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An efficient synthesis of 2-cyclopentenones from γ-ketoaldehyde acetals using lithium trimethylsilyldiazomethane. Its application to the synthesis of trichodenone C

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Abstract

The reaction of γ-ketoaldehyde acetals with lithium trimethylsilyldiazomethane afforded 2-cyclopentenones via the 1,5-C–H insertion of alkylidene carbene in high to moderate yields. Using this method, the synthesis of trichodenone C was achieved.

Keywords: alkylidene carbene; trimethylsilyldiazomethane; C–H insertion; 2-cyclopentenone; trichodenone C.

The intramolecular 1,5-C–H insertion reaction of alkylidene carbenes is a useful method for the construction of cyclopentene skeletons.[1] Alkylidene carbenes have been generated by the base-induced α-elimination of primary vinyl halides or triflates, by the nucleophilic β-addition to alkynyliodonium salts and the subsequent reductive cleavage, and by the nitrogen extrusion of diazoalkenes generated in situ.[1] Ohira et al. reported that the reaction of carbonyl compounds with lithium trimethylsilyldiazomethane in THF, which generated alkylidene carbenes via diazoalkenes through modification of the Peterson olefination, gave the cyclopentene derivatives in good yields.[2] We have also revealed that the alkylidene carbene generated from lithium trimethylsilyldiazomethane (TMSC(Li)N_2) and carbonyl compounds is used for the preparations of the homologous alkynes, aldehydes, heterocycles, and methylenecyclopropanes.[3] Although the 1,5-C–H insertion reaction into oxygen[1b] and nitrogen[4]-bearing stereogenic centers have been used to great effect, the insertion into the acetal bearing stereogenic center has not been studied. Therefore, we thought that it would be possible to extend this type of insertion to the preparation of 2-cyclopentenones using γ-ketoaldehyde acetals with TMSC(Li)N_2 (Scheme 1).

At the outset, we examined the effect of the acetal moiety in the 1,5-C–H insertion reaction. Among the acetal functionalities of dimethyl acetal, 1,3-dioxolane, and 1,3-dioxane, the 1,3-dioxane

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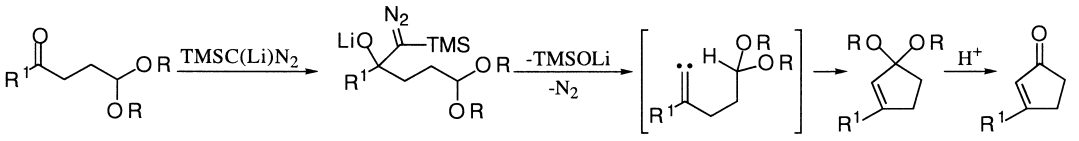
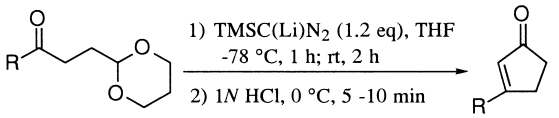
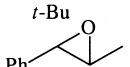
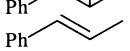


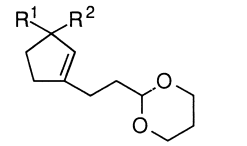
Scheme 1.

derivatives **1a** gave the best result. Thus, TMSC(Li)N_2 reacted with **1a** in THF to give the ketal-protected 2-cyclopentenone, and the ketal was easily hydrolyzed with 1N aq. HCl in one pot to furnish the 2-cyclopentenone **2a** in 82% yield (Table 1, entry 1).[5] The acyclic γ-ketoaldehyde acetals **1a–f,i** were readily prepared from the reaction of the corresponding acyl chlorides and 2-(1,3-dioxan-2-yl)-ethylmagnesium bromide in THF at –78°C.[6] While the competitive reaction of **1b** via the acetal C–H insertion and alkyl C–H insertion gave the cyclopentenone **2b** in 82% yield and the cyclopentene **3b** in 7% yield, the acetal C–H insertion versus tertiary alkyl C–H insertion showed similar reactivities (entries 2, 3).[7] The secondary alkyl ketones **1d,e**, the more sterically hindered ketone **1f**, and the α,β-epoxy ketone **1g**,[8] also afforded the corresponding 2-cyclopentenones **2d–g** in high to moderate yields (entries 4–7). When the reaction of the α,β-unsaturated ketone **1h**[8] was carried out, TLC analysis showed the complex mixtures, which were separated by silica gel column chromatography and then HPLC purification, to give the desired product **2h** in 16% yield and the alkyne **3h**, the 1,2-rearrangement product via the alkylidene carbene,[3a] in 24% yield (entry 8). The aryl ketone **1i** gave no desired product. Instead, the arylalkyne derivative **3i** was obtained in 73% yield (entry 9).[3a,9]

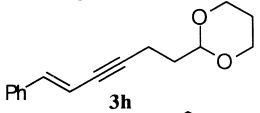
Table 1
Preparation of 2-cyclopentenones from acyclic γ-ketoaldehyde acetals



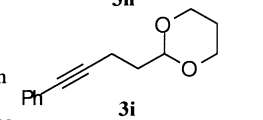
entry	substrate	R	product [a]	yield (%) [b]
1	**1a**	$PhCH_2CH_2$	**2a**	82
2	**1b**	C_5H_{11}	**2b**	82 [c]
3	**1c**	isopentyl	**2c**	41 [d]
4	**1d**	*i*-Pr	**2d**	80
5	**1e**	cyclohexyl	**2e**	89
6	**1f**	*t*-Bu	**2f**	54
7	**1g**		**2g**	50 [e]
8	**1h**		**2h**	16 [f]
9	**1i**	Ph	**2i**	- [g]



3b : R_1 = Et, R_2 = H
3c : R_1 = Me, R_2 = Me



3h

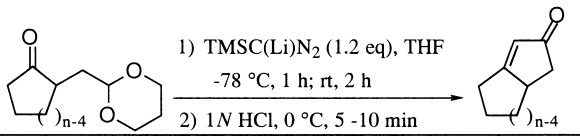


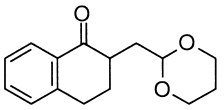
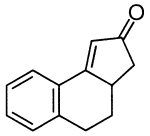
3i

a) All products gave satisfactory spectral data. b) Isolated yield. c) Cyclopentene **3b** was obtained in 7 % yield. d) Cyclopentene **3c** was obtained in 46 % yield. e) The reaction was quenched with 10 % citric acid at rt for 0.5 h instead of 1*N* HCl. f) Alkyne **3h** was obtained in 24 % yield. g) Alkyne **3i** was obtained in 73 % yield.

We next investigated the reaction of the cyclic γ-ketoaldehyde acetals **1j–n**.[10] The five-, seven-, and eight-membered ketones **1j,l,m** smoothly afforded the two-ring fused 2-cyclopentenones **2j,l,m** in

Table 2
Preparation of 2-cyclopentenones from cyclic γ-ketoaldehyde acetals

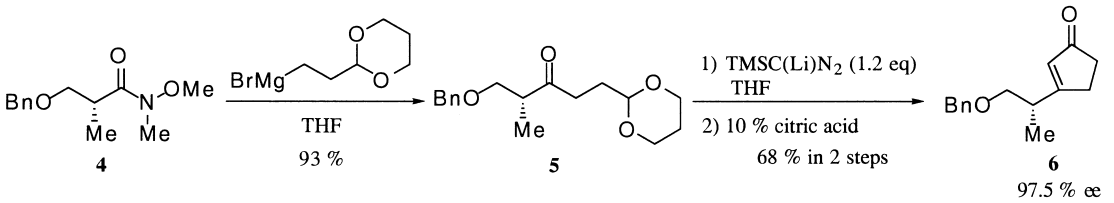


entry	substrate	n	product [a]	yield (%) [b]
1	**1j**	5	**2j**	64
2	**1k**	6	**2k**	15 [c]
3	**1l**	7	**2l**	89
4	**1m**	8	**2m**	73
5	 **1n**	-	 **2n**	57 [c,d]

a) All products gave satisfactory spectral data. b) Isolated yield. c) The unidentified product was isolated. d) The reaction was quenched with 10 % citric acid at rt for 1 h instead of 1*N* HCl.

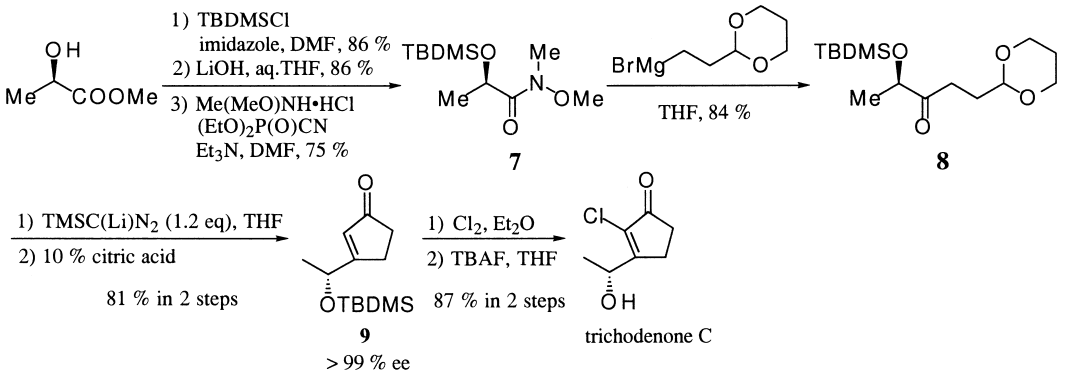
high to moderate yields (Table 2, entries 1, 3, 4). However, we were surprised to find that the cyclohexanone derivative **1k** produced complex mixtures under the same reaction conditions. In fact, the desired **2k** was obtained in only 15% yield along with the labile unidentified product (entry 2). Although the intra[3c] and intermolecular[11] oxonium ylide formation of the electrophilic alkylidene carbene was reported, the spectral data of the product was not in accord with the one derived from the oxonium ylide. Further investigation revealed that the reaction of 2-(3-phenyl-propyl)-cyclohexanone with TMSC(Li)N_2 also gave no 2-cyclopentene product and the same type of unknown products were isolated. Interestingly, when the α-tetralone derived ketone **1n** was employed, **2n** was the main product in 57% yield along with a small amount of by-product (entry 5). These results could be explained by the intramolecular reaction of the α-substituted cycloalkanone derivatives that is proceeded by another pathway in terms of the differences in the conformation.[12]

Also, the reaction of optically active α-methyl-β-benzyloxyketone **5**, which was prepared from **4**[13] and 2-(1,3-dioxan-2-yl)-ethylmagnesium bromide in THF, with TMSC(Li)N_2 in THF followed by acidic hydrolysis, provided **6** in 68% yield with 97.5% ee by chiral HPLC analysis (Scheme 2).



Scheme 2.

Using this methodology, the synthesis of trichodenone C,[14,15] isolated from a strain of *Trichoderma harzianum* OUPS-N115 and which exhibited cytotoxicity against cultured P388 cells, was accomplished. Thus, the Weinreb amide **7** prepared by protection, hydrolysis, and condensation with diethyl phosphorocyanidate[16] from methyl (*R*)-lactate reacted with 2-(1,3-dioxan-2-yl)-ethylmagnesium bromide in THF to give the ketone **8** in 84% yield. The reaction of **8** with TMSC(Li)N_2 in THF and then acidic hydrolysis gave the desired 2-cyclopentenone **9** in 81% yield with >99% ee by chiral HPLC analysis. Finally, the chlorination of **9** followed by deprotection of the silyl group with TBAF gave trichodenone C ($[\alpha]_D^{26.0}$ –12.6 (*c* 1.09, $CHCl_3$)) in 87% yield in two steps (Scheme 3). The synthetic trichodenone C was identical to the natural trichodenone C based on a comparison of their ^1H NMR, ^{13}C NMR, IR, HREIMS, and optical rotation (natural trichodenone C; $[\alpha]_D$ –10.8 (*c* 1.11, $CHCl_3$),[14] synthetic trichodenone C; $[\alpha]_D$ –12.4 (*c* 0.39, $CHCl_3$)[15]).



Scheme 3.

In conclusion, the present method using commercially available trimethylsilyldiazomethane ($TMSCHN_2$) will provide a new preparation of 3-substituted-2-cyclopentenones from γ-keto-aldehyde acetals. Using this method, we achieved the efficient synthesis of trichodenone C in eight steps.

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References

1. For reviews, see: (a) Stang, P. *Chem. Rev.* **1978**, *78*, 383. (b) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.
2. Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.
3. (a) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107. (b) Miwa, K.; Aoyama, T.; Shioiri, T. *ibid.* **1994**, 109. (c) Miwa, K.; Aoyama, T.; Shioiri, T. *ibid.* **1994**, 461. (d) Ogawa, H.; Aoyama, T.; Shioiri, T. *ibid.* **1994**, 757. (e) Ogawa, H.; Aoyama, T.; Shioiri, T. *Heterocycles* **1996**, *42*, 75. (f) Yagi, T.; Aoyama, T.; Shioiri, T. *Synlett*

1997, 1063. (g) Ito, Y.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, 1163. (h) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 3687. (i) For a review, see: Shioiri, T.; Aoyama, T. *J. Synth. Org. Chem. Japan* **1996**, *54*, 918.

4. Gabaitsekgosi, R.; Hayes, C. J. *Tetrahedron Lett.* **1999**, *40*, 7713.
5. A typical experimental procedure is as follows: To a solution of $TMSCHN_2$ (1.67 M hexane solution, 0.36 ml, 0.60 mmol) in THF (4 ml), *n*-BuLi (1.57 M hexane solution, 0.38 ml, 0.60 mmol) was added dropwise at –78°C under argon and the mixture was stirred at –78°C for 30 min. A solution of the γ-ketoaldehyde acetal **1** (0.50 mmol) in THF (1 ml) was then added dropwise at –78°C. The mixture was stirred at –78°C for 1 h, then stirred at room temperature for 2 h. After acidic work-up with 1N aq. HCl at 0°C for 5–10 min or 10% aq. citric acid at room temperature for 0.5–1 h, the mixture was extracted with ethyl acetate. The organic extracts were washed with sat. brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the 2-cyclopentenone **2**.
6. Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560.
7. It has been reported that the order of the reactivity for the C–H insertion of alkylidene carbene is primary < secondary < tertiary carbon–hydrogen bond, see: Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251.
8. The reaction of *trans*-cinnamaldehyde and 2-(1,3-dioxan-2-yl)-ethylmagnesium bromide in THF afforded the allyl alcohol, which was epoxided by *m*CPBA and then oxidized by TPAP/NMO to give **1g**. The oxidation of the former allyl alcohol by CMD (Chemical Manganese Dioxide)[17] gave **1h**.
9. In this case, the chain-homologated ketone, 2-(4-phenyl-3-oxobutyl)-1,3-dioxane, was also isolated in 13% yield. For the homologation of the ketones with $TMSCHN_2$ and boron trifluoride etherate, see: Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119.
10. The compounds **1j**–**n** were prepared from the corresponding 2-allylcycloalkanones through oxidative cleavage of the olefin followed by acetalization.
11. (a) Gilbert, J. C.; Weerasooriya, U. *Tetrahedron Lett.* **1980**, *21*, 2041. (b) Sueda, T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141.
12. Hauske, J. R.; Guadliana, M.; Desai, K. *J. Org. Chem.* **1982**, *47*, 5019.
13. (a) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (b) Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182.
14. Isolation and structure elucidation of trichodenone C: Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; Numata, A. *J. Antibiotics* **1998**, *51*, 33.
15. Synthesis of trichodenone C: Usami, Y.; Numata, Y. *Synlett* **1999**, 723.
16. Takuma, S.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3147.
17. Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35.