Communications

A New and Mild System for the Generation of Nonstabilized Carbonyl Ylides: Synthetically Practical Use in Reactions with Electron-Deficient Dipolarophiles

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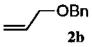
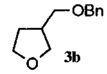
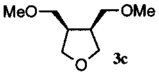
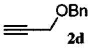
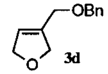
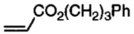
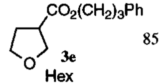
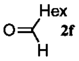
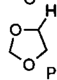
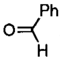
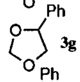
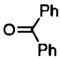
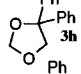
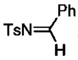
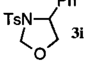
Extensive study has been devoted to the chemistry of carbonyl ylides, and considerable attention has focused on their use for the selective construction of oxygen-containing five-membered heterocycles.[1] We recently found the generation of nonstabilized carbonyl ylides[2] from iodohydrin silyl ethers or bis(chloromethyl) ethers through the 1,3-elimination pathway using samarium diiodide as a reductant.[3] This protocol realized the practical generation of carbonyl ylides bearing only alkyl substituents that react intermolecularly with alkenes and alkynes to afford stereodefined tetrahydrofurans and dihydrofurans, respectively, in high yields. On the other hand, in cycloadditions to electron-deficient dipolarophiles, the yields for cycloadducts were low because of the competitive direct-reduction of these dipolarophiles by the samarium reagent.[4] We report a new system that does not reduce dipolarophiles for the generation and reactions of nonstabilized carbonyl ylides using a manganese species where alkenes, aldehydes, ketones, and aldimine can be used as dipolarophiles.[5]

At the outset of our investigation, samarium diiodide was the only reductant known to generate nonstabilized carbonyl ylides. We searched for other effective reductants in cycloadditions of carbonyl ylides with carbon dipolarophiles. Alkali metals, alkaline earth metals, lithium naphthalenide, $CrCl_2$, and Rieke zinc were not effective for the generation of the carbonyl ylide from bis(chloromethyl) ether **1a**.[6,7] Of all the reductants examined, only manganese metal successfully afforded the corresponding cycloadducts. In the reaction with 3-butenyl 3-phenylpropyl ether (**2a**), cycloadduct **3a** was obtained in 44% yield using manganese activated by the Rieke method.[8] The manganese species prepared by the Takai method[9] was better as a reductant and gave the tetrahydrofuran **3a** in 76% yield (eq 1, Table 1).[10]

The ylide generated in this way reacted with *cis*-alkene **2c** to produce the *syn*-substituted tetrahydrofuran **3c**. We

Table 1

dipolarophile 2	conditions[a]	cycloadduct 3	yield of 3 (%)[b]
2a	A	**3a**	76
2a	B	**3a**	44
 **2b**	A	 **3b**	93
2b	C	**3b**	0
 **2c**	A	 **3c**	63
 **2d**	A	 **3d**	81
 **2e**	A[c]	 **3e**	85
 **2f**	A	 **3f**	79
 **2g**	A	 **3g**	78
 **2h**	A	 **3h**	98
 **2i**	A	 **3i**	73

[a] Conditions A: a suspension of manganese (6 mmol) and $PbCl_2$ (0.12 mmol) in THF (1 mL) was stirred at rt for 1 h. A dipolarophile (0.5 mmol), NaI (4 mmol), and bis(chloromethyl) ether (**1a**) (2 mmol) were successively added to the flask, and the mixture was stirred at rt for 4 h. Conditions B: Rieke manganese (2.5 mmol) was prepared from $MnBr_2$ (2.5 mmol) and lithium naphthalenide (5 mmol) in THF (2 mL). A dipolarophile (0.5 mmol) and bis(chloromethyl) ether (**1a**) (3 mmol) were added to the refluxing suspension, and the mixture was stirred at reflux temperature for 3.5 h. Conditions C: Rieke zinc (3 mmol) was prepared from $ZnCl_2$ (3 mmol) and lithium naphthalenide (6 mmol) in THF (4.5 mL). A dipolarophile (1 mmol) and bis(chloromethyl) ether (**1a**) (2 mmol) were added to the suspension, and the mixture was stirred at reflux temperature for 3 h. [b] Isolated yield. [c] After the manganese reagent was prepared (conditions A), the reagents and THF (4 mL) were added at 0 °C and the mixture was stirred at 0 °C to rt for 2 h and then at rt for 2 h.

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[1] (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; pp 1−176. For synthetic use of stabilized carbonyl ylides, see: (b) Padwa, A.; Weingarten, M. D. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 223−269.

[2] (a) Hojo, M.; Aihara, H.; Hosomi, A. *J. Am. Chem. Soc.* **1996**, *118*, 3533−3534. (b) Hojo, M.; Aihara, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9241−9244.

[3] For another method to generate nonstabilized carbonyl ylide, see: Prakash, G. K. S.; Ellis, R. W.; Felberg, J. D.; Olah, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 1341−1342.

[4] (a) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765−766. (b) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227.

[5] During this work, it was learned that Prof. K. Takai et al. also independently found the generation of nonstabilized carbonyl ylides using manganese in the course of their work with respect to activated manganese. We thank Professor Takai for communicating the results prior to publication. Takai, K.; Kaihara, H.; Higashiura, K.-i.; Ikeda, N. *J. Org. Chem.* **1997**, *62*, 8612.

[6] Buc, S. R. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 101−103. *Caution! Very high carcinogenic activity has been reported for bis(chloromethyl) ethers.* See the hazard note in *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 218.

[7] With simple alkenes, the substrates were mainly recovered when alkali metals, alkaline earth metals, lithium naphthalenide, $CrCl_2$, and the Rieke zinc were used. Unidentified polymeric products were obtained from alkynes and allenes using Zn(0) activated by 1,2-dibromoethane or Me_3SiCl and Bu_3MnLi. In the reaction with **2a** using Zn(0) activated by 1,2-dibromoethane or Me_3SiCl, the adduct **3a** was obtained in ca. 20−30% yield.

[8] Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197−2200.

[9] (a) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T *Tetrahedron Lett.* **1996**, *37*, 7049−7052. (b) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990−7991. (c) Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728−8729.

[10] $PbCl_2$ (34 mg, 0.12 mmol) and THF (1.0 mL) were added to a well-dried flask containing manganese (330 mg, 6.0 mmol), and the mixture was stirred at rt for 1 h. Dipolarophile **2** (0.5 mmol), NaI (600 mg, 4.0 mmol), and bis(chloromethyl) ether **1** (2.0 mmol) were successively added, and the mixture was stirred for 4 h. Water was added, and organics were extracted with ethyl acetate (20 mL × 3). After drying over anhydrous Na_2SO_4, evaporation of the solvents, and purification by means of column chromatography on silica gel (hexane/ethyl acetate), pure cycloadduct **3** was obtained.

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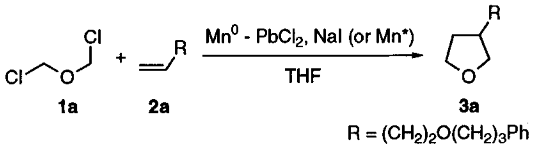
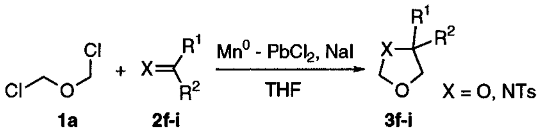


(1)

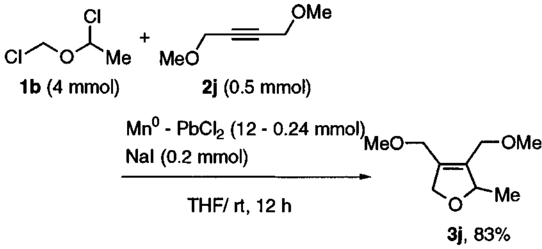
previously reported that, in the reaction with propargyl ether **2d** using a samarium reagent, a double-addition product of the parent carbonyl ylide was the main product when excess ylide was used.[2b] Interestingly, under the present conditions only the monoadduct **3d** was obtained selectively (81%) and the bis-adduct was not detected even if a 4-fold excess of ylide was used.[11] In the reaction with electron-deficient alkene **2e**, the reduction of the alkene was suppressed and the corresponding tetrahydrofuran-bearing ester function **3e** was obtained in high yield. The addition of NaI gave better results, possibly because this additive may convert **1a** to bis(iodomethyl) ether that is more reactive than **1a**, and manganese would then reduce the iodomethyl group to generate the parent carbonyl ylide preferentially to reduction of the dipolarophile.

Reactions with hetero-dipolarophiles were also examined: it was found that this manganese system can be used with a variety of carbonyl compounds, and even benzophenone, known as a good electron acceptor, was used (eq 2, Table 1). As can be seen in Table 1, the parent carbonyl ylide reacts with aldehydes **2f**−**g**, ketone **2h**, and aldimine **2i** to produce the corresponding 1,3-dioxolanes **3f**−**h** and 1,3-oxazolizine **3i**, respectively, in high yields.



(2)

We have been able to realize the reactions of the carbonyl ylide with a wide variety of dipolarophiles, including easily reducible hetero-dipolarophiles. Finally, we have also shown that this reaction system can be applied to the generation of methyl-substituted ylide from **1b**,[12−14] and this protocol leads to the generation of structural varieties of carbonyl ylides bearing various substituents (eq 3).



(3)

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR, IR, and mass spectral data of the products (16 pages).

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[11] Although the reason for the differences in reactivity is unclear at present, it is possible that metals or metal ions may interact (or coordinate) with carbonyl ylides to directly affect their reactivities.

[12] Hall, G. E.; Ubertini, F. M. *J. Org. Chem.* **1950**, *15*, 715−719. See the Supporting Information.

[13] We also examined the reactions of **1b** with unsymmetrical dipolarophiles such as benzyl propargyl ether (**2d**), benzaldehyde (**2g**), and benzophenone (**2h**). In the reaction of **2d** with **1b**, a 55:45 regioisomeric mixture of cycloadducts (**3k** + **3k′**) was obtained in 78% yield. In the reaction with **2g**, a regioisomeric mixture of cycloadducts (**3l** + **3l′**) was obtained in 86% yield where the major regioisomer was *trans*- and *cis*-2-methyl-4-phenyl-1,3-dioxolane (**(2*R**,4*R**)-3l** and **(2*R**,4*S**)-3l**) (the regioisomeric ratio was 77:23). With **2h**, the corresponding cycloadducts (**3m** + **3m′**) were obtained in 78% yield where 4,4-diphenyl-2-methyl-1,3-dioxolane (**3m′**) was a major product (the regioisomeric ratio was 94:6). For conditions, see the Supporting Information.

[14] The diastereoselectivity (2,3-*trans*:2,3-*cis* = 56:44 in 90% yield) between the unsymmetrical carbonyl ylide derived from **1b** and **2c** was almost identical in the case of the SmI$_2$-promoted reaction (2,3-*trans*:2,3-*cis* = 59:41).[2b] For conditions, see the Supporting Information.