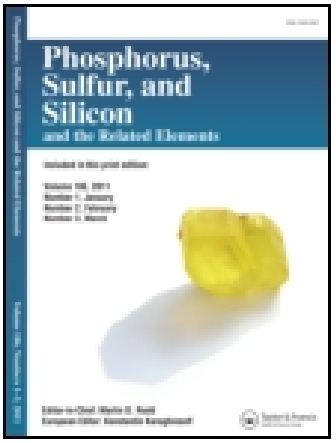
This article was downloaded by: [Florida International University]
On: 21 December 2014, At: 05:45
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Reversal Diastereoselectivity in the Benzylation of Phosphonopropanoamides

Javier Cervantes-González [a], Selene Lagunas-Rivera [a] & Mario Ordóñez [a]

[a] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Cuernavaca, Mor., México

Published online: 25 Apr 2011.

To cite this article: Javier Cervantes-González, Selene Lagunas-Rivera & Mario Ordóñez (2011) Reversal Diastereoselectivity in the Benzylation of Phosphonopropanoamides, Phosphorus, Sulfur, and Silicon and the Related Elements, 186:4, 707-711, DOI: 10.1080/10426507.2010.522638

To link to this article: http://dx.doi.org/10.1080/10426507.2010.522638

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Phosphorus, Sulfur, and Silicon, 186:707–711, 2011
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2010.522638

Downloaded by [Florida International University] at 05:45 21 December 2014

REVERSAL DIASTEREOSELECTIVITY IN THE BENZYLATION OF PHOSPHONOPROPANOAMIDES

Javier Cervantes-González, Selene Lagunas-Rivera, and Mario Ordóñez

Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Cuernavaca, Mor., México

*A convenient and efficient preparation of phosphonopropanoamides bearing (*S*)-1-(1′-naphthyl)ethylamine, (*S*)-3,3-dimethyl-2-butylamine, and (*S*)-2-amine-3-methylbutane in good yield has been achieved. The stereochemical outcome of the asymmetric benzylation reaction of their enolates changes dramatically with the LDA equivalents used. The enolization of the phosphopropanoamides with LDA (2 equiv.) followed by the reaction with benzyl bromide gives rise to the (*R,S*) quaternary phosphonoamides, whereas the (*S,S*) diastereoisomer can be obtained by enolization with LDA (≥2.5 equiv.) followed by the addition of benzyl bromide. This method provides access to both diastereoisomers changing only the base equivalents.*

Keywords Aminophosphonates; diastereoselective benzylation; phosphonoamides; quaternary stereocenter; reversal diastereoselectivity

INTRODUCTION

Optically active α-aminophosphonic acids are analogues of α-amino acids in which the planar carboxylic acid group (CO_2H) is replaced by a sterically more demanding tetrahedral phosphonic acid group (PO_3H_2). This class of compounds is currently attracting interest in the organic and medicinal chemistry, as well as in agriculture, due to their important biological and pharmacological properties.[1] Due to the tetrahedral configuration at phosphorus, α-aminophosphonic acids act as stable analogues of the unstable tetrahedral–carbon transition-state in peptide hydrolysis, and therefore act as enzyme inhibitors.[2] Many natural and synthetic α-aminophosphonic acids, α-aminophosphonates, and phosphonopeptides have potential applications, e.g., as anti-HIV,[3] antibacterial,[4] antibiotic,[5] anticancer,[6] antitumor,[7] and antiviral agents.[8] Furthermore, in agrochemistry, a number of α-aminophosphonic acids and derivatives are used as fungicidal[9] and herbicidal agents.[10]

The utility of the α-aminophosphonic acids and their peptidic derivatives as biological tools and chemical applications has stimulated during the last 35 years the need for

Received 20 August 2010; accepted 3 September 2010.

This work was carried out with the financial support of CONACYT-MEXICO (Project 62271), and (in part) by CONACYT-MEXICO-INDIA (Bilateral Project J110.501/2006).

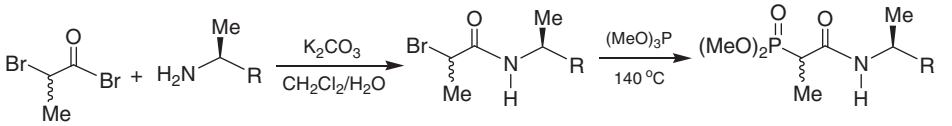
Address correspondence to Mario Ordóñez, Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62209 Cuernavaca, Mor., México. E-mail: palacios@ciq.uaem.mx

chemists to develop new methodologies for their synthesis, in racemic or enantiomerically pure form.[11] In this context, several protocols for efficient asymmetric synthesis of α-aminophosphonic acids and derivatives have emerged in recent years, especially taking into account that biological activity of these depends on the absolute configuration of the stereogenic α-carbon to the phosphorus atom.[12] All these procedures can be classified into (1) enantio- and diastereoselective hydrophosphonylation of imines (Pudovik reaction); (2) the classical Kabachnik–Fields reaction, an enantio- and diastereoselective three component reaction (aldehyde, amine, and dialkyl phosphite); (3) diastereoselective alkylation of phosphoglycinates derivatives, (4) diastereoselective amination of phosphonates; (5) chiral pool processes; (6) catalytic asymmetric hydrogenation of dehydroaminophosphonates; (7) resolution process; and (8) by convergent synthetic strategy.[13] However, the methodologies described above generally are not useful for the synthesis of quaternary α-aminophosphonic acids.

With the purpose of establishing a methodology for the synthesis of quaternary α- and β-aminophosphonic acids with a high stereoselectivity derived from the same source of chirality, recently we carried out the benzylation of the phosphonopropanoamide **3a** bearing (*S*)-α-methylbenzylamine as an chiral auxiliary, and found reversal diastereoselectivity by changing only the lithium bases equivalents (such as LDA, LiHMDS, LTMP, and *n*-BuLi), whereas when using NaHMDS and KHMDS, reversal diastereoselectivity was not observed.[14] In this article, we report the results of the synthesis and diastereoselective benzylation of the phosphonopropanoamides **3b–d** bearing (*S*)-1-(1′-naphthyl)ethylamine, (*S*)-3,3-dimethyl-2-butylamine, and (*S*)-2-amine-3-methylbutane as chiral auxiliaries.

RESULTS AND DISCUSSION

The starting phosphonopropanoamides **3a–d** used in this study were easily prepared in good yield from 2-bromopropionyl bromide employing the protocol developed in our laboratory.[15] Thus, the treatment of commercially available 2-bromopropionyl bromide with the chiral (*S*)-amines **1b–d** in the presence of K_2CO_3 at room temperature gave the diastereoisomeric mixture of α-bromopropanoamides **2b–d** in excellent yield,[16] which by reaction with trimethyl phosphite at 140°C afforded the phosphonopropanoamides **3b–d** in good yields (Scheme 1).[16] The reaction of diastereoisomerically pure **2a–d** with trimethyl phosphite at 140°C provided the phosphonopropanoamides **3a–d** with 50:50 diastereoisomeric ratio (dr), which can be explained by enolization of the α-carbon to the phosphorus atom. Similar results were obtained at 100–130°C, but under these conditions the reaction not was complete.



1a; R = Ph
1b; R = 1-Naphthyl
1c; R = *i*-Pr
1d; R = *t*-Bu

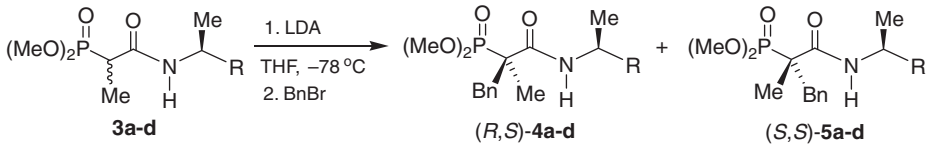
2a; R = Ph, 96%
2b; R = 1-Naphthyl, 98%
2c; R = *i*-Pr, 82%
2d; R = *t*-Bu, 95%

3a; R = Ph, 81%
3b; R = 1-Naphthyl, 72%
3c; R = *i*-Pr, 69%
3d; R = *t*-Bu, 75%

Scheme 1

Downloaded by [Florida International University] at 05:45 21 December 2014

Table 1 Benzylation of phosphonopropanoamides **3a–d**



Entry	R	LDA (equiv.)	Yield (%)	(*R*,*S*)-**4**: (*S*,*S*)-**5**[a]
1	Ph	2.0	77	90:10[b]
2	Ph	2.5	83	20:80[b]
3	1-Naphtyl	2.0	73	91:9
4	1-Naphtyl	2.5	77	31:69
5	*i*-Pr	2.0	71	75:25
6	*i*-Pr	2.5	79	40:60
7	*t*-Bu	2.0	73	89:11
8	*t*-Bu	2.5	75	18:82

[a](*R*,*S*)-**4**:(*S*,*S*)-**5** ratio was determined by ^{31}P NMR at 81 MHz in the crude product.
[b]These results were described in Ref. 13b.

In accordance with our preliminary investigations,[14] the benzylation reaction of phosphonopropanoamides **3b–d** was carried out using freshly prepared LDA (2.0 and 2.5 equiv.) in dry THF at −78°C. The results are summarized in Table 1.

With the phosphonopropanoamides **3b–d** in hand, the compound **3b** was treated with freshly prepared LDA (2.0 equiv.) in dry THF at −78°C followed by the addition of benzyl bromide (1.0 equiv), obtaining the quaternary α,α-disubstituted phosphonoamides (*R*,*S*)-**4b** and (*S*,*S*)-**5b** in 73% yield and 91:9 dr, with a predominance of (*R*,*S*)-**4b** diastereoisomer (Table 1, entry 3). However, when **3b** was treated with LDA (2.5 equiv.) at −78°C followed by the addition of benzyl bromide, the reaction afforded the phosphonoamides (*R*,*S*)-**4b** and (*S*,*S*)-**5b** in 77% yield and 31:69 dr, with a predominance of (*S*,*S*)-**5b** diastereoisomer (Table 1, entry 4). These results revealed that the benzylation step is quite sensitive to LDA equivalents used in the enolization. Initially, we anticipated that the diastereoselectivity could be increased as the size of the aryl group increased from phenyl to 1-naphthyl in the phosphopropanoamides **3a** and **3b**, respectively; however, experimentally the diastereoselectivity was similar in both cases (Table 1, entries 1–4).[17]

These results are explained assuming that the enolates **6a**,**b** derived by deprotonation of **3a** and **3b** with LDA (2.0 equiv.) adopt the same conformation, which is in accordance with the precedent in the literature and is favored by the coordination C=C−O−Li−O=P,[18] and where the orientation of the C−H bond in the methylbenzyl or methyl-1-naphthyl chiral fragments towards the oxygen atom. Therefore, the relative size of these groups determines the preferred direction of benzyl bromide addition. In this arrangement, effectively the phenyl and 1-naphthyl groups block the *re* face of the enolates **6a**,**b** towards the benzylation, and the addition of benzyl bromide would occur from the same face of the methyl group (*si* face), providing the (*R*,*S*)-**4a** and (*R*,*S*)-**4b** diastereoisomers, respectively, as principal product. On the other hand, the addition of LDA 0.5 to 2.0 equivalents more to **6a**,**b** gave the enolates **7a**,**b**, where we propose that one additional molecule of LDA is coordinated with C=C−O and N−Li fragments, and the orientation of the C−H bond in the methylbenzyl or methyl-1-naphthyl chiral fragments is directed towards C=C bond in the enolates **7a**,**b**, and the phenyl and 1-naphthyl groups now blocks the *si* face of enolates **7a**,**b**; the addition

Downloaded by [Florida International University] at 05:45 21 December 2014

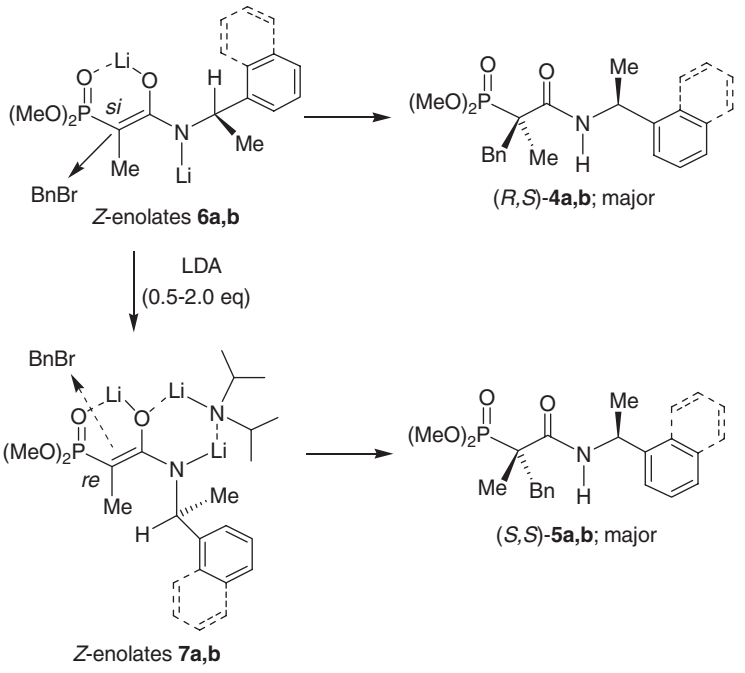


Figure 1 Mechanism proposed for the benzylation of **3a** and **3b**.

of benzyl bromide occurs by the *re* face, giving the (*S*,*S*)-**5a** and (*S*,*S*)-**5b** diastereoisomers, respectively, as major product (Figure 1).

Having established a highly efficient procedure for the benzylation of the phosphonopropanoamides **3a**,**b** bearing (*S*)-α-methylbenzylamine and (*S*)-1-(1′-naphthyl)ethylamine with reversal diastereoselectivity, we turned our attention to the benzylation of the phosphonoamides **3c**,**d** bearing (*S*)-3,3-dimethyl-2-butylamine and (*S*)-2-amine-3-methylbutane as a chiral auxiliaries, and found that the benzylated phosphonoamides (*R*,*S*)-**4c**,**d** were obtained as principal diastereoisomers 75:25 and 89:11 dr, respectively (Table 1, entries 5 and 7), when LDA (2.0 equiv.) were used in the enolization, whereas when using LDA ($\geq$2.5 equiv), the (*S*,*S*)-**5c**,**d** diastereoisomers were obtained as major product (Table 1, entries 6 and 8).

CONCLUSION

Reversal diastereoselectivity in the benzylation of the phosphopropanoamides **3a–d** is strongly dependent of LDA equivalents used in the enolization, which can be attributed to effects of the aggregation states of the enolates. This methodology provides access to both diastereoisomers from the same source of chirality, changing only the LDA equivalents.

REFERENCES

1. (a) Kukhar, V. P.; Hudson, H. R. In *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; V. P. Kukhar, Ed.; John Wiley & Sons: Chichester, UK, 2000; (b) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur* **1991,** *63*, 193–215; (c) Dhawan, B.; Redmore, D.

Downloaded by [Florida International University] at 05:45 21 December 2014

Phosphorus, Sulfur **1987,** *32*, 119–144; (d) Sieńczyk, M.; Oleksyszyn, J. *Curr. Med. Chem.* **2009,** *16*, 1673–1687.
2. (a) Rozenfeld, R.; Iturrioz, X.; Okada, M.; Maigret, B.; Llorents-Cortes, C. *Biochemistry* **2003,** *42*, 14785–14793; (b) Hirschmann, R.; Smith, III, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994,** *265*, 234–237; (c) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989,** *32*, 1652–1661; (d) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987,** *30*, 1603–1609.
3. (a) Alonso, E.; Solis, A.; del Pozo, C. *Synlett* **2000,** 698–700; (b) Stowasser, B.; Budt, K. -H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992,** *33*, 6625–6628; (c) Camp, N. P.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem. Lett.* **1992,** *2*, 1047–1052.
4. (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978,** *272*, 56–58; (b) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986,** *29*, 29–40.
5. (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Haga, S.; Sugi, H.; Tanigawa, K.; Suzuki, Y.; Fukawa, K.; Irino, O.; Saita, O.; Yamabe, S. *Heterocycles* **1981,** *16*, 1205–1242; (b) Lejczak, B.; Kafarski, P.; Sztajer, H.; Mastalerz, P. *J. Med. Chem.* **1986,** *29*, 2212–2217.
6. Feng, Y.; Coward, J. K. *J. Med. Chem.* **2006,** *49*, 770–788.
7. (a) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.* **2001,** *1*, 301–312; (b) Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A.; Cudennec, C. A.; Pierré, A. *J. Med. Chem.* **1991,** *34*, 1998–2003.
8. Huang, J.; Chen, R. *Heteroat. Chem.* **2000,** *11*, 480–492.
9. Maier, L.; Diel, P. J. *Phosphorus, Sulfur* **1991,** *57*, 57–64.
10. (a) Kozlowski, H.; Pusino, A.; Swiatek, J.; Spychala, J.; Glowiak, T.; Micera, G.; Gessa, C. *J. Agric. Food Chem.* **1990,** *38*, 1989–1992; (b) Nska, H.; Bonarska, D.; Bielecki, K.; Sarapuk, J. *Cell. Mol. Biol. Lett.* **2002,** *7*, 929–935.
11. (a) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009,** *65*, 17–49; (b) Bhadury, P. S.; Song, B.-A.; Yang, S.; Zhang, Y.; Zhang, S. *Curr. Org. Synth.* **2008,** *5*, 134–150; (c) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008,** *350*, 1195–1208; (d) Ma, J.-A. *Chem. Soc. Rev.* **2006,** *35*, 630–636; (e) Uziel, J.; Genêt, J. P. *Russ. J. Org. Chem.* **1997,** *33*, 1521–1542; (f) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994,** *92*, 239–264.
12. (a) Drag, M.; Pawelczak, M.; Kafarski, P. *Chirality* **2003,** *15*, S104–S107; (b) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans 1* **1984,** 2845–2853; (c) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Lloyd, W. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979,** *15*, 696–705.
13. (a) Meng, F.; Xu, J. *Amino Acids* **2010,** *39*, 533–538; (b) He, F.; Meng, F.; Song, X.; Hu, W.; Xu, J. *Org. Lett.* **2009,** *11*, 3922–3925; (c) Li, B.; Cai, S.; Du, D.-M.; Xu, J. *Org. Lett.* **2007,** *9*, 2257–2260; (d) Cai, S.; Yin, W.; Ma, Y.; Liu, H.; Zhao, Y.; Hu, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007,** *182*, 25–33, and references cited therein.
14. (a) Ordóñez, M.; Hernández, E.; Rojas, A.; Labastida, V. *Tetrahedron: Asymmetry* **2008,** *19*, 2767–2770; (b) Ordóñez, M.; Hernández, E.; Xahuentitla, J.; Cativiela, C. *Chem. Commun.* **2005,** 1336–1338.
15. (a) Hernández-Fernández, E.; Fernández-Zertuche, M.; García-Barradas, O.; Muñoz-Muñiz, O.; Ordóñez, M. *Synlett* **2006,** 440–444; (b) Ordóñez, M.; Hernández-Fernández, E.; Montiel-Pérez, M.; Bautista, R.; Bustos, P.; Rojas-Cabrera, H.; Fernández-Zertuche, M.; García-Barradas, O. *Tetrahedron: Asymmetry* **2007,** *18*, 2427–2436.
16. The preparation of **2a** and **3a** have been reported in Ref. 14b.
17. The absolute configuration of the new quaternary center in (*S*,*S*)-**5a** was assigned by X-ray analysis, Ref. 14b, and extrapolated for the diastereoisomers (*S*,*S*)-**5c-d**.
18. Schickli, C. P.; Seebach, D. *Liebigs Ann. Chem.* **1991,** 655–668.

Downloaded by [Florida International University] at 05:45 21 December 2014