ELSEVIER

www.elsevier.nl/locate/jorganchem

Journal of Organometallic Chemistry 606 (2000) 75–78

Journal of Organometallic Chemistry

Note

Ring closing alkyne metathesis: stereoselective synthesis of civetone

Alois Fürstner *, Günter Seidel

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim, Ruhr, Germany

Received 17 December 1999

Abstract

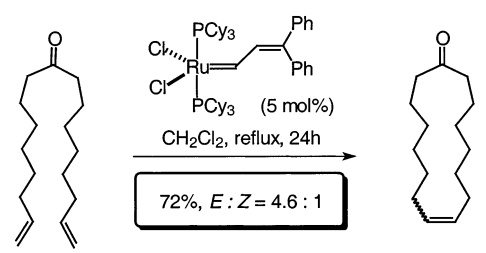
A concise and stereoselective synthesis of the macrocyclic musk civetone **6** is reported starting from readily available 9-undecynol. The key steps comprise a ring closing metathesis of diyne **4** followed by Lindlar reduction of the resulting cycloalkyne **5**. The cyclization can be effected either by using catalytic amounts of the Schrock alkylidyne complex $(t\text{-BuO})_3W{\equiv}CCMe_3$ or by means of an in situ catalyst mixture generated from $Mo(CO)_6$ and *p*-trifluoromethylphenol. Both catalyst systems turned out to be compatible with the unprotected ketone function of the substrate.

Keywords: Alkylidynes; Alkynes; Macrocycles; Metathesis; Molybdenum; Tungsten

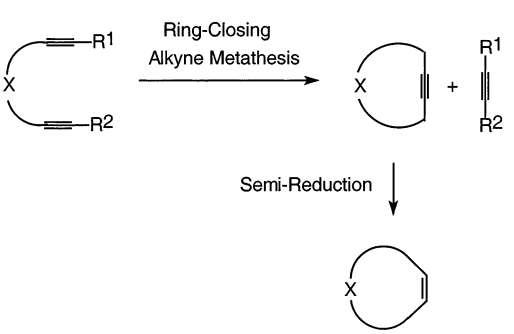
1. Introduction

The insight that ring closing metathesis (RCM) [1] of suitably substituted dienes provides a convenient entry into macrocycles, even if the substrates are conformationally unbiased for ring closure, has enabled successful applications of this methodology to the preparation of macrocyclic musks and other economically important perfume ingredients [2]. While these syntheses turned out to be unprecedentedly short and efficient and can be carried out under conditions amenable to scale-up [3], the cycloalkene products are usually formed as (*E*,*Z*)-mixtures which are difficult to separate by conventional means. Scheme 1 depicts a representative example which illustrates both aspects [2b], i.e. the good yield on the one hand and the stereounselective course on the other hand with the (*E*)-isomer prevailing in most of the recorded cases [1,4].

The olfactory nuances of the macrocyclic products depend, in a subtle way, on the configuration of the double bonds in their backbones. In view of the fact that several naturally occurring musks incorporate (*Z*)-configurated alkene entities [5], the development of a complementary and *stereoselective* entry into this series is called for. We have demonstrated recently that ring closing *alkyne* metathesis followed by Lindlar reduction



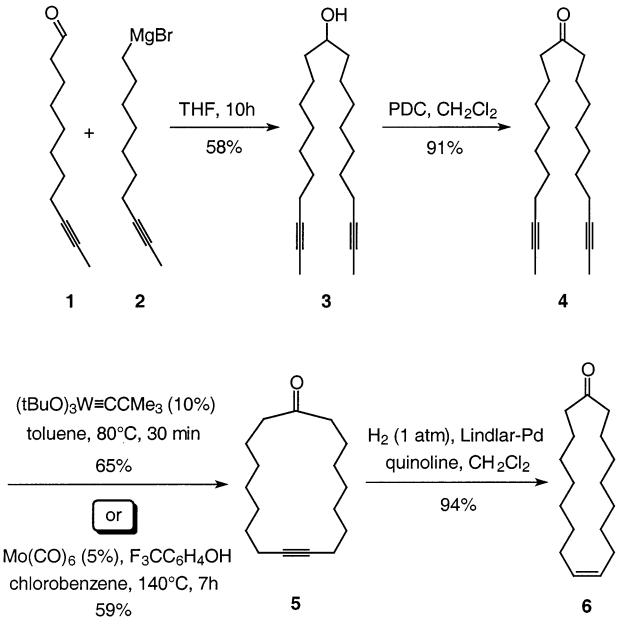
Scheme 1.



Scheme 2.

* Corresponding author.

0022-328X/00/$ - see front matter
PII: S0022-328X(00)00096-6



Scheme 3.

of the resulting cycloalkyne products may serve this purpose very well (Scheme 2) [6–8]. The Schrock alkylidyne complex $(t\text{-BuO})_3W{\equiv}CCMe_3$ [9] turned out to be an excellent pre-catalyst for this conceptually novel transformation.

A literature report, however, showing that closely related tungsten alkylidynes are highly nucleophilic and react instantaneously with carbonyl compounds, such as acetone [10], suggests that this methodology will either fail or will require lengthy protecting group manipulations in applications to odoriferous ketones. Gratifyingly, however, we found that this is not the case, as can be seen from the stereoselective synthesis of the valuable fragrance civetone **6** summarized below.

2. Results and discussion

Readily available 9-undecynol [6b] is oxidized with PDC in CH_2Cl_2 to the corresponding aldehyde **1** which reacts with 8-decynylmagnesium bromide **2** in THF to afford alcohol **3** in 58% isolated yield as a crystalline compound. Oxidation of the secondary alcohol group to ketone **4** under standard conditions sets the stage for the crucial macrocyclization. We were pleased to find that this functionalized diyne converts smoothly into the desired cycloalkyne **5** when exposed to catalytic amounts of $(t\text{-BuO})_3W{\equiv}CCMe_3$ (10 mol%) [9] in toluene at 80°C (Scheme 3). The desired 17-membered macrocycle is isolated in 65% yield as a colorless syrup together with 4% of the cyclodimeric product, i.e. the 34-membered cyclodiyne-dione. This outcome shows that the carbonyl functions of **4** and **5** are at least kinetically inert toward the tungsten alkylidyne. Another noteworthy feature of this cyclization is the exceptionally short reaction time of 30 min which indicates a very high turnover frequency of the catalyst; note that the closely related ring closing alkene metathesis depicted in Scheme 1 takes 24 h to go to completion.

The ring closing alkyne metathesis reaction can also be performed with a structurally unknown catalyst formed in situ from $Mo(CO)_6$ (5 mol%) and *p*-trifluoromethylphenol (one equivalent) in refluxing chlorobenzene according to a procedure optimized by Bunz et al. [11–13]. Despite of the rather forcing reaction conditions, the targeted product **5** is obtained in respectable 59% yield after 7 h reaction time. Although this result indicates that the activity of this instant catalyst mixture is significantly lower than that of the well defined tungsten alkylidyne complex $(t\text{-BuO})_3W{\equiv}CCMe_3$, the user friendly low-tech set-up of this experiment which employs only off-the-shelf reagents and does not require any precautions as to the drying and handling of the reagents is quite appealing from the practical point of view. Cycloalkyne **5** thus obtained can be transformed into civetone **6** by standard Lindlar hydrogenation. This example underscores the exceptional performance and wide scope of the ring closing alkyne metathesis/semi-reduction concept which complements conventional RCM with regard to stereoselectivity and rivals its efficiency in terms of most other preparatively relevant aspects [6,7]. Specifically, our studies have shown so far that this methodology is compatible with a large array of functional groups (i.e. ketones, esters, enoates, amides, sulfones, sulfonamides, urethanes, ethers, silyl ethers, alkenes, furans) and is therefore relevant for applications to advanced organic synthesis [14]. Further examples illustrating this aspect are underway and will be reported in due course.

3. Experimental

3.1. General considerations

All reactions were carried out under Ar in pre-dried glassware using Schlenk techniques. The solvents were dried by distillation over the following drying agents and were transferred under Ar: toluene (Na–K), CH_2Cl_2 (CaH_2), THF (Mg–anthracene). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a Bruker DMX 300 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. IR: Nicolet FT-7199, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV). Elemental analyses: Dornis and Kolbe, Mülheim. All commercially available chemicals were used as received.

3.2. Preparation of 2,19-heneicosadiyn-11-ol (3)

A solution of aldehyde **1** (3.33 g, 20 mmol) in THF (50 ml) is added dropwise over a period of 1 h to a solution of 8-decynylmagnesium bromide **2** (0.14 M in THF, 142 ml, 21 mmol) at −30°C. Once the addition is complete, the reaction mixture is stirred at ambient temperature for 10 h. Standard extractive work-up using *tert*-butyl methylether for the extraction of the aqueous phase followed by flash chromatography (hexane–ethyl acetate, 30/1 → 10/1) of the crude material provides alcohol **3** as colorless crystals (3.50 g, 58%). m.p. = 60–61°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.58 (m, 1H), 2.11 (tq, J = 6.8, 2.6, 4H), 1.78 (t, J = 2.6, 6H), 1.55–1.2 (m, 24 H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 79.3, 75.3, 71.9, 37.4, 29.5, 29.1, 29.0, 28.8, 25.6, 18.7, 3.4. MS: m/z (rel. intensity): 304 ([M^+], < 1), 271 (4), 257 (3), 243 (1), 229 (1), 201 (2), 189 (2), 175 (5), 161 (10), 149 (30), 135 (23), 121 (30), 107 (45), 95 (63), 81 (92), 67 (74), 55 (100), 41 (59). IR (neat): 3322, 3238, 2929, 2849, 1509, 1463, 1427, 1146, 1121, 1067, 1049, 1005, 925, 866, 812, 724, 665.

3.3. Preparation of 2,19-heneicosadiyn-11-one (4)

PDC (6.50 g, 17 mmol) is added in portions to a solution of alcohol **3** (3.40 g, 11 mmol) in CH_2Cl_2 (300 ml) and the resulting suspension is stirred for 16 h at ambient temperature. Filtration of the mixture through a short pad of silica, thorough washing of the insoluble residues with CH_2Cl_2 (200 ml in several portions) and evaporation of the combined filtrates affords analytically pure ketone **4** as colorless crystals (3.03 g, 91%). m.p. = 55–56°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.38 (t, J = 7.5, 4H), 2.11 (tq, J = 6.8, 2.6, 4H), 1.77 (t, J = 2.6, 6H), 1.56 (m, 4H), 1.22–1.50 (m, 16H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 211.5, 79.2, 75.3, 42.7, 29.1, 29.0, 28.9, 28.6, 23.8, 18.6, 3.4. MS: m/z (rel. intensity): 302 ([M^+], 2), 287 (3), 273 (5), 165 (23), 147 (21), 133 (15), 122 (42), 107 (33), 95 (62), 81 (100), 67 (66), 55 (73), 41 (60). IR (neat): 2929, 2850, 1700, 1470, 1421, 1385, 1253, 1113, 1060, 717. Anal. Calc. ($C_{21}H_{34}O$): C, 83.40; H, 11.33. Found: C, 82.89; H, 11.44.

3.4. Preparation of cycloheptadec-9-yn-1-one (5) by ring closing alkyne metathesis

3.4.1. Method A

A solution of diyne **4** (556 mg, 1.80 mmol) and (t-BuO)$_3$W≡CCMe$_3$ (85 mg, 10 mol%) in toluene (300 ml) is stirred at 80°C for 30 min. The reaction mixture is filtered through a pad of silica, the insoluble residues are carefully washed with CH_2Cl_2 (100 ml in several portions), the combined filtrates are evaporated and the residue is chromatographed (hexane–ethyl acetate, 50/1 → 30/1) affording cycloalkyne **5** as a colorless syrup (299 mg, 65%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (t, J = 6.9, 4H), 2.17 (m, 4H), 1.65 (m, 4H), 1.44 (m, 8H), 1.32 (m, 8H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 212.9, 80.5, 42.3, 28.7, 28.6, 28.2, 27.9, 24.0, 18.5. MS: m/z (rel. intensity): 248 ([M^+], 11), 230 (3), 219 (5), 205 (5), 193 (7), 179 (6), 166 (19), 151 (11), 135 (16), 121 (27), 107 (32), 93 (47), 81 (65), 79 (64), 67 (74), 55 (79), 41 (100). IR (neat): 2928, 2856, 1710, 1460, 1437, 1357, 1331, 1276, 1113, 1053, 722. Anal. Calc. ($C_{17}H_{28}O$): C, 82.20; H, 11.36. Found: 82.35; H, 11.20. A second more polar fraction was eluated which consists of the cyclodimeric product cyclotetratriacont-9,26-diyn-1,18-dione (20 mg, 4%) exhibiting the following spectroscopic properties: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.40 (t, J = 7.3, 8H), 2.14 (m, 8H), 1.57 (m, 8H), 1.43 (m, 16H), 1.30 (m, 16H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 211.5, 80.3, 42.7, 29.2, 28.83, 28.75, 28.4, 23.8, 18.6. MS: m/z (rel. intensity): 496 ([M^+], 35), 478 (5), 413 (4), 355 (3), 315 (4), 301 (6), 287 (5), 233 (2), 187 (3), 165 (11), 147 (13), 135 (17), 121 (29),107 (31), 95 (56), 81 (81), 67 (89), 55 (100), 41 (54).

3.4.2. Method B

A solution of diyne **4** (369 mg, 1.2 mmol), $Mo(CO)_6$ (16 mg, 5 mol%) and p-trifluoromethylphenol (198 mg, 1.2 mmol) in chlorobenzene (150 ml) is stirred for 7 h at 130–140°C. During this time, a gentle stream of argon is bubbled through the reaction mixture. Evaporation of the solvent at reduced pressure (ca. 10 mbar) followed by chromatographic purification of the residue (hexane–ethyl acetate, 50/1) affords the title compound as a colorless syrup (180 mg, 59%).

3.5. Preparation of civetone (6)

A suspension of cycloalkyne **5** (169 mg, 0.68 mmol), quinoline (40 μl) and Lindlar catalyst (40 mg) in CH_2Cl_2 (50 ml) is stirred under an atmosphere of H_2 (1 atm.) for 2 h at ambient temperature. The catalyst is filtered off through a short pad of silica, the solvent is evaporated and the crude product is purified by flash chromatography (hexane–ethyl acetate, 50/1) affording compound **6** as a colorless syrup which slowly crystallizes upon standing to afford a waxy solid (159 mg, 94%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.34 (ddd, J = 5.9, 4.5, 1.1, 2H), 2.39 (t, J = 6.8, 4H), 2.01 (dt, J = 6.4, 5.9, 4H), 1.62 (m, 4H), 1.29 (m, 16 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 212.4, 130.1, 42.4, 29.0, 28.6, 28.2, 28.1, 26.6, 23.8. MS: m/z (rel. intensity): 250 ([M^+], 95), 232 (4), 221 (2), 207 (2), 149 (5), 135 (11), 121 (14), 109 (19), 95 (37), 81 (53), 67 (63), 55 (94), 41 (100). IR (neat): 3003, 2925, 2853, 1711, 1654, 1460, 1409, 1364, 1275, 1124, 1056, 719.

Acknowledgements

Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz program) and by the Fonds der Chemischen Industrie is acknowledged with gratitude.

References

[1] Recent reviews: (a) R. H. Grubbs, S. Chang, Tetrahedron 54 (1998) 4413. (b) A. Fürstner, Top. Catal. 4 (1997) 285. (c) M. Schuster, S. Blechert, Angew. Chem. Int. Ed. Engl. 36 (1997) 2036. (d) A. Fürstner, Top. Organomet. Chem. 1 (1998) 37.

[2] (a) A. Fürstner, K. Langemann, J. Org. Chem. 61 (1996) 3942. (b) A. Fürstner, K. Langemann, Synthesis (1997) 792.

[3] A. Fürstner, D. Koch, K. Langemann, W. Leitner, C. Six, Angew. Chem. Int. Ed. Engl. 36 (1997) 2466.

[4] For further examples from our laboratory illustrating this aspect see: (a) A. Fürstner, N. Kindler, Tetrahedron Lett. 37 (1996) 7005. (b) A. Fürstner, K. Langemann, J. Am. Chem. Soc. 119 (1997) 9130. (c) A. Fürstner, K. Langemann, J. Org. Chem. 61 (1996) 8746. (d) A. Fürstner, T. Müller, Synlett (1997) 1010. (e) A. Fürstner, T. Müller, J. Org. Chem. 63 (1998) 424. (f) A. Fürstner, T. Müller, J. Am. Chem. Soc. 121 (1999) 7814. (g) A. Fürstner, G. Seidel, N. Kindler, Tetrahedron 55 (1999) 8215. (h) A. Fürstner, T. Gastner, H. Weintritt, J. Org. Chem. 64 (1999) 2361. (i) A. Fürstner, J. Grabowski, C. W. Lehmann, J. Org. Chem. 64 (1999) 8275.

[5] For reviews see: (a) G. Ohloff, Riechstoffe und Geruchssinn, Springer, Berlin 1990. (b) K. Bauer, D. Garbe, H. Surburg, in: Ullmann's Encyclopedia of Industrial Chemistry, fifth ed., vol. A11, VCH, Weinheim, 1988, p. 141. (c) A. S. Williams, Synthesis (1999) 1707. (d) G. Fráter, J.A. Bajgrowicz, P. Kraft, Tetrahedron 54 (1998) 7633.

[6] (a) A. Fürstner, G. Seidel, Angew. Chem. 110 (1998) 1758; Angew. Chem. Int. Ed. Engl. 37 (1998) 1734. (b) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, J. Am. Chem. Soc. 121 (1999) 11108.

[7] A. Fürstner, C. Mathes, C.W. Lehmann, J. Am. Chem. Soc. 121 (1999) 9453.

[8] For a short review on alkyne metathesis see: U.H.F. Bunz, L. Kloppenburg, Angew. Chem. Int. Ed. Engl. 38 (1999) 478.

[9] (a) R.R. Schrock, D.N. Clark, J. Sancho, J.H. Wengrovius, S.M. Rocklage, S.F. Pedersen, Organometallics 1 (1982) 1645. (b) J.H. Freudenberger, R.R. Schrock, M.R. Churchill, A.L. Reingold, J.W. Ziller, Organometallics 3 (1984) 1563. (c) R.R. Schrock, Polyhedron 14 (1995) 3177.

[10] $(RO)_3W{\equiv}CCMe_3$ (R = 2,6-diisopropylphenyl) is reported to react rapidly with acetone, benzaldehyde, paraformaldehyde, ethyl formate, DMF and acetonitrile in Wittig-like reactions, cf.: J.H. Freudenberger, R.R. Schrock, Organometallics 5 (1986) 398.

[11] The combination of $Mo(CO)_6$ and phenol additives has been originally proposed as alkyne metathesis catalyst by Mortreux et al., cf.: (a) A. Mortreux, M. Blanchard, J. Chem. Soc. Chem. Commun. (1974) 786. (b) A. Mortreux, N. Dy, M. Blanchard, J. Mol. Catal. 1 (1975) 101. (c) A. Mortreux, J.C. Delgrange, M. Blanchard, B. Lubochinsky, J. Mol. Catal. 2 (1977) 73. (d) For comments on the reactive intermediates formed under these conditions see: L.G. McCullough, R.R. Schrock, J. Am. Chem. Soc. 106 (1984) 4067.

[12] For applications of the Mortreux system see: (a) D. Villemin, P. Cadiot, Tetrahedron Lett. 23 (1982) 5139. (b) J.A.K. Du Plessis, H.C.M. Vosloo, J. Mol. Catal. 65 (1991) 51. (c) N. Kaneta, T. Hirai, M. Mori, Chem. Lett. (1995) 627. (d) N. Kaneta, K. Hikichi, S.-I. Asaka, M. Uemura, M. Mori, Chem. Lett. (1995) 1055.

[13] For further optimizations and applications see: (a) L. Kloppenburg, D. Song, U.H.F. Bunz, J. Am. Chem. Soc. 120 (1998) 7973. (b) N.G. Pschirer, U.H.F. Bunz, Tetrahedron Lett. 40 (1999) 2481.

[14] For an account on our objectives in catalysis based synthesis see: A. Fürstner, Synlett (1999) 1523.