The Journal of
Organic Chemistry

VOLUME 54, NUMBER 3 FEBRUARY 3, 1989

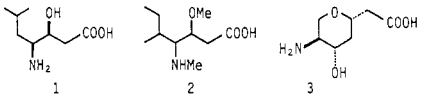
© Copyright 1989 by the American Chemical Society

Communications

New Diastereoselective Synthesis of Oxazolidin-2-ones through Carbon–Carbon Bond Formation on Cyclic Carbamoyloxy Radicals

Summary: Photoinitiated radical alkylation by using 5-(phenylthio)oxazolidin-2-ones, derived from (*S*)-α-amino acids, afforded the corresponding trans 4,5-disubstituted oxazolidin-2-ones with high diastereoselectivity. As an application of this C–C bond formation on the cyclic carbamoyloxy radical species, (3*S*,4*S*)-statine was effectively synthesized.

Sir: Development of methods for stereocontrolled synthesis of biologically important compounds containing the 2-amino alcohol moiety such as amino sugars[1] and unusual amino acids[2] continues to receive significant attention. Among various procedures, selective heterofunctionalization of acyclic olefinic systems to yield 4,5-disubstituted oxazolidin-2-ones, a protected form of 2-amino alcohols, has been widely investigated in recent years.[3] Direct stereoselective alkylation of an oxazolidinone at the 5-position provides a new, convergent methodology for the synthesis of 2-amino alcohols.[4] In this paper, we disclose a new and highly diastereoselective synthesis of 4,5-*trans*-4-substituted-5-allyloxazolidin-2-ones and thus valuable for the preparation of biologically important unusual amino acids having the 2-amino alcohol moiety such as statine (**1**),[2a,5] dolaisoleucine (**2**) in dolastatin **10**,[6] and galantinic acid (**3**) in galantin I.[7] Our synthesis involves a highly diastereoselective carbon–carbon bond formation using a novel cyclic carbamoyloxy radical[8] generated from 5-(phenylthio)oxazolidin-2-one possesses major advantages for the synthesis of 2-amino alcohols from α-amino acids, since it does not involve α-amino aldehydes, which are prone to racemization.



1 2 3

Our initial effort was focused on examining the feasibility and efficiency of the sulfonium ion induced cyclocarbamation. (*S*)-*N*-Cbz- or (*S*)-*N*-Boc-amino alcohols **4a–j**[9] were easily converted to the sulfides **5a–j**[10,11] in 80–95% yield by the conventional method (diphenyl disulfide, *n*-Bu_3P, THF, or DMF, room temperature).[12]

(1) (a) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondeli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335. (b) Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* **1969**, 1007.

(2) (a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259. (b) Nakamura, H.; Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 102. (c) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263.

(3) (a) Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079. (b) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797. (c) Roush, W.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752. (d) Hirama, M.; Shigemoto, T.; Ito, S. *J. Org. Chem.* **1987**, *52*, 3342. (e) Trost, B. M.; Sudhaker, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

(4) (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (b) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261. (c) Mukaiyama, T.; Goto, Y.; Shoda, S. *Chem. Lett.* **1985**, 671. (d) Claremon, D. A.; Lumma, P. K.; Philips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265. (e) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Lett.* **1987**, 1531.

(5) Recent publication on a synthesis of statine: (a) Woo, P. W. K. *Tetrahedron Lett.* **1985**, *26*, 2973. (b) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311. (c) Juoin, P.; Poncet, J.; Pontaroni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1895. (d) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987. (e) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1988**, *53*, 3865 and references cited therein.

(6) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuiman, A. A.; Boettner, F. E.; Kizu, H.; Tomer, K. B.; Bontomes, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883. Relative and absolute configuration of **2** was not verified.

(7) (a) Shoji, R.; Sakazaki, R.; Wakisaka, Y.; Koizumi, K.; Mayama, M.; Matsuura, *J. Antibiot.* **1975**, *28*, 122. (b) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.

(8) Reviews on radicals: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Organic Chemistry Series*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1986; Vol. 5, p 281.

(9) Compounds **4a–j** were easily available from L-amino acids. For **4h**: Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *24*, 1071.

(10) All new compounds were fully characterized by spectroscopic analyses (IR, NMR, MS) and gave satisfactory high-resolution MS and or satisfactory microanalyses.

(11) Selected physical data for **5** are as follows. **5a**: mp 47–49 °C; $[\alpha]_D$ +13.8° (*c* 0.99, $CHCl_3$). **5b**: mp 82–84 °C; $[\alpha]_D$ +26.3° (*c* 1.01, $CHCl_3$). **5c**: oil; $[\alpha]_D$ −9.2° (*c* 1.4, $CHCl_3$). **5d**: mp 80–83 °C; $[\alpha]_D$ +26.2° (*c* 0.99, $CHCl_3$). **5e**: mp 89–91 °C; $[\alpha]_D$ +23.1° (*c* 0.97, $CHCl_3$). **5f**: mp 59–62 °C; $[\alpha]_D$ +29.8° (*c* 0.91, $CHCl_3$). **5g**: mp 49–51 °C; $[\alpha]_D$ +35.8° (*c* 0.9, $CHCl_3$). **5h**: oil; $[\alpha]_D$ −4.1° (*c* 0.68, $CHCl_3$). **5i**: mp 54–56 °C; $[\alpha]_D$ −5.6° (*c* 2.14, $CHCl_3$). **5j**: oil; $[\alpha]_D$ +18.5° (*c* 0.9, $CHCl_3$).

(12) Nakagawa, T.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

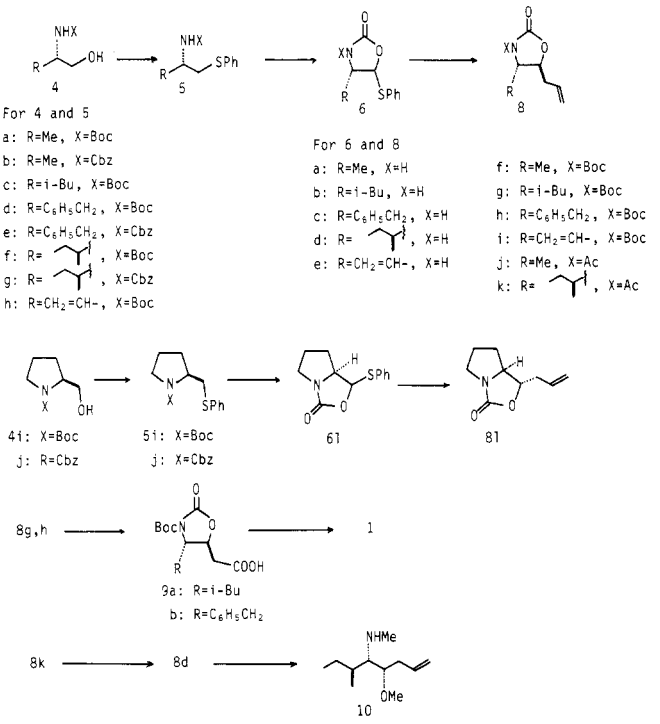
0022-3263/89/1954-0513$01.50/0 © 1989 American Chemical Society

Table I. 5-(Phenylthio)oxazolidin-2-ones

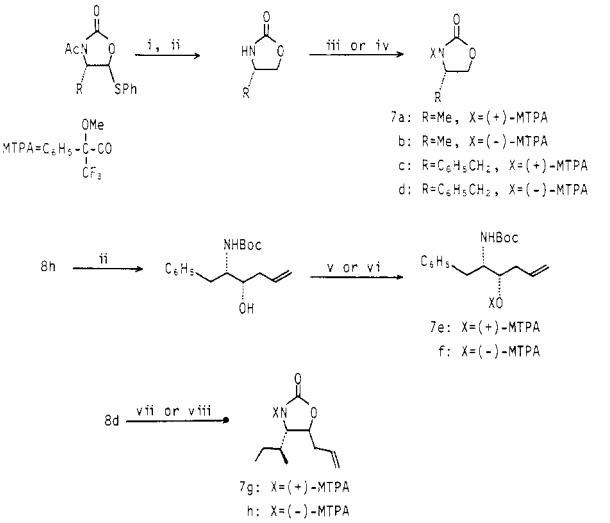
entry	sulfide	product	yield, %	trans:cis	mp, °C	$[\alpha]_D$, deg (c, $CHCl_3$)
1	**5a**	**6a**	79	10:1[a] (3:1)[b]	125–128	−302.8 (0.93)
2	**5b**	**6a**	72	10:1[a]		
3	**5c**	**6b**	80	20:1[a] (3:1)[b]	oil	−263.8 (0.6)
4	**5d**	**6c**	85	20:1[a] (4:1)[b]	107–108	−207.5 (1.0)
5	**5e**	**6c**	72	20:1[a]		
6	**5f**	**6d**	82	30:1[a] (3:1)[b]	80–83	−276.2 (0.8)
7	**5g**	**6d**	70	30:1[a]		
8	**5h**	**6e**	67	1.2:1[b,c]	oil	−241.4 (0.5)[d]
					102–104[e]	+284.4 (0.7)[e]
9	**5i**	**6l**	50	2.4:1[b]	oil	−126.6 (0.6)[f]
10	**5j**	**6l**	0[g]			

[a] Based on the signals due to 4-H and 5-H in ^1H NMR ($CDCl_3$, 90 and 400 MHz) spectra. [b] The reaction was quenched at −78 °C rather than 20 °C. [c] Based on the yields for isolation products. [d] Obtained from pure trans isomer. [e] Obtained from pure cis isomer. [f] Obtained from 2.4:1 trans/cis mixture. [g] *N*-Cbz (*S*)-prolinal was obtained.

Scheme I

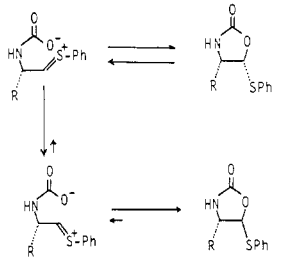


Scheme II[a]



[a] (i) Bu_3SnH, 500-W Hg lamp, Pyrex filter, CH_3CN–toluene (3:7); (ii) Cs_2CO_3, MeOH; (iii) (+)-MTPA-Cl, Et_3N, DMAP, THF; (iv) (−)-MTPA-Cl, Et_3N, DMAP, THF; (v) (+)-MTPA-OH, DCC, DMAP, CH_2Cl_2; (vi) (−)-MTPA-OH, DCC, DMAP, CH_2Cl_2; (vii) *n*-BuLi, THF, then (+)-MTPA-Cl; (viii) *n*-BuLi, THF, then (−)-MTPA-Cl.

Treatment of **5a–g** with *N*-chlorosuccinimide (CCl_4, room temperature, 0.5–2 h), followed by cyclization ($SnCl_4$, CH_2Cl_2, −78 °C for **5a,c,d,f**, −30 °C for **5b,e,g**, 20 min, then 20 °C, 30 min) afforded the corresponding (4*S*,5*S*)-5-(phenylthio)oxazolidin-2-ones **6a–d**[13] with high diastereoselectivity in good yields as shown in Table I. The diastereoselectivity was diminished when the reaction was quenched without elevating the reaction temperature to 20 °C (entry 1, 3, 4, 6). Under these low-temperature conditions, poor selectivity for **6e,l** (1.2:1 for **6e** and 2.4:1 for **6l**[14]) was obtained from **5h** and **5i**, respectively (entry 8, 9). *N*-Boc sulfides are superior to *N*-Cbz derivatives in yields for **6** (Table I, entry 1:2, 4:5, 6:7). Formation of cyclization products was observed at the chlorination step in *N*-Boc sulfides by partial cyclocarbamation. In the case of **5j**, the *N*-Cbz prolinal was obtained without formation of the desired cyclization product (entry 10). An interesting feature of this cyclocarbamation is that it involves equilibrium between cis and trans isomers (see eq 1) and



eq 1

results in predominant formation of the thermodynamically more stable trans isomers under the conditions applied. The cis isomer can be easily isomerized to the trans isomer by treatment with $SnCl_4$ as illustrated by conversion of the 1.5:1 mixture of 4*S*,5*S*/4*S*,5*R* isomer of **6a** with $SnCl_4$ (CH_2Cl_2, 20 °C, 0.5 h) to 4*S*,5*S* isomer (4*S*,5*S*:4*S*,5*R* = 10:1) without racemization. The optical purity of the cyclization products was determined as >99% ee by ^1H NMR (400 MHz) analysis of (+)- and (−)-α-methoxy-α-(trifluoromethyl)acetyl (MTPA)[15] imide **7a,b** and **7c,d**

(13) The signals due to 4-H and 5-H in their ^1H NMR ($CDCl_3$) spectra of *trans*-**6a–d** and cis isomers are as follows. *trans*-**6a**: δ 5.37 (d, *J* = 6 Hz, 5-H), 3.79 (dq, *J* = 6, 6 Hz, 4-H). *cis*-**6a**: δ 5.93 (d, *J* = 7 Hz, 5-H), 4.29 (dq, *J* = 7, 6 Hz). *trans*-**6b**: δ 5.42 (d, *J* = 6 Hz, 5-H), 3.73 (dt, *J* = 6, 6 Hz, 4-H). *cis*-**6b**: δ 5.89 (d, *J* = 8 Hz, 5-H), 4.07–4.29 (m, 4-H). *trans*-**6c**: δ 5.50 (d, *J* = 5 Hz, 5-H), 4.00–3.79 (m, 4-H). *cis*-**6c**: δ 5.94 (d, *J* = 7.5 Hz, 5-H), 4-H signals were not clearly assigned. *trans*-**6d**: δ 5.52 (d, *J* = 5 Hz, 5-H), 3.54 (dd, *J* = 4, 5 Hz, 4-H). *cis*-**6d**: δ 5.86 (d, *J* = 7 Hz, 5-H), 3.88 (dd, *J* = 7, 7 Hz, 4-H). *trans*-**6e**: δ 5.40 (d, *J* = 5 Hz, 5-H), 4.14 (br t, *J* = 5 Hz, 4-H). *cis*-**6e**: δ 5.95 (1 H, d, *J* = 8 Hz, 5-H), 4.79 (dd, *J* = 7, 7 Hz, 4-H).

(14) Attempts to cis/trans isomerization for **6l** under equilibrium conditions was unsuccessful due to undesired polimerization.

Table II. Allylation of 6

entry	substrate	product[a]	yield, %	$[\alpha]_D$, deg (c, $CHCl_3$)
1	**6a**	**8a**	45	-39.4 (0.4)
2	**6b**	**8b**[4e]	71	-71.7 (0.8)
3	**6c**	**8c**[4e]	55	-74.2 (0.9)
4	**6f**	**8f**	72	-5.4 (0.6)
5	**6g**	**8g**[18]	76	+8.2 (1.1)
6	**6h**	**8h**	81	-31.2 (0.9)
7	**6i**	**8i**	60	-43.4 (0.6)
8	*cis*-**6i**	**8i**	20	
9	**6j**	**8j**	62	-3.7 (0.6)
10	**6k**	**8k**	81	-15.9 (0.7)
11	*cis*-**6k**	**8k**	30	
12	**6l**[b,c]	**8l**	57	-63.5 (1.0)

[a] All products were obtained as an oil except **8h**. **8h**: mp 80-81 °C. [b] 2.4:1 trans/cis mixture was used. [c] The reaction was continued for 40 h.

derived from **6a** and **6c**, respectively, by the procedure as outlined in Scheme II. *tert*-Butoxycarbonylation of **6a-c,e** (Boc_2O, Et_3N, 4-(dimethylamino)pyridine, THF) afforded **6f-i**, respectively, and acetylation of **6a,d** (Ac_2O, Et_3N, 4-(dimethylamino)pyridine, THF) gave **6j,k**, respectively.

Allylation of **6a-c,f-l** by modification of Keck's conditions[16] (0.5 M solution in toluene-CH_3CN (7:3), 4 equiv of allyltri-*n*-butylstannane, 1 equiv of $(Bu_3Sn)_2$, *hν*, 24 h, Pyrex filter, 300-W Hg lamp, 24 h) gave the corresponding 5-allyloxazolidin-2-ones **8a-l** as single diastereomers in the yields shown in Table II. The stereochemical assignment was clearly determined as 4*S*,5*S*-trans based on the ^1H NMR spectra.[3a,4e,5c] The optical purity of the allylation products was >99% ee by ^1H NMR (400 MHz) analysis of *N*-Boc Mosher esters[15] **7e,f** and MTPA imides **7g,h** prepared from **8h** and **8k**, respectively. Yields for 5-allylation products were increased by protection of nitrogen with Boc or acetyl groups (compare Table II, entry 1-3 with 4-6, 9). It is noteworthy that the reactivity of the 4,5-cis isomers toward generation of radical species is remarkably low compared with that of the trans isomers. This was clearly demonstrated by using **6i** and **6k**, which stereo isomers were available in a pure state (Table II, entry 8 and 11). These results indicate that the reaction is strongly affected by the stereochemistry and that the trans-oriented phenylthio group is more active than the cis-oriented one. The low reactivity of the cis isomers could be due to steric congestion, which restricts attack of the tri-*n*-butyltin radical on the sulfur atom.

These 5-allyloxazolidin-2-ones should be useful for the synthesis of β-oxygenated γ-amino acids. Oxidation of **8g** and **8h** ($RuCl_3$-$NaIO_4$, H_2O, CH_3CN, CCl_4)[17] under Sharpless conditions afforded the corresponding acids **9a**[18] (80%), $[\alpha]_D$ +23.3° (*c* 0.90, $CHCl_3$) (lit.[18] $[\alpha]_D$ +23.32° (*c* 0.92, $CHCl_3$)), and **9b** (45%), respectively. Compound **9a** was converted to (3*S*,4*S*)-statine (**1**) through hydrolysis[18] (80% yield) of **9a** and deprotection.[5a] Hydrolysis of **8k** (catalytic amount of Cs_2CO_3, MeOH, room temperature) gave **8d** (100%), which was converted to **10** ((1) $LiAlH_4$; (2) MeI/KH,[19] THF, 50% yield from **8d**), which should be a potentially useful intermediate for one isomer of **2**.

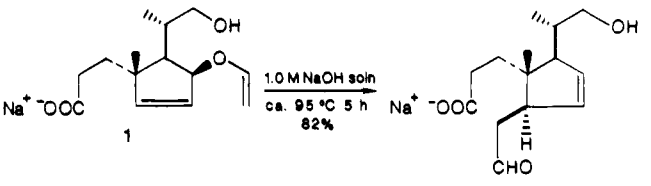
Shinzo Kano,* Tsutomu Yokomatsu
Shiroshi Shibuya
Tokyo College of Pharmacy
1432-1 Horinouchi, Hachioji
Tokyo 192-03, Japan
Received August 9, 1988

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(16) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.
(17) Carlsen, E.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(18) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331.
(19) Selective O-methylation of 2-amino alcohol system: Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

Effect of Polar Solvents on the Rates of Claisen Rearrangements: Assessment of Ionic Character

Summary: The first-order rate constants for Claisen rearrangement of carboxylate **3** and its methyl ester were determined in solvents ranging in polarity from cyclohexane to water.

Sir: The discovery by White[1] and the Cornell group[2] that polar solvents increase the rate of Claisen rearrangements has a profound consequence in synthetic methodology. While the vinyl ethers of cyclic allylic alcohols are most reluctant to undergo the 3,3-sigmatropic shift to the appropriate aldehyde in the gas phase or in hydrocarbon solvents, remarkably, compound **1** rearranges completely after only 5 h in boiling water.[3] From a mechanistic point of view, the nature of the transition state responding to the polar environment is of concern.



The Cornell group examined the rearrangement of allyl vinyl ethers in media as polar as 2:1 methanol-water.[2] However, the data could not be correlated with solvent E_t values. Further, more polar solvent systems could not be used because of solubility problems. The Cornell group interpreted the solvent response data in terms of an ionic-like transition state. In addition, Knowles has suggested that a dipolar or tight ion pair transition state is involved in the rearrangement of chorismate, **2**, and its diacid on the basis of faster rates in water relative to methanol solvent.[4] A dipolar transition state is also suggested by

(1) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196, 3585.
(2) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.
(3) Unpublished observations, E. Brandes, Indiana University.
(4) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008.

0022-3263/89/1954-0515$01.50/0 © 1989 American Chemical Society