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Highly chemoselective Pummerer reactions of sulfinyldiacetic acid derivative

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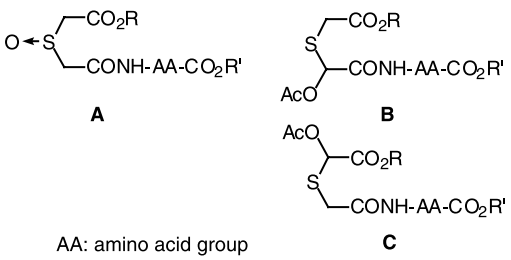
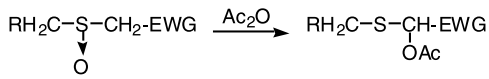
Abstract—Sulfinyldiacetic acid amide ester *rac*-**1** was efficiently synthesized starting from thiodiacetic acid **4**. Treatment of *rac*-**1** with Ac_2O and TMSOTf in CH_2Cl_2 at –40°C gave chemoselectively amide site α-acetoxy sulfide *rac*-**2** in a ratio (91:9) of *rac*-**2** and *rac*-**3** and in a 90% total yield. Similar treatment of **1** with Ac_2O and TMSOTf in DMF at room temperature furnished ester site α-acetoxy sulfide *rac*-**3** in a highly chemoselective manner (*rac*-**2**:*rac*-**3** = 3:97) and in a 92% total yield.

Pummerer reactions,[1] providing various α-substituted sulfides from the corresponding sulfoxides, have been attractive in regard to their value in the synthesis of natural products and biologically active compounds,[2] and in regard to their reaction mechanisms.[3] Thus, numerous Pummerer-type reactions have been reported.[1–3] The Pummerer reaction of dicarboxylic acid derivatives **A** bearing a sulfinyl group must be interested in the viewpoint of the development of new enzyme inhibitors; α-acetoxy sulfides **B** or **C** having rationally designed D- or L-amino acid amide group(s) (vide infra).



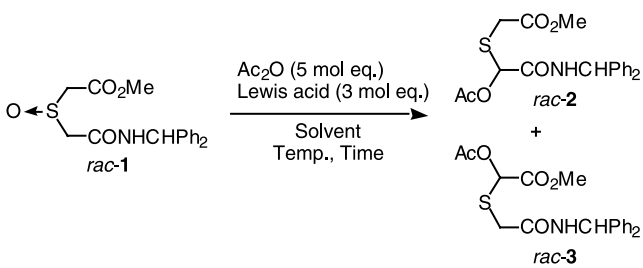
In general, regio- and chemoselective Pummerer reactions of the sulfoxides having two kinds of α-methylene groups can be performed at the more acidic methylene site with an electron-withdrawing group (EWG), as illustrated in Eq. (1).[4]



(1)

However, there have been a few reports of the Pummerer-type reaction of the sulfoxide having similarly acidic two α-methylene groups such as CH_2CO_2R and CH_2CONHR ones.[5] We herein describe highly chemoselective Pummerer reactions of sulfinyldiacetic acid amide ester *rac*-**1** as a model for **A** giving amide site α-acetoxy sulfide *rac*-**2** or ester site α-acetoxy sulfide *rac*-**3** each having high selectivity, as shown in Scheme 1 and Tables 1–3.

The synthesis of *rac*-**1** was efficiently performed by exploiting the synthetic route represented in Scheme 2. Thiodiacetic acid **4** was treated with Ac_2O (2.0 mol equiv.) under reflux for 3 h to give anhydride **5** [mp 92–95°C (AcOEt)] in an 87% yield. The compound **5** was allowed to react with aminodiphenylmethane (1.1 mol equiv.) in the presence of pyridine (0.1 mol equiv.) in Et_2O under reflux to give mono amide **6** [mp 115–117°C (AcOEt)] in a quantitative yield. After esterifica-



Scheme 1.

Keywords: Pummerer reactions; sulfoxides; chemoselectivity; Lewis acid; solvents and solvent effects.

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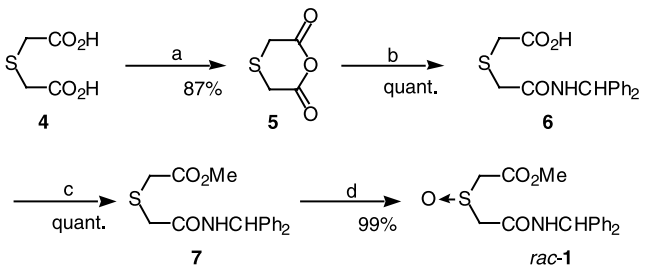
Table 1. Investigation of Lewis acids in the Pummerer reaction of *rac*-**1**[a]

Entry	Lewis acid	Time	Yield (%)[b]	Ratio[c]		
				rac-**2**	:	*rac*-**3**
1	$BF_3{\cdot}OEt_2$	1 h	97	76	:	24
2	TMSOTf	5 min	90	76	:	24
3	TBDMSOTf	5 min	63	80	:	20
4	$Zn(OTf)_2$	48 h	18	16	:	84
5	$TiCl_4$	16 h	–[d]		–	
6	BBr_3	3 h	–[d]		–	

[a] All reactions with the use of Ac_2O (5 mol equiv.) and Lewis acid (3 mol equiv.) were carried out in CH_2Cl_2 at room temperature.
[b] Total yield of *rac*-**2** and *rac*-**3**.
[c] Determined by ^1H NMR (200 MHz, $CDCl_3$) analysis.
[d] Reduction product **7** was obtained in 63% (entry 5) or 12% (entry 6) yield.

tion of **6** with MeOH in the presence of a catalytic amount of H_2SO_4 under reflux, the resultant methyl ester **7** [mp 55–56°C (*n*-hexane–$CHCl_3$)] (quantitative yield) was submitted to oxidation with $NaIO_4$ (1.5 mol equiv.) in an aqueous MeOH solution at room temperature to afford *rac*-**1** [mp 112–113°C (*n*-hexane–$CHCl_3$)] in a 99% yield.



Scheme 2. (a) Ac_2O (2.0 mol equiv.) reflux, 3 h; (b) Ph_2CHNH_2 (1.1 mol equiv.), pyridine (0.1 mol equiv.), Et_2O, reflux, 45 min; (c) H_2SO_4 (cat.) MeOH, reflux, 1 h; (d) $NaIO_4$ (1.5 mol equiv.), MeOH–H_2O, rt, 5 h.

In order to determine a suitable Lewis acid, we first examined the Pummerer reactions of *rac*-**1** by using Ac_2O (5 mol equiv.) and several Lewis acids (3 mol equiv.) in CH_2Cl_2 at room temperature. All experimental results are summarized in Table 1. The desired chemoselective reactions proceeded to give *rac*-**2** and *rac*-**3** in ratios of 76:24 ($BF_3{\cdot}OEt_2$ and TMSOTf), 80:20 (TBDMSOTf) and 16:84 [$Zn(OTf)_2$], respectively (entries 1–4 in Table 1). In the cases using $TiCl_4$ and BBr_3, a reduction product **7** was obtained in 63 and 12% yields (entries 5 and 6 in Table 1).[6] Among the results described above, the reaction conditions employing TMSOTf [7] intrigued us for further investigation toward the development of highly chemoselective Pummerer reactions.

Subsequently, an effect of the solvent on the Pummerer reactions of *rac*-**1** was examined by using Ac_2O (5 mol equiv.) and TMSOTf (3 mol equiv.) in the indicated solvents (Table 2) at room temperature. All of the reactions were carried out for 5 min to give *rac*-**2** and *rac*-**3** with good to high chemoselectivities in ratios of 76:24 (CH_2Cl_2 and $ClCH_2CH_2Cl$), 67:33 (Et_2O), 32:68 (AcOEt), 2:98 (MeCN) and 6:94 (DMF), respectively (entries 1–6 in Table 2). Surprisingly, the direction of chemoselectivity in the aprotic dipolar solvents ('electron-donating solvents')[8] involving an amide carbonyl group or a cyano group is reverse to that in CH_2Cl_2, $ClCH_2CH_2Cl$ or Et_2O.

Finally, an effect of the reaction temperature on the Pummerer reactions of *rac*-**1** was investigated by using Ac_2O (5 mol equiv.) and TMSOTf (3 mol equiv.) in CH_2Cl_2 or DMF at the indicated temperatures for the arbitrary reaction times, as shown in Table 3. In CH_2Cl_2, a clear trend toward higher chemoselectivity for production of *rac*-**2** was observed to be dependent on a lower reaction temperature (entries 1–5 in Table 3). In DMF, a remarkably high chemoselectivity for yielding *rac*-**3** was recognized even at room temperature (entry 6).

Consequently, we have achieved the chemoselective Pummerer reactions of *rac*-**1** to obtain the amide site α-acetoxy sulfide *rac*-**2**[9] in a ratio (91:9) of *rac*-**2** and *rac*-**3** and in a 90% total yield but also the ester site α-acetoxy sulfide *rac*-**3**[9] in a highly chemoselective manner (*rac*-**2**:*rac*-**3** = 3:97) and in a 92% total yield.

This complementary chemoselective Pummerer reaction can be rationalized in terms of an affinity of TMSOTf and certain other Lewis acids except for $Zn(OTf)_2$ with

Table 2. Effect of the solvent on the Pummerer reaction of *rac*-**1** using TMSOTf[a]

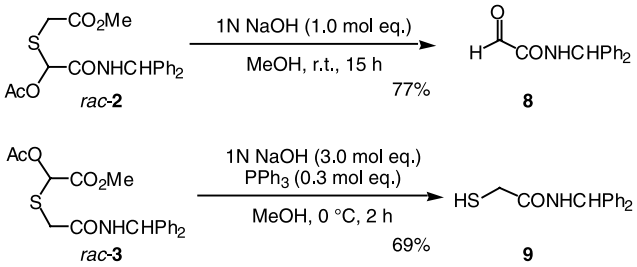
Entry	Solvent	Yield (%)[b]	Ratio[c]		
			rac-**2**	:	*rac*-**3**
1	CH_2Cl_2	90	76	:	24
2	$ClCH_2CH_2Cl$	67	76	:	24
3	Et_2O	63	67	:	33
4	AcOEt	46	32	:	68
5	MeCN	41	2	:	98
6	DMF	12[d]	6	:	94

[a] All reactions with the use of Ac_2O (5 mol equiv.) and TMSOTf (3 mol equiv.) were carried out at room temperature for 5 min.
[b] Total yield of *rac*-**2** and *rac*-**3**.
[c] Determined by ^1H NMR (200 MHz, $CDCl_3$) analysis.
[d] *Rac*-**1** was obtained in 77% recovery.

Table 3. Effect of the reaction temperature on the Pummerer reaction of *rac*-**1** using TMSOTf[a]

Entry	Solvent	Temp (°C)	Time	Yield (%)[b]	Ratio[c]	
					rac-**2** :	*rac*-**3**
1	CH_2Cl_2	Reflux	2 min	60	60 :	40
2	CH_2Cl_2	Rt	5 min	90	76 :	24
3	CH_2Cl_2	0	5 min	95	82 :	18
4	CH_2Cl_2	−20	24 h	94	88 :	12
5	CH_2Cl_2	−40	24 h	90	91 :	9
6	DMF	Rt	3 h	92	3 :	97
7	DMF	0	12 h	41[d]	4 :	96
8	DMF	−40	30 h	–[e]	–	

[a] All reactions with the use of Ac_2O (5 mol equiv.) and Lewis acid (3 mol equiv.) were carried out in CH_2Cl_2 or DMF.
[b] Total yield of *rac*-**2** and *rac*-**3**.
[c] Determined by ^1H NMR (200 MHz, $CDCl_3$) analysis.
[d] *Rac*-**1** was obtained in 33% recovery.
[e] No reaction.



Scheme 3.

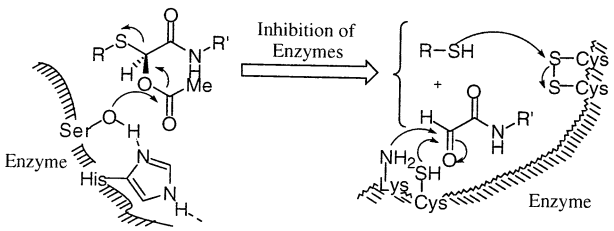


Figure 1. Design of new enzyme inhibitors.

the amide carbonyl and cyano groups. In CH_2Cl_2, TMSOTf, TBDMSOTf and $BF_3{\cdot}OEt_2$ may be predominantly coordinated by the amide carbonyl group of *rac*-**1** causing a more acidic outcome of the methylene protons of $CH_2CONHCHPh_2$ than that of the methylene protons of CH_2CO_2Me.[10] In DMF and MeCN, their amide carbonyl and cyano groups may exclusively coordinate to TMSOTf, TBDMSOTf and $BF_3{\cdot}OEt_2$, and thus a higher acidic property of the methylene protons of CH_2CO_2Me than that of the methylene protons of $CH_2CONHCHPh_2$ in *rac*-**1** must furnish the high chemoselectivity to give *rac*-**3**.

The sutructures of *rac*-**2** and *rac*-**3** were explicitly determined by their alkaline hydrolyses, as shown in Scheme 3. Treatment of *rac*-**2** or *rac*-**3** with 1N NaOH in MeOH gave each characteristic product, glyoxylic amide **8** (77% yield) or mercaptoacetic amide **9** (69% yield). These particular reactions seem to be useful for a molecular design of new suicide substrates as the esterase and protease inhibitors, as illustrated in Fig. 1.[11]

Acknowledgements

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9. Pure compound *rac*-**2** or *rac*-**3** was obtained by recrystallization of each crude solid in *n*-hexane–$CHCl_3$. *rac*-**2**: colorless needles; mp 111–112°C; IR (KBr) 1746, 1657, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.39 (d, $J=13.4$ Hz, 1H), 3.66 (d, $J=13.4$ Hz, 1H), 3.69 (s, 3H), 6.24 (d, $J=6.3$ Hz, 1H), 6.26 (s, 1H), 7.26–7.34 (m, 11H). Anal. calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.88; H, 5.51; N, 3.51. *rac*-**3**: colorless crystals; mp 94–96°C; IR (KBr) 1746, 1640, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 (s, 3H), 3.45 (d, $J=16.1$ Hz, 1H), 3.56 (d, $J=16.1$ Hz, 1H), 3.67 (s, 3H), 5.94 (s, 1H), 6.26 (d, $J=8.1$ Hz, 1H), 7.28–7.31 (m, 11H); Anal. calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 61.93; H, 5.61; N, 3.56.
10. In the ^1H NMR (300 MHz) spectrum analysis of a mixture of DMF (0.1 mmol), $MeCO_2Me$ (0.1 mmol) and TMSOTf (0.1 mmol) in $CDCl_3$, downfield shifts of CH_3 ($\Delta\delta$+0.32), CH_3 ($\Delta\delta$+0.49) and CHO ($\Delta\delta$+0.53) signals of DMF were recognized in comparison with those of a mixture of DMF and $MeCO_2Me$ without TMSOTf. However, significant downfield shifts of CH_3O ($\Delta\delta$+0.00) and CH_3CO ($\Delta\delta$+0.00) signals of $MeCO_2Me$ were not observed in the same manner as described above.
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