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[4 + 3] Cycloaddition of Cyclopropanone Hemiacetals[1]

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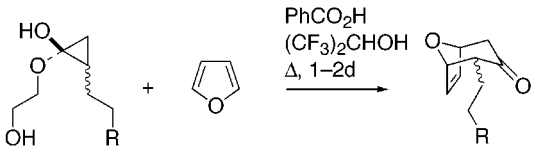
ABSTRACT

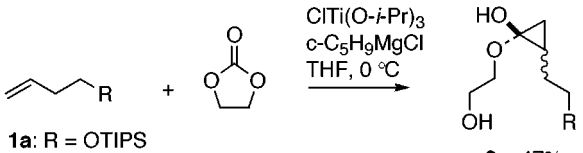


Intermolecular and intramolecular [4 + 3] cycloaddition reactions of readily available cyclopropanone hemiacetals with furans are described.

Cyclopropanone has attracted considerable attention from theoretical and synthetic chemists because of its severe strain energy and exceptional reactivity.[2] Among several ring opening reactions, the [4 + 3] cycloaddition of cyclopropanone to a 1,3-diene is of particular mechanistic and synthetic interest and closely related to that of oxyallyl, which has provided a useful method for the stereocontrolled construction of seven-membered carbocycles.[3] However, the difficulties in the preparation and handling of labile cyclopropanones have limited their use in synthesis. Cyclopropanone chemistry has subsequently been expanded by the utilization of cyclopropanone hemiacetals as a suitable surrogate.[4] As expected, cyclopropanone hemiacetals are susceptible to ring cleavage reactions, and many of these reactions can be explained in terms of a cyclopropanone hemiacetal−cyclopropanone equilibrium. Nonetheless, no example of the [4 + 3] cycloaddition of a cyclopropanone hemiacetal to a 1,3-diene such as furan or cyclopentadiene was previously known.[5] Herein we report the successful [4 + 3] cycloadditions between cyclopropanone hemiacetals and furans in both intermolecular and intramolecular reactions.[6]

The requisite cyclopropanone hemiacetals **2a**−**d** were conveniently prepared as a ca. 2:1 diastereomeric mixture by the titanium-mediated coupling of ethylene carbonate with terminal olefins **1a**−**d** (Scheme 1).[7] Moderate (43−58%) yields were offset by a one-step, convenient procedure that employed readily available starting materials and was also tolerant of a wide range of functional groups.

Scheme 1



1a: R = OTIPS
1b: R = CH_2Br
1c: R = CH_2-2'-furan
1d: R = CH_2CH_2-2'-furan

2a: 47%
2b: 58%
2c: 43%
2d: 49%

An intermolecular [4 + 3] cycloaddition reaction of **2a** with furan was first investigated. Of paramount importance

(1) Part 16 in the series of synthetic studies on [4 + 3] cycloadditions of oxyallyls. See also: (a) Part 15. Lee, K.; Cha, J. K. *Tetrahedron Lett.* **2001**, *42*, 6019. (b) Part 14. Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590. (c) Part 13. Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 3243.

(2) For reviews, see: (a) Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25. (b) Wasserman, H. H.; Clark, G. M.; Turley, P. C. *Top. Curr. Chem.* **1974**, *47*, 73. (c) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 23.

(3) For reviews on oxyallyls, see: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (e) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.

(4) For a comprehensive review, see: Salaün, J. *Chem. Rev.* **1983**, *83*, 619.

(5) Compare p 629 and footnote 137 of ref 4.

(6) Taken in part from: Cho, S. Y., Ph.D. dissertation, The University of Alabama, 2000.

(7) Lee, J.; Kim, Y. G.; Bae, J. G.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878.

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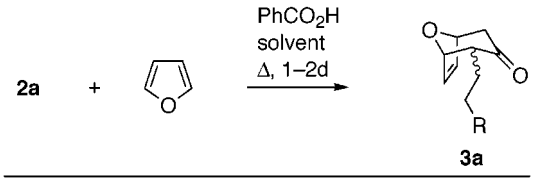
to the successful implementaion was the use of a non-nucleophilic, high ionizing solvent such as 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-2-propanol.[8] Several typical organic solvents were uniformly ineffective in inducing the [4 + 3] cycloaddition. As can be seen in Scheme 2, the

Scheme 2

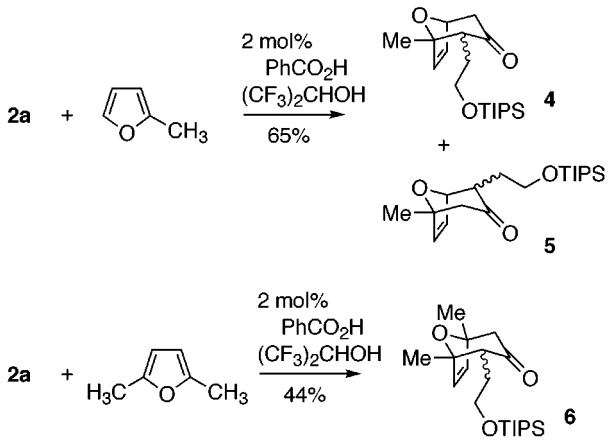


entry	solvent	$PhCO_2H$ (mol%)	rxn time	yield
1	CF_3CH_2OH	0	2 d	36%
2	CF_3CH_2OH	2	1 d	59%
3	CF_3CH_2OH	2	2 d	60%
4	CF_3CH_2OH	10	1 d	46%
5	CF_3CH_2OH	20	1 d	46%
6	$(CF_3)_2CHOH$	2	2d	82%
7	$(CF_3)_2CHOH$	5	2d	78%

addition of a small amount of benzoic acid proved to be advantageous. Thus, the optimal conditions comprised 2 mol % of benzoic acid and 1,1,1,3,3,3-hexafluoro-2-propanol as the reaction solvent, where **3a** (R = OTIPS) was obtained in 82% yield as a 1.3:1 diastereomeric mixture. Under identical conditions, **3b** (R = CH_2Br; structure not shown) was obtained in 51% as a 1:1 diastereomeric mixture.

Regioselectivity in the cycloaddition of **2a** was examined by utilizing 2-methylfuran as the diene partner (Scheme 3).

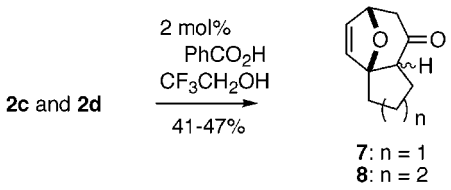
Scheme 3



It was surprising that all of the four possible stereoisomers **4** and **5** were obtained in 65% in a 1:0.9:0.6:0.6 ratio. In view of the disappointing lack of regio- and diastereocontrol, no attempt was made to make their unequivocal stereochemical assignment. With sterically more encumbered 2,5-dimethylfuran, the cycloadduct **6** was obtained in lower (44%) yield as a 1.5:1 diastereomeric mixture.

An intramolecular [4 + 3] cycloaddition of the furan-tethered cyclopropanone hemiacetals **2c** and **2d** was next studied (Scheme 4). Under unoptimized conditions employing 2 mol % benzoic acid and 2,2,2-trifluoroethanol as the solvent, the cycloadducts **7** and **8** were obtained as a 1:1 mixture of both diastereomers in 41% and 47% yield, respectively. The yields of these cycloadducts could undoubtedly be improved by further experimentation. However, this research has demonstrated that tricyclic carbocycles containing useful fuctionalities can be rapidly assembled by sequential application of the titanium-mediated cyclopropanation of ethylene carbonate and the [4 + 3] cycloaddition of the resulting cyclopropanone hemiacetals.

Scheme 4



From mechanistic and synthetic viewpoints, there are several unique characteristics in the [4 + 3] cycloaddition reactions of cyclopropanone hemiacetals, especially compared to the well-known [4 + 3] cycloaddition of oxyallyls. The observed lack of diastereoselectivity in the intermolecular and intramolecular cycloadditions of cyclopropanone hemiacetals was surprising, since those of oxyallyls have been shown to proceed with an exceptional level of diastereocontrol as a consequence of the compact transition states of W-shaped oxyallyls.[3] This unexpected discrepancy between the two cycloaddition methods may be attributed to the high temperature (e.g., refluxing 1,1,1,3,3,3-hexafluoro-2-propanol or 2,2,2-trifluoroethanol) required for the cyclopropanone hemiacetal route, whereas the oxyallyl approach generally entails room temperature or below. Similarly, the unexpected absence of regiocontrol in the intermolecular cycloaddition reactions of cyclopropanone hemiacetals might be related to the higher temperature conditions. In practice, the above-mentioned lack of diastereocontrol can be easily dealt with by base-induced equilibration to stereoselectively afford the alkyl-substituted cycloadducts at the pseudoequatorial position.[9] Finally, it is noteworthy that the present

(8) Föhlisch has previously reported a convenient generation of oxyallyl from α-chloroketones by the action of Et_3N or $LiClO_4$−Et_3N in CF_3CH_2-OH: (a) Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976. (b) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Henle, G. H.; Korfant, H.; Reiner, S.; Föhlisch, B. *J. Org. Chem*. **1999**, *64*, 3398 and references therein. See also: (c) Jin, S.-j.; Choi, J.-R.; Oh, J.; Lee, D.; Cha, J. K. *J. Am. Chem. Soc*. **1995**, *117*, 10914.

(9) In our recent formal synthesis of (+)-phorbol, such base-induced equilibration was successfully applied to appropriate [4 + 3] cycloadducts.[1b]

cycloaddition method allows the direct preparation of the [4 + 3] cycloadducts containing a monoalkyl substituent. On the other hand, other known methods for the [4 + 3] cycloadditions require the presence of suitable, removable substituents (e.g., a chloro group) to facilitate the generation of the corresponding parent or monoalkyl-substituted oxyallyl intermediates.

In summary, we have developed the intermolecular and intramolecular [4 + 3] cycloaddition reactions of readily available cyclopropanone hemiacetals.[10] This cycloaddition protocol could provide a new, convenient method for preparing monoalkyl-substituted [4 + 3] cycloadducts. Further mechanistic and synthetic studies will be reported in due course.

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(10) It is presumed that the [4 + 3] cycloaddition proceeds via cyclopropanone or ring-opened oxyallyl.

(11) **Typical Cycloaddition Procedure.** To a solution of cyclopropanone hemiacetal **2a** (60 mg, 0.2 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (2 mL) were added sequentially furan (0.4 mL, 6 mmol) and benzoic acid (0.4 mg, 4 mmol). The reaction mixture was heated at reflux for 2 d, cooled to room temperature, and treated with water (5 mL). The aqueous layer was extracted twice with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography afforded 51 mg (82%) of the cycloadduct **3a** as a colorless oil: IR ($CHCl_3$) 1715 cm^{-1}; (the data for one diastereomer) ^1H NMR (360 MHz, $CDCl_3$) δ 1.08 (m, 21 H), 2.08 (m, 2 H), 2.30 (d, J = 15.4 Hz, 1 H), 2.76 (dd, J = 4.8, 15.4 Hz, 1 H), 2.91 (m, 1 H), 3.80 (m, 2 H), 5.02 (d, J = 4.1 Hz, 1 H), 5.09 (d, J = 4.8 Hz, 1 H), 6.29 (s, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 11.9, 18.0, 28.8, 46.0, 54.5, 61.7, 78.0, 80.9, 132.3, 134.4, 207.1; HRMS ($M^+ - i$-Pr) calcd for $C_{15}H_{25}O_3Si$ 281.1599, found 281.1573.