Enantioselective Synthesis of 2,3-Disubstituted Succinic Acids by Oxidative Homocoupling of Optically Active 3-Acyl-2-oxazolidones

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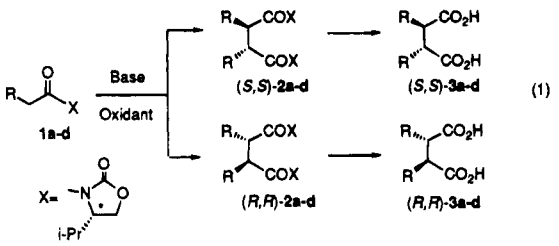
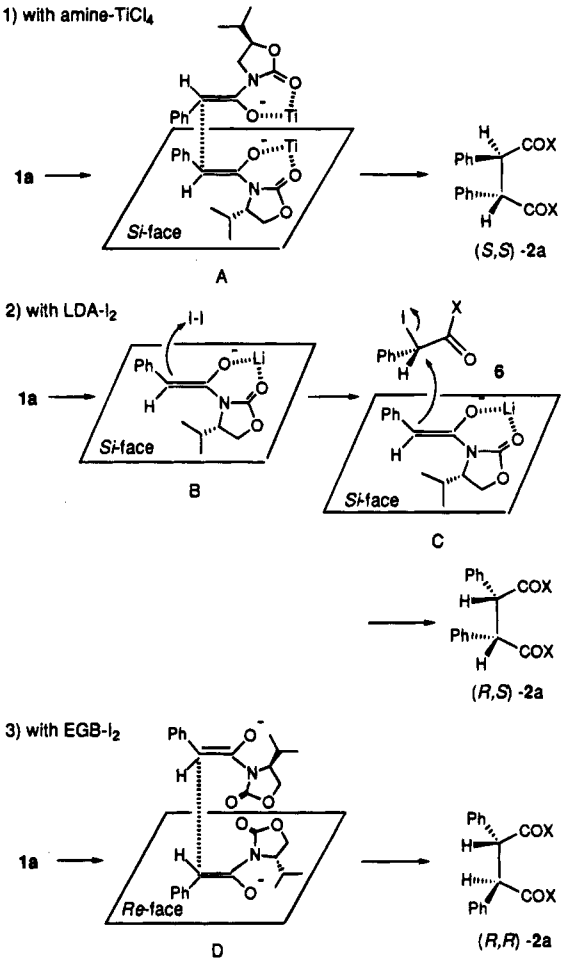
The oxidative homocoupling of enolate anions of esters is a useful reaction for the synthesis of 2,3-disubstituted succinic acids.[1] Enantioselective coupling of this type has yet to be reported,[2] although diastereoselectivity in homocoupling reactions has been studied and improved (maximum ~92%) by using carboxylic acid dianions[4a] or thioamide α-anions[4b] instead of ester enolate anions. Optically active 2,3-disubstituted succinic acids **3** are useful intermediates in the synthesis of chiral compounds as exemplified by the recent use of optically active 2,3-diphenylsuccinic acid (**3a**) as a chiral source for the preparation of optically active crown ether[5a] and diphosphine ligand.[5b] In these cases, optically pure **3a** was obtained by optical resolution.[6] We wish to report herein a first oxidative homocoupling reaction using optically active 3-acyl-2-oxazolidones **1** to afford the homocoupling products **2** which can be easily converted to enantiomerically pure 2,3-disubstituted succinic acids **3** (eq 1).



a: R=Ph b: R=Et c: R=PhCH$_2$ d: R=(3,4-methylenedioxyphenyl)methyl

Since the homocoupling of lithium enolates by $TiCl_4$[1g] and I_2[1c,2,3] is known, we attempted the oxidative coupling of (*S*)-4-isopropyl-3-(phenylacetyl)-2-oxazolidone (**1a**)[7] under several reaction conditions using these oxidants. The results are shown in Table 1. The reaction of **1a** with LDA–$TiCl_4$ did not proceed at −78 °C (run 1) and gave a complex mixture of products when the reaction temperature was raised to 0 °C (run 2). Also, treatment of the lithium enolate of **1a** with I_2 resulted in the formation of the (*R,S*)-isomer[9] as the main product (94% of the products) with a small amount of (*S,S*)-isomer (6%) (run 3). On the other hand, we found that the reaction of **1a** with a combination of amine–$TiCl_4$ at room temperature gave only the desired (*S,S*)-**2a**[10] in yields that were dependent on the kind of amine. DABCO or DMAP gave satisfactory yields (runs 4 and 5), while Et_3N, i-Pr_2EtN, and TMEDA resulted in low yields (runs 6–8). Furthermore, it was found that the treatment of **1a** with EGB (electrogenerated base)[11]–I_2 afforded (*R,R*)-**2a**,[12] though it was contaminated with a small amount of (*R,S*)-isomer (run 9). Thus, our two reaction conditions for homocou-

Scheme 1



(1) (a) Kofron, W. G.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 2085. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Brocksom, T. J.; Petragnani, N.; Rodrigues, R.; LaScala Teixeira, H. *Synthesis* **1975**, 396. (d) Tokuda, M.; Shigei, T.; Itoh, M. *Chem. Lett.* **1975**, 621. (e) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009. (f) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125. (g) Ojima, I.; Brandstadter, S. M.; Donovan, R. J. *Chem. Lett.* **1992**, 1591.

(2) Recently, the stereoselective synthesis of (2*R*,3*R*)-diethyl succinamide derivative by oxidative coupling of optically pure oxazolidine derivative with LDA-I_2 or $CuCl_2$ has been reported.[3]

(3) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457.

(4) (a) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (b) Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1978**, *100*, 1923.

(5) (a) Naemura, K.; Komatsu, M.; Adachi, K.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1675. (b) Krause, H.; Sailer, C. *J. Organomet. Chem.* **1992**, *423*, 271.

(6) (a) Wren, H.; Still, C. J. *J. Chem. Soc.* **1915**, *444*, 1449. (b) Krause, H. W.; Meinicke, C. *J. Prakt. Chem.* **1985**, *6*, 1023.

(7) Optically active 3-acyl-2-oxazolidones were prepared by *N*-acylation of optically active 2-oxazolidones.[8]

(8) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Gage, J. G.; Evans, D. A. *Organic Syntheses*; Wiley: New York, 1993; Vol. VIII, p 339.

(9) (*R,S*)-**2a**: mp 253–254 °C; $[\alpha]^{20}_D$ +46.5 (*c* 1.00, $CHCl_3$).

(10) (*S,S*)-**2a**: mp 208–209 °C; $[\alpha]^{20}_D$ +388 (*c* 1.03, $CHCl_3$).

(11) (a) Shono, T.; Kashimura, S.; Ishizaki, K.; Ishige, O. *Chem. Lett.* **1983**, 1311. (b) Shono, T.; Kashimura, S.; Nogusa, H. *J. Org. Chem.* **1984**, *49*, 2043.

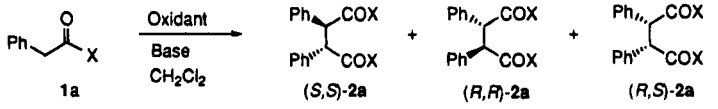
(12) (*R,R*)-**2a**: mp 237–238 °C; $[\alpha]^{20}_D$ −242 (*c* 1.00, $CHCl_3$).

(13) The conversion of **2a** to **3a** was easily achieved in good yields by the reported method.[14] The absolute stereoconfiguration and ee (~100%) of (*S,S*)- and (*R,R*)-**2a** were determined by converting those products to dimethyl (2*S*,3*S*)- and (2*R*,3*R*)-2,3-diphenylsuccinates followed by the measurement of the optical rotations and ^1H NMR analyses with Eu(hfc)$_3$. Dimethyl (2*S*,3*S*)-2,3-diphenylsuccinate derived from (*S,S*)-**2a**: mp 165–166 °C (lit.[6a] mp 165–166 °C); $[\alpha]^{20}_D$ +342 (*c* 1.25, acetone) (lit.[6a] $[\alpha]^{20}_D$ +341.9). Dimethyl (2*R*,3*R*)-2,3-diphenylsuccinate derived from (*R,R*)-**2a**: mp 164–165 °C [lit.[6a] mp 165–166 °C); $[\alpha]^{20}_D$ −340 (*c* 1.15, acetone) (lit.[6a] $[\alpha]^{20}_D$ −342.1).

(14) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

0022-3263/95/1960-1100$09.00/0

Table 1. Oxidative Coupling of (S)-4-Isopropyl-3-(phenylacetyl)-2-oxazolidone 1a

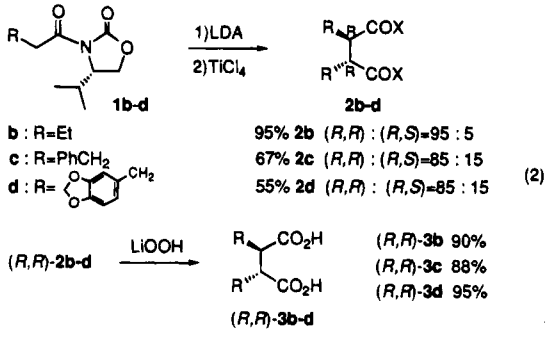


run	1	base	oxidant	reaction condns (°C)	yield (%) of 2a[a]	distribution[b] (%)[b] (S,S)-2a	(R,R)-2a	(R,S)-2a
1	1a	LDA	$TiCl_4$	−78	no reaction			
2	1a	LDA	$TiCl_4$	−78 → 0	c			
3	1a	LDA	I_2	−78 → rt	80	6	0	94
4	1a	DABCO	$TiCl_4$	0 → rt	69	~100	0	0
5	1a	DMAP	$TiCl_4$	0 → rt	76	~100	0	0
6	1a	i-Pr_2EtN	$TiCl_4$	0 → rt	46	~100	0	0
7	1a	TMEDA	$TiCl_4$	0 →rt	28	~100	0	0
8	1a	Et_3N	$TiCl_4$	0 → rt	24	~100	0	0
9	1a	EGB	I_2	−50 → 0	64	0	84	16

[a] Isolated yields. [b] Determined by ^1H NMR analysis. [c] A complex mixture of products was formed.

pling make it possible to prepare both (*S,S*)- and (*R,R*)-**3a** selectively from **1a**.[13,15]

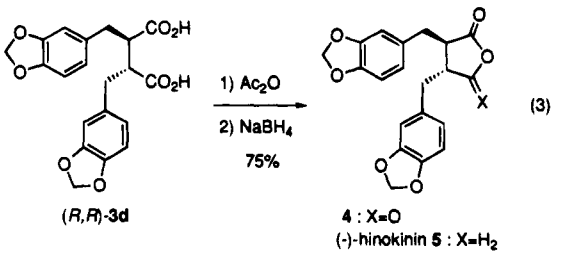
In contrast with **1a**, other (*S*)-3-alkanoyl-4-isopropyl-2-oxazolidones **1b−d** did not react with amine−$TiCl_4$ possibly because the basicity of the amine was not enough to generate the enolate anions of **1b−d**. Accordingly, LDA was examined as a base in place of amine, and fortunately, the homocoupling of **1b−d** was found to take place with LDA−$TiCl_4$.[16] The enolate anions of **1b−d** seem to be more oxidizable than that of **1a** in the reaction with $TiCl_4$. The predominant products from **1b−d** were (*R,R*)-**2b−d**, although a small amount of each (*R,S*)-isomer was formed (5% from **1b** and 15% from **1c,d**) (eq 2). The stereochemistry of (*R,R*)-**2b−d** was determined



from that of the (2*R*,3*R*)-2,3-dialkylsuccinic acids **3b−d**, which were obtained by hydrolysis of **2b−d** (eq 2).[17]

The products (*S,S*)- and (*R,R*)-**3** are useful as chiral intermediates for organic synthesis. One application is the preparation of (−)-hinokinin (**5**) from (*R,R*)-**3d**. Treatment of (*R,R*)-**3d** with Ac_2O and subsequent reduction of the resultant anhydride **4** with $NaBH_4$ gave **5**[19,20] (eq 3).

The stereoselectivities observed in the oxidative coupling of **1a−d** can be reasonably explained in terms of the radical and S_N2 mechanisms as shown in Scheme 1 for **1a**, although this is only a working hypothesis. In



(3)

the reaction of **1a** with amine−$TiCl_4$, the Ti-chelated enolate of **1a** is oxidized with Ti(IV) to generate a radical. The radicals then couple at the less hindered side (*Si* face), as depicted in A, to give (*S,S*)-**2a** stereospecifically (radical mechanism). On the other hand, in the oxidative coupling of an enolate anion with iodine,[21] the iodide **6** formed by the attack of iodine on the Li-enolate from the less hindered side (*Si* face), as depicted in B, reacts with another Li-enolate, as depicted in C, to yield (*R,S*)-**2a** (S_N2 mechanism). The formation of a small amount of (*S,S*)-**2a** in this coupling reaction can be explained only by a radical mechanism in which the radical is generated from enolate anion by single electron transfer to iodine. In contrast with these two cases, nonchelated enolate may be generated in the reaction of **1a** with EGB. The nonchelated enolate is oxidized with iodine, and the resulting radicals couple at the less hindered side (*Re* face), as depicted in D, to give (*R,R*)-**2a** (radical mechanism). The formation of a small amount of (*R,S*)-**2a** in this case can also be explained by the S_N2 mechanism.

Supplementary Material Available: Experimental details and compound characterization data (6 pages).

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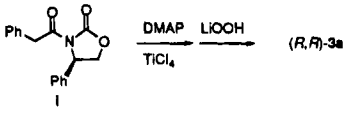
(15) Although (*R,R*)-**2a** could be also obtained by the reaction of (*R*)-4-isopropyl-3-(phenylacetyl)-2-oxazolidone, the (*R*)-isomer of **1a**, with amine−$TiCl_4$, (*R,R*)-**3a** was more conveniently prepared from (*R*)-4-phenyl-3-(phenylacetyl)-2-oxazolidone (**i**) because (*R*)-4-phenyl-2-oxazolidone was more easily available than (*R*)-4-isopropyl-2-oxazolidone. The coupling product of **i**: 76% yield with DMAP−$TiCl_4$; mp 94−96 °C; $[\alpha]^{20}_D$ −488 (*c* 1.00, $CHCl_3$).



(16) The reaction was carried out by the known method.[1g] (*R,R*)-**2b**: mp 146−148 °C; $[\alpha]^{20}_D$ +93.5 (*c* 1.00, $CHCl_3$). (*R,R*)-**2c**: mp 202−203 °C; $[\alpha]^{20}_D$ −200 (*c* 1.00, $CHCl_3$). (*R,R*)-**2d**: mp 176−177 °C; $[\alpha]^{20}_D$ +145 (*c* 1.09, $CHCl_3$).

(17) Hydrolysis of dimers was carried out according to the reported method.[14] The (2*R*,3*R*) configuration and ee (>95%) of **3b** were determined by the comparison of its optical rotation with reported data.[18] The absolute configuration of the major isomer of **3d** was assigned as (2*R*,3*R*) at the (−)-hinokinin (**5**) stage. Although the stereochemistry of **3c** could not be confirmed, it was assumed to be (2*R*,3*R*) on the basis of the data of **3d**. (*R,R*)-**3b**: mp 124−125 °C (lit.[18a] mp 126 °C); $[\alpha]^{20}_D$ +28.0 (*c* 1.00, acetone) (lit.[18a] $[\alpha]^{20}_D$ +28.9). (*R,R*)-**3c**: mp 141−142 °C; $[\alpha]^{20}_D$ −15.7 (*c* 1.00, acetone). (*R,R*)-**3d**: mp 169−170 °C; $[\alpha]^{20}_D$ −11.4 (*c* 1.08, acetone).

(18) (a) Wren, H.; Crawford, J. *J. Chem. Soc.* **1937**, 230. (b) Nagarajan, K.; Weissmann, C.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1963**, *137*, 1212. (c) Schickaneder, H.; Grill, H.; Wagner, J. *Liebigs Ann. Chem.* **1979**, 1205.

(19) **5**: $[\alpha]^{20}_D$ −33.0 (*c* 0.63, $CHCl_3$) (lit.[20a] $[\alpha]^{20}_D$ −34.0).

(20) (a) Haworth, R. D.; Woodcock, D. *J. Chem. Soc.* **1938**, 1985. (b) Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717 and references cited therein.

(21) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745.