Pergamon

Tetrahedron Letters 43 (2002) 3739–3741

TETRAHEDRON LETTERS

Cyclocarbonylation of silicon tethered enynes derived from propargylic alcohols and vinylsilanes: a new reductive Pauson–Khand reaction with a traceless tether

John F. Reichwein, Scott T. Iacono, Mittun C. Patel and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712, USA

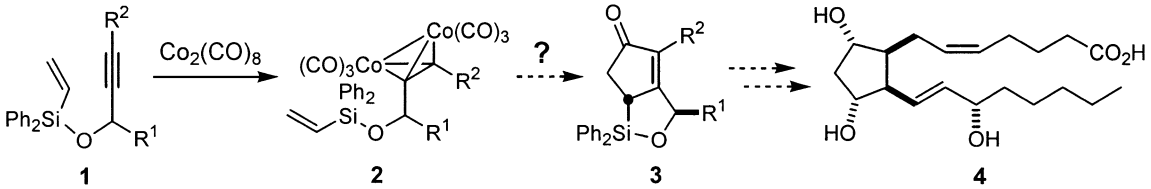
Received 18 February 2002; accepted 25 March 2002

Abstract—In nitrile solvents vinylsilyl ethers of propargylic alcohols undergo Pauson–Khand reaction with polysiloxane extrusion and concomitant reduction of the propargylic C–O bond. The product enones are formally the result of an intermolecular PKR reaction with ethylene.

The isoprostanes (e.g. **4**) are receiving considerable attention for their ability to mimic the biological activity of the prostaglandins.[1] It seemed that a Pauson–Khand reaction with a silicon tethered[2] enyne **1** suitably functionalized at R^1 and R^2 could provide an enantioselective and efficient route to the isoprostane core (Scheme 1). While the Pauson–Khand reaction (PKR) is a popular strategy for cyclopentenone synthesis,[3] the utilization of vinyl silanes as the olefinic component in this reaction has seen little use. In this regard, Saigo reported that under standard Pauson–Khand conditions 3-sila-1,7-enynes undergo cycloisomerization to eight-membered cyclic dienylsilanes (**5**→**6**, Scheme 2), but cyclopentenones **7** were not detected.[4]

At the onset of this project the prospect of the 4-silacyclopentenones undergoing Lewis acid-catalyzed desilylation was an obvious potential challenge to the successful implementation of the strategy outlined in Scheme 1.[5] Structurally related enones have been prepared by Whitby through a zirconocene-mediated cyclization/carbonylation sequence,[6] but the general effectiveness of the Tamao–Fleming oxidation with enones of general structure **3** has not been fully explored.

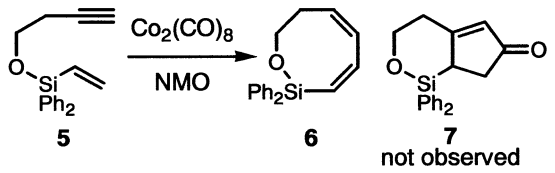
Enyne **8**, an internal alkyne with an aliphatic substituent at the propargylic position, was selected as a model substrate for the isoprostane synthesis (Scheme 3). Enyne **8** was readily prepared by silylation of the corresponding alcohol (Et_3N, CH_2Cl_2, 0°C to rt, >85% yield) with commercially available $Me_2SiCl(CH{=}CH_2)$. In the initial experiments to identify optimum conditions for the PKR, many experimental variants were explored, including the use of catalytic[7–10] conditions and the addition of adjuncts reported to facilitate the PKR: silica,[11] amine *N*-oxides,[12] DMSO,[13] primary amines,[14] molecular sieves,[15] sulfides[16] and oxygen. However, none of these methods provided the desired cyclopentenone **9**, but instead metal decomplexation, hydrolysis of the silyl ether and/or decomposition occurred. In contrast, *the use of damp nitrile solvents had a dramatic effect on the course of the reaction*, and in refluxing acetonitrile (30 min) the $Co_2(CO)_6$ complex of enyne **8** was converted to enone **10** in 62% isolated yield.[17,18] The beneficial effect of nitrile solvents on the



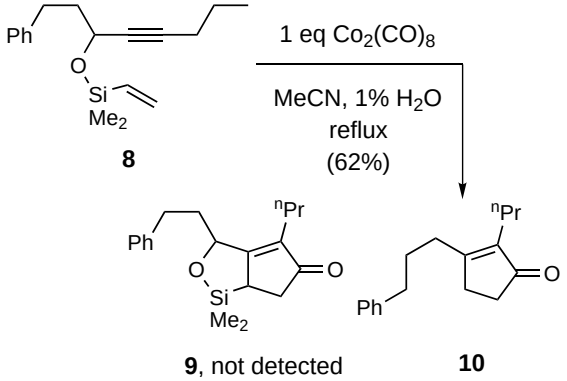
Scheme 1.

* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00634-2



Scheme 2.



Scheme 3.

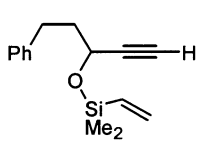
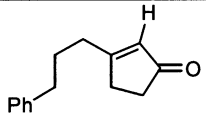
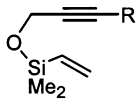
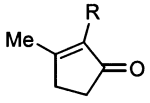
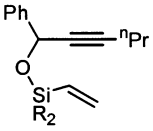
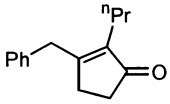
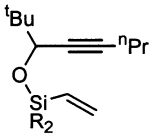
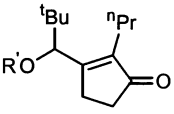
PKR has been documented.[19] The use of anhydrous acetonitrile had a deleterious effect on the efficiency of the reaction.[20]

To explore the generality of this new reaction, a variety of substrates with substituents offering different electronic and steric properties at the alkynyl and propargylic positions were examined.[21] The results of these studies are presented in Table 1. Entry 1 showed that terminal alkynes participate in the reaction, although this substrate required 24 h for consumption of starting material. In entries 2 and 3, enynes without substitution at the propargylic position were shown to undergo analogous cyclization. In entries 4 and 5, enynes with a doubly activated benzylic and propargylic ether each provided enone **18** in moderate yield. Throughout these investigations, and illustrated specifically with entries 4 and 5, both the dimethyl and diphenyl silyl tethers behaved similarly. The reaction of the pivaldehyde enynes **20** and **22** were anomalous in that no reduction at the propargylic position occurred in these substrates. The diphenyl silanol group in product **23** helped secure crystals (mp 95–98°C, hexanes) suitable for X-ray analysis (Fig. 1).[22] Bicyclic enones (e.g. **3**) were not observed in any of the reactions reported in Table 1.

The enone products in Table 1 are formally the result of an intermolecular PKR with an alkyne and ethylene gas.[23,24] For most laboratory preparations this new method is superior to the reaction with ethylene for several reasons. Specifically, the reaction does not require high pressures or special equipment, and the propargylic oxygen ensures that only one of the two possible isomeric enones is formed during the reaction.

In summary, we have reported the first Pauson–Khand reactions of silicon-tethered enynes in which the carbons bound to the silicon tether were reduced during the course of the reaction. This new method offers a convenient alternative to the intermolecular Pauson–Khand reaction with ethylene gas. In these reactions, the reduction of the propargylic oxygen indicates a process more complicated than mere Lewis acid mediated desilylation. Further details providing insight into

Table 1. Pauson–Khand reaction of vinylsilane-derived enynes[a]

Entry	Substrate	Product	Yield[b]
1	 **11**	 **12**	45%[c]
2	 **13**, R = ^{n}Pr	 **14**, R = ^{n}Pr	75%
3	**15**, R = Ph	**16**, R = Ph	74%
4	 **17**, R = Me	 **18**	65%
5	**19**, R = Ph	**18**	69%
6	 **20**, R = Me	 **21**, R′ = H	65%
7	**22**, R = Ph	**23**, R′ = $SiPh_2(OH)$	37%

[a] Reaction conditions: 1 eq $Co_2(CO)_8$, 1 eq enyne, 1% H_2O, refluxing MeCN (0.25 M), 30 min. [b] Isolated yields. [c] 24 h reaction time.

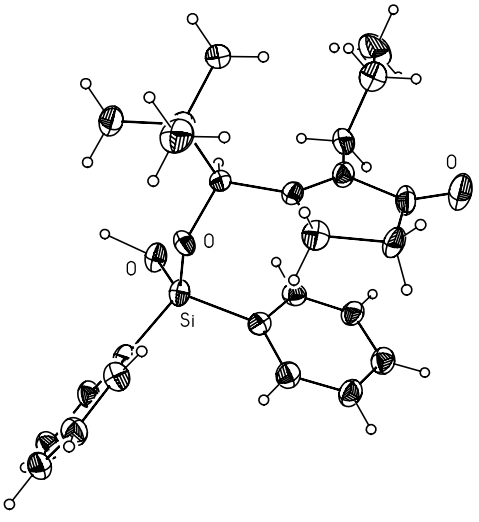


Figure 1. ORTEP representation of **23**.

the reaction mechanism and full experimental details will be reported elsewhere.[20]

Acknowledgements

We thank the Robert A. Welch Foundation for financial support and Vincent Lynch for determination of the X-ray structure. M.C.P. thanks the University of Texas at Austin for an undergraduate research fellowship.

References

1. Liu, T.; Stern, A.; Roberts, L. J.; Morrow, J. D. *J. Biomed. Sci.* **1999**, *6*, 226–235.
2. (a) Gauthier, D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289–2338; (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813–854; (c) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253–1277.
3. (a) Schore, N. E. *Org. React.* **1991**, *40*, 1–90; (b) Shore, N. E. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Elsevier: Oxford, 1995; Vol. 12, p. 703; (c) Ingate, S. T.; Marco-Contelles, J. *Org. Prep. Proced. Int.* **1998**, *30*, 121–143; (d) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911–914; (e) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297–341; (f) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283; (g) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 1657–1668; (h) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589–1595.
4. Kagoshima, H.; Hayashi, M.; Hashimoto, Y.; Saigo, K. *Organometallics* **1996**, *15*, 5439–5441.
5. Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377–2396.
6. Probert, G. D.; Harding, R.; Whitby, R. J.; Coote, S. J. *Synlett* **1997**, 1371–1374.
7. Jeong, N.; Hwang, S. H.; Lee, Y. S.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159–3160.
8. (a) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285–2286; (b) Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637–7640; (c) Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7641–7644; (d) Pagenkopf, B. L.; Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Synthesis* **2000**, 1009–1019.
9. Krafft, M. E.; Bonaga, L. V. R.; Hirosawa, C. *J. Org. Chem.* **2001**, *66*, 3004–3020.
10. Other metal catalysts explored with these silicon tethered enynes included $[Ir(COD)Cl]_2$·2(*S*)-tolBINAP: Shibata, T.; Takagi, K. *J. Am. Chem. Soc.* **2000**, *122*, 9852–9853; $Mo(CO)_6$: Jeong, N.; Lee, S. J. *Tetrahedron Lett.* **1993**, *34*, 4027–4030; $[RhCl(CO)dppp]_2$: Jeong, N. *Organometallics* **1998**, *17*, 3642–3644; Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609–4610; $Ru_3(CO)_{12}$: Kondo, T.; Nobuyoshi, S.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187–6188; Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762–3765; 'Cp_2Ti': Hicks, F. A.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 2713–2718; 'Cp_2Zr': Negishi, E.; Cederbaum, F. R.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832. Negishi, E.; Swanson, D. R.; Cederbaum, F. R.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917–920. Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421–4438.
11. Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245–1248.
12. (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289–5292; (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E. *Synlett* **1991**, 204–206.
13. Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220–223.
14. Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801–2804.
15. Perez-Serrano, L.; Blanco-Urgoiti, J.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *J. Org. Chem.* **2000**, *65*, 3513–3519.
16. Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771–773.
17. All products were fully characterized by IR, ^1H and ^{13}C NMR and HRMS.
18. Representative procedure: 2-propyl-3-phenylpropyl-2-cylcopenten-1-one (**10**). To a solution of $Co_2(CO)_8$ (342 mg, 1.00 mmol) in MeCN (4 mL, containing 1% H_2O) under an atmosphere of nitrogen was added enyne **8** (287 mg, 1.00 mmol) in MeCN (1 mL). After stirring for 1 h at rt, the reaction flask was placed into a preheated oil bath (135°C) to bring the reaction mixture quickly to reflux. After 30 min the reaction flask was removed from the oil bath and allowed to cool to rt. The volatile components were removed in vacuo, and the residue was purified by flash chromatography on silica gel using 40% EtOAc/hexanes for elution to afford the title compound **10** as a pale yellow oil (149 mg, 62%). R_f 0.65 (40% EtOAc/hexanes); IR (thin film) ν 3447 (br, m), 2930 (m), 1706 (s), 1614 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H), 2.69 (t, $J=7.8$ Hz, 2H), 2.50–2.45 (m, 4H), 2.39–2.36 (m, 2H), 2.13 (t, $J=7.5$ Hz, 2H), 1.91–1.85 (m, 2H), 1.43–1.36 (m, 2H), 0.88 (t, $J=7.5$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3 (C), 173.7 (C), 141.7 (C), 140.8 (C), 128.7 (CH), 128.6 (CH), 126.3 (CH), 36.1 (CH_2), 34.5 (CH_2), 31.0 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 25.4 (CH_2), 22.1 (CH_2), 14.4 (CH_3); HRMS m/z calcd for $C_{17}H_{23}O$ $[M+H]^+$ 243.1749, found 243.1741.
19. Hoye, T. R.; Suriano, J. A. *J. Org. Chem.* **1993**, *58*, 1659–1660.
20. Reichwein, J. F.; Iacono, S. T.; Pagenkopf, B. L. *Tetrahedron* **2002**, in press.
21. For a 'reductive Pauson–Khand' variant, see: Krafft, M. E.; Bonaga, L. V. R.; Wright, J. A.; Hirosawa, C. *J. Org. Chem.* **2002**, *67*, 1233–1246.
22. Crystallographic data for structure **23** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 175779. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].
23. Khand, I. U.; Pauson, P. L. *J. Chem. Res. (M)* **1977**, 168–177.
24. (a) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *Chem. Commun.* **1999**, 2171–2172; (b) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104–117.