

tent with known reactions of cyclopropylcarbinyl cations and explains the results in this system.

Formation of 2-ethyl-1,1-dithiophenylcyclobutane, 2a: To 5.4 g (24.3 mmol) of anhydrous $ZnBr_2$ in 4.6 mL of 48% HBr was added 1.4 g (6.8 mmol) of **1a** in 2.9 mL (5 eq.) of thiophenol. After stirring for 2 hour, the mixture was poured into 0.25 L of ice cold water overlaid with 0.5 L of pentane. Further extraction with pentane was followed by drying with $MgSO_4$. Removal of solvents under reduced pressure was followed by chromatography (SiO_2 /pentane) to give 1.9 g (6.5 mmol, 95.2%) of **2a** as a clear oil ($R_f=0.3$, pentane/silica gel). 1H -NMR ($CDCl_3$) 7.77-7.17 (10H, m), 2.55 (1H, m), 2.20-1.45 (6H, m), 0.82 (3H, t); ^{13}C -NMR ($CDCl_3$): 136.24 (s), 134.06 (s), 128.76 (d), 128.63 (d), 127.70 (d), 66.31 (s), 50.24 (d), 32.70 (t), 24.19 (t), 23.17 (t), 11.58 (q); Infrared (neat); 3200 (s), 2950 (s), 1570 (m), 1470 (m), 1450 (m), 1060 (s), 900, 745, 670 cm^{-1} ; Mass Spectrum (m/z , rel. intensity): P^+ 300 (7), 271 (2), 244 (16.8), 223 (11), 191 (100), 135 (73), 109 (35.3), 91 (44.8), 81 (69.1). 65 (34).

References

- Presented in part at the 3rd Chemical Congress of North America, *ORGN*, 197, 6/8/88, Toronto.
 - T. W. Kwon and M. B. Smith, *J. Org. Chem.*, **54**, 4250 (1989).
 - R. T. Hrubiec and M. B. Smith, *Tetrahedron*, **40**, 1457 (1984); R. T. Hrubiec and M. B. Smith, *J. Org. Chem.*, **49**, 385 (1984).
 - M. B. Smith, R. T. Hrubiec, and C. A. Zezza, *J. Org. Chem.*, **50**, 4815 (1985); R. T. Hrubiec and M. B. Smith, *Tetrahedron Lett.*, 5031 (1983).
 - B. M. Trost, D. E. Keeley, H. C. Arndt, and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **99**, 3088 (1977).
 - M. Julia, S. Julia, and R. Geugan, *Bull. Soc. Chim. Fr.*, 1072 (1960); S. F. Brady, M. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).
 - T. W. Kwon and M. B. Smith, *Chemistry Letters*, 2027 (1989).
- | Alcohol | R | Dithioketal | % 2 | |
|-----------|---|-------------|-----------------|-------------------|
| 1a | Et | 2a | 95 ^e | 45 ^{e,e} |
| 1b | iPr | 2b | 92 ^e | 59 ^{e,f} |
| 1c | \underline{c} -C ₆ H ₁₁ | 2c | 92 ^e | |
| 1d | Ph | 2d | 27 ^d | |
| | | | 36 ^e | |
| | | | 67 ^b | |
- ^aRT, 5 eq. PhSH. ^b65°C, 25 eq. PhSH. ^cRT, no PhSH. ^dRT, 1 eq. PhSH. ^e48% **3a**. ^f10% **3b**.
- T. W. Kwon and M. B. Smith, *Synth. Commun.*, 2273 (1992).
 - R. D. Miller and D. R. McKean, *Tetrahedron Lett.*, 583 (1979).
 - J. R. Salaun and J. M. Conia, *Tetrahedron Lett.*, 2849 (1972); H. H. Wasserman and D. C. Clagett, *J. Am. Chem. Soc.*, **88**, 5368 (1986).
 - B. M. Trost, *Accounts Chem. Res.*, **7**, 85 (1974).
 - M. J. Bogdanowicz, T. Ambelang, and B. M. Trost, *Tetrahedron Lett.*, 923 (1973).
 - R. C. Gadwood, *Tetrahedron Lett.*, **25**, 5851 (1984).

A Convenient Method for β -Lactam Formation from β -Amino Acids Using (3-Nitropyridyl) Dialkyl Phosphate

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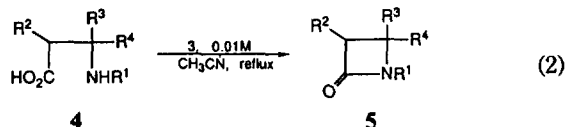
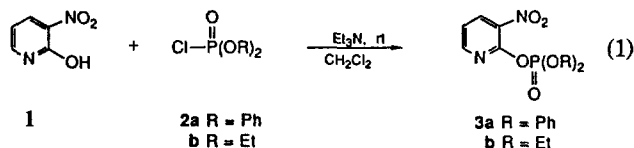
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Intramolecular condensation is one of the important reactions which are frequently used in the formation of β -lactam rings from β -amino acids in the presence of suitable condensing reagents¹. Recently, new organophosphate type condensing reagents have been introduced² for the construction of β -lactams, esters, and peptides.

In the course of our work in developing new effective condensing reagents³, we have examined the β -lactams (**5**) formation from β -amino acids (**4**) using organophosphate compounds. Compounds studied in this work involve (3-nitropyridyl)diphenyl phosphate (**3a**, **3-NDP**) and (3-nitropyridyl) diethyl phosphate (**3b**, **3-NDE**). These reagents can be easily prepared by the reaction of 2-hydroxy-3-nitropyridine (**1**) with dialkyl chlorophosphate (**2a**, or **2b**), and triethylamine in dichloromethane at room temperature for 1 h (Eq. (1)). **3-NDP** reagent was obtained as an orange crystal in essentially quantitative yield (92-94%) and can be stored in a refrigerator for several weeks without any decomposition. However, **3-NDE** reagent was obtained as a reddish oil and was easily decomposed into the starting material (**1**) within two weeks.



We have briefly studied solvent and concentration effects using 3-benzylaminobutanoic acid, 1.2 equivalent of **3-NDP** reagent and triethylamine at room temperature or at refluxing condition. The best result was obtained in case of the substrate concentration of 0.01 M in acetonitrile with refluxing for 24 h.

Some experimental results are summarized in Table 1 to illustrate the efficiency of the present method. N-Substituted β -amino acids were cleanly cyclized into the corresponding β -lactams in moderate to high yields whereas N-unsubstituted β -amino acids gave poor results due to the poor solubility.

In conclusion, **3a** is a crystalline solid having excellent

Table 1. Synthesis of β -Lactams from β -Amino Acids

β -Amino acids				Yield (%) of β -Lactams ^a	
R ¹	R ²	R ³	R ⁴	3-NDP(3a)	3-NDE(3b)
PhCH ₂	H	CH ₃	H	86	90
PhCH ₂	H	CH ₃	CH ₃	97	
PhCH ₂	H	(CH ₂) ₂ CH ₃	H	83	85
PhCH ₂	H	CH ₂ CH ₃	H	82	
PhCH ₂	H	COCH ₃	H	72	78
PhCH ₂	CH ₃	H	H	54	63
PhCH ₂ CH ₂	H	CH ₃	CH ₃	95	
C ₆ H ₅ (OCH ₃) ₂ CH ₂ ^b	H	CH ₃	H	84	
C ₆ H ₅ (OCH ₃) ₂ CH ₂ ^b	CH ₃	H	H	80	
H	H	H	Ph	^c	30

^a Isolated yields by column chromatography. ^b 3,4-Dimethoxybenzyl. ^c Less than 10%.

hydrolytic stability and therefore is handled more easily than **3b**. Both **3a** and **3b** are applicable to the formation of β -lactams from *N*-substituted β -amino acids. Further utility of the reagent as dehydrating and condensing reagents is being explored.

Experimental

Melting points were determined with Buchi 510 apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on Silica gel 60 F₂₅₄ (Merck) plates, and spots were detected by ultraviolet (UV) irradiation. ¹H-NMR spectra were measured with a Bruker AC 100 spectrometer. Tetramethylsilane (TMS) in CDCl₃ was used as an internal reference. ¹³C-NMR spectra was obtained on a Gemini-300 spectrometer

Preparation of (3-nitropyridyl) diphenyl phosphate (3a). A mixture of 2-hydroxy-3-nitropyridine (**1**) (14.01 g, 0.1 mol) and triethylamine (10.12 g, 0.1 mol) in dichloromethane (300 ml) was stirred at room temperature and a solution of diphenyl chlorophosphate (26.86 g, 0.1 mol) in dichloromethane (100 ml) was added dropwise. Stirring was continued for 1 h. The mixture was evaporated and the residue was extracted with chloroform. The organic layer was washed successively with 5% NaHCO₃ (100 ml) and brine (200 ml) and dried with Na₂SO₄. The solvent was removed under reduced pressure and the residue was crystallized from chloroform-hexane. Yield 92-94%, mp. 76-78°C; ¹³C-NMR (acetone-d₆) δ 119.52, 119.58, 121.55, 125.04, 129.08, 135.57, 139.17, 141.40, 151.16.

Preparation of (3-nitropyridyl) diethyl phosphate (3b). Compound **3b** was prepared from **1** and diethyl chlorophosphate (**2b**) as described above. Yield 93%, ¹H-NMR (100 MHz, CDCl₃) δ 1.19 (t, 6H, *J*=7.2 Hz), 4.19 (q, 4H, *J*=7.2 Hz), 7.15-8.34 (m, 3H).

The representative experimental procedure for the reaction of β -amino acid with (3-nitropyridyl) dialkyl phosphate (Eq. (2)); To a mixture of 3-benzyl aminobutanoic acid (289 mg, 1.5 mmol) and **3-NDP** (670 mg, 1.8 mmol) in acetonitrile (150 ml) was added triethylamine (360 mg, 3.6 mmol) at room temperature. After being stirred for 24 h at 80°C. Usual

work-up 2 : 1 ether-chloroform afforded 1-benzyl-4-methylazetid-2-one in 86% yield (150 mg) as an oil.

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References

- (a) N. S. Isaacs, *Chem. Soc. Rev.*, **15**, 181 (1976); (b) A. K. Mukerjee and A. K. Singh, *Tetrahedron*, **34**, 1731 (1978); (c) K. Hirai, *Yuki Gosei Kagaku Kyokai Shi*, **38**, 97 (1980).
- (a) M. Ueda and H. Oikawa, *J. Org. Chem.*, **50**, 760 (1985); (b) S. Kim, H. Chang, and Y. K. Ko, *Tetrahedron Lett.*, **26**, 1341 (1985); (c) S. Kim and S. S. Kim, *J. Chem. Soc. Chem. Commun.*, 719 (1986); (d) S. Kim, S. B. Chang, and P. H. Lee, *Tetrahedron Lett.*, **28**, 2735 (1983); (e) C. W. Kim, B. Y. Chung, J. Y. Namkung, J. M. Lee, and S. Kim, *ibid.*, **31**, 2905 (1990); (f) C. Palomo, J. M. Aizpurua, R. Urchequi, M. Iturburn, A. O. de Retana, and C. Cuevas, *J. Org. Chem.*, **56**, 2244 (1991); (g) B. Y. Chung, K. C. Paik, and C. S. Nah, *Bull. Korean Chem. Soc.*, **12**, 589 (1991).
- For our recent reports: (a) Y. H. Lee, W. S. Choi, and D. S. Lho, *Bull. Korean Chem. Soc.*, **10**, 474 (1989); (b) Y. H. Lee, K. Y. Chai, C. H. Lee, and W. S. Choi, *ibid.*, **12**, 710 (1991).

Revised Assignment of the ¹³C-NMR Spectra of Bicyclo[3.1.1]heptane Derivatives

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A unique rigid geometry of bridged bicyclic compounds has received considerable attention from NMR spectroscopists because their geometry is ideal to study the relationships between configuration and the magnitude of NMR parameters.^{1,2} Because the proton spectra were restricted for the conformational studies by complexity, the carbon-13 spectra of these derivatives were used as a mean of determining their conformations.^{1,3} One of the interesting qualitative application of carbon-13 chemical shift is the conformational analysis of bicyclo[3.1.1]heptane derivatives (**1**) which has the conformational flexibility in the three carbon bridge.⁴

