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A Novel Cyclopentane Annulation by [3+2] Cycloaddition of Substituted Methylenecyclopropyl Ketones with Allyltrimethylsilane

Honoré Monti*, Denis Rizzotto, Gilbert Léandri
Laboratoire de Réactivité Organique Sélective associé au CNRS
Faculté des Sciences de St Jérôme 13397 Marseille cedex 20 - France

Jean-Pierre Monti
Laboratoire de Biophysique 80037 Amiens - France

Abstract : Reaction of subtituted methylenecyclopropyl ketones with allyltrimethylsilane affords functionalized methylene or alkylidenecyclopentanes in good yield via a $TiCl_4$ mediated cleavage of the carbocycle followed by a [3+2] cycloaddition of the resultant 1,3-zwitterion with allyltrimethylsilane which acts as the 1,2-partner.

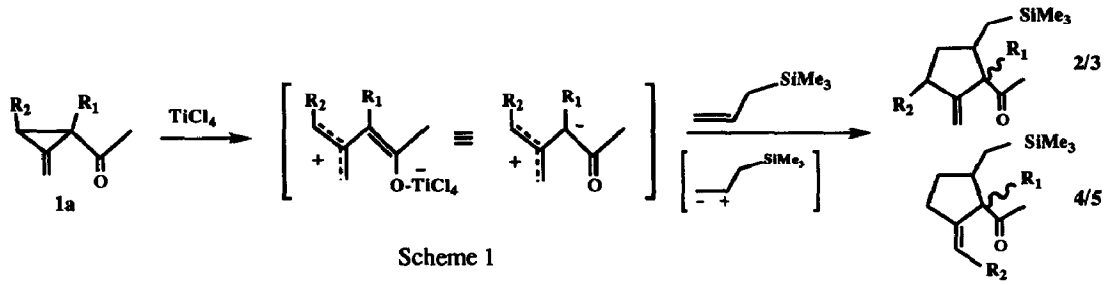
The great occurrence of cyclopentanoid natural products[1] has spurred on the development of new methods for the synthesis of highly functionalized cyclopentanes and the topic is of current interest.

Among these methods, the transition metal mediated [3+2] one-stage cycloaddition offers a synthetically attractive tool. In this context, trimethylenemethane (TMM) and its derivatives are versatile C_3 synthons for preparing a wide range of methylene or alkylidenecyclopentanes. The two major types of precursors used are methylenecyclopropanes[2] and bifunctional conjunctive reagents[2a,3]. Likewise, vicinally donor-acceptor substituted cyclopropanes have attracted attention as a useful 1,3-synthetic building block[4] and allylsilanes can function as three-carbon components with 1,2-silyl shift[5].

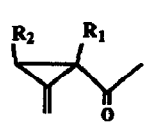
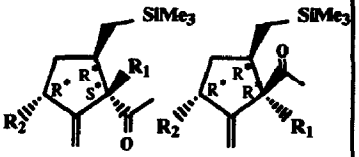
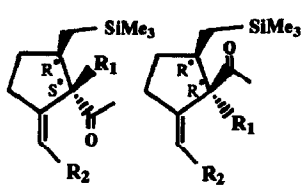
We report here a novel [3+2] cyclopentane annulation resulting from an hitherto unprecedented mode of reactivity between allyltrimethylsilane and substituted methylenecyclopropyl ketones.

We have investigated the reaction using three diversely substituted methylenecyclopropyl ketones **1a-c**. Results are shown in the Table.

Contrarily to its reaction with enones in which the competitive cyclisation *vs* Sakurai 1,4-addition involves a 2-silyl- substituted 1,3-dipole[6], in our case allyltrimethylsilane is the formal 1,2-partner and reacts without sila-Wagner-Meervein rearrangement[5] (Scheme 1).



Scheme 1

Substrates [a]	Products [b,c] (ratio)		Yields [d]
	Methylenecyclopentanes [e]	Ethylidenecyclopentanes [f]	
			
1a R_1=CH_3,R_2=H	**2a** (44%) + **3a** (56%)	— —	80%
1b R_1=R_2=CH_3	**2b** (11 %) + **3b** (13 %)	**4b** (38%) + **5b** (38%)	76%
1c R_1=H,R_2=CH_3	**2c** (traces) + **3c** (traces)	**4c** (35%) **5c** (65%)	72%

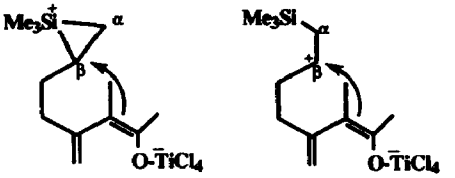
[a] Synthesized from ref. 11. [b] All compounds showed analytical and spectroscopic data consistent with the assigned structure. [c] Typical procedure: a solution of **1** (5mmol, 1 equiv.) and allyltrimethylsilane (20 mmol, 4 equiv.) in dry dichloromethane (15 ml) was added at room temperature to a stirred solution of titanium tetrachloride (1M in dichloromethane, 6 ml, 1.2 equiv.). After addition was complete, the reaction mixture was stirred for 15 minutes, then quenched by addition of aqueous sodium carbonate solution. After the usual work-up, the residue was subjected to chromatography (silica). [d] Yields refer to purified mixture of the different isomers after column chromatography. [e] Ratio mixture of diastereomers determined by ^1H NMR. [f] Ratio (**4b+5b**) mixture of diastereomers determined by ^1H NMR after separation from (**2b+3b**) by preparative GLC (Carbowax 20M). **4c** and **5c** are pure stereomers separated by preparative GLC (Carbowax 20M).

In the examples of the literature, the success of these annulations depends critically on the structure of the allylsilane annulation component. Only derivatives with bulky trialkylsilyl groups such as i-Pr_3Si undergo the desired ring formation process in appreciable yields. Me_3Si derivatives afford cyclopentane skeletons as minor by-products of the "normal" conjugate allylation.

Here, methylene or ethylidenecyclopentanes are the single products[7]. The assignment of these structures was made based on the analysis of the ^1H, ^{13}C and DEPT NMR spectra. All data are in complete agreement with the cyclopentane structure[8].

The assignment of the cis/trans stereochemistry of the acetyl and CH_2SiMe_3 groups for all the products, the relative configuration of R_2 (R_2 = CH_3) for **2b** and **3b**, and the Z configuration of the trisubstituted double bond (R_2 = CH_3) for **4b**, **5b** and **4c**, **5c** are based on 2D-NOESY experiments.

In our case, the initially Si-stabilized cation[9] doesn't rearrange or suffer desilylation. The direct *5-exo-tet* (bridged non-classical pentavalent silicon cation, non vertical stabilization according to Traylor) or *5-exo-trig* (carbon-silicon σ bond stabilize the carbocation by hyperconjugation, vertical stabilization according to Traylor) cyclization is by far the kinetically favoured procedure[10] (Scheme 2).



5-exo-tet cyclization *5-exo-trig* cyclization

Scheme 2

If, according to the numerous examples of the literature, we propose the siliranium ion as an intermediate, one can point out that the nucleophilic attack of the titanium enolate at the kinetically favored unsubstituted C_α position, with 1,2-shift of the trimethylsilyl group, doesn't occur (Scheme 2).

Further studies are under way in our laboratory so as to investigate the regio and stereoselectivity of the reaction and to carry out further applications.

References and Notes

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5. For recent examples, see: (a) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew . Chem. Int. Ed. Engl.* **1993**, *32*, 1081-1083. (b) Danheiser, R.L.; Takahashi, T.; Bertòk, B.; Dixon, B.R. *Tetrahedron Lett.* **1993**, *34*, 3845-3848. (c) Knölker, H.-J.; Graf, R. *Tetrahedron Lett.* **1993**, *34*, 4765-4768. (d) Knölker, H.-J. ; Foitzik, N.; Graf, R. ; Pannek, J.-B. ; Jones, P. G. *Tetrahedron* **1993**, *49*, 9955-9972.
6. The by-products of the Sakurai reaction, originally described as silylmethylcyclobutanes, are in fact silylcyclopentanes. For a discussion, see: Knölker, H.-J.; Jones, P.G.; Pannek, J.-B. *Synlett* **1990**, 429-430.
7. In the case of **1a**, intermolecular attack of a chloride anion at the cyclopropane ring leads always to some formation of the corresponding allylic chloride.
8. (**2a** + **3a**) structures supported by ^1H, ^{13}C NMR and DEPT experiments.
   ^1H-NMR (200MHz, $CDCl_3$) : **2a** δ -0.11 (s, 9H), 0.32 (d, 2H, J = 7.5 Hz), 1.10 (s, 3H), 1.40-1.55 (m, 1H), 1.60-1.75 (m, 1H), 1.94 (s, 3H), 2.22-2.35 (m, 1H), 2.35-2.60 (m, 2H), 4.57 (broad t, 1H, J = 2.3 Hz), 4.69 (broad t, 1H, J = 2.4 Hz). **3a** δ –0.10 (s, 9H), 0.22 and 0.60 (ABX, 2H, J = -14.4, 12.1, 2.4 Hz), 0.90 (s, 3H), 1.12-1.30 (m, 1H), 1.75-1.95 (m, 2H), 1.98 (s, 3H), 2.35-2.60 (m, 2H), 4.83 (broad t, 1H, J = 2.1 Hz), 4.90 (broad t, 1H, J = 2.0 Hz).

^{13}C NMR and DEPT (50 MHz, $CDCl_3$) : δ -1.13 ($SiCH_3$) ; 16.59, 17.13 (CH_2) ; 17.78 (CH_3 **2a**) ; 22.63 (CH_3 **3a**) ; 25.23, 29.16 (CH_3) ; 31.71, 31.82, 32.22, 32.62 (CH_2) ; 43.76, 48.53 (CH) ; 107.38, 107.64 (CH_2) ; 156.68, 157.10 (C) ; 209.80, 210.36 (C=O).

(**4b** + **5b**) structures supported by ^1H, ^{13}C NMR and DEPT experiments ([a], [b] these assignments may be interchanged)

^1H-NMR (200MHz, $CDCl_3$) : **4b** δ -0.16 (s, 9H), 0.24 (d, 2H, J = 7.7 Hz), 0.86 (s, 3H), 1.29[a] (dt, 3H, J = 7.2 Hz and two J = 2.3 Hz), 1.35-1.50 (m, 1H), 1.65-1.80 (m, 1H), 1.95[b] (s, 3H), 2.02 (ddd, 1H, J = 11.9, 7.7 and 5.4 Hz), 2.25-2.40 (m, 2H), 5.19 (qt, 1H, J = 7.2 Hz and two J = 2.0 Hz). **5b** δ -0.15 (s, 9H), 0.08 and 0.52 (ABX, 2H, J = -14.2, 12.7, 2.0 Hz), 1.07 (s, 3H), 1.31[a] (dt, 3H, J = 7.1 Hz and two J = 1.9 Hz), 1.10-1.25 (m, 1H), 1.65-1.80 (m, 2H), 1.91[b] (s, 3H), 2.25-2.40 (m, 2H), 5.26 (qt, 1H, J = 7.1 Hz and two J = 2.0 Hz).

^{13}C NMR and DEPT (50 MHz, $CDCl_3$) : δ -1.23, -1.29 ($SiCH_3$) ; 13.71, 14.02 (CH_3) ; 15.45, 16.54 (CH_2) ; 14.69 (CH_3 **4b**) ; 22.61 (CH_3 **5b**) ; 24.79, 29.49 (CH_3) ; 31.71, 33.06, 33.67, 34.57 (CH_2) ; 45.11, 50.12 (CH) ; 60.93, 61.66 (C) ; 117.70 (CH) ; 147.26, 147.38 (C) ; 211.21, 211.57 (C=O).

4c and **5c** structures supported by IR, ^1H, ^{13}C NMR, DEPT experiments and elemental analysis.

4c : IR (film, NaCl) : ν 3040, 1700, 1350, 1245, 860, 835 cm^{-1}.

^1H-NMR (200MHz, $CDCl_3$) : δ -0.10 (s, 9H), 0.46 and 0.80 (ABX, 2H, J = -14.6 Hz, J = 4.4 Hz, J = 10.9 Hz), 0.97-1.17 (m, 1H), 1.40 (dq, 3H, J = 6.5 Hz and three J = 1.4 Hz), 1.79-1.94 (m, 1H), 1.98 (s, 3H), 1.96-2.12 (m, 1H), 2.24-2.32 (m, 2H), 2.85 (broad d, 1H, J = 8.0 Hz), 5.36 (qq, 1H, J = 6.5 Hz and three J = 2.0 Hz). ^{13}C NMR and DEPT (50 MHz, $CDCl_3$) : δ -1.06 ($SiCH_3$), 14.42 (CH_3), 22.78 (CH_2), 26.44 (CH_3), 34.40 (CH_2), 34.49 (CH_2), 41.48 (CH), 65.69 (CH), 118.49 (CH), 141.88 (C), 209.85 (C=O). Anal. Calcd. for $C_{13}H_{24}OSi$: C, 69.64 ; H, 10.71. Found : C, 69.70 ; H, 10.65.

5c : IR (film, NaCl) : ν 3040, 1710, 1360, 1250, 870, 840 cm^{-1}.

^1H-NMR (200MHz, $CDCl_3$) : δ -0.07 (s, 9H), 0.35 and 0.72 (ABX, 2H, J = -14.4 Hz, J = 3.8 Hz, J = 11.6 Hz), 1.43 (dq, 3H, J = 6.8 Hz and three J = 1.5 Hz), 1.40-1.60 (m, 1H), 1.73-1.87 (m, 1H), 2.02 (s, 3H), 2.08-2.20 (m, 1H), 2.22-2.45 (m, 2H), 3.45 (broad d, 1H, j = 8.3 Hz), 5.35 (qq, 1H, J = 6.8 Hz and three J = 2.1 Hz). ^{13}C NMR and DEPT (50 MHz, $CDCl_3$) : δ -1.08 ($SiCH_3$), 15.00 (CH_3), 18.30 (CH_2), 31.05 (CH_3), 32.38 (CH_2), 32.50 (CH_2), 40.59 (CH), 60.65 (CH), 118.49 (CH), 142.43 (C), 210.35 (C=O). Anal. Calcd. for $C_{13}H_{24}OSi$: C, 69.64 ; H, 10.71. Found : C, 69.67 ; H, 10.68.

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