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Studies on Organophosphorus Compounds 80. Stereoselective Synthesis of Fused Carbocyclic and Isoxazoline Rings via Intramolecular Cycloaddition of Nitrile Oxides Derived from α-Nitroalkenes

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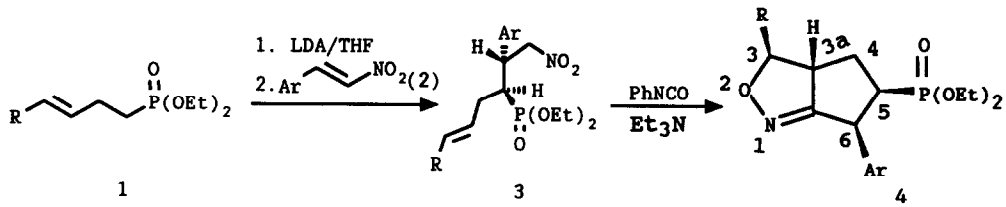
Abstract: Stereoselective condensation of alk-3-en-1-ylphosphonates with α-nitroalkenes gave the corresponding nitro compounds, which led to the stereoselective synthesis of 6-aryl-3,3a,4,5,6-pentahydrocyclopent[c]-isoxazole-5-ylphosphonates via intramolecular nitrile oxide -olefin cylco-addition in good yield. Cyclohex-2'-en-1'-ylmethylphosphonate behaves analogously.

In recent years intramolecular nitrile oxide - olefin cycloaddition (INOC) has been of considerable interest in ring constructions due to its high stereoselectivity.[1] Meanwhile, the resulting isoxazoline derivatives can be converted into β-hydroxy ketones, γ-amino alcohols, and other functional groups and can therefore provide a useful entry into natural product synthesis.[2-4] On the other hand, the presence of a phosphonate moiety should extend the scope of the applications via Horner-Emmons reaction. Herein we wish to report a novel and convenient method for the synthesis of these kind of compounds **4** by intramolecular nitrile oxide - olefin cycloaddition starting from α-nitroalkenes.

The chemistry of α-nitroalkenes has attracted synthetic chemists' interest because of their versatile reactivities[5-6] and convenient methods for their preparations.[7-10] The conjugated additions of α-nitroalkenes by various nucleophiles lead to functionalized nitro compounds, which can be transformed to amino or hydroxyamino groups. By use of Mukaiyama-Hoshino method,[11] nitro compounds can be converted into the corresponding nitrile oxides, which give 2-isoxazoline derivatives upon reaction with alkenes. Based on these transformations, we carried out the reactions of alk-3-en-1-ylphosphonates (**1**) with 2-aryl-1-nitroethylenes (**2**).

As shown in Scheme 1, Michael condensation of phosphonates **1** with α-nitroalkenes **2** exhibited high diastereoselectivity and provided exclusively the erythro isomers **3**. This result may be ascribed to the low reac-

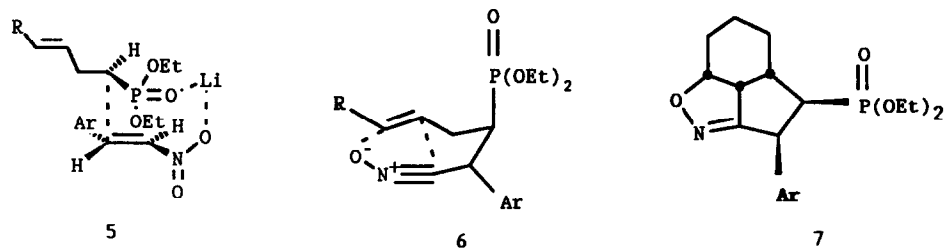
tivity of α-nitroalkenes **2**, which tended the reaction to proceed via the transition state **5** of the least steric hindrance. As for the reaction of 1-nitroalk-1-enes, the diastereoselectivity was not obvious, probably because of their higher reactivity and smaller differences in steric effect of the related groups.



Scheme 1.

The second step was the INOC reaction of **3** using standard Mukaiyama - Hoshino method. Treatment with phenyl isocyanate in the presence of catalytic amount of triethylamine, **3** can be readily converted into the corresponding bicylic compounds **4** in good yield. The ^{1}H-,^{13}C-,^{31}P NMR, NOESY and ^{1}H-^{13}C COSY spectra demonstrated that the hydrogen at C-3a was in cis to both the phosphonate group at C-5 and the aryl substituent at C-6. The R group at C-3 was also in cis to the hydrogen at C-3a due to the E-olefin in **3**. This stereoselectivity might be rationalized by the formation of sterically less hindered transition state **6** in the INOC process. The results of the reactions are summarized in Table 1.

As an extension of the reaction, cyclohex-2'-en-1'-ylmethylphosphonate behaved analogously under similar experimental conditions, and tricyclic compounds **7** (Ar = Ph, p-F-C_6H_4, p-Me-C_6H_4) were achieved with high stereoselectivity in good yield.



In conclusion, The above two stereoselective reactions provide a novel strategy for the direct synthesis of fused ring system of isoxazoline and cyclopentane bearing a phosphonate moiety. By subsequent transformations,

compounds **4** may be converted stereoselectively into polysubstituted cyclopentanone derivatives, studies of which are presently in progress.

Table 1. Compounds **3** and **4** synthesized.

Entry	R	Ar	Yield(%)		Time/Temp. (h/°C)[c]
			3[a]	**4**[b]	
a	H	Ph	90	84	24/20
b	H	p-F-C_6H_4	86	78	24/20
c	H	p-Me-C_6H_4	83	76	24/20
d	Me	Ph	81	74	2/80
e	Me	p-F-C_6H_4	77	75	2/80
f	Me	p-Me-C_6H_4	70	71	2/80
g	Ph	Ph	58	52	36/30
h	Ph	p-F-C_6H_4	54	50	36/30
i	Ph	p-Me-C_6H_4	57	52	36/30

a. Isolated yield based the corresponding phosphonates **1**.
b. Isolated yield based the corresponding compounds **3**.
c. Refer to the experimental conditions in the synthesis of compounds **4**.

As a typical procedure, diethyl but-3-en-1-ylphosphonate (0.96 g, 5 mmol) was added dropwise at -68°C to LDA solution prepared by n-butyllithium (3.13 mL, 5 mmol, 1.6 M solution in hexanes) and diisopropylamine (0.7 mL, 5 mmol) in THF (20 mL) in-situ. After the complete addition the solution was stirred for an additional 30 min and then 2-phenyl-1-nitroethylene (0.782 g, 5.25 mmol) in THF (4 mL) was added dropwise. The solution was sitrred at -68°C for 1 h and then at r.t. for 10 h. Hydrochloric acid (1 N) was added until the pH of the solution was slightly acidic. The resulting mixture was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica with the eluent of petroether/acetone (2/1, v/v) to give the pure compound **3a** as a colorless oil. Yield: 1.53 g (90%).[12]

A mixture of compound **3a** (0.34 g, 1 mmol), phenyl isocyanate (0.33 mL, 3 mmol) and triethylamine(10 drops) in benzene (20 mL) was stirred at r.t. for 24 h. The white precipitate was filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica with the eluent of petroether/acetone (2/1, v/v)

to give the pure product **4a** as a colorless oil. Yield: 0.27 g(84%).[13]

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11. Mukaiyama, T. and Hoshino, T. J.Am.Chem.Soc. **1960**, 82, 5339.
12. Diethyl 5-phenyl-6-nitrohex-1-en-4-ylphosphonate (**3a**):IR (film) ν 3070, 1705, 1600, 1550, 1500, 1450, 1250, 1025, 960, 740, 700. EIMS: m/z 342 (M^++H), 204. ^{1}H NMR($CDCl_3$) δ 1.12,1.30 (2×3H, 2t, J=7, CH_3CH_2O), 2.15-2.55 (3H, m, CH_2CHP), 3.85-4.15 (5H, m, CH_2O+CHPh), 5.00 (1H, dd, J=9, 13.4, CH_2NO_2), 5.10 (2H, m, CH_2=), 5.25 (1H, dd, J=6.5, 13.4, CH_2NO_2), 5.80(1H, m, CH=), 7.35(5H, m, C_6H_5). ^{31}P NMR($CDCl_3$) δ 29.50. Anal.Calcd for $C_{16}H_{24}NO_5P$:C,56.31; H,7.09; N,4.11. Found:C,56.07; H,7.21; N,4.12.
13. Diethyl 6-phenyl-3,3a,4,5,6-pentahydrocyclopent[c]isoxazole-5-ylphosphonate (**4a**): IR (film) ν 3030, 1490, 1450, 1240, 1020, 740, 700. EIMS: m/z 324 (M^++H), 186. ^{1}H NMR ($CDCl_3$) δ 1.21, 1.27 (2×3H, 2t, J=7, CH_3) 1.86 (1H, m, 4-H), 2.42 (1H, m, 4-H), 2.96(1H, m, 5-H), 3.95-4.15 (6H, m, CH_2O + 6-H + 3-H), 4.20 (1H, dd, J=7, 16, 3a-H), 4.65 (1H, dd, J=7, 8, 3-H), 7.35 (5H, m, C_6H_5). ^{31}P NMR ($CDCl_3$) δ 28.33. ^{13}C NMR ($CDCl_3$) δ 16.38,16.45 (CH_3), 29.98(4-C), 40.95 (3a-C), 48.45 (d, J_{C-P}=147, C-P), 55.23 (d, J_{C-P}=12.8, 6-C), 62.21, 62.34 (CH_2O), 74.88 (3-C), 127.4, 128.3, 128.8, 139.8 (Ph), 171.4 (C=N). Anal.Calcd for $C_{16}H_{22}NO_4P$: C,59.44; H.6.86; N,4.33. Found: C,59.35; H,6.91; N,4.03.

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