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Facile synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate from L-proline

Shigeo Hirata, Masami Kuriyama, Osamu Onomura *

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

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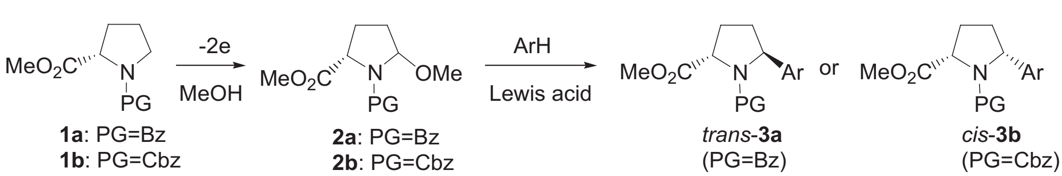
Diastereoselective introduction of phosphono groups into L-proline derivatives at the 5-position was achieved with suitable selection of *N*-protecting group. *N*-Benzoyl-L-prolinate preferentially gave *trans*-phosphorylated products, which could be easily transformed into (*S*)-(pyrrolidin-2-yl)phosphonates. On the other hand, *N*-benzyloxycarbonyl-L-prolinate reacted with phosphite to give *cis*-substituted products, which could be easily transformed into (*R*)-(pyrrolidin-2-yl)phosphonates.

1. Introduction

Optically active α-amino phosphonates and their derivatives are biologically important compounds structurally analogous to α-amino acids.[1] A lot of useful methods have been developed for the diastereo- or enantio-selective synthesis of acyclic α-amino phosphonates.[2] On the other hand, there are fewer methods for the diastereoselective synthesis of optically active cyclic α-amino phosphonates, which have found promising applications as surrogates of proline.[3] These methods use (+)- or (−)-2-hydroxy-3-pinenone,[3b] (+)-camphor,[3c] (*R*)- or (*S*)-phenylglycinol,[3d,e] L-menthol,[3f] (*S*)-(+)-*p*-toluenesulfinamide[3g] as chiral auxiliaries, while easily available L-proline on manufacturing scale has not used for the synthesis.

Recently, we have reported Lewis acid-catalyzed arylation of *N*-acylated 5-methoxy-L-proline **2**, which are electrochemically prepared from L-proline derivatives **1** proceeded diastereoselectively. Namely, *N*-benzoylated prolinate **2a** afforded *trans*-5-arylated L-proline *trans*-**3a**, while *N*-benzyloxycarbonylated prolinate **2b** afforded *cis*-5-arylated L-proline *cis*-**3b** (Eq. 1).[4]



(1)

* Corresponding author. Tel.: +81 95 819 2429; fax: +81 95 819 2476; e-mail address: onomura@nagasaki-u.ac.jp (O. Onomura).

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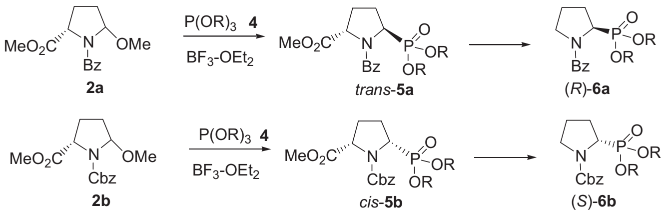
We wish herein to report the effect of *N*-acyl groups on the diastereoselective introduction of phosphonate groups into L-proline derivatives **2** at the 5-position and its application to synthesis of both enantiomers of (pyrrolidin-2-yl)phosphonate **6** (Scheme 1).

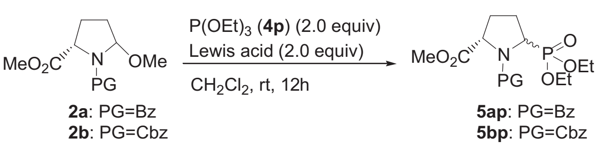


Scheme 1.

2. Results and discussion

2.1. Effect of Lewis acid on the Arbusov reaction

First, we investigated effect of Lewis acid on introduction of triethyl phosphite **4p**[5] into *N*-benzoylated or *N*-benzyloxycarbonylated 5-methoxylated L-prolinate[6] **2a** or **2b** (Eq. 2). The results are shown in Table 1. In the case of **2a**, $TiCl_4$ mediated α-phosphorylation in good yield but with low diastereoselectivity (entry 1). $BF_3 \cdot OEt_2$ promoted the phosphorylation in moderate diastereoselectivity (entry 2), while $SnCl_4$ did not work as an effective Lewis acid (entry 3).[7] Using $Cu(OTf)_2$, $AlCl_3$, $Hf(OTf)_4$, or $In(OTf)_3$ as Lewis acid afforded phosphorylated product **5ap** in low yields (entries 4–7).[7] In the case of **2b**, similar tendency for tested Lewis acids was observed (entries 8–14), and $BF_3 \cdot OEt_2$ afforded the best result (entry 9).



(2)

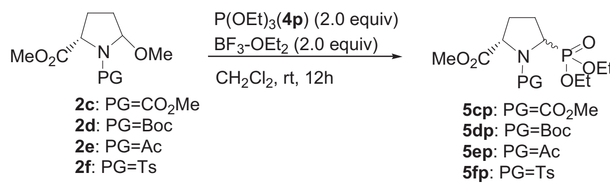
Table 1
Effect of Lewis acid on the Arbusov reaction

Entry	Substrate	PG	Lewis acid	Product	Yield[a] (%)	de[b] (%)	Major isomer
1[c]	**2a**	Bz	$TiCl_4$	**5ap**	66	26	trans
2	**2a**	Bz	$BF_3 \cdot OEt_2$	**5ap**	59	43	trans
3	**2a**	Bz	$SnCl_4$	**5ap**	0	—	—
4	**2a**	Bz	$Cu(OTf)_2$	**5ap**	27	30	trans
5	**2a**	Bz	$AlCl_3$	**5ap**	37	53	trans
6	**2a**	Bz	$Hf(OTf)_4$	**5ap**	32	15	trans
7	**2a**	Bz	$In(OTf)_3$	**5ap**	14	32	trans
8[c]	**2b**	Cbz	$TiCl_4$	**5bp**	49	51	cis
9	**2b**	Cbz	$BF_3 \cdot OEt_2$	**5bp**	45	78	cis
10	**2b**	Cbz	$SnCl_4$	**5bp**	0	—	—
11	**2b**	Cbz	$Cu(OTf)_2$	**5bp**	35	55	cis
12	**2b**	Cbz	$AlCl_3$	**5bp**	44	29	cis
13	**2b**	Cbz	$Hf(OTf)_4$	**5bp**	33	61	cis
14	**2b**	Cbz	$In(OTf)_3$	**5bp**	26	70	cis

[a] Yield of isolated product as a mixture of diastereomers after purification by column chromatography.
[b] The diastereomer excess was determined by ^1H NMR spectroscopy after purification.
[c] Reaction temperature: −78 °C to rt.

2.2. Effect of *N*-protective group

Next, we investigated effect of *N*-protecting group on the diastereoselectivity for the Arbusov reaction of **2c**–**f** with **4p** in the presence of $BF_3 \cdot OEt_2$ (Eq. 3). The results are shown in Table 2. Diastereoselectivities of phosphorylated products **5cp** and **5dp**, which were obtained from *N*-methoxycarbonylated proline **2c** and *N-tert*-butoxycarbonylated proline **2d**[8] (entries 1 and 2 in Table 2) lowered compared with that of *N*-benzyloxycarbonylated proline **5bp** (entry 9 in Table 1). Similarly, diastereoselectivities of phosphorylated products **5ep** and **5fp**, which were obtained from *N*-acetylated proline **2e** and *N*-*p*-toluenesulfonylated proline **2f** (entries 3 and 4 in Table 2) did not exceed that of *N*-benzoylated proline **5ap** (entry 2 in Table 1).



(3)

Table 2
Effect of *N*-protective group on the Arbusov reaction

Entry	Substrate	PG	Product	Yield[a] (%)	de[b] (%)	Major isomer
1	**2c**	CO_2Me	**5cp**	68	50	nd
2	**2d**	Boc	**5dp**	20	41	nd
3	**2e**	Ac	**5ep**	60	15	nd
4	**2f**	Ts	**5fp**	98	29	nd

[a] Yield of isolated product as a mixture of diastereomers after purification by column chromatography.
[b] The diastereomer excess was determined by ^1H NMR spectroscopy after purification.

2.3. Effect of ester group in phosphite

Next, we investigated effect of ester group of phosphites on the diastereoselectivity for the Arbusov reaction of **2a** or **2b** in the presence of $BF_3 \cdot OEt_2$ (Eq. 4). The results are shown in Table 3. *N*-Benzoylated proline **2a** reacted with trimethyl phosphite **4q** gave *trans*-phosphorylated product **5aq** in similar yield and diastereoselectivity (entry 1 in Table 3) to those of **5ap** (entry 2 in Table 1). Although triphenyl phosphite **4r**, tribenzyl phosphite **4s**, and tri-*n*-butyl phosphite **4u** were ineffective (entries 2, 3, and 5 in Table 3),[7] triisopropyl phosphite **4t** was effective to afford *trans*-phosphorylated product **5at** in good yield with high diastereoselectivity (entry 4 in Table 3). In the case of *N*-benzyloxycarbonylated proline **2b**, similar tendencies were observed with respect to effect of phosphites (entries 6–10 in Table 3).[7] The reaction of **2b** with **4t** gave the best result to afford *cis*-**5bt** in 50% yield with 85% de (entry 9 in Table 3).

2.4. Determination of stereoconfiguration

Transformation of **5bp** into diethyl (*S*)-(pyrrolidin-2-yl)phosphonate (*S*)-**9p** shown in Eq. 5 revealed that the relative stereoconfiguration of **5bp** was cis-form. Namely, removal of 2-methoxycarbonyl group of **5bp** was accomplished by alkaline hydrolysis of **5bp** to afford carboxylic acid **7bp**, and decarboxylative methoxylation[9] of **7bp**, followed by reduction of *N*,*O*-acetal **8bp**[10] to give *N*-benzyloxycarbonyl-2-pyrrolidinylphosphonate **6bp**. Successive debenzyloxycarbonylation of **6bp** afforded (*S*)-**9p**.[3c,11]

Opposite diastereoselectivity for the reaction of **2b** with **4p** was confirmed by transformation of *cis*-**5bp** into *cis*-**5ap** shown in Eq. 6. The major diastereomer of *cis*-**5ap** in Eq. 6 was consistent with the minor diastereomer obtained in entry 1 of Table 1. Accordingly, **5ap** shown in entry 1 in Table 1 was trans-configuration.