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Reaction of Alkynes with Tetracarbonyl[Methoxy(2,4-Dimethoxyphenyl)Carbene]chromi A Formal Synthesis of 7-Methoxyeleutherin

Karl Heinz Dötz $^{\rm a}$, William A. Donaldson $^{\rm b}$ & Werner Sturm $^{\rm a}$

^a Kekulé-Institut für Organischen Chemie und Biochemie der Universität Bonn Gerhard-Domagk-Straße 1, D-53121, Bonn, Germany

^b Chemistry Department, Marquette University, P.O. Box 1881, Milwaukee, WI, 53201--1881, USA Published online: 04 Dec 2007.

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REACTION OF ALKYNES WITH TETRACARBONYL[METHOXY(2,4-DIMETHOXYPHENYL)CARBENE]CHROMIUM: A FORMAL SYNTHESIS OF 7-METHOXYELEUTHERIN¹

Karl Heinz Dötz,*† William A. Donaldson,*§ and Werner Sturm†

[†]Kekulé-Institut für Organischen Chemie und Biochemie der Universität Bonn Gerhard-Domagk-Straße 1, D-53121 Bonn, Germany

[§]Chemistry Department, Marquette University, P.O. Box 1881, Milwaukee, WI 53201-1881 USA

Abstract: The reaction of alkynes with tetracarbonyl[methoxy(2,4-dimethoxyphenyl)carbene]chromium, followed by oxidation, gives naphthoquinones as well as other cyclized products. This has been utilized in the preparation of (3) an intermediate in the synthesis of 7-methoxyeleutherin.

7-Methoxyeleutherin is a *cis*-dimethyl pyranonaphthoquinone (1) isolated from the seeds of *Karwinskia humboldtiana* Zucc.² A structurally related naphthoquinone lactol, thysanone (2), has been shown to be an effective inhibitor (IC_{50} 13 µg/mL) of the human rhinovirus 3C-protease.³ Compound 1 and its *trans* isomer were prepared from naphthoquinone 3 (Scheme 1),⁴ and this same precursor might be of utility in the synthesis of 2. The naphthoquinone 3 was synthesized in 7 steps (8.8%) from tetralone 4.⁴



^{*} To whom correspondence should be addressed.

The thermal reaction of chromium aryl carbene complexes with alkynes, followed by oxidative workup, produces predominantly naphthoquinone products (Scheme 2), however indanones, indenones, cyclobutenones, and/or furans have also been isolated.⁵ The annulation of unsymmetrically substituted alkynes occurs in a regioselective fashion such that the larger substituent is next to the phenolic group. An alternative preparation of 3 was envisioned from the reaction of tetracarbonyl[methoxy(2,4-dimethoxyphenyl)carbene]chromium (5)⁶ with the THP ether of 4-pentyn-2-ol,⁷ followed by oxidative workup.



Results. [Methoxy(2,4-dimethoxyphenyl)carbene]Cr(CO)₅ was prepared by the reaction of $Cr(CO)_6$ with 4-lithio-1,3-dimethoxybenzene followed by alkylation with Me₃O⁺BF₄⁻. Decarbonylation gave the chelated carbene complex 5 according to the literature procedure.⁶ The reactions of complex 5 with 3-hexyne and with 1-pentyne have been previously reported.⁸

In our hands, the reaction of 5 (0.033 <u>M</u> in MTBE) with 3-hexyne (3 equivalents) at 45°C, followed by oxidation with CAN, gave a mixture of naphthoquinone **6a** and indenone **7a** (ca. 1:1, Scheme 3). Indenone **7a** was identified in the crude reaction mixture by comparison of its ¹H NMR signals with the literature data.⁸ A pure sample of **6a** was isolated by column chromatography followed by recrystallization. While the melting point and the majority of the spectral data for the present sample matched the literature data, the ¹H NMR signals of the 5- and 7-methoxy groups which we observed (δ 3.90 and 3.88 ppm) are considerably different than those reported⁸ (δ 3.49 and 3.48 ppm). On the basis of ¹H NMR spectral data for other 5,7-dimethoxynaphthoquinones (*vide infra*), our values appear to be more reasonable.

The reaction of 5 (0.1 <u>M</u> in THF) with 1-hexyne (2.3 equivalents) at 45°C, followed by oxidation with CAN, gave a mixture of naphthoquinone **6b** and indanone **7b** (Scheme 3) which were separable by flash chromatography. The

structures of **6b** and **7b** were assigned by comparison their spectral data with that reported for the known corresponding n-propyl derivatives.⁸



The reaction of 5 (ca. 0.1 <u>M</u> in THF) with 1-ethoxypropyne (4.3 equivalents) at 62 °C, followed by oxidation with CAN, gave a mixture of products from which **6c** was isolated after chromatography. A 5,7-dimethoxy-1,4-naphthoquinone skeleton was assigned on the basis of IR (1660, 1594 cm⁻¹) and ¹H NMR spectral data [δ 7.24 (d), 6.65 (d) ppm]. The 2-methyl-3-ethoxy substitutent pattern was assigned by comparison of the ¹³C NMR spectral data of

6c with naphthoquinones 8 and 9 (regiospecifically prepared in an unambiguous fashion).⁹ In particular, the spectral data for the naphthoquinone ring carbons of 8 and 9 are relatively similar ($\Delta \delta \le 0.9$ ppm) except for three signals (Table 1). The signals for 6c more closely match those of 8 than of 9. It should be noted that the annulation of a pyrrole carbene Cr complex with 1-methoxypropyne proceeds with the same regioselectivity for insertion of the alkyne into the Cr-carbene bond.¹⁰



Finally, the reaction of 5 (0.1 <u>M</u> in hexanes) with the THP ether of 4pentyn-2-ol (2 equivalents) at 50 °C, followed by oxidation with CAN, gave a mixture of products from which 3 and 10 were isolated after chromatography (Scheme 3). The spectral data for 3 obtained in this work was identical with that reported in the literature,⁴ and its isolation constitutes a formal total synthesis of 1. Product 10 was identified as a diastereomeric mixture of lactones on the basis of its ¹H NMR spectral data. In particular, the appearance of three aryl protons indicated the 1,2,4-trisubstitued ring, while the appearance of two multiplets at 8 4.74 and 4.54 ppm are indicative of a R₂CHOC(O)R' functionality. The ¹³C NMR spectrum of 10 contains signals for both the aryl ketone carbonyl (ca. 8 196 ppm) and the lactone carbonyl (ca. 8 179 ppm).

Discussion. The reaction between chromium carbene complexes and an alkyne occurs via a multi-step, multi-pathway mechanism (Scheme 4). Insertion of an alkyne into the chromium carbene generates the vinylcarbene complex 11. Further reaction of 11 proceeds either by carbonyl insertion to give the vinylketene complex 12 (and eventually naphthoquinones) or by competing cyclization to give 13 (and eventually indanones/indenones). The relative rate of these steps is dependent on substitutents present on the aryl ring,⁸ oxygen and other substituents present in the alkyne component,¹¹ and the solvent and

concentration at which the reaction is run.¹² Shortly after the present studies were undertaken, the formation of naphthoquinones and indenones/indanones from the reaction of alkoxyphenyl methoxy carbene chromium complexes with 3-hexyne or 1-pentyne was reported.⁸ These authors found that the ratio of six-membered ring formation vs. five-membered ring formation is influenced by varying reaction temperature and the initial concentration of the carbene complex; high concentrations (0.5 M) and lower temperature (45 °C) favor formation of six-membered ring products, while low concentration (0.005 M) and high temperatures (110 °C) favor formation of five-membered ring products. Our results are consistent with these findings; at concentrations which are intermediate (ca. 0.03 to 0.1 M) nearly equivalent amounts of both naphthoquinone and indenone/indanone were formed.



The reaction of chromium aryl carbenes with alkynyl alcohols¹³ and the reaction of chromium carbene complexes with trimethylsilyloxy alkynes¹⁴ is reported to afford lactone products. These products arise via intramolecular

attack of the hydroxyl/ether group on the vinyl ketene complex to form a lactol species 14. Oxidative workup and the presence of acid results in hydrolysis of the enol ethers to give lactone products. In the present work, the diastereomeric lactone products 10 are presumably formed by a similar mechanism.

In summary, the reaction of [methoxy(2,4-dimethoxyphenyl)carbene]-Cr(CO)₄ (5) with alkynes gives naphthoquinone products, albeit in low yield. While the yields are low, the present one-step preparation affords a higher yield of 3 than the 7-step literature procedure.⁴

Experimental Section

Reaction of (5) with 3-hexyne. A solution of 5 (231 mg, 0.671 mmol) and 3hexyne (0.22 mL, 2.0 mmol) in TBME (20 mL) was degassed by three freezepump-thaw cycles. The reaction mixture was then heated at 45 °C for 8 h. The reaction mixture was cooled to rt and the solvent evaporated under high vacuum. The residue was dissolved in acetic acid (50 mL) and excess (NH₄)₂Ce(NO₃)₆ was added. The mixture was stirred for 1 h and then diluted with H₂O (30 mL) and extracted with ether (2 x 30 mL). The combined ether extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) and the solvent evaporated to afford a golden yellow semi-solid. Purification of the residue by chromatography (flash SiO₂, Et₂O) followed by recrystallization from Et₂O/petroleum ether gave **6a** as a golden yellow solid (37 mg, 20%).

6a: mp 158-160 °C (lit.⁸ mp 154-156 °C); IR (CH₂Cl₂, cm⁻¹) 1655, 1597; ¹H NMR (300 MHz, CDCl₃) & 7.19 (d, J = 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 3.90 and 3.88 (2 x s, 6H), 2.55 and 2.53 (2 x q, J = 7.7 Hz, 4H), 1.08 and 1.07 (2 x t, J = 7.7 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) & 185.2, 183.2, 164.1, 161.5, 150.0, 145.1, 136.2, 114.7, 103.8, 102.4, 56.3, 55.8, 20.2, 19.9, 14.0, 13.7; MS (m/z, rel int) 274 (100, M⁺), 259 (97), 237 (78), 106 (45); Anal. calcd for C₁₆H₁₈O₄: C, 70.06; H, 6.61. Found: C, 69.68; H, 6.35.

Reaction of (5) with 1-hexyne. A solution of 5 (705 mg, 2.05 mmol) and 1-hexyne (383 mg, 4.66 mmol) in THF (20 mL) was degassed by three freezepump-thaw cycles. The reaction mixture was heated at 45 °C for 6 h and then cooled to rt and stirred for 12 h. Additional 1-hexyne (50 mg, 0.61 mmol) was added and the reaction mixture was heated at 45 °C for an additional 6 h. The reaction mixture was cooled to rt and the solvent evaporated under high vacuum. The residue was dissolved in acetic acid (40 mL) and excess $(NH_4)_2Ce(NO_3)_6$ was added. The mixture was stirred at rt for 90 min and then diluted with H₂O (30 mL) and extracted with ether (2 x 30 mL). The combined ether extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) and the solvent evaporated. Purification of the residue by chromatography (flash SiO₂, Et₂O) gave **6b** as a yellow solid (31 mg, 6%). Further elution (Et₂O-CH₂Cl₂, 2:1) gave **7b** as a pale yellow oil (95 mg, 19%).

6b: mp 109-114 °C; IR (CH₂Cl₂, cm⁻¹) 1653, 1596; ¹H NMR (300 MHz, CDCl₃) δ 7.24 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.61 (t, J = 1.3 Hz, 1H), 3.95 and 3.93 (2 x s, 6H), 2.48 (dt, J = 1.3, 7.6 Hz, 2H), 1.57-1.32 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 185.5, 183.6, 164.5, 161.6, 148.5, 137.3, 136.4, 104.1, 103.5, 56.4, 55.9, 29.9, 28.6, 22.4, 13.8 (signal for C5a too weak to be observed); MS (m/z, rel int) 274 (100, M⁺), 256 (33), 203 (56), 165 (45), 106 (35); Anal. calcd for C₁₆H₁₈O₄·0.75 H₂O: C, 66.77; H, 6.83. Found: C, 66.62; H, 6.56.

7b: ¹H NMR (300 MHz, CDCl₃) & 6.48 (d, J = 1.7 Hz, 1H), 6.29 (d, J = 1.8 Hz, 1H), 3.89 and 3.87 (2 x s, 6H), 3.19 (m, 1H), 2.78 (dd, J = 7.6, 18.6 Hz, 1H), 2.32 (dd, J = 3.3, 18.6 Hz, 1H), 1.8-1.2 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) & 202.5, 166.9, 164.2, 159.1, 119.0, 100.8, 97.3, 55.7, 55.6, 43.7, 37.9, 35.6, 29.4, 22.7, 13.9; MS (m/z, rel int) 248 (100, M⁺), 219 (39), 205 (35), 192 (98), 191 (48).

Reaction of (5) with 1-ethoxy-1-propyne. A solution of 5 (818 mg, 2.37 mmol) and 1-ethoxy-1-propyne (870 mg, 10.3 mmol) in THF (25 mL) was degassed by three freeze-pump-thaw cycles. The reaction mixture was then heated at 62 °C for 34 h, and then stirred at rt for 11 h. The solvent was evaporated under high vacuum and the residue was dissolved in a mixture of acetic acid/CH₂Cl₂. After stirring for 90 min, excess (NH₄)₂Ce(NO₃)₆ was added and the mixture was stirred for 90 min. The mixture diluted with H₂O and the layers separated. The aqueous layer was extracted with ether (2 x 30 mL) and the combined CH₂Cl₂ layers were washed with H₂O. The CH₂Cl₂ layer was diluted with an equal volume of H₂O, and solid NaHCO₃ was added until the aqueous layer was basic. The layers were separated and the organic layer was washed with brine, dried

(MgSO₄) and the solvent evaporated. Purification of the residue by chromatography (SiO₂, Et₂O) gave **6c** as a golden yellow solid (143.6 mg, 22%). **6c**: mp 135-138 °C; Rf = 0.44 (Et₂O); IR (CH₂Cl₂, cm⁻¹) 1660, 1594; ¹H NMR (300 MHz, CDCl₃) δ 7.24 (d, J = 2.4, 1H), 6.65 (d, J = 2.4 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.94 and 3.91 (2 x s, 6H), 2.01 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 185.8, 179.2, 164.7, 161.8, 158.6, 136.4, 128.9, 113.7, 103.6, 103.2, 69.5, 56.4, 55.9, 16.1, 9.0; MS (m/z, rel int) 276 (84, M⁺), 261 (31), 232 (100); Anal. calcd for C₁₅H₁₆O₅: C, 65.21; H, 5.84. Found: C, 64.80; H, 5.70.

1-Pentyn-4-yl tetrahydropyranyl ether was prepared from 4-pentyn-2-ol and dihydropyran according to the literature procedure.⁶ The spectral data for this complex is consistent with the 60 MHz ¹H NMR spectral data. All of the other spectral data is reported for the first time. ¹H NMR (300 MHz, CDCl₃) & 4.68 (dd, J = 2.7, 4.9 Hz) and 4.64 (t, J = 3.5 Hz, total 1H), 3.94-3.78 (m, 2H), 3.45-3.39 (m, 1H), 2.48 (ddd, J = 2.7, 5.1, 16.5 Hz, 0.5H), 2.40-2.18 (m, 1.5H), 1.92 and 1.90 (2 x t, J = 2.8 Hz, total 1H), 1.80-1.40 (m, 6H), 1.25 and 1.18 (2 x d, J = 6.2 Hz, total 3H); ¹³C NMR (75 MHz, CDCl₃) & 97.6 [96.6], 81.3 [81.0], 77.4, 76.9, 76.5, 70.7 [70.4], 69.6, 62.4 [62.1], 30.8 [30.7], 26.9, 25.6, 25.3, 20.8, 19.5 [19.3], 18.7; MS (m/z, rel int) 168 (0.5, M⁺), 153 (1.5), 129 (9), 110 (8), 101 (44), 95 (13), 86 (39), 85 (100); Anal. calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.15; H, 7.93.

Reaction of (5) with 1-pentyn-4-yl tetrahydropyranyl ether. A solution of 5 (0.733 g, 2.13 mmol) and (0.717 g, 4.26 mmol) in n-hexane (20 mL) was degassed by three freeze-pump-thaw cycles. The reaction mixture was then heated at 50 °C for 3.5 h. The reaction mixture was cooled to rt and stirred for 3 d. The solvent was evaporated under high vacuum and the residue was dissolved in acetic acid (40 mL) and excess (NH₄)₂Ce(NO₃)₆ was added. The mixture was stirred for 24 h and then diluted with H₂O (30 mL) and extracted with ether (2 x 30 mL). The combined ether extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) and the solvent evaporated. Purification of the residue by chromatography (SiO₂, CH₂Cl₂-Et₂O (1:1) gave **10** as an oil (103 mg, 22%). Further elution (Et₂O-MeOH (4:1)) gave **3** as a golden yellow solid (58.2 mg, 10%). This latter fraction was purified by preparative TLC (20 cm x 20 cm SiO₂, CHCl₃-Et₂O (1:1)).

10: Rf 0.24 (CHCl₃-Et₂O (1:1)); ¹H NMR (300 MHz, CDCl₃) δ 7.86 (2 x d, J = 8.8 Hz, 1H), 6.52 (2 x dd, J = 2.4, 8.8 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 4.74 (m) and 4.54 (qd, J = 6.1, 16.1 Hz, total 1H), 3.88 and 3.84 (2 x s, 6H), 3.60 (m, 2H), 3.20 (m, 1.5 H), 2.67 and 2.25-2.02 (m, 1.5 H), 1.41 and 1.38 (2 x d, J = 6.2 Hz, total 3H); ¹³C NMR (75 MHz, CDCl₃) δ 196.4 [196.3], 179.6 [179.1], 164.9, 161.2, 132.8, 119.9 [119.8], 105.3, 98.2, 75.5 [75.1], 55.5 [55.4], 44.7 [44.5], 37.7 [37.6], 35.1, 21.3 [20.9]; diastereometric signals in brackets.

3: ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, J = 2.4 Hz, 1H), 6.73 (narrow t, 1H), 6.72 (d, J = 2.4 Hz, 1H), 4.09 (m, 1H), 3.95 and 3.94 (2 x s, 6H), 2.72 (ddd, J =1.2, 4.2, 13.9 Hz, 1H), 2.57 (ddd, J = 1.0, 7.8, 13.9 Hz, 1H), 1.27 (d, J = 6.0 Hz, 3H), signal for OH not observed; ¹³C NMR (75 MHz, CDCl₃) δ 184.9, 164.6, 161.6, 144.9, 139.6, 136.0, 114.4, 104.3, 103.6, 65.8, 56.5, 55.9, 29.7, 14.1; EI-HRMS *m*/z 276.0983 (calcd for C₁₅H₁₆O₅ *m*/z 276.0998).

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