# An Efficient Synthesis of 3,4-Dihydropyran-2-one Derivatives by Lewis Base-catalyzed Tandem Michael Addition and Lactonization

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

(Received August 10, 2004; CL-040943)

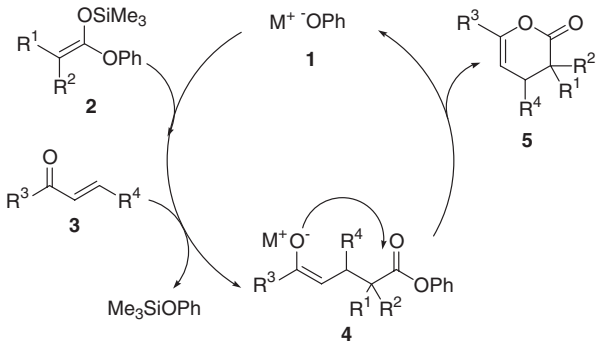
A convenient one-pot preparation of 3,4-dihydropyran-2-one derivatives by Michael addition of silyl enolate derived from phenyl ester with $\alpha,\beta$-unsaturated ketones in the presence of a Lewis base catalyst such as tetrabutylammonium phenoxide was developed. In this catalytic cycle, 3,4-dihydropyran-2-ones were produced in good to excellent yields via intramolecular cyclization of in situ formed Michael-adducts.

3,4-Dihydropyran-2-ones are widely used as useful synthetic intermediates for the preparation of 2-pyranones,[1] $\gamma$-lactones,[2] cyclic enamines,[3] and so on. In spite of the approaches developed for the synthesis of 3,4-dihydropyran-2-ones, effective ones are not many. Among the few, an intramolecular cyclization via Michael addition has often been considered as one of the most synthetically efficient and powerful strategies because it allows a wide variety of 3,4-dihydropyran-2-one derivatives to be prepared by one-pot procedure.[4] For example, nucleophilic Michael additions of metalated enolates such as lithium enolate of ester,[5] silyl enolates derived from thioesters,[4a] and lithium enolates of *N*-acylbenzotriazoles[4b] to $\alpha,\beta$-unsaturated ketones afforded 3,4-dihydropyran-2-ones.

Recently, several Lewis base-catalyzed Michael reactions between silyl enolates and $\alpha,\beta$-unsaturated carbonyl compounds were introduced from our laboratory.[6] They are useful methods for the synthesis of various 1,5-dicarbonyl compounds since they proceed smoothly by using readily available Lewis base catalysts such as lithium benzamide,[6a] lithium succinimide,[6a] and lithium acetate.[6b] In order to demonstrate the usefulness of these Lewis base-catalyzed reactions further, the application of the Michael addition to the synthesis of 3,4-dihydropyran-2-one derivatives was planned.

In this communication, a convenient one-pot preparation of 3,4-dihydropyran-2-one derivatives by tandem Michael addition and lactonization between silyl enolate derived from phenyl ester and $\alpha,\beta$-unsaturated ketones in the presence of a Lewis base catalyst such as tetrabutylammonium phenoxide is described.

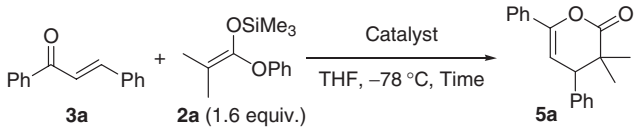
A proposed catalytic cycle for the Lewis base-catalyzed Michael addition and sequential lactonization is illustrated in Scheme 1: namely, trimethylsilyl (TMS) enolates **2**, activated by a nucleophilic attack of the phenoxide ion on the silicon atom, react with the $\alpha,\beta$-unsaturated ketones **3** in the presence of a Lewis base catalyst such as metal or ammonium phenoxide **1** to form enolate intermediates **4** and TMS ether of phenol. The in situ formed enolate intermediates **4** attack intramolecularly the ester carbonyl group to form the corresponding 3,4-dihydropyran-2-ones **5** along with elimination of phenoxide ion. The TMS enolate derived from phenyl ester was chosen as a starting material since it was considered that the phenoxy group would work as a suitable leaving group to facilitate the intramolecular cyclization of in situ formed enolate intermediates **4** and behave, at the same time, as active species **1** via regeneration in the above catalytic cycle.




**Scheme 1.**

In the first place, reaction of chalcone **3a** and TMS enolate **2a** was tried, and various catalysts were screened (Table 1). In the case when a catalytic amount of potassium or tetrabutylammonium phenoxide was used, the reactions completed immediately at $-78\,^{\circ}C$ in THF and afforded the corresponding 3,4-dihydropyran-2-one **5a** in excellent yields even when 1 mol % of tetrabutylammonium phenoxide was used (Entries 3–6). On the other hand, the lithium phenoxide-catalyzed reaction resulted in low conversion (Entry 1). In addition, the reactions were initiated similarly by potassium *tert*-butoxide or tetrabutylammonium fluoride (TBAF) (Entries 7 and 8). These results indicated that the yields of the above reaction were dependent on the nature of the counter cations, and tetrabutylammonium was found

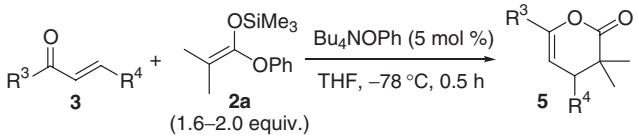
**Table 1.** Effect of a variety of catalysts




| Entry | Catalyst/mol % | Time/h | Yield[a]/% |
|---|---|---|---|
| 1 | LiOPh (10) | 5 | <20 |
| 2 | NaOPh (10) | 3 | 91 |
| 3 | KOPh (10) | 0.5 | 92 |
| 4 | $Bu_4NOPh$ (10) | 0.5 | 98 |
| 5 | $Bu_4NOPh$ (5) | 0.5 | 99 |
| 6 | $Bu_4NOPh$ (1) | 0.5 | 91 |
| 7 | KO*t*-Bu (10) | 0.5 | 92 |
| 8 | TBAF (10) | 0.5 | 98 |

[a]Isolated yield.

**Table 2.** Synthesis of various 3,4-dihydropyran-2-ones




| Entry | $R^3$ | $R^4$ | Yield[a]/% |
|---|---|---|---|
| 1 | Ph | Ph | 99 |
| 2 | Ph | 4-$ClC_6H_4$ | 99 |
| 3 | Ph | 4-$MeOC_6H_4$ | 92 |
| 4 | Ph | 4-$Me_2NC_6H_4$ | 72 |
| 5 | Ph | 1-Naphthyl | 70 |
| 6 | Ph | Me | 89 |
| 7 | Ph | *i*-Pr | 87 |
| 8 | Ph | PhCO | 71 |
| 9 | 4-$ClC_6H_4$ | Ph | 85 |
| 10 | 4-$MeOC_6H_4$ | Ph | 98 |
| 11 | 4-$Me_2NC_6H_4$ | Ph | 84 |
| 12 | *i*-Pr | Ph | 78 |
| 13 | *i*-Bu | Ph | 52 |
| 14 | *t*-Bu | Ph | 80 |
| 15 | PhCH=CH | Ph | 77 |

[a]Isolated yield.

to be particularly effective.

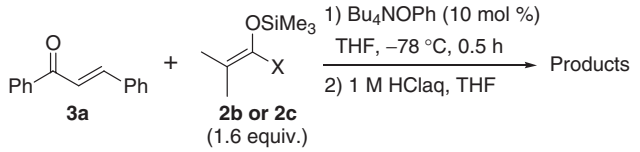
Next, the reactions of TMS enolate **2a** with various $\alpha,\beta$-unsaturated ketones by using 5 mol % of tetrabutylammonium phenoxide were tried at −78 °C in THF (Table 2).[7] In most cases, the reactions proceeded smoothly to provide the desired 3,4-dihydropyran-2-ones in good to excellent yields. It was found that various types of $\alpha,\beta$-unsaturated ketones having alkyl or aryl substituents at the $R^3$ or $R^4$ positions could successfully be employed in this procedure.

Then, the influence of other TMS enolates that are derived from methyl ester or thioester on this Michael addition and sequential lactonization process was investigated (Table 3). When the reaction of TMS enolate derived from methyl isobutyrate **2b** with chalcone was carried out by using 10 mol % of tetrabutylammonium phenoxide, the cyclized product was not detected at all although the Michael-adduct **6** was obtained in 85% yield together with 1,2-addition product, silyl ether **7**, in 15% yield (Entry 1). On the other hand, a similar reaction of TMS enolate derived from *S-tert*-butyl thioisobutyrate **2c** proceeded to afford the 3,4-dihydropyran-2-one **5a** in moderate yield with undesired formation of a conjugate adduct of thiolate **8** (Entry 2). These results showed that the TMS enolate derived from phenyl ester worked effectively for this catalytic tandem reaction.

Thus, an efficient method for the synthesis of 3,4-dihydropyran-2-one derivatives via phenoxide-catalyzed tandem Michael addition and lactonization between silyl enolate derived from phenyl ester and $\alpha,\beta$-unsaturated ketones was developed. The present reaction presents new possibility in the field of Lewis base-catalyzed reactions and, in addition, catalytic tandem addition–cyclization procedures. Further investigation on this reaction is now in progress.

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

**Table 3.** Reactions of TMS enolate **2b** or **2c** with chalcone **3a** in the presence of tetrabutylammonium phenoxide




| Entry | X | Products (Yield[a]/%) |
|---|---|---|
| 1 | OMe (**2b**) | **6** (85) + **7** (15) |
| 2 | S*t*-Bu (**2c**) | **5a** (59) + **8** (39) |

[a]Isolated yield.

## References and Notes

1 a) D. Rosenthal, P. Grabowich, E. F. Sabo, and J. Fried, *J. Am. Chem. Soc.*, **85**, 3971 (1963). b) T. Kume, H. Iwasaki, Y. Yamamoto, and K. Akiba, *Tetrahedron Lett.*, **29**, 3825 (1988).
2 A. K. Mandal and D. G. Jawalkar, *J. Org. Chem.*, **54**, 2364 (1989).
3 S. H. Thang and D. J. Rigg, *Synth. Commun.*, **23**, 2355 (1993).
4 a) S. Kobayashi and M. Moriwaki, *Synlett*, **1997**, 551. b) A. R. Katritzky and O. V. Denisko, *J. Org. Chem.*, **67**, 3104 (2002).
5 D. A. Oare and C. H. Heathcock, *J. Org. Chem.*, **55**, 157 (1990).
6 a) T. Mukaiyama, T. Nakagawa, and H. Fujisawa, *Chem. Lett.*, **32**, 56 (2003). b) T. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Chem. Lett.*, **33**, 1016 (2004).
7 Typical experimental procedure is as follows (Table 2, Entry 1): a) Preparation of a THF solution of tetrabutylammonium phenoxide;[8] To phenol (198 mg, 2.1 mmol) was added tetrabutylammonium hydroxide in methanol (37 wt %, 1.40 g, 2.0 mmol). After the mixture was stirred for 0.5 h, the solvent was removed under reduced pressure. The residue was azeotroped with toluene (2 mL × 3), and then dissolved in THF (20 mL) to give a 0.1 M solution of tetrabutylammonium phenoxide. b) General procedure for the preparation of 3,4-dihydropyran-2-ones from TMS enolate **2a** and $\alpha,\beta$-unsaturated ketones; To a THF solution of tetrabutylammonium phenoxide (0.15 mL, 0.015 mmol) was added a solution of chalcone (62.5 mg, 0.3 mmol) in THF (1.2 mL) and a solution of TMS enolate **2a** (113 mg, 0.48 mmol) in THF (0.65 mL) at −78 °C. After the mixture was stirred for 0.5 h at the same temperature, it was quenched with 1 M HCl aq and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated. The crude product was purified by preparative TLC to give the corresponding 3,4-dihydropyran-2-one (83.0 mg, 99%).
8 a) I. B. Dicker, G. M. Cohen, W. B. Farnham, W. R. Hertler, E. D. Laganis, and D. Y. Sogah, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, **28**, 106 (1987). b) M. A. Rahim, Y. Matsui, T. Matsuyama, and Y. Kosugi, *Bull. Chem. Soc. Jpn.*, **76**, 2191 (2003).

Published on the web (Advance View) October 9, 2004; DOI 10.1246/cl.2004.1454