Pergamon

Tetrahedron Letters, Vol. 35, No. 3, pp. 363-366, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0232-9

A Novel and Efficient Synthesis of Cyclic and Acyclic 1,5-Alkadiynes by Selective Coupling of $Co_2(CO)_6$-Complexed Propargyl Radicals

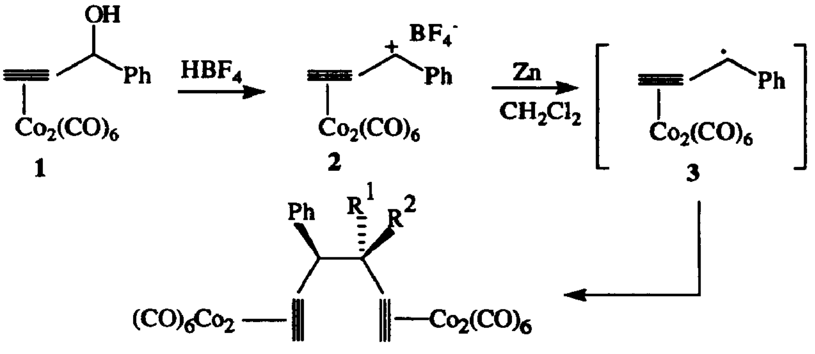
Gagik G. Melikyan*, Richard C. Combs, John Lamirand, Masood Khan and Kenneth M. Nicholas*

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, USA

Abstract: Intra- and intermolecular coupling reactions of $Co_2(CO)_6$-complexed propargyl radicals have been realized providing cyclic and acyclic 1,5-alkadiynes in moderate yield and moderate to good diastereoselectivity (44-80%).

The ability of organometallic fragments to dramatically influence the stability/reactivity of coordinated molecules and ions is well-documented and of central importance in organic synthesis. However, despite the recent renaissance in organic radical chemistry, the reactivity of carbon-centered organometallic radicals is almost unknown.[1] While investigating the chemistry and synthetic utilization of $Co_2(CO)_6$-complexed propargyl cations (e.g. **2**),[2] we have turned our attention to the chemistry of the corresponding radicals **3**. First postulated as intermediates in the reaction of propargyl halides with $Co_2(CO)_8$[3] and in some coupling reactions of **2**,[4] the involvement of these radicals has been implicated recently in Mn-promoted additions to Co-complexed 1,3-en-ynes.[5] We now report that reduction of the readily available propargylium salts **2**[6] provides a novel and convenient source of (propargyl)$Co_2(CO)_6$ radicals[7] and that these species enter into efficient inter- and intramolecular coupling reactions, affording a useful route to acyclic and cyclic 1,5-alkadiynes.

Initial experiments utilized the phenyl-substituted complex **2** and granular zinc (30-100 mesh) as the reductant. Thus, **2** (0.1M in CH_2Cl_2), derived from protonation of alcohol **1** at -40 °C,[6] was stirred at r.t. with an equimolar amount of Zn. Complete conversion was achieved within an hour, producing easily separable (SiO_2, pentane) *dl/meso* diastereomers **4** and **5**[8] (75:25) in 76% overall yield from **1**.



4 (R^1=Ph; R^2= H), **5** (R^1=H; R^2= Ph)

Scheme 1

The configuration of the major isomer **4** was established as *dl* by X-ray diffraction (Fig. 1).

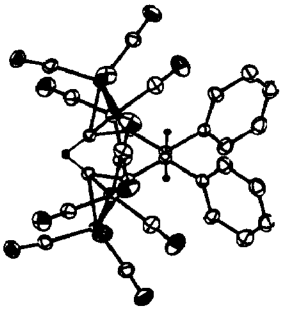
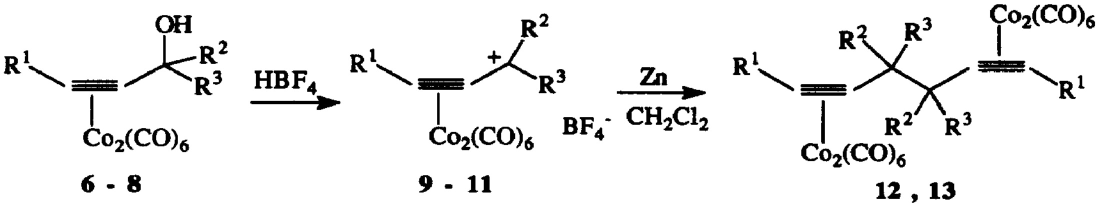


Figure 1. ORTEP diagram of dl-4

Decomplexation of **4** and **5** with cerium(IV) ammonium nitrate (CAN)[9] produced *dl*- and *meso*-3,4-diphenyl-1,5-hexadiynes, respectively, each in 87% yield.

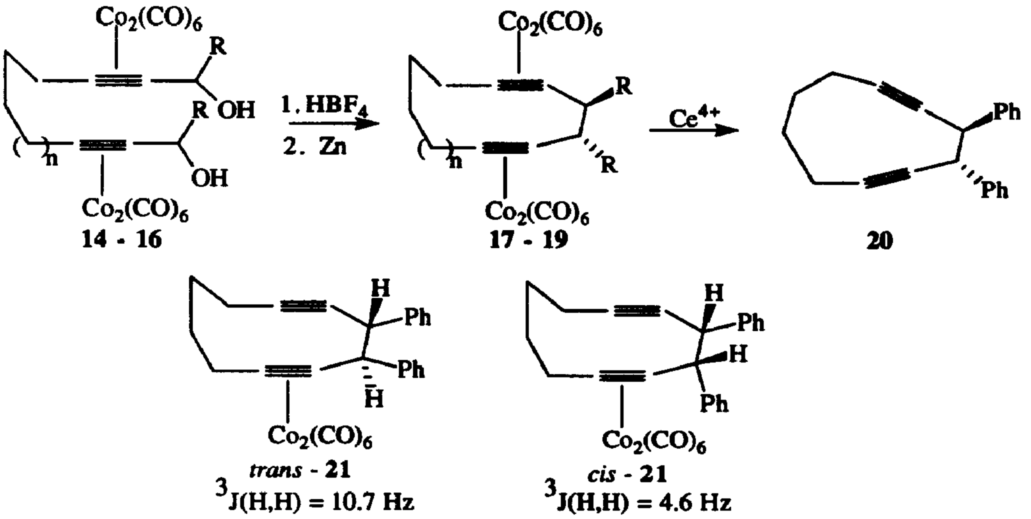
A preliminary assessment of the scope of the intermolecular reactions was carried out using the above (unoptimized) conditions. Thus, the primary cation complex **9** ($R^1=C_7H_{15}$, $R^2=R^3=H$) produced from **6** reacted with Zn to give both coupling and H-atom abstraction products- 8,12-eicosadiyne complex **12** (21 % from **9**) and (2-decyne)$Co_2(CO)_6$ (3.5 %). The secondary complex **10** ($R^1=R^2=H$; $R^3=CH_3$) underwent reductive coupling exclusively to **13** (21% from alcohol **7**) with a diastereoselectivity (72:28) similar to the Ph-analog **2**. Reductive dimerization of tertiary complex **11** ($R^1=H$; $R^2=R^3=CH_3$) derived from **8** was unsuccessful, however, with the products of H-atom abstraction, $[HC{\equiv}CCH(CH_3)_2]Co_2(CO)_6$ (19 %), and electrophilic coupling, $[HC{\equiv}CC(CH_3)_2CH_2C(=CH_2)C{\equiv}CH]\{Co_2(CO)_6\}_2$ (18 %), only being isolated.



Scheme 2

These intermolecular dimerizations are noteworthy in several respects. Firstly, due to the protection of the triple bond by the $Co_2(CO)_6$-group, the radical(oid) species generated undergo regiospecific *propargyl-propargyl* coupling in contrast to the regioisomeric mixtures observed in reductions of conventional propargyl or allenyl substrates.[10] Secondly, reduction occurs under mild conditions (-40° --> +20°C) allowing the metal cluster to survive and coupling to occur as the dominant pathway for primary and secondary substrates. Thirdly, the significant diastereoselectivity observed (de 44, 50%) with the secondary substrates is rather unusual for organic radical dimerizations, which typically show no stereoselectivity.[11] Additionally, reductive dimerization of (pentadienylium)iron- and (propargylium)Mo_2- salts and reduction of (benzylium)$Cr(CO)_3$ complexes with Grignard reagents produce dimerization products stereorandomly.[1]

Perhaps of greater synthetic impact are *intra*molecular variants of the reductive coupling process involving bis-radicals (Scheme 3).[12] Thus the Ph-substituted dication complex derived from **14** (R=Ph, n=1) was reduced [excess zinc (1:70), 0.005 M CH_2Cl_2[13] at 20 °C] producing 3,4-diphenyl-1,5-cyclodecadiyne complex **17** (51%) as a 90:10 ratio of diastereomers. The stereochemistry of the products **17** was determined by ^{1}H NMR analysis of the lower symmetry derivatives, *mono*-$Co_2(CO)_6$ complexes *cis*- and *trans*-**21**, which were obtained by controlled oxidation of **17** (CAN addition rate: 1eq/0.5hr at -78°C). The $^{3}J(H,H)$ values of 10.7 Hz and 4.6 Hz, respectively, allowed assignment of the *dl*-stereochemistry to the major isomer.



Scheme 3

This intramolecular coupling reaction exhibits remarkably high stereoselectivity (de 80%),[14] although the moderate yield does not exclude the possibility of selective destruction of the *meso*-isomer. Decomplexation of **17** with CAN proceeds rapidly at -78 °C (8 eq, 15 min) producing 3,4-diphenyl-1,5-cyclodecadiyne (**20**, *dl/meso* 88:12) in 91% yield. The present macrocyclization process has general promise for the efficient synthesis of medium-sized 1,5-diynes as evidenced by the successful generation of the parent 10- and 9-membered rings from primary alcohols **15** (R=H, n=1) and **16** (R=H, n=0), affording **18** (46%) and **19** (20%). Previously, 1,5-cyclodecadiyne and 1,5-cyclononadiyne have been synthesized by multistep schemes in low overall yields (8 steps, 1.9% and 7 steps, 0.5%, respectively).[15] *In contrast, the Co-mediated approach furnishes 10-membered monocyclic 1,5-alkadiynes in 4 steps with an overall yield of 20-23 %.* These reactions may benefit from the bent geometry of the coordinated $C{\equiv}C$[16] which serves to bring the reactive radical centers in closer proximity and decreases ring strain in the macrocycle.

1,5-Alkadiynes and 1,5-cycloalkadiynes are important classes of organic compounds, serving as substrates in the Co-mediated [2+2][17]- and [2+2+2][18]- construction of fused and bridged polycyclic systems, as models for studying the through-space electronic interaction of two triple bonds,[19] and because of their relationship to the cyclic ene-diyne core of the potent antitumor antibiotics esperamicin, calicheamicin, neocarzinostatin and dynemicin.[20] The present reductive cyclization process provides a novel, flexible (i.e. ring size and substitution pattern), and improved route to cycloalkadiynes along with new evidence of the unique reactivity associated with π-complexed radicals. Studies are underway to fully define the scope of these radical coupling reactions, including their potential for producing cyclic ene-diynes.

Acknowledgement. We are indebted to the U.S. National Institutes of Health (Grant No. GM 34799) for support of this research.

References and Notes.

1. Evidence for the following organometallic radicals has been presented: a) (pentadienyl)Fe$(CO)_3$: Mahler, J.E.; Gibson, D.H.; Pettit, R. *J.Am.Chem.Soc.* **1963**, *85*, 3959-3963; b) Pearson, A.J.; Chen, Y.; Daroux, M. L.; Tanaka, A. A.; Zettler, M. *Chem.Soc.Chem.Comm.* **1987**, 155-157; c) (propargyl)$Cp_2Mo_2(CO)_4$: Berre-Cosquer, N.; Kergoat, R; L'Haridon, P. *Organometallics* **1992**, *11*, 721-728; d) (benzyl)Cr$(CO)_3$: Top, S.; Jaouen, G. *J.Organomet.Chem.* **1987**, *336*, 143-151.
2. Nicholas, K.M. *Acc. Chem. Res.* **1987**, *20*, 207-214.
3. Tirpak, M.R.; Hollingsworth, C.A.; Wotiz, J.H. *J.Org.Chem.* **1960**, *25*, 687-690.
4. Padmanabhan, S.; Nicholas, K.M. *J.Organomet.Chem.* **1981**, *212*, 115-124.
5. Melikyan, G.G.; Vostrowsky, O.; Bauer, W.; Bestmann, H.J. *J.Organomet.Chem.* **1992**, *423*, C24-27; Melikyan, G.G.; Vostrowsky, O.; Bauer, W.; Bestmann, H.J.; Khan, M.; Nicholas, K.M. *J. Org. Chem.* (submitted).
6. Varghese, V.; Saha, M.; Nicholas, K.M. *Org. Syn.* **1988**, 141-147.
7. Although direct evidence for the generation of "free" radicals is presently lacking, the observed reactions (*vide infra*) are consistent with the involvement of such species.
8. Satisfactory spectroscopic and analytical data were obtained for all Co-complexes and decomplexation products.
9. a) Seyferth, D.; Nestle, M.O.; Wehman, A.T. *J.Am.Chem.Soc.* **1975**, *97*, 7417-7426; b) Saha, M.; Muchmore, S.; van der Helm, D.; Nicholas, K.M. *J.Org.Chem.* **1986**, *51*, 1960-1966.
10. Badanyan, Sh.O.; Voskanyan, M.G.; Chobanyan, Zh.A. *Russ,Chem.Rev.* **1981**, *50*, 1074-1086.
11. Ruchardt, C. *Top.Curr.Chem.* **1980**, *88*, 1-32; Porter, N.A.; Krebs, P.J. *Top.Stereochem.* **1988**, *18*, 97-127.
12. The bis-cationic salts were generated according to the standard mono-cation protocol (ref. 6) from the corresponding bis-carbinol complexes **14-16**. These, in turn, were synthesized in two steps (48-52% overall yield) via deprotonation(BuLi)/addition of commercially available 1,6- and 1,7-alkadiynes to the appropriate aldehydes followed by treatment with $Co_2(CO)_8$.
13. Maximum concentration since the bis-cation salts are sparingly soluble in CH_2Cl_2.
14. High diastereoselectivity has also been found in one other case involving reductive cyclization of a bis-[tricarbonyl(pentadienylium)iron] complex to a 5-membered carbocycle. Sapienza, R.S.; Riley, P.E.; Davis, R.E.; Pettit, R. *J. Organomet. Chem.* **1976**, *121*, C35-40.
15. Gleiter, R.; Kratz, D.; Schafer, W.; Schehlmann, V. *J. Am. Chem. Soc.* **1991**, *113*, 9258-9264.
16. For other illustrations and exploitations of this effect see e.g.: ref. 9b; Magnus, P.; Pitterna, T. *J. Chem. Soc., Chem. Commun.*, **1991**, 541-543; Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.*, **1989**, *30*, 309-312.
17. King, R.B.; Efraty, A. *J. Am. Chem.Soc.* **1972**, *94*, 3021-3025.
18. Vollhardt, K.P.C. *Angew. Chem. Int. Ed.* **1984**, *23*, 539-644.
19. Gleiter, R.; Schafer, W. *Acc. Chem. Res.* **1990**, *23*, 369-375.
20. Nicolaou, K.C.; Dai, W.M. *Angew. Chem. Int. Ed.* **1991**, *30*, 1387-1530.

(*Received in USA* 24 *September* 1993; *accepted* 10 *November* 1993)