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Reaction of 3-Phenylglycidic Esters. III.[1] Reaction of *cis*-3-Arylglycidic Esters with Various Thiophenols

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The reaction of the *cis*-3-arylglycidic esters **2** and **10** with thiophenols (**3**) has been investigated. The reactivity and stereoselectivity of the oxirane ring-opening of these *cis*-glycidic esters were lower than those of the *trans*-analogues (**1** and **9**). These tendencies were more apparent in the 4-MeO derivative (**2**). On the other hand, the tin-catalyzed reaction of **2** with **3a** was highly stereospecific and afforded the *cis*-opening product (**5a**).

Keywords——*cis*-3-arylglycidic ester; thiophenol; oxirane ring-opening; tin catalyst; stereoselectivity

In our previous studies,[1,2] we investigated the mode of oxirane ring opening of the *trans*-3-arylglycidic ester **1** by various thiophenols (**3**) under a variety of reaction conditions and established a new efficient method of producing either the *threo*- (**4**) or the *erythro*-ester (**5**) stereoselectively. Thus, *cis*-opening of the oxirane ring of **1** by 2-nitrothiophenol (**3a**) proceeded stereoselectively in the presence of a catalyst such as tin or zinc compounds to give the *threo*-isomer (**4a**), a key intermediate for the synthesis of diltiazem.[2c] On the other hand, in the presence of a catalytic amount of $NaHCO_3$ or $MgCl_2$, stereoselective *trans*-opening of **1** occurred to give the *erythro*-isomer (**5**). Highly stereoselective *cis*-opening of the corresponding *cis*-glycidate (**2**) by **3a** in the presence of stannous 2-ethylhexanoate was reported to give the *erythro*-isomer (**5a**).[1a]

In the present study, in order to shed more light on the mode of ring opening of *cis*-3-arylglycidic esters and to find an alternative route to **4a**, we investigated the reaction of **2**[1a] or its demethoxy analogue (**10**)[3] with thiophenols (**3a**—**d**) under a variety of conditions. The results obtained are summarized in Table I together with the comparative data[1a,b] for the corresponding *trans*-glycidates (**1** and **9**). The ratio of *cis*- to *trans*-opening of the *cis*-glycidate (**2** and **10**) represents the product ratio of the *erythro*- (**5** and **12**) to *threo*- (**4** and **11**) esters, while the reverse is the case for the reaction of the *trans*-glycidate (**1** and **9**). The ratios of **5** to **4** and **12** to **11** were determined by the method described previously.[1a]

Generally, both the reactivity[4] and stereoselectivity of the oxirane ring opening of the *cis*-glycidate (**2**) were lower than those of the *trans*-glycidate (**1**). As regards the effect of the substituents in thiophenols on the reaction of **2** in the absence of catalyst, the total yield of **4** and **5** was higher with more acidic thiophenols, and this was also the case for the *cis*-opening ratio. This parallels the reported observation in the *trans*-glycidate (**1**).[1b] Thus, the reaction of **2** with 2-NO_2-substituted, 2-NH_2-substituted, and unsubstituted thiophenols (**3a**, **d**, **c**) gave mainly the *threo*-isomers (**4**) by *trans*-opening in the absence of catalysts. Only the reaction of **2** with 4-nitrothiophenol (**3b**) gave the *cis*-opening product (**5b**) as a major product. The *cis*- to *trans*-opening ratio (2.1), however, was much lower than that in the reaction of the *trans*-glycidate (**1**) (entry 12). The interesting effect of temperature on the stereoselectivity seen in

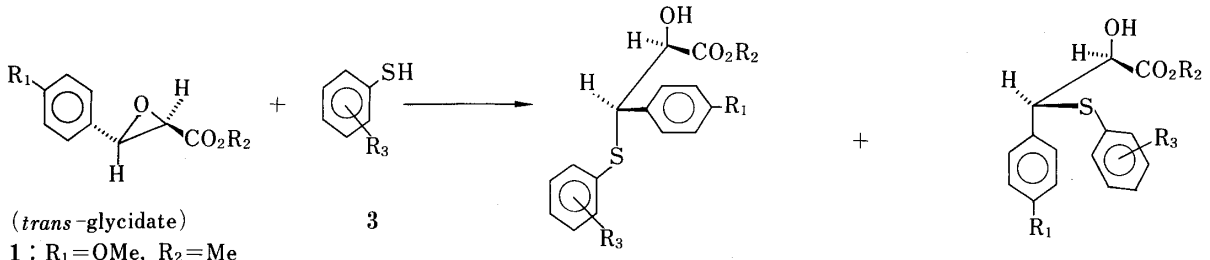
the reaction of the *trans*-glycidate (**1**)[1b] was not observed with the *cis*-isomer (**2**) (entries 1 and 2).

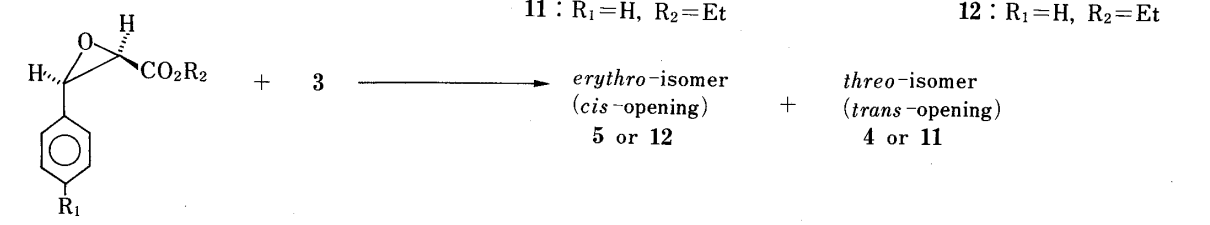
With regard to the effect of catalysts, $BF_3 \cdot Et_2O$ greatly accelerated the reaction of the *cis*-glycidate (**2**), but the stereoselectivity remained as low as that in the reaction without catalyst (entries 5 and 6). In contrast, stannous chloride showed good catalytic activity with a high *cis*-opening ratio (entry 4) in accordance with the reported observation with stannous 2-ethylhexanoate.[1a] The remarkable catalytic activity of tin derivatives even in the reaction of the *cis*-glycidate (**2**) is noteworthy. The $NaHCO_3$-catalyzed reaction of **2** proceeded mainly by *trans*-opening, but the selectivity was not as one-sided as that seen with the *trans*-glycidate (**1**) (entries 7 and 16). $MgCl_2$ showed no catalytic effect (entry 9).

In the reaction of the *trans*-glycidate (**1**) with **3** in hexamethylphosphoramide (HMPA), considerable formation of the regioisomer (**6**) was observed previously.[1b] The *cis*-glycidate (**2**) scarcely reacted with **3a** in this solvent, and no formation of the regioisomer (**6**) was observed (entry 10).

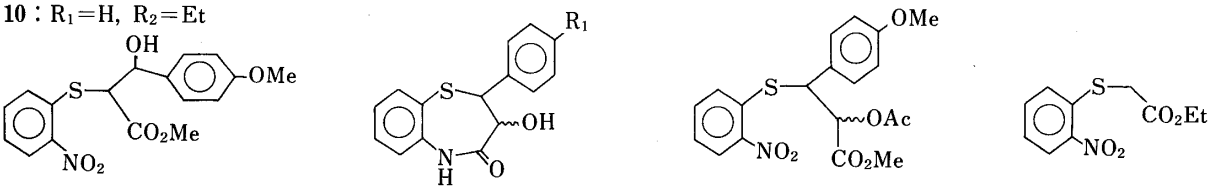
No difference in reactivity and stereoselectivity was apparent between the *trans*- and *cis*-isomers of the less reactive glycidates (**9** and **10**) without an electron-donating substituent.[1a] The reaction of the *cis*-glycidate (**10**) with **3d** at 155—160 °C gave a mixture of the lactams (**14a**, **b**) and the amino esters (**11d** and **12d**). On the basis of the sum of the ratios of the respective isomers, *trans*-opening occurred rather predominantly in this case in contrast to the complete *cis*-opening of the *trans*-glycidate (**9**).[2] In the $NaHCO_3$-catalyzed reaction of **10** with **3a**, formation of **13**, the *retro*-aldol product of the regioisomer corresponding to **6**, was observed in addition to the normal *trans*-opening product (**11a**).

Thus, the *cis*-3-arylglycidates (**2** and **10**) generally react with thiophenols less easily and





a : R_3=2-NO_2, **b** : R_3=4-NO_2, **c** : R_3=H, **d** : R_3=2-NH_2



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8a : R_1=OMe, *cis*
8b : R_1=OMe, *trans*
14a : R_1=H, *cis*
14b : R_1=H, *trans*

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13

with a decreased *cis*-opening ratio as compared with the *trans*-counterparts (**1** and **9**), and this tendency is more apparent in the reaction of the 4-MeO derivative (**2**).

TABLE I. Reaction of the *cis*-Glycidic Ester **2** or **10** with Thiophenols **3**[a]

Entry	Glycidic ester	Thiophenol	Solvent	Catalyst (eq)	Conditions	Total yield of the *threo*- and *erythro*-esters (%)	*cis*-Opening / *trans*-Opening[b]
1	**2**	**3a**	CH_3CN	—	r.t., 4 d	2.0	0.78
					(r.t., 3 d)	(37.2)	(0.33)
2	**2**	**3a**	CH_3CN	—	50—55 °C, 4 d	63.9	0.62
					(50—60 °C, 3 d)	(84.6)	(3.0)
3	**2**	**3a**	Dioxane	$Sn(OCOC_7H_{15})_2$ (0.1)	r.t., 18 h	84.0[c]	23.5
					(r.t., 19 h)	(82.0)	(9.3)
4	**2**	**3a**	Toluene	$SnCl_2$ (0.1)	r.t., 18 h	81.1	6.0
					(r.t., 18 h)	(80.0)	(14.5)
5	**2**	**3a**	Dioxane	$BF_3 \cdot Et_2O$ (0.07)	r.t., 5 h	74.9	0.75
					(r.t., 0.3 h)	(69.2)[d]	(4.2)
6	**2**	**3a**	Dioxane	—	r.t., 22 h	13.8	0.75
					(r.t., 48 h)	(46.2)	(0.25)
7	**2**	**3a**	EtOH	$NaHCO_3$ (0.1)	r.t., 4 d	30.9	0.35
					(r.t., 18 h)	(80.0)	(*trans*-Opening)
8	**2**	**3a**	EtOH	—	r.t., 4 d	3.7	0.5
9	**2**	**3a**	Toluene	$MgCl_2$ (0.1)	r.t., 17 h	8.6	0.63
					(r.t., 16 h)	(65.0)	(*trans*-Opening)
10	**2**	**3a**	HMPA	—	r.t., 4 h	Trace[e]	—
					(r.t., 6.5 h)	(13.5)[f]	(*trans*-Opening)
11	**2**	**3a**	Toluene	—	60 °C, 3 d	35.9	0.72
					(60 °C, 3 d)	(41.6)	(2.1)
12	**2**	**3b**	Toluene	—	60 °C, 3 d	57.8	2.1
					(60 °C, 3 d)	(67.9)	(5.0)
13	**2**	**3c**	Toluene	—	60 °C, 3 d	7.6	0.77
					(60 °C, 3 d)	(44.6)	(3.75)
14	**2**	**3d**	—	—	165 °C, 6 h	43.2[g]	0.6
					(165 °C, 6 h)	43.5)[h]	(30.0)
15	**2**	**3d**	Benzene	—	50—55 °C, 4 d	44.7	0.31
					(50—55 °C, 3 d)	(77.0)	(*cis*-Opening)
16	**2**	**3d**	EtOH	$NaHCO_3$ (0.1)	r.t., 4 d	33.8	0.14
					(r.t., 3 d)	(40.2)	(*trans*-Opening)
17	**10**	**3a**	EtOH	$NaHCO_3$ (0.2)	Reflux, 4 h	22.6	*trans*-Opening[i]
					(Reflux, 8 h)	(55.6)[j]	(*trans*-Opening)
18	**10**	**3a**	Dioxane	$BF_3 \cdot Et_2O$ (0.1)	r.t., 3 d	21.9	1.0
					(r.t., 3 d)	(22.7)	(0.33)
19	**10**	**3a**	CH_3CN or dioxane	—	r.t., 3 d	—[k]	
					(r.t., 3 d)	(—)[k]	
20	**10**	**3d**	—	—	155—160 °C, 7 h	46.6[l,m]	0.25
					(155—160 °C, 6 h)	(27.6)[n]	(*cis*-Opening)

a) Values in parentheses are the results obtained in the reaction of the corresponding *trans*-glycidate (**1** or **9**). See reference 1. *b*) The ratio of *cis*- to *trans*-opening of the *cis*-glycidate (**2** or **10**) represents the product ratio of the *erythro*- (**5** or **12**) to *threo*- (**4** or **11**) esters, while the reverse is the case for the reaction of the *trans*-glycidate (**1** or **9**). *c*) See reference 1*a*. *d*) Et_2O was used as the solvent. *e*) No regioisomer (**6**) was obtained. *f*) The regioisomer (**6**) was isolated in 19.9% yield. *g*) This is the total yield of the *cis*- and *trans*-lactam (**8a, b**). The amino ester (**4d** or **5d**) was not detected. *h*) This is the sum of the yields of the *threo*-ester (**4d**, 6.9%) and the lactams (**8a, b**, 36.6%). *i*) Compound (**13**) was obtained in 17.9% yield. *j*) Methyl ester was used. See reference 1*a*. *k*) **11a** or **12a** was not obtained. *l*) A mixture of the *cis*- and *trans*-lactams (**14a** and **b**) and a mixture of the *threo*- and *erythro*-amino esters (**11d** and **12d**) were obtained in 14.2 and 32.4% yields, respectively. *m*) In the reaction at 125—130 °C, only the amino esters (**11d** and **12d**) was obtained in 68.0% yield (*cis*-opening/*trans*-opening = 0.09). *n*) The *threo*-ester (**11d**) and the *cis*-lactam (**14a**) were obtained in 14.4 and 13.2% yields, respectively. See reference 2*a*.

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX-100S spectrometer. Chemical shifts are given as δ values from tetramethylsilane as an internal standard. Preparative thin-layer chromatography (preparative TLC) were carried out on Kieselgel PF_{254} (Merck). Kieselgel 60 (230—400 mesh) (Merck) was used for flash column chromatography. 2-Nitrothiophenol, 4-nitrothiophenol, thiophenol, and 2-aminothiophenol were used without further purification. All compounds obtained were identified by comparison with authentic samples.[1] The ratios of the isomeric esters (**4** to **5** or **11** to **12**) were determined by the method described previously.[1]

Reaction of Methyl *cis*-3-(4-Methoxyphenyl)glycidate (2) with 2-Nitrothiophenol (3a) (Table I, Entry 2)——A mixture of the *cis*-glycidate (**2**)[1a] (1 g, 4.80 mmol) and 2-nitrothiophenol (**3a**) (750 mg, 4.83 mmol) in CH_3CN (7 ml) was stirred at 50—55 °C for 4 d under an argon atmosphere. The yellow crystals of the *threo*-nitro ester (**4a**) (540 mg, mp 155—156 °C) that precipitated after cooling were filtered off, and the mother liquor was concentrated. The residual oil was separated by preparative TLC (developed with benzene–AcOEt (4 : 1)) to give a mixture of the *threo*- and *erythro*-nitro esters (**4a** and **5a**) (580 mg) as an oil.

The *threo*/*erythro* ratio of this mixture was 0.36 as determined by comparison of the intensities of the $COCH_3$ proton signals in the NMR spectrum of the corresponding 2-acetoxy derivatives (**7**) (Me protons of OAc of *threo*- and *erythro*-isomers appeared at 2.12 (s) and at 2.20 (s), respectively.[1a]). Therefore, the ratio of *cis*-opening/*trans*-opening (**5a**/**4a**) of the oxirane ring of **2** was 0.62.

The other experiments listed in Table I were carried out similarly.

Reaction of Ethyl *cis*-3-Phenylglycidate (10) with 2-Aminothiophenol (3d) (Table I, Entry 20)——A mixture of the *cis*-glycidate (**10**) (1.2 g, 6.24 mmol) and **3d** (780 mg, 6.23 mmol) was heated at 155—160 °C for 7 h under an argon atmosphere. The resulting oil was dissolved in AcOEt, washed with conc. HCl–H_2O (1 : 1) and water, dried, and evaporated to give an oil (900 mg). The oil was separated by preparative TLC (developed with benzene–AcOEt (8 : 1)). The *cis*-lactam (**14a**) and *trans*-lactam (**14b**) were obtained in 10.5% (178 mg, mp 194—197 °C) and 3.7% (63 mg, mp 201—204 °C) yields, respectively.

The conc. HCl–H_2O (1 : 1) layer was made basic with K_2CO_3 and extracted with $CHCl_3$. The extracts were washed with water, dried, and evaporated to give an oil (900 mg) which was purified by flash column chromatography. The eluate with benzene–AcOEt (10 : 1) gave a mixture of the *threo*- and *erythro*-amino esters (**11d** and **12d**) as an oil (640 mg, 32.4%). This mixture was converted to the corresponding *cis*- and *trans*-lactams (**14a** and **14b**),[5] by the method described in our previous report[2] and separated by preparative TLC to give **14a** (232 mg) and **14b** (48 mg). Therefore, the total ratio of *cis*-opening/*trans*-opening of the oxirane ring was 0.25.

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References and Notes

1) Part of this work was presented at the 42nd Symposium on Synthetic Organic Chemistry (Japan), Tokyo, November 1982: *a*) Part I: T. Hashiyama, H. Inoue, M. Konda, and M. Takeda, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1725. *b*) Part II: T. Hashiyama, H. Inoue, K. Aoe, K. Kotera, and M. Takeda, *ibid.*, in press.
2) *a*) H. Kugita, H. Inoue, M. Ikezaki, and S. Takeo, *Chem. Pharm. Bull.*, **18**, 2028 (1970); *b*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda, and S. Takeo, *ibid.*, **18**, 2284 (1970); *c*) T. Nagao, M. Sato, H. Nakajima, and A. Kiyomoto, *ibid.*, **21**, 92 (1973).
3) C. C. Tung and A. J. Speziale, *Chem. Ind.* (London), **1963**, 1985.
4) The reactions of the *cis*-glycidic esters (**2** and **11**) with thiophenols (**3**) proceeded more slowly than those of the *trans*-counterparts in all cases (TLC). This tendency was especially marked with the 4-MeO derivative (**2**).
5) The ratio of *cis*- to *trans*-opening determined by conversion to the isomeric lactams in another case was in good accord with that estimated from the NMR spectrum of the *O*-acetyl ester. The results should, therefore, be reliable. See ref. 1*a*.