Facile Unmasking of Dicobalt Hexacarbonyl Complexes of 1-Cyclodecene-3,9-diynes (Enediynes)

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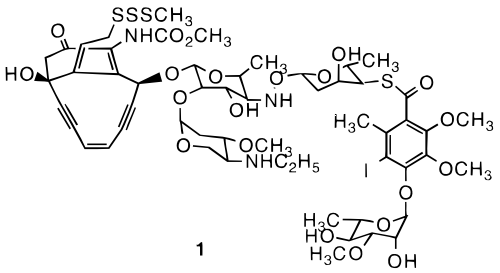
Introduction

Cyclic enediynes have become increasingly important over the past decade since the isolation of naturally ocurring enediyne antitumor agents including calicheamicin (**1**),[1] a derivative of which is currently undergoing clinical trials for the treatment of myeloid leukemia.[2] The



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pharmacophore of the enediyne antibiotics is described either by a 9- or 10-membered cyclic enediyne subgroup, many of which show antitumor activity in their own right.[3] The origin of antitumor activity of cyclic C-10 enediynes resides in the ability of the enediyne subgroup to undergo Bergman cyclization resulting in a reactive 1,4-diyl radical. These diyl intermediates are capable of causing single- and double-stranded DNA breaks and possibly protein lesions. These two events presumably play a dominant role in the biological activity of enediynes.[1]

The half-lives for unstrained 10-membered carbocyclic enediynes is around 8−24 h at physiological temperature; thus, any attempted chemical synthesis of cyclic enediynes must be mindful of this thermal lability. We recently developed a direct synthetic route to cyclic C-10 enediynes **2**, based on a low-temperature carbenoid coupling−elimination strategy, and found it desirable to mask the product enediynes to enable handling and manipulation at ambient temperature.[4] Encouraged by literature reports,[5] we elected to protect the products as the corresponding dicobalt hexacarbonyl complexes **3**. As expected, the complex **3** (X = CH_2) proved thermally stable over extended periods and was amenable to routine manipulation and spectroscopic analysis, which confirmed that both alkynes had undergone complexation. Though methods to effect decomplexation to give **2** had been described, we were particularly interested in minimizing in situ thermal decomposition of the enediyne product and, thus, desired a convenient method that worked rapidly at low temperature.

Results and Discussion

To assay the biological effects of enediyne-derived diyls **4** effectively, it was essential for us to employ a rapid method for unmasking of the complexes **3**. Such a method would then allow shelf-stable precursors **3** to be converted to the enediyne immediately, allowing batch-style bioassay methods to be employed. Due to the thermal lability of the enediyne **2** (X = CH_2), we elected to initially study unmasking methods using a model compound of comparable molecular weight and, thus, prepared and investigated the cobalt carbonyl complex of 5-decyne, **7** (Scheme 2). The results of the decomplexation study are presented in Table 1. Established methods such as oxidative decomplexation using trimethylamine *N*-oxide,[6] while effective at low temperature, required multiple equivalents to achieve quantitative recovery of alkyne (Table 1, entries 1−3). Ferric nitrate proved sluggish with multiple equivalents (Table 1, entry 4),[7] and potassium nitrosodisulfonate (Fremy's salt) gave only moderate yields with 10 equiv of agent (Table 1, entry 5). Ceric ammonium nitrate (CAN), however, worked extremely well at low temperature with 1 equiv of agent (Table 1, entry 6).[8] In an effort to find a convenient system that could work quantitatively using minimal amounts of reagent, a range of other ammonium salts were investigated, and it was eventually discovered that TBAF/THF could induce decomplexation (Table 1, entries 8−13). Reactions were smooth at low temperature, giving a near-quantitative yield of product within 3 h at −10 °C (Table 1, entry 14). Given the commercial availability of this agent as a stock solution[9] and the potential for few side reactions with its use,[10] it was thus adopted as the agent of choice for all subsequent deprotections. With mild and efficient methods for decomplexation in hand, bis(dicobalt hexacarbonyl) complexes of the known enediynes **2** (X = CH_2, S, O) were prepared, and TBAF/THF-induced deprotection was investigated. As demonstrated in the model system, this method worked extremely well at −10 °C and allowed isolation of essentially pure enediyne following brief workup (Table 2). Half-lives of the enediynes (37 °C) were in agreement with reported/calculated values (X = CH_2 18 h,[11] X = S

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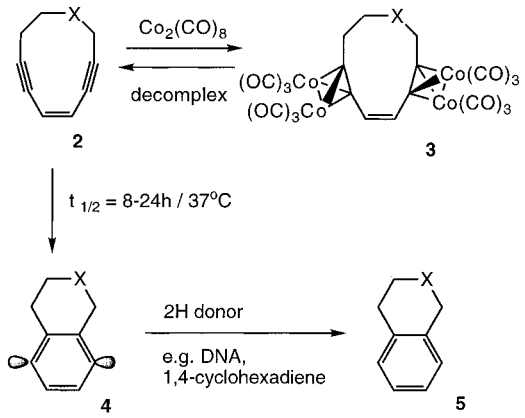
Scheme 1. Thermal Decomposition of Unstrained Enediynes



Scheme 2. Decomplexation of 5-Decyne·$Co_2(CO)_6$

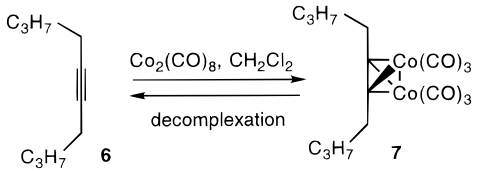


Table 1. Decomplexation of Dicobalt Hexacarbonyl Complex 7

entry	reagents	equiv	solvent	*T* (°C)	% **6**
1	$(CH_3)_3NO$	1	THF	−10/4	61
2	$(CH_3)_3NO$	1	THF	−78/2	32
3	$(CH_3)_3NO$	5	CH_3COCH_3/THF	−78/4	>99
4	$Fe(NO_3)_3·H_2O$	5	CH_3COCH_3/THF	+25/12	90
5	$(KSO_3)_2NO$	10	CH_3COCH_3/THF	−78/3	33
6	$Ce(NH_4)_2(NO_3)_6$	6	CH_3COCH_3/THF	−78/3	>99
7	$Ce(NH_4)_2(NO_3)_6$	1	CH_3COCH_3/THF	−78/3	77
8	Bu_4NHSO_4	10	H_2O/THF	+25/12	20
9	Bu_4NClO_4	10	H_2O/THF	+25/48	5
10	Bu_4NCl	10	H_2O/THF	+25/12	10
11	Bu_4NBr	10	H_2O/THF	+25/48	10
12	Bu_4NPF_6	10	THF	+25/12	5
13	Bu_4NF	10	THF	+25/1	>99
14	Bu_4NF	5	THF	−10/3	>99
15	Bu_4NF	1	THF	−10/4	98
16	Bu_4NF	1	THF	−78/5	96

Table 2. TBAF/THF Decomplexation of Enediyne Complexes 3

entry	X	equiv	*T* (°C)	% **2**
1	CH_2	2	−10/2	93
2	CH_2	2	−78/4	84
3	CH_2	10	−10/20 min	>95
4	CH_2	10	−78/1	>95
5	O	2	−10/2	92
6	S	2	−10/2	81

22 h,[12] X = O 15 h[13]), confirming the utility of the protection strategy.[14,15] Since the entire deprotection strategy can be completed in less than 30 min, it thus allows biological evaluation of the enediynes **2** and diyls **4** that they generate to be conducted on demand and is expected to find application in other thermally labile enediyne-type systems where conventional methods are ineffective.[16] Significantly, deprotection of **3**, X = CH_2, using CAN required >6 equiv of reagent at −10 °C and required chromatographic purification of the product (70%).

In summary, a facile method for decomplexation of cobalt carbonyl-complexed acetylenes has been developed. The method provides the opportunity for rapid unmasking of thermally labile cyclic enediyne derivatives and may also find application in the deprotection of other useful substrates.[7,17]

Experimental Methods

Unless stated otherwise, all reactions described herein were performed in glassware that had been oven dried (140 °C/12 h) and then flame dried prior to use. Reactions were conducted under an atmosphere of nitrogen, with flasks sealed using dried septa (P_2O_5). The tips of the cannulas were flame dried under a stream of dry nitrogen gas prior to use. THF was distilled immediately prior to use from sodium−benzophenone ketyl. Methylene chloride was distilled from P_2O_5. Dicobalt octacarbonyl was obtained from Strem Chemicals. All other reagents and solvents were commercial grade and purified according to standard convention. Chromatography was perfomed on Brockmann grade I neutral alumina. Analytical TLC was performed on glass-backed 250 μm plates visualized with anisaldehyde and phosphomolybdic acid.

5-Decyne−Dicobalt Hexacarbonyl Complex 7. 5-Decyne (0.97 g, 7.0 mmol) was dissolved in cold CH_2Cl_2 (120 mL) in a 1000 mL round-bottomed flask. The contents of the flask were slowly cannulated into a solution of dicobalt octacarbonyl (3.00 g of 90 wt %/wt in hexane, 8.8 mmol) in CH_2Cl_2 (300 mL) that had been precooled to −10 °C. The resulting solution was allowed to stir in the dark for 12 h at −10 °C, after which time the red liquid was filtered (under an atmosphere of nitrogen) by cannula through a plug of neutral alumina and concentrated in vacuo. Column chromatography (alumina, hexane eluent) afforded 2.55 g (93% yield) of the complexed 5-decyne as a deep red oil: ^{1}H NMR (300 MHz, $CDCl_3$) 2.82 (t, J = 7.5 Hz, 4H), 1.53 (m, 8H), 0.958 (t, J = 6.9, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 99.9, 33.8, 22.7, 13.8; IR (CCl_4) 3412, 2970, 2025, 1472 cm^{-1}; MS (EI) 138 (14), 95 (53), 81 (82), 67 (100), 54 (95). Anal. Calcd for $C_{16}H_{18}Co_2O_6$: C, 45.31; H, 4.28. Found: C, 45.34; H, 4.33.

1-Cyclodecene-3,9-diyne−bis(dicobalt hexacarbonyl) complex 3, X = CH_2 was prepared from 1-cyclodecen-3,9-diyne:[4,11] mp 105−110 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 2H), 3.24 (s, 4H), 1.89 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 125.7, 97.4, 83.8, 33.0, 29.2; IR (CCl_4) 2935, 2085, 2050 cm^{-1}.

3,4,7,8-Tetradehydro-9,10-dihydro-2*H*-oxecine−bis(dicobalt hexacarbonyl) complex 3, X = O was prepared from 3,4,7,8-tetradehydro-9,10-dihydro-2*H*-oxecine:[13] mp 45−50 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (q, J = 10.5 Hz, 2H), 4.98 (s, 2H), 3.93 (t, J = 6.54 Hz, 2H), 3.35 (t, J = 6.51 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 126.9, 124.9, 94.2, 92.0, 84.9, 83.0, 70.0 (d), 34.9; IR (CCl_4) 3429, 2944, 2068, 1651, 1097, 519 cm^{-1}; MS (EI) 134 (40), 104 (100), 77 (57).

3,4,7,8-Tetradehydro-9,10-dihydro-2*H*-thiecine−bis(dicobalt hexacarbonyl) complex 3, X = S was prepared from 3,4,7,8-tetradehydro-9,10-dihydro-2*H*-thiecine:[12] mp 65−70 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 2H), 4.15 (s, 2H), 3.49 (t, J = 6.05 Hz, 2H), 2.96 (t, J = 6.08 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 125.6, 94.6, 94.2, 84.3, 83.1, 33.8 (t), 29.7; IR (CCl_4) 3447, 2034, 1651 cm^{-1}.

General Procedure for TBAF−THF-Induced Decomplexation. Complex **3**, X = CH_2 (50.0 mg, 0.0705 mmol), was dissolved in THF (0.5 mL) and the resulting solution cooled to −10 °C. With stirring at −10 °C, TBAF (0.705 mmol of 1.0 M

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(14) Enediynes **2** were incubated with 1,4-cyclohexadiene (30 equiv) at 37 °C in benzene-d_6 and formation of the corresponding tetrahydronaphthalenes **5** monitored by ^{1}H NMR.

(15) Nicholas has developed an elegant decomplexation strategy involving reduction via sodium−benzophenone ketyl followed by reoxidation and demonstrated its utility using cycloocta-1,5-diyne complexes (Melikyan, G. G.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1995**, *14*, 2170).

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(17) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737.

in THF) was added over 1 min. The reaction mixture was allowed to stir for 20 min and then filtered through a plug of neutral alumina and the plug washed with Et_2O (2 × 10 mL). The resulting ethereal solution was shaken with water (2 × 10 mL) and then dried over $MgSO_4$, filtered through a pad of Celite, and concentrated in vacuo to give cyclodec-3-ene-1,5-diyne (8.9 mg, 95%) as a thermally unstable oil, spectroscopically identical with previously prepared samples:[4,11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 2H), 2.37 (m, 4H), 1.93 (pent, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.2, 104.1, 82.4, 28.8, 21.6.

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