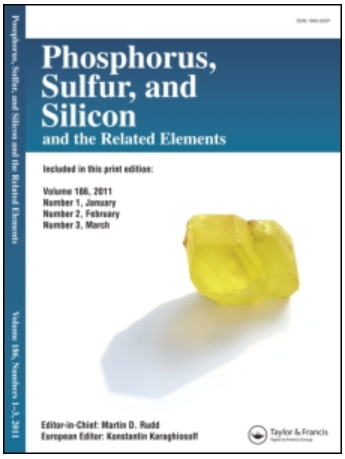


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Nitrogen-Containing 3-Phosphonoalkylcyclohexenones

Malose J. Mphahlele

To cite this Article Mphahlele, Malose J.(1999) 'Synthesis of Nitrogen-Containing 3-Phosphonoalkylcyclohexenones', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 351 — 354
To link to this Article: DOI: 10.1080/10426509908546253
URL: http://dx.doi.org/10.1080/10426509908546253

Phosphorus, Sulfur and Silicon, 1999, Vol. 144-146, pp. 351-354
Reprints available directly from the publisher
Photocopying permitted by license only

Synthesis of Nitrogen-Containing 3-Phosphonoalkylcyclohexenones

MALOSE J. MPHAHLELE

Department of Chemistry and Biochemistry, Medical University of Southern Africa, P.O. Box 235, Medunsa 0204, South Africa

With a view of preparing compounds with potential biological activity and to study structure-activity relationship, the ring and side chain substituted 3-phosphonomethylcyclohexenones were transformed to aminophosphonic acid derivatives using Schmidt, Beckmann and Neber rearrangement reactions.

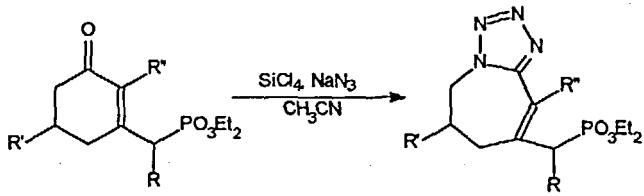
Keywords: 3-Phosphonoalkylcyclohexenones; Schmidt; Beckmann and Neber rearrangement

INTRODUCTION

The applications of aminophosphonic acids as antibacterial, antiviral, pesticidal, insecticidal and herbicidal agents in pharmacological and agrochemical industries has led to increased interest in the synthesis of nitrogen-containing phosphonic acid derivatives with increased potency.[1] Our interest in this field is focused on analogues of the medicinally useful aminoalkylphosphonic acids that include such structural modifications as different relative location of heteroatoms and the degree of unsaturation in the phosphonic skeleton. In our research on the synthetic applications of the ring and side chain substituted 3-phosphonomethylcyclohexenones **1**,[2] we investigated their conversion into N-containing systems using Schmidt, Beckmann and Neber rearrangement reactions. Systems **1** used as starting materials in our investigations were synthesised as described in our previous communications from lithioalkylphosphonates and β-chloro- and/ or β-methoxycyclohexenones.[2,3]

RESULTS AND DISCUSSION

The ring and side chain substituted 3-phosphonomethylcyclohexenones **1** were treated with triazidochlorosilane in acetonitrile, the reaction conditions previously applied to the non-phosphorus cyclohexenone derivatives (Scheme 1).[4] ^{31}P NMR spectroscopic analysis of the crude reaction mixture revealed the presence of only one phosphorus-containing product. In all cases, only tetrazolo derivatives **2** resulting from the migration of the methylene (6-CH_2) group were isolated in moderate yields (42 - 65%) and no products of the vinylic carbon (2-CH) shift were detected. [5] The selectivity of the migration was clear from the significant downfield shift (*ca.* 4.30ppm) of the ^1H NMR signal of the 6-CH_2 group in **1** upon migration to the position adjacent to the nitrogen atom corresponding to **2**.

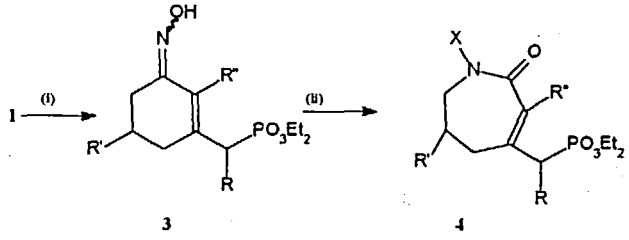


1 **2**

Scheme 1

An attempt to synthesise the ring-enlarged lactam(s) derived from systems **1** using Me_3SiN_3-TFA mediated Schmidt rearrangement resulted in the recovery of the starting materials.[5] An alternative approach using the Beckmann rearrangement of a mixture of *syn* and *anti* (predominant) oxime derivatives of **1** was then investigated. Oximes **3** were treated with $SOCl_2$ in 1,4-dioxane to afford only lactams **4** (X = H) resulting from methylene (6-CH_2) shift and no enamine isomers resulting from vinylic (2-CH) shift were isolated (Scheme 2). The isolation of the pure product presented some problems (eg., chromatography on SiO_2 drastically reduced the yields) and the products were isolated only in moderate yields when Al_2O_3 was used for column

chromatography. In some cases isolated lactams **4** still contained some impurities and further purification led to extensive decomposition. Those products were converted into N-acetyl derivatives (X = $COCH_3$) which could be purified and characterised by NMR (^1H, ^{13}C, ^{31}P) and IR spectroscopy, mass spectrometry and elemental analyses. The results of this reaction have recently been published.[6]

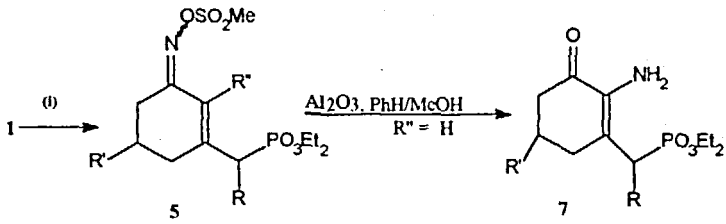


(i) NH_2OH/HCl, NaOAc. $3H_2O$, EtOH; (ii) $SOCl_2$, Dioxane

Scheme 2

The sensetivity of some oximes to strongly acidic media and their isolation problems complicate the application of Beckmann rearrangement. It has been established that the conversion of the oximes to the corresponding O-mesylate[7] or O-tosylate[8] derivatives promote the Beckmann rearrangement under relatively mild basic conditions. We converted the oximes **3** to the corresponding mixture of *syn* (minor) and *anti* O-mesyloxime derivatives **5** and subjected the latter to Al_2O_3 induced Beckmann rearrangement. However, instead of the expected α,β-unsaturated lactams **4** (X = H) or their enamine isomers, we isolated the 2-amino-3-phosphonoalkylphosphonates **7** formed via the Neber rearrangement of **5** (Scheme 3).[9] Although products **7** contain the cyclohexenonealkylphosphonate framework, they were easily distinguished from the corresponding precursors **1**, **3** and **5** by the lack in the ^1H NMR spectra of the olefinic proton and the mesylate signals.

The N-containing derivatives of **1** described in this communication contain the allylic phosphonate moiety and are thus valuable sytems for further transformation and for biological activity studies.



(i) CH_3SO_2Cl, NEt_3, THF

Scheme 3

ACKNOWLEDGEMENTS

Financial support from the Foundation of Research and Development is gratefully acknowledged.

References

[1] M. Mikolajczyk, P. Lyzwa, J. Drabowicz and M. Wiczorek, *Chem. Commun.*, 1503 (1996) and references cited therein.
[2] M.J. Mphahlele, A. Pienaar and T.A. Modro, *J. Chem. Soc. Perkin Trans.* **2.**, 1455 (1996).
[3] M.J. Mphahlele and T.A. Modro, *J. Org. Chem.*, **60**, 8236 (1995).
[4] A.S. El-Ahl, S.S. Elmorsy, H. Soliman and F.A. Amer, *Tetrahedron Lett.*, **36**, 7337 (1995).
[5] M.J. Mphahlele and T.A. Modro, *Phosphorus, Sulfur and Silicon*, **118**, 145 (1996).
[6] M.J. Mphahlele and T.A. Modro, *J. Chem. Res.*, (S), 198 (1998).
[7] H. Hu, G.E. Jagmann Jr., P.F. Hughes and J.B. Nichols, *Tetrahedron Lett.*, **36**, 3659 (1995).
[8] E. Alberti, A. Barco, S. Benetti, C. De Risi, G.P. Pollini and V. Zanirato, *Synlett.*, 29 (1996).
[9] M.J. Mphahlele and T.A. Modro, *Phosphorus, Sulfur and Silicon*, in press.