

Accepted Manuscript



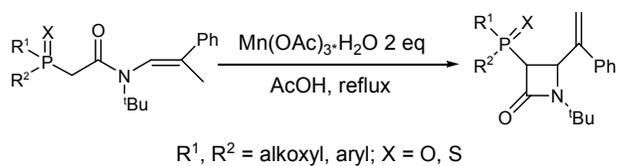
This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard [Terms & Conditions](#) and the [ethical guidelines](#) that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.



Radical cyclization of phosphono-acetenamides promoted by manganese (III) acetate leads exclusively to the formation of 3-phosphoryl-β-lactams.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A simple and novel synthesis of 3-(thio)phosphoryl- β -lactams by radical cyclization

Pawel Punda^a, Sławomir Makowiec^{*a}

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

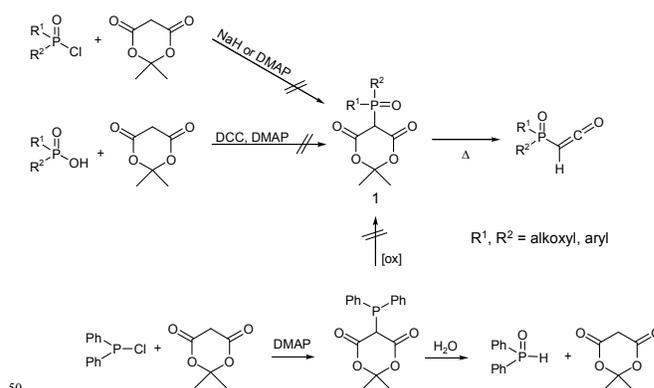
DOI: 10.1039/b000000x

Radical cyclization of phosphono-acetenamides promoted by manganese (III) acetate leads exclusively to the formation of 3-phosphoryl- β -lactams. The thiophosphoryl analogues were also prepared using this method. In particular, the presented protocol doesn't require the use of noble metals, while comparable methods do.

Modification of the β -lactams ring is still the focus of organic chemists, mainly due to the well-known antimicrobial activity of this class of compounds¹. However, this is not only the biological activity of azetidones that attracts attention; β -lactams also exhibit: cholesterol absorption activity², anti-cancer activity³, muscarinic agonist properties⁴ or inhibition of human leukocyte elastase responsible for autoimmune diseases⁵. In light of the β -lactam synthon method developed by Ojima, synthetic application of azetidones have shown increasing importance in synthetic organic chemistry⁶. Recently we have focused on the carbamoyl and thiocarbamoyl modification of the azetidine ring in position 3, based on Meldrum's acid derivative type of Staudinger cycloaddition⁷. As an extension of this topic we have undertaken attempts to develop a similar method for the preparation of 3-phosphoryl β -lactams. In the chemical literature, three methods can be found for the preparation of 3-phosphoryl β -lactams: first, the simplest involving direct metalation of the α -position in 3-unsubstituted β -lactams following by reaction with three coordinated phosphorus electrophiles and oxidation to five coordinated phosphorus. However, this process sometimes leads to a mixture of mono and di-phosphorylated products^{2c, 8}; another promising method is a Staudinger type cycloaddition of imines with ketenes generated from the phosphono-acetates activated with CDI⁹. Despite the attractive simplicity this method, it is limited only to reaction with N-aryl imines. The last known method for the preparation of 3-phosphoryl β -lactams is based on rhodium catalysed intramolecular C-H insertion of carbenes generated from diazocompounds¹⁰. However, the carbene insertion process usually leads to forming a mixture of five and four membered lactams and selectively 3-phosphoryl β -lactams can be obtained only when specific substituents on nitrogen are present¹¹.

In the light of our own experience⁷ it seemed obvious that a convenient alternative approach for the synthesis of 3-phosphoryl β -lactams should assume the use of 5-phosphoryl-2,2-dimethyl-1,3-dioxane-4,6-diones as a source for thermal generation of phosphoryloketenes and subsequently their cycloaddition to aldimines. However, no example of preparation and reactivity of phosphoryl Meldrum's acid is known in the

literature.



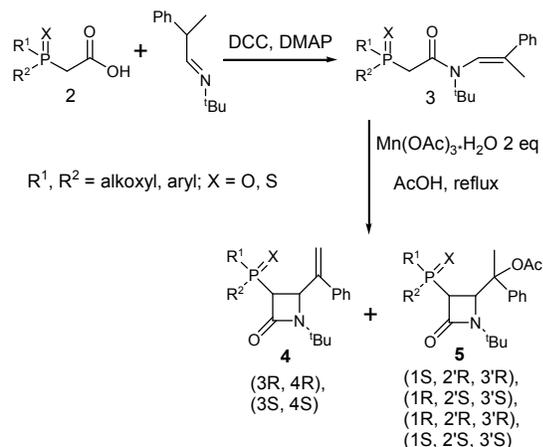
Scheme 1 Attempts for preparation of 5-phosphorylo-2,2-dimethyl-1,3-dioxane-4,6-dione **1** a potential source of phosphorylketenes

Hence we undertook a systematical study in the preparation of any 5-phosphoryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**); unfortunately, the reactions with five coordinated phosphorus electrophiles did not give the desired product, while reaction with three coordinated derivative means diphenyl chlorophosphine lead to an unstable compound, which decomposes during purification to phosphine oxide and Meldrum's acid (Scheme 1). These unpublished and unsatisfactory attempts for preparation of 5-phosphorylo-2,2-dimethyl-1,3-dioxane-4,6-dione forced us to search a new strategy for the synthesis of 3-phosphoryl β -lactams. On the other hand, an alternative to the typical Staudinger method of construction a β -lactam ring involves the oxidation and radical cyclization of derivatives of acetyl acetenamides¹². However, to the best of our knowledge, this type of reactions was never tested for the preparation of 3-phosphoryl β -lactams from phosphonoacetenamides, which due to different position of the ketol-enol equilibrium, may cause problems during oxidation.

In this paper we wish to report the application of the manganese (III) acetate as a reagent for the cyclization of

phosphono-acetatenamides to β -lactams. The key substrate **3** was obtained in the classic carbodiimide coupling of phosphonoacetic acids with enolizable imine (Scheme 2).

In the first experiment we oxidized diethyl 2-[methyl(2-phenylprop-1-enyl)amino]-2-oxoethylphosphonate (**3a**) in acetic acid with $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ added in small portions to determine the minimum required amount of oxidizer, leaving other conditions the same as those optimal for oxidation of acetyl acetenamides¹². However, in the case of **3a** we observed the rate of oxidation indicated as a manganese (III) colour disappearance was much slower, and the yield obtained was low (Entry 1, Table 1). The next two experiments were performed with gradually increased temperature using the theoretically required amount of oxidizer (Entries 2, 4, Table 1) to give a significant increase in yield. On the other hand, we decided to check if it is possible to replace rather expensive manganese oxidizer with CAN. Unfortunately, using only CAN or a system with small amount of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ with equimolar amount of CAN for regeneration of Mn^{3+} allows to obtaining only low yields of the desired product (Entries 5, 6, Table 1).



Scheme 2 Synthesis of 3-(dialkoxyphosphoryl)- β -lactams

Knowing the optimal condition for the oxidation and

Table 1 Cyclization of phosphonoacetenamides **3** with $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$

Entry	2, 3, 4	R ¹	R ²	X	Temp (°C)	Time (min)	Mn(OAc) ₃ ·2H ₂ O (eq)	Yield ^d (%) 4:5
1	a	EtO	EtO	O	70	25	1.2	22 : 0
2	a	EtO	EtO	O	90	10	2	42 : 0
3	a	EtO	EtO	O	119	10	1.2	30 : 0
4	a	EtO	EtO	O	119	10	2	50 : 0
5 ^a	a	EtO	EtO	O	119	10	-	4 : 0
6 ^b	a	EtO	EtO	O	119	10	0.1	11 : 0
7	b	OCH ₂ C(CH ₃) ₂ CH ₂ O		O	119	10	2	70 : 0
8	c	MeO	Ph	O	119	10	2	34 : 0
9	d	t-Bu	Ph	O	119	10	2	0
10 ^c	e	n-Bu	n-Bu	O	119	120	6	0
11	f	EtO	EtO	S	119	15	2	15 : 15
12	f	EtO	EtO	S	119	15	4	7 : 0

^a 2 eq of CAN was used, instead of $\text{Mn}(\text{OAc})_3$.

^b 2 eq of CAN was added

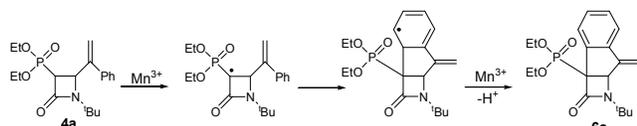
^c $\text{Mn}(\text{OAc})_3$ was added in three 2 eq portions, each after decolorization

^d isolated yields

cyclization of phosphono-acetenamides **3** we decided to apply our method to other models. The oxidation and subsequent cyclization of 1,3-neopentylidene 2-[methyl(2-phenylprop-1-enyl)amino]-2-oxoethylphosphonate (**3b**) leads to a high yield of 3-phosphoryl β -lactam (Entry 7, Table 1), whereas introduction of one aryl group instead of alkoxy results in a significant decrease in yield. It should be noted that in the case of **4c**, an additional stereocenter is introduced into the molecule, causing the formation of two pair of enantiomers, all with trans configuration in the β -lactam ring (H3 –H4 coupling constants 2.4 and 2.5 Hz respectively) whereas models with achiral phosphorus **4a, b, f** gave only one pair of enantiomers. Substrates with two P-C bond proved to be inert; even using a large excess of oxidizer and prolonged time of reaction did not allow us to obtain cyclized product; in the reaction mixture, unreacted starting material **3d, e** was still observed (Entries 9, 10, Table 1). Positive results in the cyclization of phosphono-acetenamides has raised the question of whether 3-thiophosphoryl β -lactams can also be obtained by this radical cyclization. However, it is clear that oxidative cyclization of thiophosphono-acetenamides may suffer from desulfurization caused by the oxidizing reagent¹³. Fortunately, oxidation of O,O-ethyl 2-[methyl(2-phenylprop-1-enyl)amino]-2-oxoethylphosphonothioate **3f** with Mn (III) allows obtaining the desired 3-thiophosphoryl- β -lactam (**4f**) with 15% yield; moreover, in this case 1-[3-(diethoxyphosphorothioyl)-1-tert-butyl-4-oxoazetidin-2-yl]-1-phenylethyl acetate (**5f**) with 15% yield, as a mixture of two pairs of enantiomers with a 1:2 ratio was also formed, indicating that carbocation formed after the second oxidation has two potential ways of reaction, the first with abstraction of proton, and the second, less common, leading to the formation of acetoxy derivative of β -lactam.

Generally, for the presented method, several factors which have a negative influence on the yield can be demonstrated. Firstly, phosphono or phosphino substituted acetic acid are less prone to enolization than their alkoxy carbonyl or acetyl analogues, while it is well known that enolic form is necessary for effective radical formation during manganese (III) acetate oxidation^{12c, 14}.

Additionally, introduction of alkyl or aryl substituents on a phosphorus atom causes a decrease in electrophilicity of the radical, which results in the lower yield in the cyclization step where electron rich π -bond is attacked.



Scheme 3 Subsequent oxidation of 4a

On the other hand, in all reactions, acetophenone as a by-product was observed, meaning oxidative cleavage of π -bond competes with radical formation and causes the decomposition of the substrate. The last observed drawback is due to the subsequent oxidation of already formed 3-phosphoryl β -lactam. We observed in an independent experiment that heating of 4a within 2 h with 4 eq of $Mn(OAc)_3 \cdot 2H_2O$ leads to approx. 13% conversion of 4a into 6a through, intramolecular aromatic radical substitution (Scheme 3).

In summary, we have described the method for preparing 3-phosphoryl β -lactams and 3-thiophosphoryl β -lactams based on the use of radical cyclization of phosphono-acetenamides. The method is simple, convenient and does not require the use of noble metals as in comparable literature methods that are known. The obtained yields are moderate, and depends on substitution on the phosphorus atom. Among tested oxidizers, the best results was obtained with $Mn(OAc)_3 \cdot 2H_2O$.

Experimental

Typical procedure for the preparation of diethyl 1-tert-butyl-2-oxo-4-(1-phenylvinyl)azetid-3-ylphosphonate (**4a**): To a stirred mixture of diethyl 2-[methyl(2-phenylprop-1-enyl)amino]-2-oxoethylphosphonate (**3a**) (1 mmol, 0.367 g) in acetic acid (10 mL) at reflux, was added $Mn(OAc)_3 \cdot 2H_2O$ (2 mmol, 0.535 g). After 10 min., reaction mixture was cooled and poured into 50 mL of ice water, and extracted with CH_2Cl_2 (5x20 mL). Organic layer was washed with aqueous 5% $NaHCO_3$ (3x10 mL), dried with $MgSO_4$ and concentrated. The residue was subject to column chromatography over silica gel using hexanes/EtOAc (1:1) as eluent to give **4a** with 50% yield. 1H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.24 (3 H, t, $J = 6.9$ Hz), 1.30 (3 H, t, $J = 6.9$ Hz), 1.38 (9 H, s), 3.23 (1 H, dd, $J^{PH} = 13.9$ Hz, $J^{HH} = 2.4$ Hz), 4.04-4.23 (4 H, m), 4.66 (1 H, dd, $J^{PH} = 9.2$ Hz, $J^{HH} = 2.4$ Hz), 5.51 (1 H, s), 5.59 (1 H, s), 7.33-7.49 (5 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 16.7 (d, $J^2 = 3.1$ Hz), 16.8 (d, $J^2 = 3.2$ Hz), 28.3, 54.2 (d, $J^1 = 29.3$ Hz), 55.8 (d, $J^2 = 2.2$ Hz), 56.7, 62.8 (d, $J^2 = 6.5$ Hz), 63.2 (d, $J^2 = 6.1$ Hz), 115.8, 127.1, 128.7, 129.0, 139.2, 148.3 (d, $J^3 = 2.8$ Hz), 162.6 (d, $J^2 = 6.3$ Hz). HRMS (ESI): m/z [M + Na] $^+$ calcd for $C_{19}H_{28}NO_4PNa$: 388.1654; found: 388.1665.

Acknowledgments

We thank the Gdańsk University of Technology for financial support (DS 020334 T. 001).

Notes and references

- ^a Department of Organic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland. Fax: 48-58-347-2694; Tel: 48-58-347-1724; E-mail: mak@pg.gda.pl
- [†] Electronic Supplementary Information (ESI) available: [Experimental procedures for the preparation of compounds **3a-f**, **4a-f**, **5f** and **6a** and their spectroscopic characterization]. See DOI: 10.1039/b000000x/
- (a) T. J. Dougherty, M. J. Pucci, *Antibiotic Discovery and Development*, Springer, 2012. DOI: 10.1007/978-1-4614-1400-1; (b) R. B. Morin, M. Gorman, *Chemistry and Biology of β -Lactam Antibiotics*, Academic Press: New York, 1982.
 - (a) J. Clader, D. A. Burnett, M. A. Caplen, M. S. Domalski, S. Dugar, W. Vaccaro, R. Sher, M. E. Browne, H. Zhao, R. E. Burrier, B. Salisbury, H. R. Davis, *J. Med. Chem.*, 1996, **39**, 3684. (b) S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis, N. Yumibe, J. W. Clader, D. A. Burnett, *J. Med. Chem.*, 1998, **41**, 973. (c) B. A. McKittrick, K. Ma, K. Huie, N. Yumibe, H. Davis, J. W. Clader, M. Czarniecki, *J. Med. Chem.*, 1998, **41**, 752.
 - (a) I. Banik, F. F. Becker, B. K. Banik, *J. Med. Chem.*, 2003, **46**, 12, (b) G. Geron-Navarro, J. Pérez de Vega, T. García-López, G. Andrei, R. Snoeck, E. Clercq, J. Balzarini, R. González-Muñiz, *J. Med. Chem.*, 2005, **48**, 2612, (c) F. Tripodi, R. Pagliarin, G. Fumagalli, A. Bigi, P. Fusi, F. Orsini, M. Frattini, P. Coccetti, *J. Med. Chem.*, 2012, **55**, 2112.
 - B. M. Nilsson, B. Ringdahl, U. Hacksell, *J. Med. Chem.*, 1990, **33**, 580.
 - S. K. Shah, J. C. Dorn, P. E. Finke, J. J. Hale, W. K. Hagmann, K. A. Brause, G. Chandler, A. L. Kissinger, B. M. Ashe, H. Weston, W. B. Knight, A. L. Maycock, P. S. Dellea, D. S. Fletcher, K. M. Hand, R. A. Mumford, D. A. Underwood, J. B. Doherty, *J. Med. Chem.*, 1992, **35**, 3745.
 - (a) I. Ojima, K. Nakahashi, S. M. Brandstadter, N. Hatanaka, *J. Am. Chem. Soc.*, 1987, **109**, 1798, (b) I. Ojima, S. Suga, R. Abe, *Chem. Lett.*, 1980, **9**, 853. (c) I. Ojima, H. C. Chen, X. Qiu, *Tetrahedron*, 1988, **44**, 5307.
 - K. Janikowska, N. Pawelska, S. Makowiec, *Synthesis*, 2011, 69.
 - D. F. Wiemer, Y. Du, *J. Org. Chem.*, 2002, **67**, 5709.
 - M. Nahmany, A. Melman, *J. Org. Chem.* 2006, **71**, 5804.
 - (a) Gois, M. P.; Afonso, C. A.; *Tetrahedron Letters*, 2003, **44**, 6571, (b) N. R. Candeias, M. P. Gois, C. A. Afonso, *J. Org. Chem.* 2006, **71**, 5489. (c) L. F. Gomes, A. F. Trindade, N. R. Candeias, L. F. Verios, M. P. Gois, C. A. Afonso, *Synthesis*, 2009, **20**, 3519.
 - M. P. Gois, C. A. Afonso, *Eur. J. Org. Chem.*, 2003, **19**, 3798.
 - (a) A. D'Annibale, S. Resta, C. Trogolo, *Tetrahedron Lett.*, 1995, **36**, 9039. (b) A. D'Annibale, A. Pesce, S. Resta, C. Trogolo, *Tetrahedron Lett.*, 1996, **37**, 7429. (c) A. D'Annibale, A. Pesce, S. Resta, C. Trogolo, *Tetrahedron*, 1997, **53**, 13129. (d) B. Attenni, A. Cerreti, A. D'Annibale, S. Resta, C. Trogolo, *Tetrahedron*, 1998, **53**, 12029.
 - (a) J. H. Hillhouse, I. A. Blair, L. Field, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1986, **169**, 26. (b) I. Mohammadpoor-Baltorka, M. M. Sadeghia, K. Esmayilpoura, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 61.
 - B. B. Snider, *Chem. Rev.*, 1996, **96**, 339.
 - (a) C. E. Harris, L. Y. Lee, H. Dorr, B. Singaram, *Tetrahedron Lett.*, 1995, **36**, 2921. (b) C. E. Harris, W. Chrisman, S. A. Bickford, L. Y. Lee, A. E. Torreblanca, B. Singaram, *Tetrahedron Lett.*, 1997, **38**, 981. (c) M. Takemoto, Y. Iwakiri, Y. Suzuki, K. Tanaka, *Tetrahedron Lett.*, 2004, **45**, 8061.