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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>

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K. Kellner^a; C. Preussler^a; M. Dargatz^a

^a Martin-Luther-Universität Halle-Wittenberg Sektion Chemie, Halle

To cite this Article Kellner, K. , Preussler, C. and Dargatz, M.(1990) 'Synthesis and Stereochemical Studies of P-Analogues of Aspartic Acid Derivatives', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 51: 1, 15 — 18

To link to this Article: DOI: 10.1080/10426509008040671

URL: <http://dx.doi.org/10.1080/10426509008040671>

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SYNTHESIS AND STEREOCHEMICAL STUDIES OF P-ANALOGUES OF ASPARTIC ACID DERIVATIVES

K. KELLNER, C. PREUSSLER, AND M. DARGATZ
Martin-Luther-Universität Halle-Wittenberg,
Sektion Chemie, Halle (S.), DDR-4010

Abstract A method for the synthesis of 3-phosphono 2-acylamino propionic acid and their derivatives is described. The procedure is based on methylene oxazolinones as synthons and their reaction with activated P-H compounds. By the method a diastereoselective reaction is observed. The stereochemical course and the relative configuration have been proposed on the base of nmr spectra.

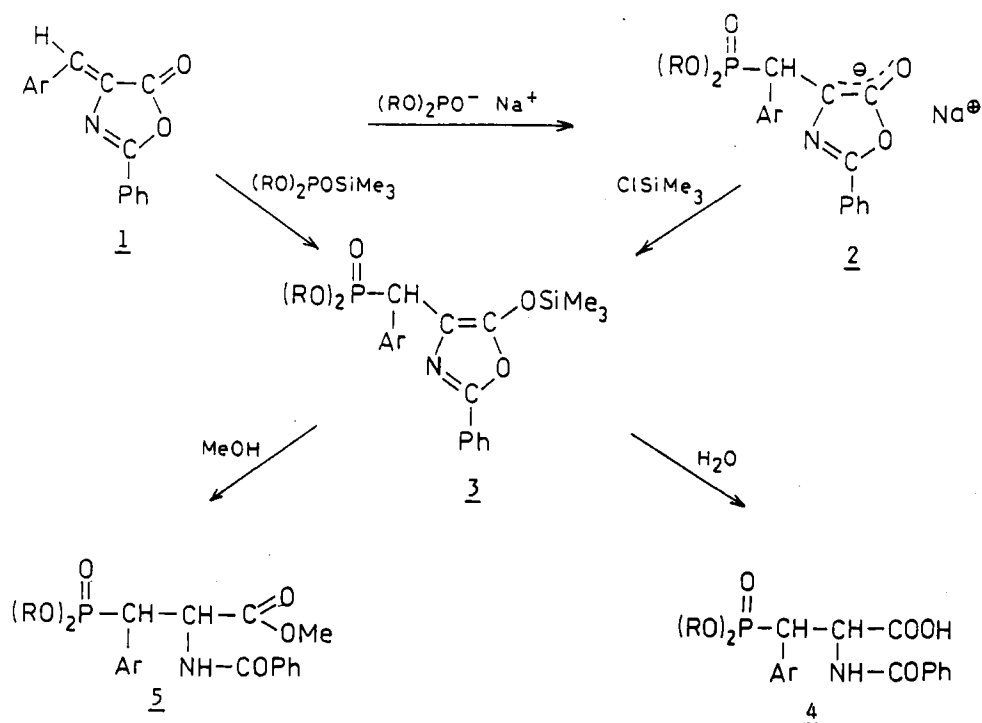
INTRODUCTION

Considerable interest has recently been focussed on P-substituted glutamic and aspartic acid derivatives. These have been shown to have a fundamental role in the synthesis of Bialaphos. In contrast to the large number of glutamic acid derivatives there are only a few methods known for the synthesis of aspartic acid derivatives. For the β -phosphorus substituted compounds, the principally used methods recall the works of Chambers and Isbell¹ and of the Mastalerz² group. The α -acylamino vinyl carbonic acids which are used in this method are weak Michael-acceptors, so the reaction requires strong reaction conditions. Substitution at the carbon chain and at the carboxylic group is also limited.

RESULTS AND DISCUSSION

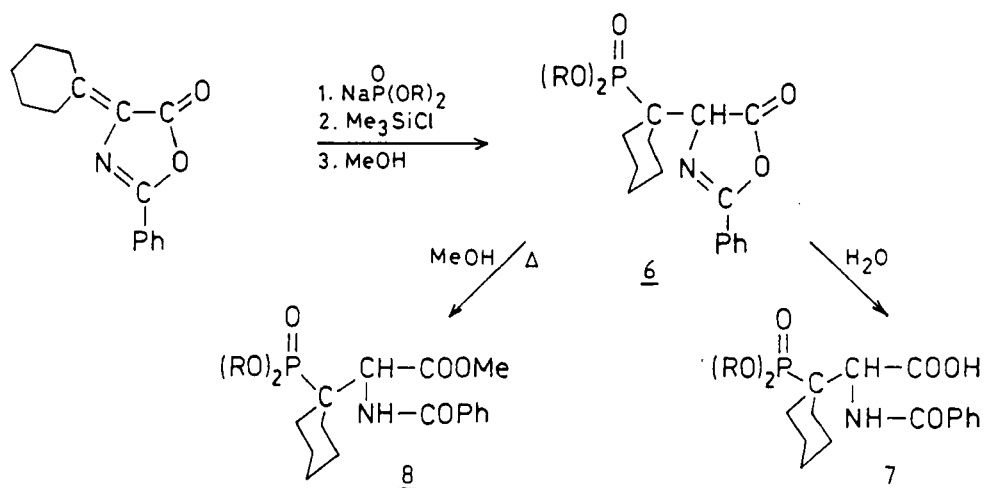
We found in the 4-arylidene 2-phenyl oxazolin-5-ones 1 useful precursors for the preparation of 3-P-substituted aspartic acid derivatives. The heterocyclic ring system has two functions in our method, namely protection of the amino group and activation of the exocyclic double bond. It has

been found that when 1 is allowed to react with alkalisalts of dialkylphosphites in aprotic solvents at room temperature, a nearly quantitative addition occurred at the exocyclic double bond. The protonation of the resulting alkali-0-oxazoles 2 with water, methanol etc. is not successful because the alkaline medium leads to many side reactions. To avoid the alkaline medium 2 is transferred into the 4-phosphonomethyl 5-siloxy oxazol 3. This intermediate can be also obtained by the reaction of 1 with dialkyl silyl esters of the phosphonous acid. By reaction of 3 with water or alcohols the 4-phosphonomethyl oxazolin-5-ones are formed in a fast reaction. After ring opening by these nucleophiles either 3-phosphonato 3-aryl 2-benzoylamino acids or the corresponding esters are produced instantaneously.



SCHEME 1

By the reaction of 4-pentamethylene oxazolinones with dialkylphosphites evidence has been found for the reaction pathway by characterization of all intermediates.



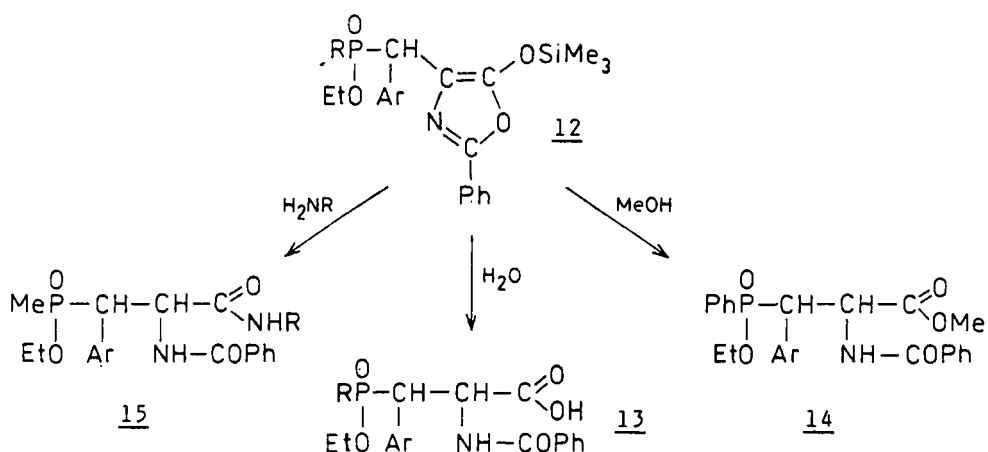
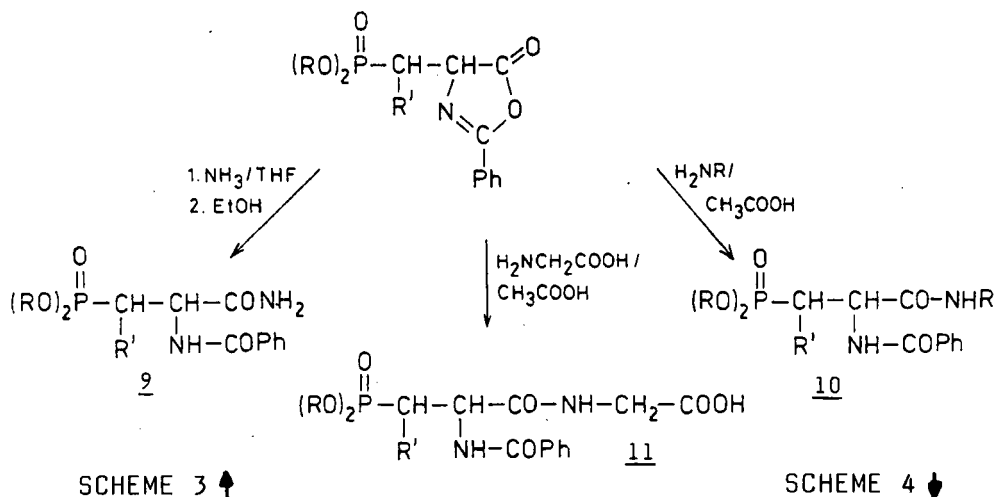
The 3-substituted 3-phosphonato aspartic acid analogues are characterized by 2 asymmetric centres, 2 diastereoisomers are thus expected. By reactions according to scheme 1 only one diastereoisomer has been isolated. That suggests that in the reaction pathway there should be a diastereoselective step. The diastereoselection observed in both derivatives is discussed in terms of the desilylation of 3 controlled by the first asymmetric centre.

The HPLC analysis of the crude product of 5 showed a ratio of diastereoisomers of 95:5. To our knowledge such a high stereoselection has not been observed in the hydrolysis of silylenolethers up to now. The second diastereoisomer can be isolated after a racemisation process at the α -carbon. Both isomers were well characterized by nmr-, ir-, and X-ray analysis.³

The key position of the siloxyoxazol 3 is demonstrated also by its reaction with ammonia, primary amines and amino acids under special conditions resulting in the formation of amides 9, 10 and dipeptides 11, respectively. Stereoselectivity is observed in these cases too. The diastereoisomers of 9 obtained in 1:4 ratio are separated by crystallization.

The significance of this approach to P-analogues of aspartic acids is further demonstrated by the synthesis of

3-phosphinato derivatives. It has been found that when 1 was allowed to react with O-alkyl O-silyl phosphonites the 4-phosphinatomethyl 5-siloxy oxazoles 12 result in high yield. By desilylation and ring opening reactions with water, alcohols and amines the 3-phosphinato 3-substituted 2-benzoylamino propionic acids, esters and amides can be prepared as shown above.



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