This article was downloaded by: [Texas A & M International University]
On: 06 October 2014, At: 09:56
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

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Reactions of N-Phosphorylated Aziridines with Dianions Derived from Ethyl Acetoacetate and 1,3-Diketones: New Route to Substituted Pyrrolines and Pyrrolidines

Krystyna Osowska-Pacewicka [a] & Andrzej Zwierzak [a]
[a] Institute of Organic Chemistry, Technical University (Politechnika) , Żwirki 36, Łódź 40, 90-924, Poland
Published online: 15 Aug 2006.

To cite this article: Krystyna Osowska-Pacewicka & Andrzej Zwierzak (1998) Reactions of N-Phosphorylated Aziridines with Dianions Derived from Ethyl Acetoacetate and 1,3-Diketones: New Route to Substituted Pyrrolines and Pyrrolidines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:7, 1127-1137, DOI: 10.1080/00397919808005953

To link to this article: http://dx.doi.org/10.1080/00397919808005953

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

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

SYNTHETIC COMMUNICATIONS, 28(7), 1127-1137 (1998)

REACTIONS OF N-PHOSPHORYLATED AZIRIDINES WITH DIANIONS DERIVED FROM ETHYL ACETOACETATE AND 1,3-DIKETONES: NEW ROUTE TO SUBSTITUTED PYRROLINES AND PYRROLIDINES

Krystyna Osowska-Pacewicka and Andrzej Zwierzak*
Institute of Organic Chemistry, Technical University (Politechnika),
Żwirki 36, 90-924 Łódź 40, Poland

Abstract: The nucleophilic ring-opening of N-(diethoxyphosphoryl)aziridines by the dianions derived from ethyl acetoacetate and 1,3-diketones has been studied. Acid-mediated cyclisation and dephosphorylation of the resulting products to a number of substituted pyrrolines and pyrrolidines has been also investigated.

It was found recently that various N-phosphorylated aziridines are effective synthetic equivalents of a^2 synthons when reacting with copper-modified Grignard reagents. Aminoethylation of organomagnesium bromides[1] as well as construction of sec-alkylamines with various carbon framework[2] could be easily accomplished by regioselective nucleophilic ring-opening of N-phosphorylated aziridines followed by hydrolytic[2] or solvolytic[1] dephosphorylation. We were interested in extending this work to similar reactions with dianions derived from ethyl acetoacetate and 1,3-diketones as the nucleophilic components, since this could allow a relatively easy access to some substituted pyrrolidines and pyrrolines.

*To whom correspondence should be addressed.

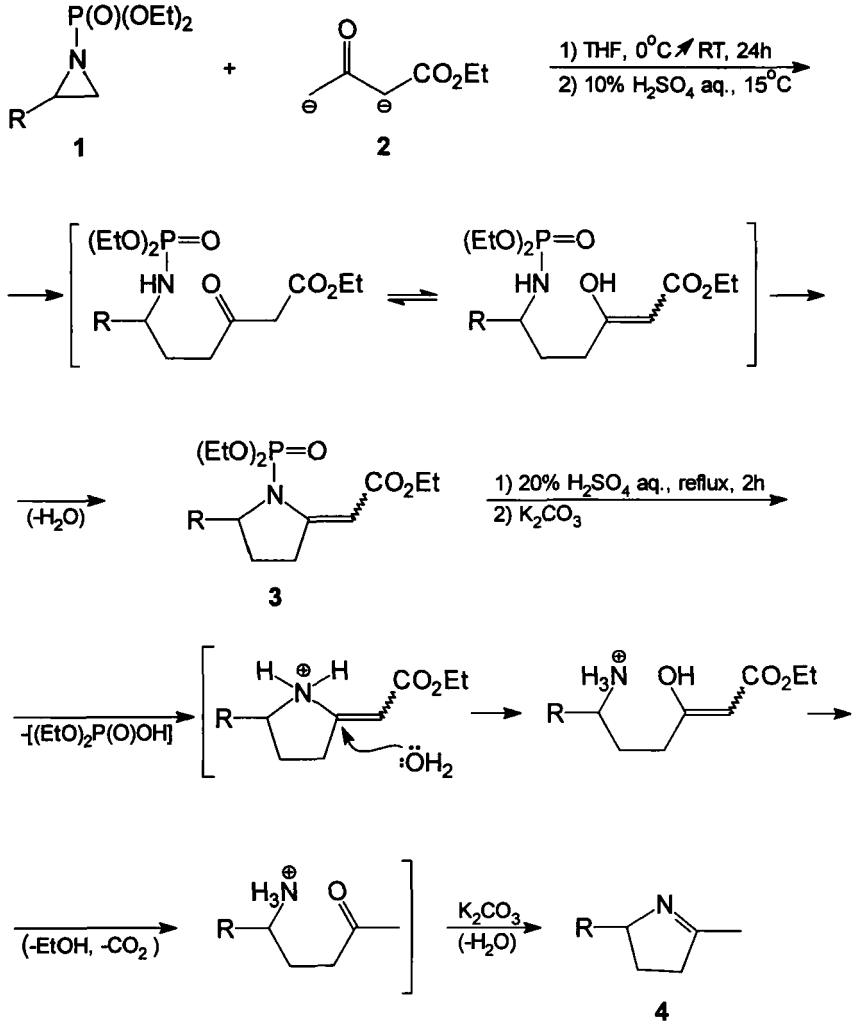
Copyright © 1998 by Marcel Dekker, Inc.

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

The ring-opening of N-tosyl substituted aziridines with dianions derived from β-ketoesters has been studied by Lygo[3], who found that in most cases acid-mediated cyclisation of the primarily formed adducts leads to N-tosylpyrrolidines. Having established that the diethoxyphosphoryl group can be easily and cleanly removed from nitrogen[1,2] we turned our attention to similar transformations employing N-(diethoxyphosphoryl) aziridines as a possible source of pyrrolidines unsubstituted at nitrogen atom.

The reaction between N-(diethoxyphosphoryl) aziridines (1a,b) and an excess of dianion (2) (prepared conventionally from one equivalent of ethyl acetoacetate, one equivalent of sodium hydride, and one equivalent of butyl lithium) was carried out by adding aziridine to the solution of dianion (2) in tetrahydrofuran at 0°C. Stirring of the reaction mixture for 24 h at room temperature followed by quenching with 10% aqueous sulfuric acid afforded N-phosphorylated pyrrolidine derivatives (3a,b). Crude (3) was subjected to dephosphorylation by refluxing with 20% aqueous sulfuric acid. Such treatment followed by addition of an excess of potassium carbonate delivered, however, not the expected pyrrolidine but the pyrroline derivative (4a,b). The formation of (4) is tentatively explained by assuming deprotection at nitrogen and consecutive pyrrolidine ring-opening, hydrolysis, decarboxylation, and recyclisation to pyrroline derivative (4) in alkaline medium. (Scheme 1).

Downloaded by [Texas A & M International University] at 09:56 06 October 2014



1, 3, 4	R
a	H
b	CH_3

Scheme 1

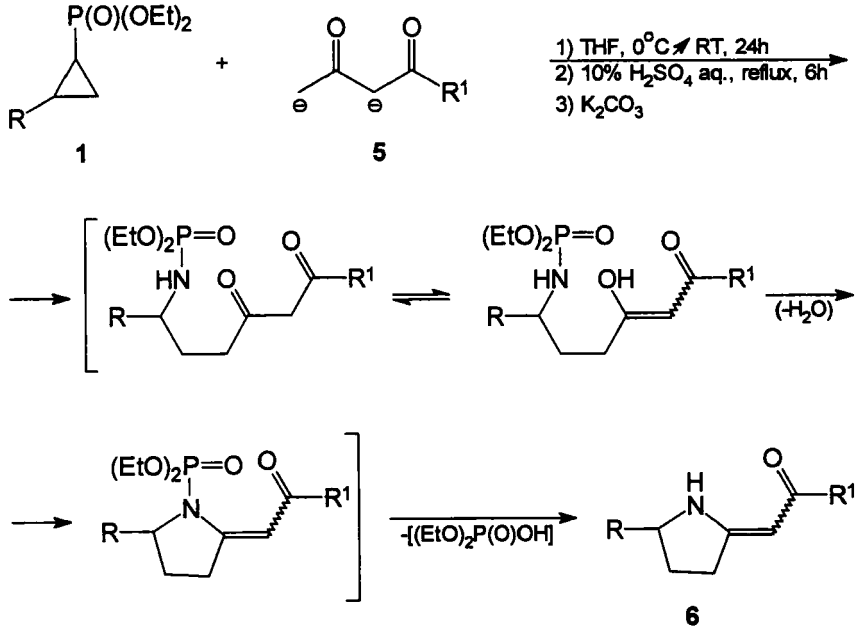
Downloaded by [Texas A & M International University] at 09:56 06 October 2014

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

It is noticeable that ring-opening of unsymmetrically substituted 2-methyl-N-(diethoxy-phosphoryl)aziridine (1b) takes place exclusively at the least substituted carbon atom of the aziridine ring giving rise to the formation of (3b) and (4b) respectively. Structures of (3a,b) were confirmed by spectroscopic methods. Spectral data of (4a,b) were fully consistent with the literature data.

The ring-opening of N-phosphorylated aziridines (1a,b) by means of dianions derived from acetylacetone (5, $R^1 = CH_3$) and benzoylacetone (5, $R^1 = Ph$) was performed under strictly the same conditions as described for ethyl acetoacetate dianion (2). Quenching and dephosphorylation of the primarily formed products (not isolated) was carried out by refluxing with 10% aqueous sulfuric acid. Progress of deprotection could be easily monitored by ^{31}P-NMR spectroscopy. Deprotection was in all cases accompanied by acid-mediated cyclisation of the primarily formed ring-opening products to give pyrrolidine derivatives (6a-d). (Scheme 2). All pyrrolidines, obtained as a mixture of diastereoisomers, were purified by "bulb-to-bulb" distillation. The Structures of all compounds were confirmed by elemental analysis and spectroscopic data.

This approach to some pyrroline and pyrrolidine derivatives, which are useful intermediates for the synthesis of a variety of natural products[4], seems to be relatively simple and convenient as compared to other methods described in the literature.



6	R	R^1
a	H	CH_3
b	CH_3	CH_3
c	H	Ph
d	CH_3	Ph

Scheme 2

EXPERIMENTAL SECTION

All reagents were purchased from Fluka and used without further purification. Melting and boiling points are uncorrected. IR spectra were measured in liquid films or nujol mulls using a Specord M 80 (C.Zeiss) instrument. ^{31}H-NMR spectra were recorded at 200 MHz with a Bruker

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

AC 200 spectrometer. ^{1}P-NMR spectra were taken on a Bruker AC 200 spectrometer at 81 MHz. Positive chemical shifts are downfield from 85% H_3PO_4 used as external reference. FABMS were recorded on a PO Electron (Ukraine) Modell M1 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). Mass spectra were recorded on a LKB 2091 mass spectrometer at 70 eV.

Preparation of N-phosphorylated pyrrolidines (3a,b). General Procedure: Ethyl acetoacetate (3.9 g, 30 mmol) was added dropwise with strirring to the suspension of sodium hydride (0.8 g, 33 mmol) in tetrahydrofuran (50 mL) at room temperature (occasional external cooling). After the evolution of hydrogen had stopped, t he resultant solution was cooled to 0°C and 1.6 M solution of butyl lithium in hexane (20.6 mL, 33 mmol) was added dropwise at this temperature. After an additional 10 min., N-phosphorylated aziridine (1, 20 mmol) was added and the mixture was stirred at room temperature for 24 h. 10% Aqueous sulfuric acid (35 mL) was then added dropwise with external cooling at 15°C, after which the organic phase was separated, washed with water, dried over anhydrous $MgSO_4$, and concentrated thoroughly in vacuo. The remaining liquid appeared to be spectroscopically pure pyrrolidine (3) (^{1}H-NMR and ^{31}P-NMR).

1-(Diethoxyphosphoryl)-2-((ethoxycarbonyl)methylidene)pyrrolidine(3a) Yield: 88%, IR(film): υ = 3000, 2950, 1720, 1675, 1620, 1400, 1255, 1175, 1050, 980 cm^{-1}.

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.24 (t, 3H, J=7.1); 1.33, 1.34 (2t, 6H, J=7.1); 2.07 (qt, 2H, J=7.0); 3.17 (dt, 2H, J=7.0, J=1.8); 3.64 (t, 2H, J=7.0); 3.98 - 4.20 (m, 6H); 5.57 (t, 1H, J=1.8).

^{31}P-NMR ($CDCl_3$): δ = 0.92.

FABMS: 292 (M+1, 76%), 246 (M-45, 100%).

1-(Diethoxyphosphoryl)-2-((ethoxycarbonyl)methylidene)-5-methyl-pyrrolidine (3b):

Yield: 96%, IR(film): υ = 3000, 2950, 1720, 1640, 1620, 1380, 1275, 1150, 1050, 1030, 980 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.22 (t, 3H, J=7.1); 1.24 (d, 3H, J=7.1); 1.30, 1.33 (2dt, 6H, J=7.1); 1.61-1.71 (m, 1H); 1.89-2.10 (m, 1H); 2.82-3.03 (m, 1H); 3.36-3.51 (m, 1H); 3.91-4.34 (m, 7H); 5.42 (br.s, 1H).

^{31}P-NMR ($CDCl_3$): δ = - 0.02.

FABMS: 306 (M+1, 71%), 260 (M-45, 100%).

Preparation of 3,4-dihydro-2H-pyrroles (Δ^1-pyrrolines) (4a,b). General Procedure:

Crude N-phosphorylated pyrrolidine (3) prepared from ethyl acetoacetate (3.9 g, 30 mmol) according to the procedure described above was refluxed for 2 h with 20% aqueous sulfuric acid (30 mL). The resultant solution was cooled to room temperature and subsequently extracted with dichloromethane (2x20 mL). The aqueous layer was made alkaline with solid potassium carbonate and crude Δ^1 - pyrroline (4a,b) was

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

extracted with dichloromethane (3x20 mL). The extracts were combined, dried over anhydrous $MgSO_4$, concentrated in vacuo, and the remaining liquid distilled to give analytically pure (4) as colorless liquid.

5-Methyl-3,4-dihydro-2H-pyrrole (5-methyl-Δ^1-pyrroline) (4a):

Yield: 75%, b.p. 103°C (Lit.[5]: b.p. - 105-106°/760 mmHg);

n_D^{20} - 1.4345 (Lit.[6]: n_D^{20} - 1.4296).

IR (film): υ = 2960, 2935, 2920, 1655, 1440, 1380, 1320, 940 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.87 (qt, 2H, J=7.8); 2.03 (s, 3H); 2.46 (t, 2H, J=8.2); 3.72-3.83 (m, 2H). The spectrum was fully consistent with the literature data[7].

FABMS: 83 (M, 48%); MS (m/z): 83 (M^+).

2,5-Dimethyl-3,4-dihydro-2H-pyrrole (2,5-dimethyl-Δ^1-pyrroline) (4b):

Yield: 58%, b.p. 114°C (Lit.[8]: b.p. - 110-112°/760 mmHg);

n_D^{20} - 1.4335 (Lit.[9]: n_D^{25} - 1.4330).

IR (film): υ = 2960, 2936, 2928, 1648, 1445, 1380, 1320, 1105, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.25 (d, 3H, J=6.8); 1.31-1.46 (m, 1H); 2.01 (s, 3H); 2.04-2.16 (m, 1H); 2.31-2.61 (m, 2H); 3.94-4.09 (m, 1H).

FABMS: 97 (M, 67%); MS (m/z): 97 (M^+).

Preparation of substituted pyrrolidines (6a-d). General Procedure:

The aziridine ring-opening was carried out by the same procedure and on the same scale as described before for the preparation of N-phosphorylated pyrrolidines (3a,b) using the dianions derived from

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

acetylacetone (compounds 6a,b) or benzoylacetone (compounds 6c,d). The reaction product was quenched with 10% aqueous sulfuric acid (65 mL) and the resultant mixture was refluxed for 6 h with efficient stirring (until disappearance of the P-signal in the amide region of ^{31}P-NMR spectrum). The aqueous layer was made alkaline with an excess of solid potassium carbonate and extracted with chloroform (3x20 mL). The extract was dried over anhydrous $MgSO_4$, evaporated, and "bulb to bulb" distilled in vacuo to give the pure pyrrolidine derivative (6a-d).

1-(Pyrrolidin-2-ylidene)-propan-2-one (6a):

Yield: 52%, b.p. 120-125°C /0.8 mmHg ((Lit.[10]: b.p. - 122°/0.1. mmHg)

IR (film): υ = 3300, 2980, 2890, 1625, 1555, 1360, 1300, 1250, 1035, 980, 925 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.81-2.05 (m, 2H); 1.99 (s, 3H); 2.56 (t, 2H, J=7.8); 3.53 (t, 2H, J=7.0); 5.07 (s, 1H); 9.76 (br.s.,1H).

MS (m/z): 125 (M^+, 100%), 110 (M-15, 97%).

Anal.Calcd for $C_7H_{11}NO$ (125.2): C, 67.1; H, 8.8; N, 11.2. Found: C, 67.0; H, 8.9; N, 11.4.

1-(5-Methylpyrrolidin-2-ylidene)-propan-2-one (6b):

Yield: 61%, b.p. 122-126°C /0.8 mmHg .

IR (film): υ = 3290, 2970, 2930, 2870, 1620, 1550, 1537, 1500, 1355, 1305, 1245, 945, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.21 (d, 3H, J=6.3); 1.38-1.53 (m, 1H); 1.98 (s, 3H); 1.99-2.21 (m, 1H,); 2.53-2.61 (m, 2H); 3.83-3.99 (m,

1H); 5.00 (s, 1H); 9.71 (br.s., 1H).

MS (m/z): 139 (M^+, 33%); 124 (M-15, 100%).

Anal.Calcd for $C_8H_{13}NO$ (139.2): C, 69.0; H, 9.3; N, 10.1. Found: C, 68.8; H, 9.5; N, 10.3.

1-Phenyl-(2-pyrrolidin-2-ylidene)-ethanone (6c):

Yield: 48%, m.p. 97-110°C (Lit.[10]: m.p. 109°C).

IR (nujol): υ = 2995, 2950, 2880, 1620, 1540, 1300, 1275, 745, 715 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.95-2.10 (m, 2H); 2.72 (t, 2H, J=7.8); 3.64 (t, 2H, J=7.0); 5.80 (s, 1H,); 7.35-7.45 (m, 3H); 7.83-7.91 (m, 2H); 10.27 (br.s., 1H).

MS (m/z): 186 (M -1, 100%); 110 (M-77, 52%).

Anal.Calcd for $C_{12}H_{13}NO$ (187.2): C, 76.9; H, 6.9; N, 7.5. Found: C, 76.7; H, 7.0; N, 7.2.

1-Phenyl-2-(5-methylpyrrolidin-2-ylidene)-ethanone (6d):

Yield: 48%, m.p. 75-86°C.

IR (nujol): υ = 2990, 2950, 2900, 1620, 1600, 1540, 1270, 730 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.30 (d, 3H, J=6.3); 1.48-1.67 (m, 1H); 2.11-2.27 (m, 1H); 2.70-2.79 (m, 2H); 3.98-4.08 (m, 1H); 5.75 (s, 1H); 7.27-7.46 (m, 3H); 7.78-7.89 (m, 2H); 10.23 (br.s., 1H).

MS (m/z): 200 (M-1, 100%); 124 (M-77, 52%).

Anal. Calcd for $C_{13}H_{15}NO$ (201.2): C, 77.5; H, 7.5; N, 7.0. Found: C, 77.2; H, 7.8; N, 7.0.

Downloaded by [Texas A & M International University] at 09:56 06 October 2014

Acknowledgements

Financial support by a grant 3T-09A/095/08 from the Polish Committee of Scientific Research (KBN) is gratefully acknowledged.

References

1. Osowska-Pacewicka, K. and Zwierzak, A. *Synthesis* **1996**, 333.
2. Gajda, T., Napieraj, A., Osowska-Pacewicka, K., Zawadzki, S. and Zwierzak, A. *Tetrahedron* **1997**, *53*, 4935.
3. Lygo, B. *Synlett* **1993**, 764.
4. References cited in ref. 3.
5. Vaultier, M., Lambert, P.H. and Carrie, R. *Bull.Soc.Chim. France* **1986**, 83.
6. Burckhalter, J.H. and Short, J.H. *J.Org.Chem.* **1958**, *23*, 1281.
7. Hua, D.H., Bharathi, S.N., Robinson, P.D. and Tsujimoto, A. *J.Org.Chem.* **1990**, *55*, 2128.
8. Evans, G.G. *J.Am.Chem.Soc.* **1951**, *73*, 5230.
9. Logothetis, A.L. *J.Am.Chem.Soc.* **1965**, *87*, 749.
10. Delbecq, P., Bacos, D., Celerier, J.P. and Lhommet, G. *Can.J.Chem.* **1991**, *69*, 1201.

(Received in The Netherlands 03 November 1997)

Downloaded by [Texas A & M International University] at 09:56 06 October 2014