Stereoselective Synthesis of *trans*-3,4-Dihydropyran-2-ones by Phenoxide ion-catalyzed Tandem Michael Addition and Lactonization

Takashi Tozawa,[†,††] Yoshinobu Yamane,[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

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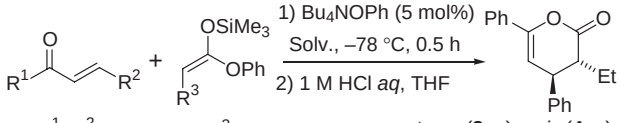
Phenoxide ion-catalyzed tandem Michael addition and lactonization between α,β-unsaturated ketones and silyl enolates derived from phenyl carboxylates proceeded smoothly to afford the corresponding 3,4-dihydropyran-2-ones in high yields with good to excellent trans-selectivities.

An intramolecular cyclization via Michael addition is one of the most synthetically efficient and powerful strategies in constructing 3,4-dihydropyran-2-one skeleton.[1] For example, Katritzky et al. reported that the reactions between the lithium enolates of *N*-acylbenzotriazoles and α,β-unsaturated ketones afforded previously unknown 3,4-dihydropyran-2-one derivatives in good yields.[1c] However, the scope of this method for the preparation of substituted 3,4-dihydropyran-2-ones was essentially limited to the derivatives with non-α-branched alkyl substituents at 3-position. Recently, it was reported from our laboratory that a convenient one-pot preparation of 3,4-dihydropyran-2-ones by Michael addition of silyl enolate derived from phenyl isobutyrate to various α,β-unsaturated ketones and sequential lactonization was accomplished in the presence of a Lewis base catalyst such as tetrabutylammonium phenoxide in THF at $-78\,^{\circ}C$.[2] In this reaction, the phenoxy group on the silyl enolate behaves as an effective leaving group to facilitate intramolecular cyclization of in situ formed Michael-adduct, and the liberated phenoxide ion serves also as a Lewis base catalyst to activate silyl enolate. In order to extend the synthetic utility of the phenoxide ion-catalyzed tandem Michael addition and lactonization, diastereoselective synthesis of 3,4-dihydropyran-2-ones using various silyl enolates derived from phenyl carboxylates was studied. In this communication, we would like to report on trans-selective synthesis of 3,4-dihydropyran-2-ones by phenoxide ion-catalyzed tandem Michael addition and lactonization between various silyl enolates derived from phenyl carboxylates and α,β-unsaturated ketones.

In the first place, reaction of chalcone **1a** and (*E*)-trimethylsilyl (TMS) enolate **2a** (R^3 = Et) was tried in THF at $-78\,^{\circ}C$ by using 5 mol % of tetrabutylammonium phenoxide under the conditions reported in our previous report.[2] A diastereomeric mixture of 3,4-dihydropyran-2-ones, **3aa** and **4aa**, was obtained in 96% yield with the predominant formation of trans-isomer **3aa** (the ratio of 88:12).[3] Next, effects of other solvents were examined (Table 1). When the reaction was carried out in Et_2O, high diastereoselectivity was attained although the yield of the de-

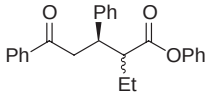
Table 1. Effects of solvents[a]



1a: R^1, R^2 = Ph **2a**: R^3 = Et (1.6 equiv.) *trans* (**3aa**) + *cis* (**4aa**)

Entry	Solv.	Yield[b]/%	*trans* (**3aa**):*cis* (**4aa**)[c]
1	THF	96	88:12
2	Et_2O	69[d]	93:7
3	DMF	66[e,f]	60:40
4	CH_2Cl_2	19[g]	68:32
5	toluene	98	92:8

[a]Reactions were carried out according to the typical procedure (Ref. 2). [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Michael-adduct **5** was afforded as a by-product (18% yield). [e]The reaction was carried out at $-50\,^{\circ}C$. [f]Compound **6** was afforded as a by-product (20% yield). [g]Compound **6** was afforded as a by-product (75% yield).



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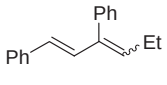

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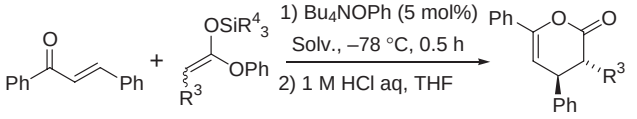
In the first place, reaction of chalcone **1a** and (*E*)-trimethylsilyl (TMS) enolate **2a** (R^3 = Et) was tried in THF at $-78\,^{\circ}C$ by using 5 mol % of tetrabutylammonium phenoxide under the conditions reported in our previous report.[2] A diastereomeric mixture of 3,4-dihydropyran-2-ones, **3aa** and **4aa**, was obtained in 96% yield with the predominant formation of trans-isomer **3aa** (the ratio of 88:12).[3] Next, effects of other solvents were examined (Table 1). When the reaction was carried out in Et_2O, high diastereoselectivity was attained although the yield of the de-

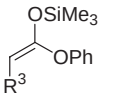
Table 2. Phenoxide ion-catalyzed tandem Michael addition and lactonization using various silyl enolates[a]



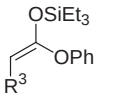
1a **2** (1.6 equiv.) *trans* (**3**) + *cis* (**4**)

Entry	Enolate[b]	Solv.	Yield[c]/% (*trans*:*cis*)[d]
1	**2b**: R^3 = Me, R^4 = Me	THF	78 (**3ab**:**4ab** = 90:10)
2	**2c**: R^3 = *i*-Pr, R^4 = Me	THF	96 (**3ac**:**4ac** = 71:29)
3	**2d**: R^3 = *t*-Bu, R^4 = Me	THF	90 (**3ad**:**4ad** = >95:5)
4	**2b**: R^3 = Me, R^4 = Me	toluene	82 (**3ab**:**4ab** = 90:10)
5	**2c**: R^3 = *i*-Pr, R^4 = Me	toluene	99 (**3ac**:**4ac** = 71:29)
6	**2e**: R^3 = Et, R^4 = Et	THF	93[e] (**3ae**:**4ae** = 93:7)
7	**2f**: R^3 = *i*-Pr, R^4 = Et	THF	86[e] (**3af**:**4af** = 82:18)
8	**2g**: R^3 = Et, R^4 = Et	THF	47[e] (**3ag**:**4ag** = 47:53)

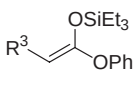
[a]Reactions were carried out according to the typical procedure (Ref. 2). [b]Structures are shown below. cIsolated yield. [d]Determined by ^{1}H NMR analysis. [e]2 equivalents of enolate were used.



2a: R^3 = Et **2c**: R^3 = *i*-Pr
2b: R^3 = Me **2d**: R^3 = *t*-Bu
(*E*:*Z* = >95:5)



2e: R^3 = Et (*E*:*Z* = 90:10)
2f: R^3 = *i*-Pr (*E*:*Z* = >95:5)



2g: R^3 = Et (*E*:*Z* = 7:93)

sired product decreased because of the formation of the non-cyclized product, Michael-adduct **5** (Entry 2). In the case when DMF or CH_2Cl_2 was used, on the other hand, the side reaction of forming conjugated 1,3-diene **6** proceeded via an undesired 1,2-addition pathway, and the yields lowered significantly (Entries 3 and 4).[1c] Among the solvents examined, toluene gave the best result (Entry 5). These results showed that both yield and selectivity of this tandem reaction were influenced considerably by the solvent, and toluene was found to be effective just as well as THF.

Next, phenoxide ion-catalyzed tandem Michael addition and lactonization was studied by using various silyl enolates derived from phenyl carboxylates in THF or toluene (Table 2). It was found then that the reaction of chalcone **1a** and (*E*)-TMS enolates **2** having various alkyl substituents at R^3 position afforded trans-isomers predominantly (Entries 1–5). It was remarkable to note that trans-isomer **3ad** was obtained almost exclusively when sterically hindered (*E*)-TMS enolate **2d** ($R^3 = t$-Bu) was used (Entry 3). In addition, the similar predominant formation of trans-isomers was observed when (*E*)-triethylsilyl (TES) enolates were employed in place of the above (*E*)-TMS enolates (Entries 6 and 7). On the other hand, the use of (*Z*)-TES enolate **2g** led to a considerable decrease in the yield and also in its selectivity (Entry 8).

Then, reactions of (*E*)-TMS enolates, **2a** and **2b**, with various α,β-unsaturated ketones were further tried by using 5 mol% of tetrabutylammonium phenoxide in toluene at $-78\,^{\circ}C$ (Table 3). In most cases, the reactions proceeded smoothly to provide the desired 3,4-dihydropyran-2-ones in high yields with good to excellent trans-selectivities (Entries 1–9). It was found that substituents at R^1 or R^2 positions of α,β-unsaturated ketones played an important role on controlling the stereoselectivity of this reaction, and the trans-selectivities became higher when their bulkness, particularly that of R^1, increased. The detailed stereochemical trends and transition states are now under investigation.

The relative configuration at newly created stereocenters of diastereomers was clearly identified by X-ray crystallographic analysis of major trans-isomer **3ba** (Figure 1).[4,5]

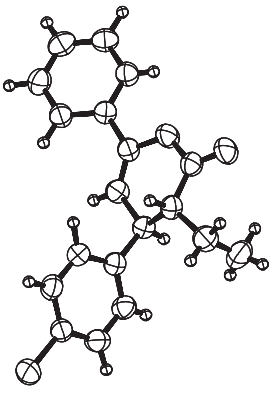


Figure 1. ORTEP drawing of compound **3ba**.

Thus, a direct and trans-selective synthesis of 3,4-dihydropyran-2-ones via phenoxide ion-catalyzed Michael addition of various silyl enolates derived from phenyl carboxylates to α,β-unsaturated ketones and successive lactonization was established. Further study on this type of tandem reaction is now in progress.

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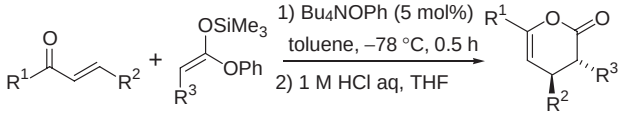
Table 3. Phenoxide ion-catalyzed tandem Michael addition and lactonization using various α,β-unsaturated ketones[a]



1 **2a or 2b** (1.6 equiv.) *trans* (**3**) + *cis* (**4**)

Entry	Enone	Enolate	Yield[b]/% (*trans*:*cis*)[c]
1	**1b**: R^1 = Ph, R^2 = 4-ClC_6H_4	**2a** (R^3 = Et)	81 (**3ba**:**4ba** = 92:8)
2	**1c**: R^1 = Ph, R^2 = 4-$MeOC_6H_4$		97 (**3ca**:**4ca** = >95:5)
3	**1d**: R^1 = Ph, R^2 = Me		89 (**3da**:**4da** = 71:29)
4	**1e**: R^1 = mes[d], R^2 = Me		97 (**3ea**:**4ea** = >95:5)
5	**1f**: R^1 = *i*-Pr, R^2 = Ph		75 (**3fa**:**4fa** = >95:5)
6	**1g**: R^1 = *t*-Bu, R^2 = Ph		85 (**3ga**:**4ga** = >95:5)
7	**1d**: R^1 = Ph, R^2 = Me	**2b** (R^3 = Me)	82 (**3db**:**4db** = 72:28)
8	**1e**: R^1 = mes[d], R^2 = Me		85 (**3eb**:**4eb** = 91:9)
9	**1g**: R^1 = *t*-Bu, R^2 = Ph		83 (**3gb**:**4gb** = >95:5)

[a]Reactions were carried out according to the typical procedure (Ref. 2). [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]2,4,6-Trimethylphenyl.

References and Notes

1 a) D. A. Oare and C. H. Heathcock, *J. Org. Chem.*, **55**, 157 (1990). b) S. Kobayashi and M. Moriwaki, *Synlett*, **1997**, 551. c) A. R. Katritzky and O. V. Denisko, *J. Org. Chem.*, **67**, 3104 (2002).

2 T. Tozawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 1454 (2004).

3 Structural assignment of diastereomeric 3,4-dihydropyran-2-ones was based on the ^{1}H NMR chemical shift of the characteristic vinyl proton, which resonates at a lower magnetic field in the cis-isomer than in the trans-isomer (See Ref. 1a, 4, and 5).

4 trans-Isomer **3ba** was recrystallized from EtOAc/hexane. Crystal data: $C_{19}H_{17}ClO_2$ ($M_r = 312.80$), monoclinic, $P2_1/a$, $a = 11.332(1)$, $b = 15.528(2)$, $c = 9.1979(9)$ Å, $\beta = 95.404(8)^{\circ}$, $V = 1611.2(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.289$ g cm^{-3}, $T = 298$ K. X-ray intensities were measured on a Rigaku AFC7R diffractometer with Cu Kα radiation ($\lambda = 1.54178$ Å), $R = 0.048$.

5 trans-Isomer **3ba**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.5$ Hz, 3H), 1.62–1.82 (m, 2H), 2.69 (dd, $J = 12.6$, 6.9 Hz, 1H), 3.70 (dd, $J = 6.9$, 4.5 Hz, 1H), 5.80 (d, $J = 4.5$ Hz, 1H), 7.17 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.34–7.43 (m, 3H), 7.64–7.68 (m, 2H). The signal for the vinyl proton of minor cis-isomer **4ba** appears at 6.02 ppm (d, $J = 6.6$ Hz). However, according to the report by Katritzky et al., the compound **3ba** was assigned to be cis (See Ref. 1c). On the basis of X-ray crystallographic analysis, their assignment about the relative configuration should be revised.

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