

New Access to Carbonyl Ylides by the Silicon-Based 1,3-Elimination and their [3 + 2] Cycloadditions to Activated Alkenes and Alkynes: One-step Synthesis of Dihydrofurans and Tetrahydrofurans¹

Makoto Hojo, Masakazu Ohkuma, Naruyasu Ishibashi, and Akira Hosomi*

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

Key Words: carbonyl ylide; chloromethyl trimethylsilyl(α -aryl)methyl ether; 1,3-elimination; [3 + 2] cycloaddition; dihydrofuran; tetrahydrofuran

Abstract: Simple aryl-substituted carbonyl ylides are generated by the silicon-based 1,3-elimination of chloromethyl trimethylsilyl(α -aryl)methyl ethers promoted by fluoride ion under mild and neutral conditions which provide an one-step synthesis of dihydrofurans and tetrahydrofurans via [3 + 2] cycloadditions to activated multiple π -bonds such as α,β -unsaturated alkenes and alkynes.

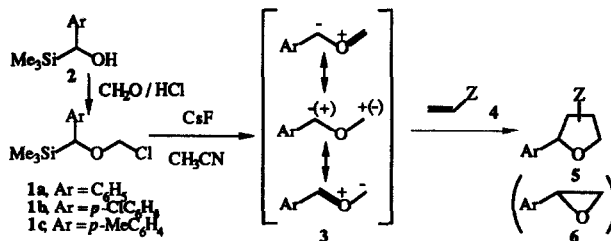
1,3-Dipolar reagents are important and interesting chemical species from both synthetic and theoretical points of view.² Among them, we have already reported that nonstabilized 1,3-dipoles such as azomethine ylides and thiocarbonyl ylides have been prepared by the silicon-based 1,3-elimination under mild and neutral conditions, however, granted, not for carbonyl ylides.³ Especially the practical efficient methods for the generation of carbonyl ylides and their applications to synthesis of tetrahydrofurans and related furans have remained still unexplored, due to extremely reactive transient species that have been generated by thermal or photochemical ring-cleavage of oxiranes and oxadiazolidines and carbene additions to carbonyls.⁴ Recently Padwa and his co-workers made considerable progress in the generation and synthetic use of stabilized carbonyl ylides by the rhodium (II)-catalyzed reaction of α -diazo ketones with carbonyl compounds,⁵ however, the results have so far been restricted to stabilized α -keto carbonyl ylides and the efficient methods for the generation of carbonyl ylides are still unsuccessful. To overcome these limitations, for convenience sake, Linderman and his co-workers have recently described the stepwise synthesis of tetrahydrofurans using both nucleophilic and electrophilic carbonyl ylide synthons, but not carbonyl ylides themselves.⁶ In view of the above background, we report herein the novel findings that simple carbonyl ylides are indeed expediently generated by the silicon-based 1,3-elimination under mild and neutral conditions which provide a powerful one-step synthesis of dihydrofurans and tetrahydrofurans⁷ via [3 + 2] cycloadditions to multiple π -bonds (Scheme I).

The starting chloromethyl trimethylsilyl(α -aryl)methyl ethers **1** were readily prepared by the reaction of trimethylsilyl(α -aryl)methanols **2**⁸ with formaldehyde in water by passing through hydrochloric acid at 0 °C in reasonable yields.⁹

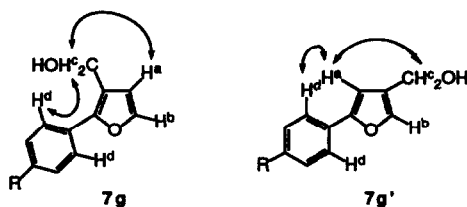
Table I summarized the results of the [3 + 2] cycloaddition of carbonyl ylides **3** generated from the ethers **1** induced by cesium fluoride to activated alkenes and alkynes **4**.^{10,11} As a general procedure, a solution of a dipolarophile **4** (2 mmoles), an ether **1** (1 mmol), and cesium fluoride (1.2 mmol) was stirred in dry acetonitrile (5 ml) at room temperature for 7.5 h under a nitrogen atmosphere. Saturated NaHCO₃ and ether were added,

and then the organic layer was separated and dried over Na_2SO_4 . Evaporation of the solvent yielded a crude product which was purified by column chromatography on silica gel.

Scheme 1



Among the promoters examined, cesium fluoride exhibited the excellent activity to afford the adduct **5** in good yield. For example, the ether **1a** reacts smoothly with dimethyl acetylenedicarboxylate (**4a**) in the presence of cesium fluoride (dried under vacuum at 90–110 °C for 2 h) in acetonitrile to give exclusively 3,4-bis(methoxycarbonyl)-2-phenyl-2,5-dihydrofuran (**5a**) in 65% yield (entry 1). With methyl propiolate (**5b**), a regioisomeric mixture of 3- and 4-methoxycarbonyl-2-phenyl-2,5-dihydrofurans (**5b**) (76:24) was obtained in 79% yield (entry 2). To ascertain the regiochemistry of the CsF -promoted cycloaddition products, the isolated adducts **5b** and **5b'** were converted to the corresponding hydroxymethyl-substituted furan derivatives **7g** and **7g'**, respectively, by oxidation with *N*-bromosuccinimide (NBS) followed by reduction with lithium aluminum hydride. The NOE between ortho-proton (H^d) and hydroxymethylene protons (H^c), furan ring proton (H^a) in **7g** and **7g'** was observed by the ^1H NMR spectroscopy. The ratio of regioisomers was determined by the peak of benzylic protons.



Reaction of **1a** with dimethyl fumarate (**4c**) and dimethyl maleate (**4d**) gave selectively the corresponding stereoisomeric mixture¹² of 3,4-*trans*- and 3,4-*cis*-methoxycarbonyl-2-phenyltetrahydrofurans (**5e**) and (**5f**), respectively, with retention of the stereochemistry in a stereo-controlled mode. Likewise all alkenes **4** having electron-withdrawing group(s) examined undergo cycloaddition very efficiently.¹³

Precursors **1b** and **1c** of other aryl-substituted carbonyl ylides (*p*-Cl and *p*-Me) are all suitable reagents for this [3 + 2] cycloaddition toward activated π -bonds such as methyl propiolate, and good yields of furan derivatives **5** can be obtained (entries 3 and 4). It is worth to note that the reactivities of **1b** and **1c** toward methyl propiolate and the regioselectivity in this cycloaddition are almost similar to those of unsubstituted **1a**.

In summary, this work describes a short and efficient generation of aryl-substituted carbonyl ylides, which has been achieved by the novel 1,3-elimination of chloromethyl silylmethyl ethers,¹³ and thus provides a straightforward and stereospecific access to dihydro- and tetrahydrofurans which were often found in useful biologically active materials. The ethers **1** can be viewed as synthetic reagents to carbonyl ylides **3**, storable and easy to handle. The usefulness of the present reaction was mostly displayed by a simple way to access to carbonyl ylides and their one-pot cycloaddition to dipolarophiles, as well as ready accessibility of the starting materials and simple manipulation of the conversion under mild and neutral conditions required for the

generation of the ylides. Further related study including the generation of the parent carbonyl ylide¹⁴ is focusing on both details of mechanisms of this [3 + 2] cycloaddition promoted by fluoride ion and further synthetic use of carbonyl ylides generated by the new method.

Table 1. Reaction of Chloromethyl Silylmethyl Ether **1** with Electron-deficient Alkene **4**^a

entry	ether 1	alkene 4	products 5 ^b	%yield ^c
1 ^d	1a (Ar = C ₆ H ₅)	4a	5a	65
2	1a	4b	5b + 5b' (76:24) ^e	79
3	1b (Ar = <i>p</i> -ClC ₆ H ₄)	4b	5c + 5c' (80:20) ^e	85
4	1c (Ar = <i>p</i> -MeC ₆ H ₄)	4b	5d + 5d' (75:25) ^e	76
5 ^f	1a	4c	5e (3,4- <i>trans</i>) (52:48) ^f	81
6 ^h	1a	4d	5f (3,4- <i>cis</i>) (54:46) ^g	92
7	1a	4e	5g + 5g' (52:48) ^g	74
8	1a	4f	5h + 5h' (30:26:25:19) ^{g,h}	65
9 ⁱ	1a	4g	5i + 5i' (47:53) ^g	81
10	1a	4h	5j + 5j' (59:16:14:11) ^{g,h}	43

^a Conditions: **1** (1.0 mmol), **4** (2.0 mmol), CsF (1.2 mmol) in CH₃CN (5 mL) at rt for 7.5 h, unless otherwise noted. For details, see footnote 9 and the supplementary material. ^b A mixture of stereoisomers. ^c Isolated yield by silica gel chromatography. ^d Conditions: **1a** (1.0 mmol), **4a** (4.0 mmol), CsF (2.4 mmol) for 15 h. ^e The ratio of regioisomers determined by NMR. ^f 15.5 h. ^g The ratio of stereoisomers determined by NMR. ^h Conditions: **1a** (1.4 mmol), **4d** (1.0 mmol). ⁱ Conditions: **1a** (1.4 mmol), **4g** (1.0 mmol), CsF (1.5 mmol) for 16 h.

Acknowledgment. Financial support for our work is provided by Grants-in-Aid for Scientific Research and Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan, Sumitomo Chemical Co., Ltd., and the Chemical Materials Research and Development Foundation. We thank Dow Corning Toray Silicone Co. Ltd. and Shin-Etsu Chemical Industries, Co. Ltd., for a gift of organosilicon compounds.

References and Notes

1. Studies on organosilicon chemistry. 119.
2. (a) Kellogg, R. M. *Tetrahedron* **1976**, *32*, 2165. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (c) *1,3-Dipolar Cycloaddition Chemistry, Vol. 1 and 2*; Padwa, A., Ed.: John Wiley & Sons, New York, 1984. (d) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.
3. (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117. (b) Hosomi, A.; Matsuyama, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1073. (c) Hosomi, A.; Miyashiro, Y.; Yoshida, R.; Tominaga, Y.; Yanagi, T.; Hojo, M. *J. Org. Chem.* **1990**, *55*, 5308. (d) Tominaga, Y.; Hojo, M.; Hosomi, A. *J. Syn. Org. Chem., Japan*, **1992**, *50*, 48 and references cited therein.
4. (a) Huisgen, R.; DeMarch, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953. (b) L'Esperance, R. P.; Ford, T. M.; Jones, M. Jr. *J. Am. Chem. Soc.* **1988**, *110*, 209. (c) Padwa, A.; Carter, S. P.; Nimmegern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894.
5. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100 and references cited therein.
6. (a) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438.
7. For a recent review on the synthesis of tetrahydrofurans, see: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
8. Brook, A. G. *J. Am. Chem. Soc.* **1957**, *79*, 4373. The alcohol **2c** was prepared by the Linderman's procedure. Linderman, R. J.; Ghannam, A. F. *J. Am. Chem. Soc.* **1990**, *112*, 2392.
9. Chloromethyl trimethylsilyl(α -aryl)methyl ethers **1** were prepared by the modified method according to the literature: Hill, A. J.; Keach, D. T. *J. Am. Chem. Soc.* **1926**, *48*, 257. **1a**: Yield 63 %; bp 108-110 °C / 0.7mmHg. ¹HNMR (CDCl₃) δ 0.02 (s, 9H), 4.63 (s, 1H), 5.26 (d, $J=5.3$ Hz, 1H), 5.60 (d, $J=5.3$ Hz, 1H), 7.10-7.33 (m, 5H); ¹³CNMR (CDCl₃) δ -4.1 (q, 3C), 76.0 (d), 82.7 (t), 126.3 (d, 2C), 126.5 (d), 128.4 (d, 2C), 139.0(s). **1b**: Yield 42 %; bp 135 °C / 0.55mmHg. ¹HNMR (CDCl₃) δ 0.07 (s, 9H), 4.67 (s, 1H), 5.29 (d, $J=5.3$ Hz, 1H), 5.66 (d, $J=5.3$ Hz, 1H), 7.13(d, $J=7.2$ Hz, 2H), 7.35 (d, $J=7.2$ Hz, 2H); ¹³CNMR (CDCl₃) δ -4.2 (q, 3C), 75.4 (d), 82.4 (t), 125.7 (d, 2C), 128.6 (d, 2C), 132.1(s), 137.7(s). **1c**: Yield 24 %; bp 130 °C / 0.6 mmHg. ¹HNMR (CDCl₃) δ 0.01 (s, 9H), 2.33 (s, 3H), 4.61 (s, 1H), 5.28 (d, $J=5.0$ Hz, 1H), 5.60 (d, $J=5.0$ Hz, 1H), 7.03(d, $J=8.1$ Hz, 2H), 7.13 (d, $J=8.1$ Hz, 2H); ¹³CNMR (CDCl₃) δ -4.0 (q, 3C), 21.0 (q), 75.8 (d), 82.6 (t), 126.4 (d, 2C), 129.1 (d, 2C), 135.7 (s), 136.1 (s).
10. Satisfactory spectral and analytical data were obtained for all new compounds throughout this work.
11. In the absence of alkenes, the existence of styrene oxide (**6**) in the reaction mixture was confirmed in a considerable amount by GC, and NMR and mass spectroscopy.
12. The products were obtained as a mixture of stereoisomers between the substituents of 2 and 3 positions which could not be separated by TLC and LC, and further characterized as a mixture of isomers by the NMR spectroscopy.
13. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience, New York, 1976.
14. Chloromethyl trimethylsilylmethyl ether was similarly prepared, but unfortunately the generation and its cycloaddition to π -bonds of the expected parent carbonyl ylide was unsuccessful under the similar conditions, probably since the Si-C bond cleavage was not sufficiently induced by fluoride ion.

(Received in Japan 7 June 1993)