**1a**	*p*-MeO-C_6H_4CHO	Catalyst A[c]	CH_2Cl_2 + CH_3CN[d], 0 ° C, 18 h – r.t., 78 h	**2d**	37	12	76/24
i	**1a**	Cinnamaldehyde	Catalyst A[c]	CH_2Cl_2 + CH_3CN[d], 0 ° C, 18 h – r.t., 51 h	**2e**	21	5.9	78/22
j	**1a**	EtCHO[h]	Catalyst A[c]	CH_2Cl_2 + CH_3CN[d], r.t., 52 h	**2f**	13	2.3	85/15
k	**1b**	EtO_2CCHO[h]	$Ti(OPr^i)_4$ $TiCl_4$	CH_3CN, r.t., 13 h	**2g**	43[g] (40)[b]	8.2[g] (7.4)[b]	84/16
l	**1b**	EtO_2CCHO[h]	$Ti(OEt)_4$ $TiCl_4$	CH_3CN, r.t., 20 h	**2g**	44	16	73/27
m	**1b**	EtO_2CCHO[h]	$SnCl_4$	CH_3CN, r.t., 10.5 h	**2g**	10[g] (10)[b]	58[g] (55)[b]	15/85

a) The reaction was carried out in the presence of 1.0 equiv. of Lewis acid unless otherwise noted. b) Isolated yield by column chromatography. c) For preparation: See text of a typical experimental procedure. d) 1:1 Mixture of the solvents. e) Two equiv. of organoaluminum reagent A was used. f) Prepared *in situ* from 2,4,6-tribromophenol and $AlMe_3$ (0.99 M in hexane) in dry CH_2Cl_2. g) Determined by HPLC analysis. h) Two equiv. of the aldehyde was used. i) Recovered oxazole **1**: Run a, 4.8%[g]; Run b, 0.1%[g]; Run c, 1.1%[g]; Run d, 5.9%[g]; Run e, 0.9 %[g]; Run f, 0%; Run g, 0%; Run h, 25%; Run i, 4.8%[g]; Run j, 70%; Run k, 0%; Run l, 0.7%[g]; Run m, 0.7%[g].

Catalyst A



Catalyst B



(Run a and b). Although the reaction rate was very slow in the presence of catalyst A (1.0 equiv.) in dry CH_2Cl_2 or dry MeCN, the mixed solvent of CH_2Cl_2 and MeCN (1:1) was effective. Some *p*-substituted benzaldehydes, cinnamaldehyde and propanal also undergo regioselective [3 + 2] cycloaddition with oxazole **1a** to give the corresponding 4-methoxycarbonyl-2-oxazolines **2b** – **2f** with high cis selectivity (Table 1, cis:trans = 98:2 ~ 76:24).

A typical experimental procedure is given for the reaction of oxazole **1a** with *p*-nitrobenzaldehyde. To a solution of (±)-2,2'-dihydroxy-1,1'-dinaphthyl (0.286 g, 1.0 mmol) in dry CH_2Cl_2 (5 ml) was added a 0.99 M hexane solution of $AlMe_3$ (1.0 ml, 1.0 mmol), and the resulting solution was stirred at room temperature for 1 h. After cooled to −78 °C, a solution of oxazole **1a** (0.205 g, 1.0 mmol) and *p*-nitrobenzaldehyde (0.151 g, 1.0 mmol) in dry MeCN (5 ml) was added. The reaction mixture was stirred at 0 °C for 45 h, poured into ice cooled saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated *in vacuo*. Column chromatography of the residue on silica gel eluting with 4:1 hexane/ethyl acetate gave *trans*-2-oxazoline **trans-2b** (21 mg, 5.9%); and eluting with 7:3 hexane/ethyl acetate gave *cis*-2-oxazoline **cis-2b** (301 mg, 84%).[8)]

Ethyl glyoxylate also reacted with oxazole **1b** to give 2-oxazoline **2g** in the presence of a Lewis acid. Using 1:1 mixture of titanium(IV) chloride and titanium tetraalkoxide in dry MeCN, **cis-2g** was formed selectively (cis:trans = 84:16 ~ 73:27). On the other hand, **trans-2g** was obtained as a major isomer by use of tin(IV) chloride in dry MeCN (cis:trans = 15:85). The formation of thermodynamically more stable **trans-2a** or **trans-2g** in the presence of tin(IV) chloride occurred through epimerization of the initial adduct under the reaction conditions.[9)] In the case of the reaction of ethyl glyoxylate, catalyst A gave less satisfactory results in reactivity and stereoselectivity.

Efforts to apply the reaction to diastereoselective or enantioselective syntheses of 2-oxazolines using chiral aldehydes or chiral Lewis acid are now in progress, together with mechanistic study for the cis selectivity by using organoaluminum catalyst A.

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5) Only one example of the thermal reaction of alkoxyoxazole with carbonyl compound was reported for diethyl ketomalonate but not in regioselective manner: A. Hassner and B. Fischer, *Tetrahedron*, **45**, 3535 (1989).

6) Oxazoles **1a** and **1b** also undergo regioselective [3 + 2] cycloaddition with diethyl ketomalonate in the presence of $SnCl_4$ to give the corresponding 2-oxazolines as sole products in high yields.

7) The organoaluminum catalysts A and B were prepared according to the following method: K. Maruoka, T. Itoh, T. Shirasaka, and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 310; (1988); K. Maruoka, Y. Hoshino, T. Shirasaka, and H. Yamamoto, *Tetrahedron Lett.*, **29**, 3967 (1988); K. Maruoka, H. Banno, and H. Yamamoto, *J. Am. Chem. Soc.*, **112**, 7791 (1990); K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *ibid*, **110**, 3588 (1988); K. Nonoshita, H. Banno, K. Maruoka, and H. Yamamoto, *ibid*, **112**, 316 (1990).

8) The cis or trans geometry of **2b** was established on the basis of the coupling constant J_{4-5} (**cis-2b**: 10.9 Hz, **trans-2b**: 7.6 Hz). Other oxazolines were similarly assigned.

9) *Cis*-2-oxazoline **cis-2g** epimerized to a 9:1 mixture of **trans-2g** and **cis-2g** by treatment with 1.0 equiv. of $SnCl_4$ in dry MeCN at room temperature for 24 h.

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