CHEMISTRY LETTERS, pp. 183-186, 1986.

SYNTHESIS OF A NEW PHOSPHORUS-FUNCTIONALIZED NITRILE OXIDE, α-(DIETHYLPHOSPHONO)ACETONITRILE OXIDE, AND CYCLOADDITION LEADING TO 3-(DIETHYLPHOSPHONOMETHYL)-Δ^2-ISOXAZOLINES

Otohiko TSUGE,* Shuji KANEMASA, and Hiroyuki SUGA
Research Institute of Industrial Science, and Department
of Molecular Science and Technology, Interdisciplinary
Graduate School of Engineering Sciences, Kyushu University,
Kasugakoen, Kasuga 816

Cycloaddition of α-(diethylphosphono)acetonitrile oxide, a new phosphorus-functionalized nitrile oxide, leads to 3-phosphonomethyl-Δ^2-isoxazolines which are useful as Δ^2-isoxazoline unit-introducing reagents.

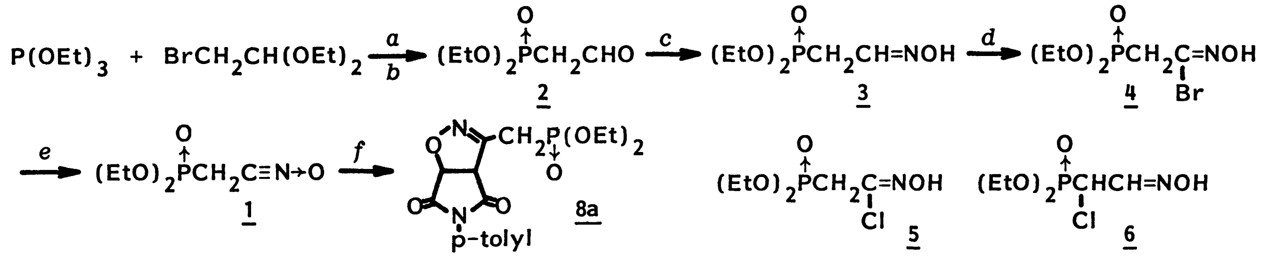
Nitrile oxides have been much more frequently used in organic synthesis, especially in the elaboration of complex molecules, than any other 1,3-dipoles.[1)] The importance of nitrile oxide is based on its high reactivity toward a wide range of olefins, both electron-poor and -rich types, forming Δ^2-isoxazolines which are synthetic equivalents of β-hydroxy ketones (aldols),[2)] γ-amino alcohols,[3)] and α,β-unsaturated ketones.[4)]

In recent years, have been reported synthetic applications of several nitrile oxides carrying such functinality as hydroxy,[5)] ester,[6)] sulfonyl,[7)] and acetal moieties.[8)] Their cycloaddition provides functionalized Δ^2-isoxazolines.

This communication describes the first synthesis of phosphorus-functionalized nitrile oxide, α-(diethylphosphono)acetonitrile oxide 1, and its cycloaddition with a variety of olefins. 3-(Diethylphosphonomethyl)-Δ^2-isoxazolines formed are useful as reagents for the introduction of a Δ^2-isoxazoline functionality into a molecule by a carbon-carbon bond forming reaction.

Our synthetic route of 1 starts from diethylphosphonoacetaldehyde 2 since it is readily available in large quantities by the Arbuzov reaction between triethyl phosphite and bromoacetaldehyde diethylacetal.[9)] The aldehyde 2 was converted into the oxime 3 (syn:anti=3:4 (^{1}H-NMR)) in 95% yield (Scheme 1).[10)] Although the oxidation of 3 with lead tetraacetate or sodium hypochlorite ended in failure, 1 was found successfully accessible by the bromination with NBS followed by dehydrobromination with triethylamine.[11)] The chlorination of 3 with NCS led to a mixture of the expected imidoyl chloride 5 and undesired α-chloro oxime 6 whose ratio varied within the range of 1:1 to 16:3 depending upon the reaction conditions.[12)]

The nitrile oxide 1 was captured as cycloadduct 8a with N-(p-tolyl)maleimide 7a. A typical procedure is as follows: A mixture of 3 and NBS (2 equiv.) in dry DMF was allowed to react at -20 °C for 1 h and then 0 °C for 0.5 h. The mixture was diluted with dry ether (half the volume of DMF),[13)] and a solution of 7a and

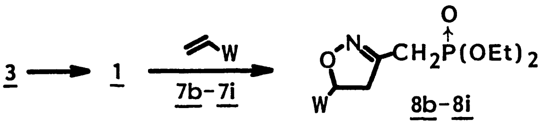


a: 185-190 °C, *b*: HCl, p-hydroquinone, 70-80 °C, *c*: $NH_2OH \cdot HCl$, EtOH, rt, *d*: NBS, *e*: NEt_3, *f*: N-(p-tolyl)maleimide 7a

Scheme 1.

triethylamine (each equimolar to 3) in dry ether was added. The reaction was continued at room temperature until 7a was all consumed (checked on TLC). The followed hydrolytic work up, extraction with dichloromethane, and column chromatography over silica gel gave 8a in 80% yield.

The cycloaddition reactions of 1 with a variety of olefinic dipolarophiles 7b-7i gave the corresponding Δ^2-isoxazolines 8b-8i all as single regioisomers (Scheme 2 and Table 1).



7 and 8:
b: W=Ph
c: W=n-Pen
d: W=COOMe
e: W=COMe
f: W=CN
g: W=SO_2Ph
h: W=CH_2Br
i: W=OCOMe

Scheme 2.

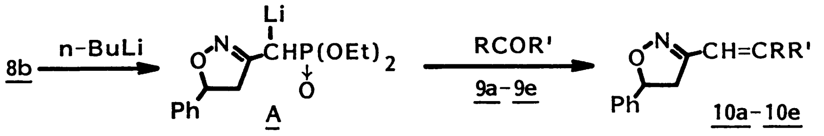
Table 1. Cycloaddition of 1 with 7[a)]

Olefin	7/3	Time/h[b)]	Product	Yield/%[c)]	Olefin	7/3	Time/h[b)]	Product	Yield/%[c)]
7a	1	18	8a	80	7f	2	18	8f	45
7b	5	18	8b	81	7g	1	18	8g	25
7c	5	18	8c	75	7h	5	18	8h	57
7d	1	18	8d	84	7i	5	18	8i	73
7e	2	48	8e	70					

a) Conditions for the formation of 4: 1+NBS (2 equiv) in DMF at -20 °C for 1 h and then at 0 °C for 0.5 h. b) At room temperature in the presence of triethylamine (one equivalent to 3). c) Isolated yield based on 3.

Unlike 3-alkyl-substituted Δ^2-isoxazolines,[14)] the 3-(diethylphosphonomethyl)-Δ^2-isoxazolines 8 are expected to undergo regioselective deprotonation at the carbon substituted by the phosphorus moiety and therefore they will be useful as Δ^2-isoxazoline unit-introducing reagents through the subsequent reaction with electrophiles. Some examples along this purpose were demonstrated below.

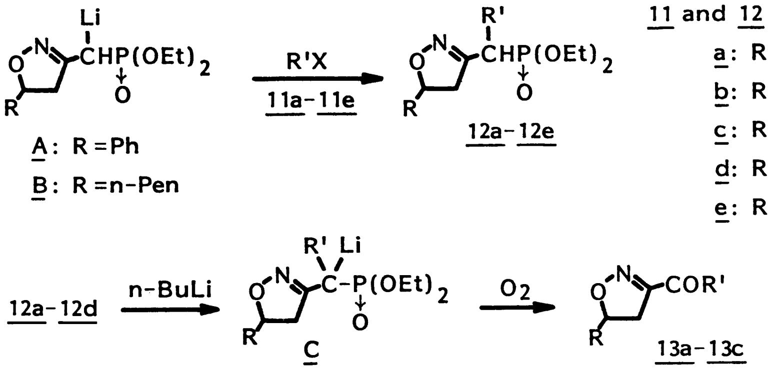
Treatment of 8b as an example with butyllithium in dry THF at -78 °C led to a smooth formation of the phosphorus-stabilized carbanion A. The subsequent reactions with aldehydes 9a-9d or a ketone 9e gave 3-(1-alkenyl)-Δ^2-isoxazolines 10a-



9 and 10: a: R=Ph, R'=H d: R=MeCH$\overset{t}{=}$CH, R'=H
b: R=Et, R'=H e: RR'=$(CH_2)_5$
c: R=n-Pen, R'=H

Scheme 3.

10e in good to excellent yields (Scheme 3 and Table 2). The anions A and B could be alkylated with a variety of alkyl halides 11a-11e giving 3-(1-diethylphosphonoalkyl)-Δ^2-isoxazolines 12a-12e (Scheme 4 and Table 2). They could be again deprotonated at the same carbon with butyllithium in THF at -78 °C forming carbanions C. These anions underwent oxidative elimination of the phosphorus moiety to provide the corresponding Δ^2-isoxazolin-3-yl ketones 13a-13c when treated with dry oxygen gas at -78 °C.



A: R=Ph
B: R=n-Pen

11 and 12:
a: R=Ph, R'=Me (X=I)
b: R=Ph, R'=n-Pen (X=I)
c: R=Ph, R'=CH_2TMS (X=I)
d: R=n-Pen, R'=CH_2Ph (X=Br)
e: R=n-Pen, R'=allyl (X=Br)

a: R=Ph, R'=Me
b: R=Ph, R'=n-Pen
c: R=n-Pen, R'=CH_2Ph

Scheme 4.

Table 2. Reaction of Δ^2-Isoxazolines 8 and 12 with Electrophiles[a)]

Δ^2-Isoxazoline	Electrophile	Temp/°C	Time/h	Product	Yield/%[b)]	
8b	9a	rt	12.5	10a	99	E only[c)]
8b	9b	rt	12.5	10b	75	E:Z=75:25[c)]
8b	9c	rt	16	10c	66	E:Z=72:28[c)]
8b	9d	rt	17	10d	81	E only[c)]
8b	9e	rt	16	10e	94	
8b	11a	rt	17	12a	80	
8b	11b	rt	11	12b	72	
8b	11c	rt	15	12c	70	
8c	11d	rt	15	12d	75	
8c	11e	rt	15.5	12e	91	recovered 12
12a	oxygen	-78	1	13a	70	12a (16%)
12b	oxygen	-78	1	13b	83	12b (15%)

Table 2 (Continued from the preceding page)

12c	oxygen	-78	1	13a	78	12c (12%)
12d	oxygen	-78	1	13c	57	12d (39%)

a) The carbanions A-C were generated with butyllithium in THF at -78 °C and then the reactions with electrophiles were carried out under the conditions listed in this table. b) Isolated yield. c) Determined by GLC.

References

1) A. P. Kozikowski, "Comprehensive Heterocyclic Chemistry," ed by A. R. Katrizky, C. W. Rees, Pergamon Press, Oxford, New York, Tronto, Sydney, Paris, Frankfurt (1984), Vol. 1, Chap. 1-16, pp. 413-491; G. Desimoni, G. Tacconi, A. Barco, G. P. Pollini, "Natural Product Synthesis Through Pericyclic Reactions," as ACS Monograph 180, ed by M. C. Caserio, American Chemical Society, Washington, D. C. (1983), Chap. 4, pp. 89-117.

2) R. H. Wollenberg and J. E. Goldstein, Synthesis, 1980, 757; D. P. Curran, J. Am. Chem. Soc., 105, 5826 (1983).

3) G. W. Perold and F. V. K. von Reiche, J. Am. Chem. Soc., 79, 465 (1957); V. Jäger, V. Buss, and W. Schwab, Tetrahedron Lett., 1978, 3133.

4) H. Grund and V. Jäger, Liebigs Ann. Chem., 1980, 80.

5) A, P. Kozikowski and A. K. Ghosh, Tetrahedron Lett., 24, 2623 (1983).

6) R. V. Stevens, C. G. Christensen, R. M. Cory, and E. Thorsett, J. Am. Chem. Soc., 97, 6865 (1975); A. P. Kozikowski and A. K. Ghosh, ibid., 104, 5788 (1982).

7) P. A. Wade and H. R. Hinney, J. Am. Chem. Soc., 101, 1319 (1979).

8) T. Kametani, S. -P. Huang, and M. Ihara, Heterocycles, 12, 1183 (1979); A. P. Kozikowski and C. -S. Li, J. Org. Chem., 50, 778 (1985).

9) A. I. Razumov and V. V. Moskva, Zh. Obshch. Khim., 34, 2589 (1964) and Chem. Abstr., 70, 140707a (1964).

10) All new compounds reported herein gave satisfied elemental and spectral data.

11) Nitrile oxide synthesis using NBS: C. Grundmann and R. Richter, J. Org. Chem., 33, 476 (1968); R. V. Stevens, Tetrahedron, 32, 1599 (1976).

12) These chlorinated products 5 and 6 are unstable but isolable through column chromatography over silica gel (hexane-ethyl acetate). The maximum yield in our experimentation was 71% (5:6=16:3 (^{1}H-NMR)).

13) The ether was used in order to remove the unreacted NBS which precipitated out of the solution. By this way, further bromination of 4 as well as bromination of the dipolarophile was suppressed to a certain extent.

14) Regioselectivity in the deprotonation of 3-methyl-Δ^2-isoxazolines has been already discussed in Ref. 4.

(Received November 5, 1985)