Notes

Facile, One-Step Conversion of Cyclic Ketals to 2-Cyclohexen-1-one Derivatives

Tae Hee Ha and Jong-Gab Jun*

Department of Chemistry, Hallym University, Chunchon 200-702, Korea

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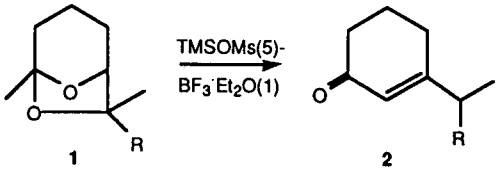
In the course of our study on the 6,8-dioxabicyclo[3.2.1] octane system, we found the facile synthesis of 1,5-diketone,[1] and the mixture of pyridine and cyclohexenone[2] from cyclic ketal in one-step. It was observed that the intermediate 1,5-diketone transformed to other structures depending on reaction conditions. Cyclic enones were easily obtained from diketone *via* aldol condensation, but the yield was not satisfactory in our one-step synthesis of cyclohexenone from 6,8-dioxabicyclo[3.2.1]octane system *via* 1,5-diketone; 9% by using Al/I_2, and 70% by using TMSCl/NaI.

Recently, we reported the trimethylsilyl methanesulfonate (TMSOMs)-boron trifluoride etherate ($BF_3 \cdot Et_2O$) system as a mild and selective Lewis acid catalyst for the synthesis of 2,3,6-trisubstituted pyridine derivatives.[3] Active species for this system is boron difluoride methanesulfonate (BF_2OMs). This catalyst was introduced in the first time for the reductive cleavage of methylated glycans.[4]

In the continuous study on this catalyst, we realized the one-pot synthesis of cyclohexenones from the cyclic ketal compounds. The ketal **1** was heated at reflux with TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.) mixture in methylene chloride for 15 hour to give cyclohexenone **2** as shown in Table 1. The plausible mechanism of this novel transformation is shown in Scheme 1. 1,5-Diketone **3** was formed through oxonium and epoxide followed by 1,2-hydride shift, and this mechanism was proved by deuterium exchange experiment.[5] The following aldol condensation of 1,5-diketone yielded the cyclohexenone in one flask. The formation of 1,5-diketone **3** as an intermediate in this reaction was confirmed by isolation of it by running the reaction at room temperature or by heating at reflux for short period of time.

Table 1. One-Step Synthesis of 2-Cyclohexen-1-one Derivative from Heterocyclic Ketal Compound



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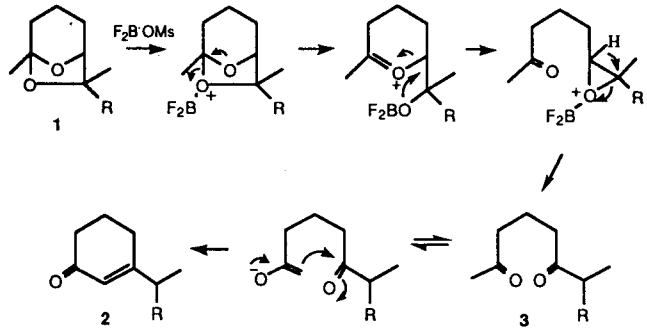
Entry	R	Yield (%)
a	Me	80
b	Et	90
c	n-Pr	88
d	i-Pr	83
e	Ph	72



Scheme 1.

The advantage of this methodology is the easy introduction of substituent, especially at α′-position of cyclohexenone.[6] Experiments are currently underway in an attempt to introduce substituent at α′-position of cyclohexenone.

Experimental

Typical Procedure. Cyclic ketal **1** (1.18 mmole) was added to distilled methylene chloride (8 mL), pre-dried with CaH_2, in 25 mL 2-neck round bottom flask. To this reaction mixture, TMSOMs (5 equiv.)-$BF_3 \cdot Et_2O$ (1 equiv.) mixture was added by syringe and heated at reflux for 15 hrs. The reaction was quenched with aqueous NaOH (5%) solution and extracted with ether. Organic layer was dried, concentrated and the residue was chromatographed (Hexane ; ether=7 : 3) to give pure liquid product.

3-Isopropyl-2-cyclohexen-1-one (2a). ^1H NMR (200 MHz, $CDCl_3$) δ 5.84 (1H, d, J=1.2 Hz), 2.45-2.23 (5H, m), 1.93 (2H, quint, J=6.4 Hz), 1.06 (6H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 200.3 (s), 171.8 (s), 123.5 (d), 37.5 (t), 35.7 (d), 27.7 (t), 22.9 (t), 20.5 (q, 2 x CH_3); IR (neat) 1669, 1621 cm^{-1}.

3-(1-Methylpropyl)-2-cyclohexen-1-one (2b). ^1H NMR (200 MHz, $CDCl_3$) δ 5.83 (1H, br s), 2.34 (2H, t, J=6.6 Hz), 2.26-2.08 (3H, m), 1.94 (2H, quint, J=6.2 Hz), 1.41 (2H, m), 1.05 (3H, d, J=6.8 Hz), 0.82 (3H, t, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 200.2 (s), 170.8 (s), 125.1 (d), 43.2 (d), 37.6 (t), 27.5 (t), 26.9 (t), 22.9 (t), 18.4 (q), 11.8 (q); IR (neat) 1671, 1622 cm^{-1}.

3-(1-Methylbutyl)-2-cyclohexen-1-one (2c). ^1H NMR (200 MHz, $CDCl_3$) δ 5.82 (1H, br s), 2.32 (2H, t, J=6.6 Hz), 2.27-2.19 (3H, m), 1.92 (2H, quint, J=6.2 Hz), 1.48-1.22 (4H, m), 1.03 (3H, d, J=6.6 Hz), 0.81 (3H, t, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 200.2 (s), 171.1 (s), 125.0 (d), 41.3 (d), 37.6 (t), 36.9 (t), 26.9 (t), 22.9 (t), 20.5 (t), 18.8 (q), 14.0 (q); IR (neat) 1670, 1621 cm^{-1}.

3-(1,2-Dimethylpropyl)-2-cyclohexen-1-one (2d). ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (1H, br s), 2.32 (2H, t, J=6.5 Hz), 2.21 (2H, t, J=5.6 Hz), 1.92 (3H, m), 1.65 (1H, m), 1.01 (3H, d, J=6.9 Hz), 0.85 (3H, d, J=6.6 Hz), 0.81 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 200.1 (s), 170.1 (s), 125.7 (d), 48.8 (d), 37.7 (t), 31.0 (d), 27.3 (t), 22.9 (t), 21.6 (q), 19.5

(q), 15.9 (q); IR (neat) 1671, 1620 cm^{-1}.

3-(1-Phenylethyl)-2-cyclohexen-1-one (2e). ^1H NMR (200 MHz, $CDCl_3$) δ 7.33-7.13 (5H, m), 6.04 (1H, d, J=1.3 Hz), 3.54 (1H, q, J=7.0 Hz), 2.34 (2H, t, J=6.7 Hz), 2.13 (2H, t, J=6.0 Hz), 1.90 (2H, quint, J=6.3 Hz), 1.42 (3H, d, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 200.2 (s), 168.7 (s), 142.8 (s), 128.7 (d, 2 x C), 126.9 (d, 2 x C), 125.0 (d), 46.9(d), 37.6 (t), 28.5 (t), 22.9 (t), 19.1 (q); IR (neat) 1669, 1623 cm^{-1}.

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A New Method for β-Lactam Formation Form β-Amino Acids Using N,N-[diethoxyphosphinyl] benzo-1,2,5-thiadiazolidine 1,1-dioxide

Young Haeng Lee*, Chai-ho Lee, and Won Sik Choi**

**Department of Chemistry, Wonkwang University, Iksan 570-749, Korea*
***Department of Life Science, Soon Chun Hyang University, Asan 330-602, Korea*

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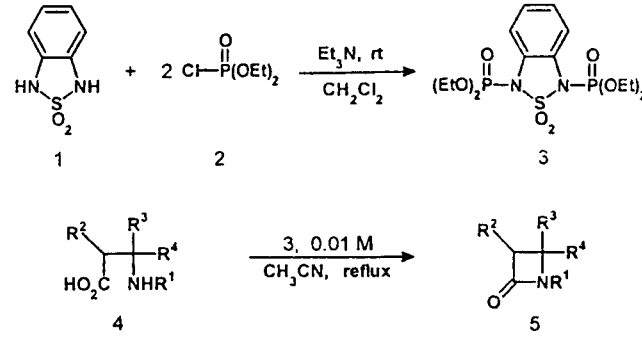
One of the most common synthetic methods the formation of β-lactams is based on the intramolecular condensation of β-amino acids in presence of suitable condensing reagents.[1] Recently, new oraganophosphate type condensing reagents have been introduced[2] for the construction of β-lactams, esters, thioesters, and peptides. The five and six-membered heterocycles such as imidazole, triazole, 2-oxazolone, and 2-thiazolidinethione play an important role in activating the carboxyl group for condensation as the bifunctional leaving moieties.[3]

In connection with our ongoing research program directed toward the development of new synthetic methodologies for the formation of β-lactam derivatives from β-amino acids and based on the excellent leaving ability of benzo-1,2,5-thiadiazolidine 1,1-dioxide skeletons, we have examined the β-lactams (**5**) formation from β-amino acids (**4**) using N,N-[diethoxyphosphinyl]benzo-1,2,5-thiadiazolidine 1,1-dioxide (**3**). Bisdiethyl phosphonate reagent (**3**) can be prepared by the reaction of benzo-1,2,5-thiadiazolidine 1,1-dioxide (**1**) with two equivalent of diethyl chlorophosphate (**2**), and triethylamine in dichloromethane at room temperature for 3 h. Reagent **3** was obtained as a reddish crystal in essentially quantitative yield (90-92%) and was generally used without further purification.



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The solvent and concentration effects were briefly studied using 3-benzylaminobutanoic acid as a model compound with 1.2 equivalent of reagent **3** and triethylamine at room temperature or at refluxing condition. Among the solvents tested, acetonitrile gave the best results, even though dichloromethane and tetrahydrofuran were also effective, under high dilution (0.01 M) and refluxing condition.

Some experimental results are summarized in Table 1 to illustrate the efficiency of reagent. β-Amino acids were cleanly cyclized into the corresponding β-lactams in high yield whether the amino group is secondary or primary. In conclusion, this report describes the preparation of bisdiethyl phos-

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

R^1	R^2	R^3	R^4	Yield (%)[a]
$PhCH_2$	H	CH_3	H	88
$PhCH_2$	H	CH_3	CH_3	90
$PhCH_2$	H	CH_2CH_3	H	80
$PhCH_2$	CH_3	H	H	87
$C_6H_3(OCH_3)_2CH_2$[b]	H	CH_3	H	85
$C_6H_3(OCH_3)_2CH_2$[b]	CH_3	H	H	81
H	H	Ph	H	80
H	H	CH_3	H	75

[a] Isolated yields by column chromatography. [b] 3,4-Dimethoxybenzyl