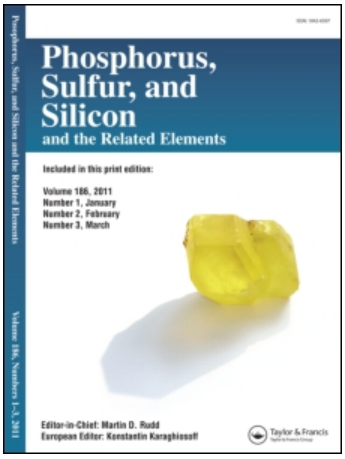
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Diastereoselective Synthesis of Enantiopure α-Aminophosphonic Acid Derivatives: Pudovik Reaction in Stereoselective Synthesis (Dedicated to A. N. Pudovik, 1916-2006)

V. A. Alfonsov[a]
[a] A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan, Russian Federation

To cite this Article Alfonsov, V. A.(2008) 'Diastereoselective Synthesis of Enantiopure α-Aminophosphonic Acid Derivatives: Pudovik Reaction in Stereoselective Synthesis (Dedicated to A. N. Pudovik, 1916-2006)', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 11, 2637 — 2644
To link to this Article: DOI: 10.1080/10426500802344022
URL: http://dx.doi.org/10.1080/10426500802344022

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 183:2637–2644, 2008
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802344022

Taylor & Francis
Taylor & Francis Group

Diastereoselective Synthesis of Enantiopure α-Aminophosphonic Acid Derivatives: Pudovik Reaction in Stereoselective Synthesis (Dedicated to A. N. Pudovik, 1916–2006)

V. A. Alfonsov
A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan, Russian Federation

In this report, we present the application of Pudovik reaction in the synthesis of chiral organophosphorus compounds and shown this reaction to be a promising way to enantiopure aminophosphonic acid derivatives. Cyclization reactions are a new, most efficient strategy for stereoselective synthesis of α-aminophosphonates, namely an intramolecular type of interaction of the P(III) atom and an imino group.

Keywords Cyclization reactions; diastereoselectivity; enantiopure α-aminophosphonates; Pudovik reaction

Downloaded At: 17:25 27 January 2011

INTRODUCTION

In 2006, A. N. Pudovik—a well-known Russian chemist—celebrated his ninetieth birthday. Scientists in our community know he made a fundamental contribution to the development of organophosphorus chemistry. One reaction in organic chemistry has been named in his honor. I dedicate this report to him, to Arkady Pudovik, to my teacher in science and life.

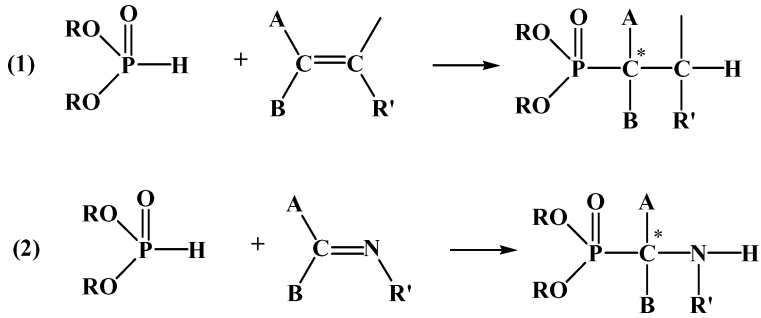
A. N. Pudovik discovered his reaction in the fourth and fifth decades of the previous century. This reaction involves the addition of the P—H bond of phosphonic acid esters to C=C (**1**) and C=N (**2**), or other double

Received 9 July 2008; accepted 15 July 2008.

This article was presented at the 17th International Conference on Phosphorus Chemistry (ICPC-17), April 15–21, 2007, Xiamen, China.

This work was supported by the Civilian Research and Development Foundation (grant no. RUC2-2638-KA-05) and the Russian Foundation for Basic Research (grant no. 07-03-00617).

Address correspondence to Prof. Vladimir Alfonsov, A. E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences, Arbuzov Str, 8, Kazan, 420088 Russia. E-mail: alfonsov@iopc.knc.ru



SCHEME 1

bonds. If the two substituents A and B at the double bond are different, an asymmetric center in α-position to the phosphorus atom is formed.[1]

The addition of phosphonic acid esters to azomethines leading to α-aminophosphonic acid derivatives is the most known among these reactions (**2**) (Scheme 1).

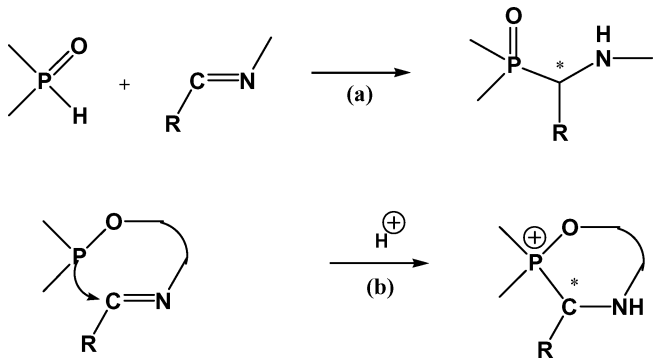
Aminophosphonates are very attractive due to their well-known biological activity. Among them substances with antibacterial, antiviral, neurotropic, antitumor, and anti-HIV activities are found. Several original articles and reviews have been devoted to these compounds and include the Pudovik reaction itself as an important part of the paper.[2] In many cases, the compounds obtained have chiral centers and could be separated into optical antipodes.

A number of methods were proposed for the asymmetric synthesis of α-aminophosphonic acid derivatives on the basis of the Pudovik reaction. However, only the intermolecular Pudovik reaction was considered in terms of this approach (route a). To develop a new, more efficient strategy for stereoselective synthesis of α-amino phosphonates we found it attractive to study reactions, which allow an intramolecular type of interaction of the P(III) atom and an imino group (route b)—an intramolecular Pudovik reaction (Scheme 2).

The subsequent transformation of the cyclic intermediate, in particular via an Arbuzov reaction intermediate, could lead to diastereomeric cyclic or acyclic α-aminophosphonates. As the realization of such a process requires a definite relative position of the P(III) atom to the imino group, possessing nonequivalent diastereotopic faces, one can anticipate a significant increase of diastereomeric excess of the reaction products in terms of this approach.

We have focused our attention on the study of the reaction of monochlorophosphites with chiral β-aldiminoalcohols.[3] To the best of our knowledge, no attempts have been made to investigate the reaction of halogen phosphites with β-iminoalcohols.

Downloaded At: 17:25 27 January 2011

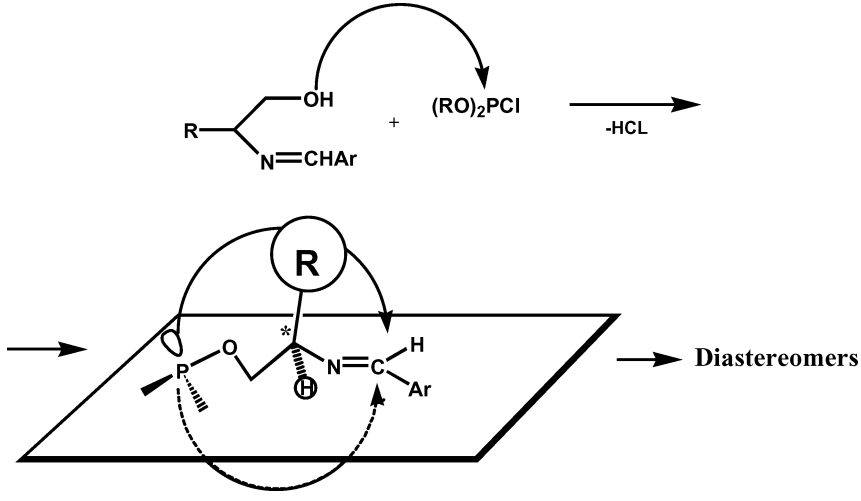


SCHEME 2

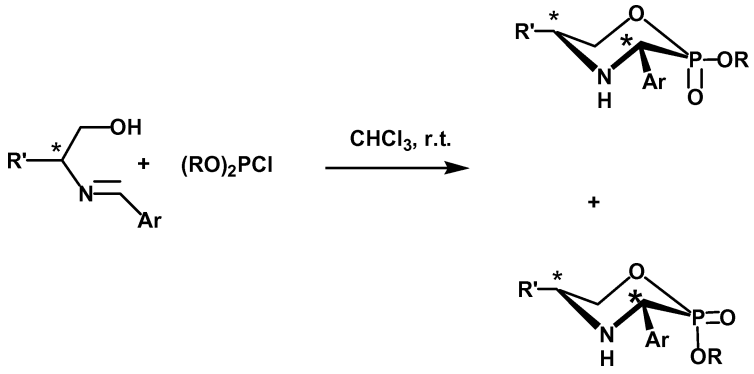
Downloaded At: 17:25 27 January 2011

The general scheme and stereochemistry of intramolecular interactions of the P(III) atom with the C=N double bond, leading to the diastereoselectivity in this reaction, is as follows: At first the interaction of the chlorophosphite with the iminoalcohol gives rise to an iminophosphite. If in this compound there is a chiral center, the two sides of the planar C=N bond become stereochemically nonequivalent. They are diastereotopic, and the cyclization reaction proceeds diastereoselectively. The subsequent transformation of the cyclic intermediate could lead to diastereomeric α-aminophosphonates (Scheme 3).

We have studied many examples of this type of reaction with different chlorophosphites and have established that this intramolecular



SCHEME 3

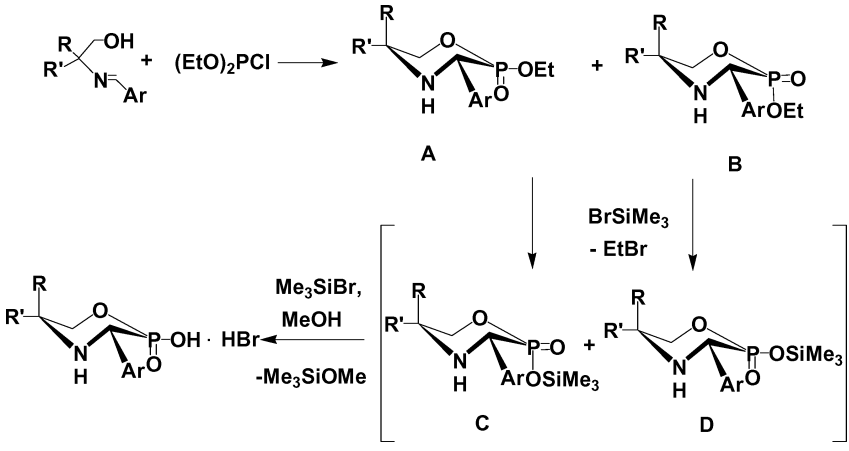


SCHEME 4

Downloaded At: 17:25 27 January 2011

Pudovik reaction is possible. It gives rise to 1,4,2-oxazaphosphorine rings and proceeds stereospecifically with the formation of a new chiral center at C3 with ee > 98 %.[3] Only one of the two possible intramolecular stereochemical interactions of the phosphorus atom with the imino group is realized (Scheme 4).

To obtain the free cyclic acids from the cyclic esters, we have developed a one-pot synthesis starting from chlorophosphite and iminoalcohol. After mixing the starting compounds trimethyl bromosilane was added to the reaction mixture and then the silyl derivatives were quenched with methanol to form the free acids. The configuration at the carbon atom C3 was preserved (Scheme 5).



SCHEME 5

This approach, based on the most stereocontrolled version of the Pudovik reaction—intramolecular cyclization—can be considered as a new strategy for the stereoselective synthesis of α-aminophosphonates.

The diastereoselective synthesis of related 1,4,2-oxazaphosphorines starting from (*R*)-(-)-phenylglycinol via reaction of the corresponding oxazolidines with trimethyl phosphite in the presence of $SnCl_4$, has been reported by Royer.[4] It should be noted that an absolute *S* configuration of the new chiral center at C3 was established. In our case, a complementary process takes place with formation of the *R* configuration of the new chiral center at C3. The absolute (*R*)-(-)-configuration of the chiral center of the parent aminoalcohol remains unchanged.

In conclusion, our method and that of *Royer* complement each other, providing α-aminophosphonic acid enantiomers and their 1,4,2-oxazaphosphorine heterocyclic precursors with a choice of configuration.

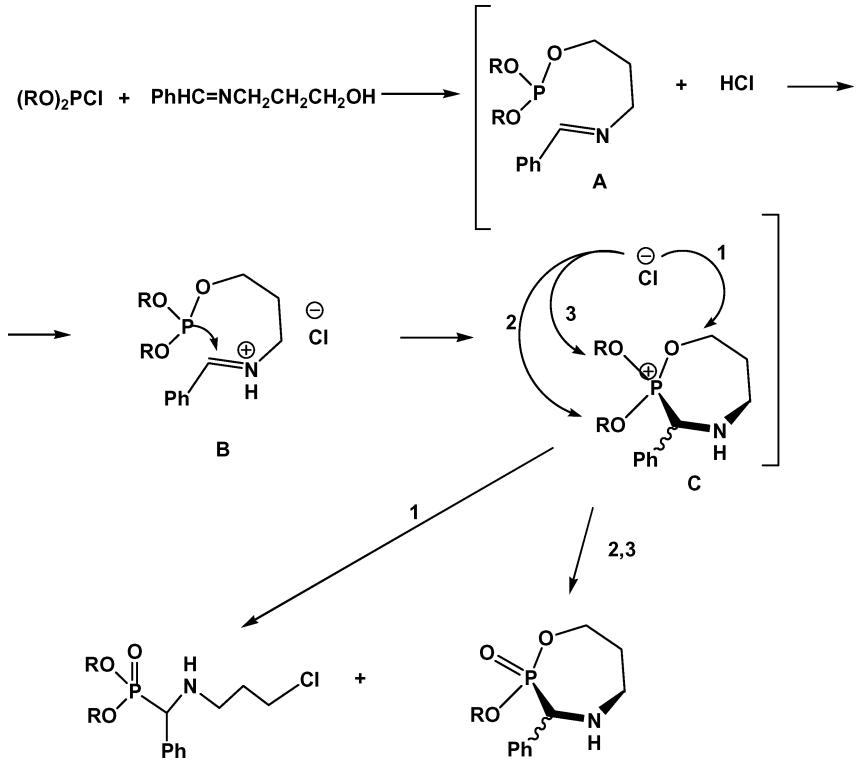
Downloaded At: 17:25 27 January 2011

To check up the possibility to use γ-iminoalkohols in this intramolecular Pudovik reaction we have studied the reaction of imino propanol with dialkylchlorophosphites.[5] The reaction proceeds with the formation of cyclic 7-membered phosphepane rings. In this case acyclic phosphonates are formed as side products, however (Scheme 6).

Considering the formal structural similarity between α-iminocarboxylic acids and 1,2-iminoalcohols, namely the same number of carbon atoms between the hydroxy and imino groups, we assumed that these compounds would also be able to close the 1,4,2-oxazaphosphorinane ring in an intramolecular Pudovik reaction with dialkyl chlorophosphites. To check this assumption, we studied the reaction of sodium *N*-benzylideneglycinate with dialkyl chlorophosphites. Unexpectedly we found that these compounds react with each other under very mild conditions to give 1,4-bis[α-(dialkoxyphosphoryl)benzyl] piperazine-2,5-diones as a statistic mixture of the diastereomeric *d,l*- and the *meso*-form (Scheme 7).[6]

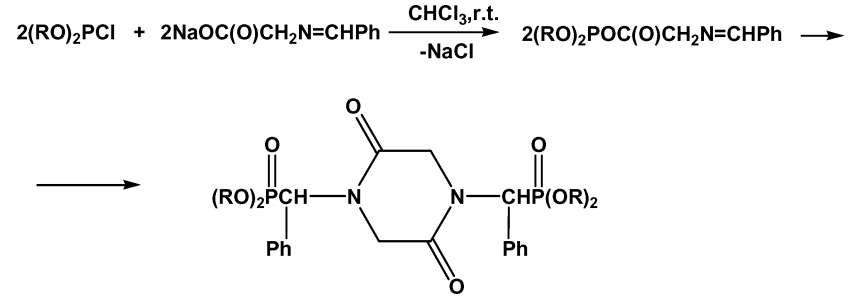
To check the possibility of using chiral amino acid derivatives in this reaction we investigated the interaction of dialkyl chlorophosphites with sodium *N*-benzylidenevalinate and phenylglycinate. It was found that in this case the reaction proceeds in an absolutely different way. The major reaction products are diastereomeric aminobisphosphonates. The interaction is followed by oxidative decarboxylation and CO_2 elimination. This method represents the direct synthesis of α-aminophosphonates from the isostructural α-benzylidene- aminocarboxylic acids, because the result is the direct replacement of a carboxy group by the phosphono group (Scheme 8).[7]

Finally we have used a new simple and available chiral inductor in the Pudovik reaction to obtain a new type of aminophosphonates.



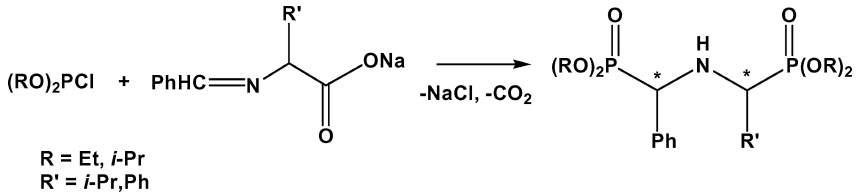
SCHEME 6

This inductor is Betti base, which is easily available from β-naphthol, bensaldehyde, and ammonia. We have developed new promising methods of synthesis and enantioseparation of these compounds[8] and have investigated the Pudovik reaction of these imino derivatives with

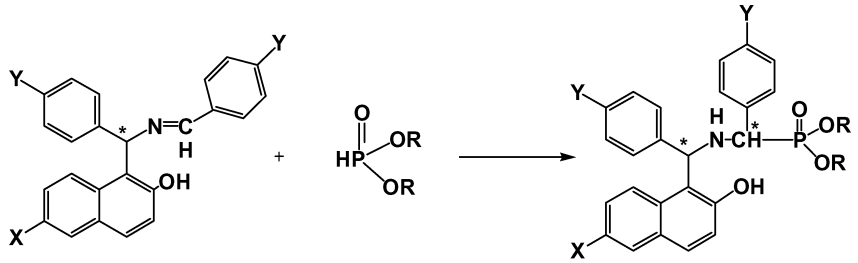


SCHEME 7

Downloaded At: 17:25 27 January 2011



SCHEME 8



SCHEME 9

dialkyl and diphenyl phosphites. The diastereoselectivity of this reaction was shown to be quite high (Scheme 9).

CONCLUSIONS

We have described the application of the Pudovik reaction in the synthesis of chiral organophosphorus compounds and showed this reaction to be a promising way to enantiopure aminophosphonic acid derivatives, the potential of which has not yet been exploited. Chiral organophosphorus compounds can be obtained in high yield and optical purity by this route.

REFERENCES

[1] I. V. Konovalova and L. A. Burnaeva, *Pudovik Reaction* (published by Kazan State University, 1991) p. 148.

[2] (a) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur*, **63,** 193 (1991); (b) A. B. Smith, K. M. Yager, and C. M. Taylor, *J. Am. Chem. Soc.*, **117,** 10879 (1995); (c) V. P. Kukhar, N. Yu. Svistunova, V. A. Solodenko, and V. A. Solojenok, *Russ. Chem. Rev.*, **62,** 261 (1993); (d) J. Uziel and J. P. Genet, *J. Org. Khim.*, **33,** 1605 (1997); (e) R. A. Cherkasov and V. I. Galkin, *Russ. Chem. Rev.*, **67,** 940 (1998); (f) H. Sasai, Sh. Arai, Y. Tahara, and M.

Downloaded At: 17:25 27 January 2011

Shibasaki, *J. Org. Chem.*, **60,** 6656 (1995); (g) M. L. Bojin and S. A. Evans, *Phosphorus, Sulfur*, **111,** 157 (1996); (h) T. Yokomatsu, Y. Yoshida, and Sh. Shibuya, *J. Org. Chem.*, **59,** 7930 (1994); (i) T. Yokomatsu, Y. Yoshida, and Sh. Shibuya, *Tetrahedron Lett.*, **38,** 2717 (1997); (j) M. C. Mitchell, A. C. Cawley, and T. P. Kee, *Tetrahedron Lett.*, **36,** 287 (1995); (k) M. Mikolaiczyk, P. Lyzwa, and J. H. Drabowicz, *Phosphorus, Sulfur, and Silicon*, **144–146,** 157 (1999).

[3] (a) M. N. Dimukhametov, E. Yu. Davydova, E. V. Bayandina, A. B. Dobrynin, I. A. Litvinov, and V. A. Alfonsov, *Mendeleev Commun.*, 222 (2001); (b) M. N. Dimukhametov, E. V. Bayandina, E. Yu. Davydova, T. A. Zyablikova, A. B. Dobrynin, I. A. Litvinov, and V. A. Alfonsov, *Russ. Chem. Bull.*, **50,** 2468 (2001); (c) M. N. Dimukhametov, E. V. Bajandina, E. Yu. Davydova, I. A. Litvinov, A. T. Gubaidullin, A. B. Dobrynin, T. A. Zyablikova, and V. A. Alfonsov, *Heteroatom Chem.*, **14,** 56 (2003); (d) M. N. Dimukhametov, E. V. Bayandina, E. Yu. Davydova, A. T. Gubaidullin, I. A. Litvinov, and V. A. Alfonsov, *Mendeleev Commun.*, 150 (2003); (e) M. N. Dimukhametov, M. A. Abaskalova, E. Yu. Davydova, E. V. Bayandina, A. B. Dobrynin, I. A. Litvinov, and V. A. Alfonsov, *Mendeleev Commun.*, 35 (2004).

[4] C. Maury, T. Gharbaoui, J. Royer, and H.-P. Husson, *J. Org. Chem.*, **61,** 3687 (1996).

[5] E. V. Bayandina, E. Yu. Davydova, M. N. Dimukhametov, A. B. Dobrynin I. A. Litvinov, R. Z. Musin, and V. A. Alfonsov, *Russ. Chem. Bull.*, **54,** 1453 (2005).

[6] M. N. Dimukhametov, M. A. Abaskalova, E. Yu. Davydova, E. V. Bayandina, A. B. Dobrynin, I. A. Litvinov, V. A. Alfonsov, *Mendeleev Commun.*, 35 (2004).

[7] E. V. Bayandina, E. Yu. Davydova, M. A. Abaskalova, R. Z. Musin, V. A. Alfonsov, *Russ. Chem. Bull.*, **54,** 1449 (2005).

[8] V. A. Alfonsov, K. E. Metlushka, C. E. McKenna, B. A. Kashemirov, O. N. Kataeva, V. F. Zheltukhin, D. N. Sadkova, and A. B. Dobrynin, *Synlett*, 488 (2007).

Downloaded At: 17:25 27 January 2011