Pergamon

Tetrahedron Letters 41 (2000) 8687–8690

TETRAHEDRON
LETTERS

Synthesis of benzofuran derivatives through the coupling of conjugated dienynes with Fischer carbene complexes

James W. Herndon,* Yi Zhang, Haixia Wang and Ke Wang

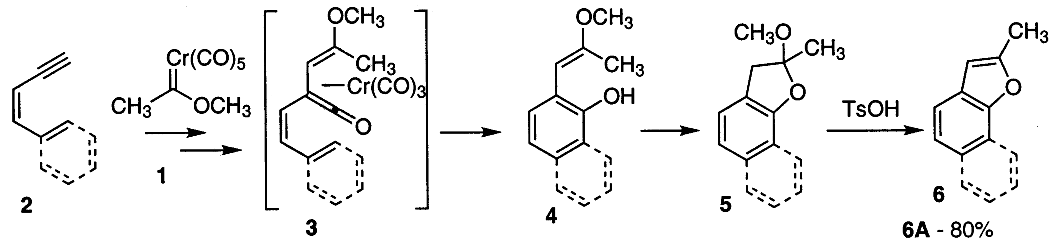
Department of Chemistry & Biochemistry, New Mexico State University, MSC 3C, Las Cruces, NM 88003, and Department of Chemistry & Biochemistry, University of Maryland, College Park, MD 20742-2021, USA

Received 30 June 2000; revised 10 August 2000; accepted 14 September 2000

Abstract

The reaction of Fischer carbene complexes with conjugated dienylacetylene derivatives followed by treatment with iodine leads to benzofuran derivatives in good-to-excellent yields. Equivalent products can be obtained from coupling of conjugated enediynes with Fischer carbene complexes in the presence of hydrogen atom donors. © 2000 Published by Elsevier Science Ltd.

In several recent publications, annulation processes employing the coupling of Fischer carbene complexes with highly conjugated acetylene derivatives have been demonstrated. Specific classes of conjugated acetylenes include arylvinylacetylenes,[1] cyclopropylvinylacetylenes,[1] enediynes,[2] enyne aldehydes,[3] and *o*-alkynylbenzoyl derivatives.[4] The coupling of Fischer carbene complex **1** (Scheme 1) with arylvinylacetylenes (e.g. **2A**) results in benzannulation, ultimately affording naphthofuran derivatives **5A** or **6A**, depending upon the reaction conditions. This process is mechanistically related to the Dötz benzannulation reaction[5] in that a chromium carbene-generated arylvinylketene complex (e.g. **3A**) cyclizes to a phenol derivative (**4A**), which ultimately converts to the observed products **5A** or **6A**, depending upon the workup procedure.



Scheme 1. Compounds **2**–**6**: (A) Dashed atoms included (phenyl series). (B) Dashed atoms omitted (vinyl series)

---

* Corresponding author. E-mail: jherndon@nmsu.edu

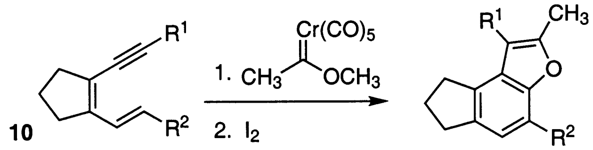
PII: S0040-4039(00)01574-4

In this manuscript the focus is on coupling of Fischer carbene complexes with dienylacetylenes (e.g. **2B**), which should in theory provide simple benzofuran derivatives (**6B**). The benzofuran ring system is a very important pharmacophore and is present in numerous biologically-active natural and synthetic compounds.[6] Most syntheses of benzofurans emphasize annulation of a furan ring onto a preexisting benzene ring,[7] however, the synthetic approach in Scheme 1 involves a simultaneous single-pot construction of both the furan and benzene rings which occurs in conjunction with the formation of three carbon–carbon bonds and one carbon–oxygen bond.

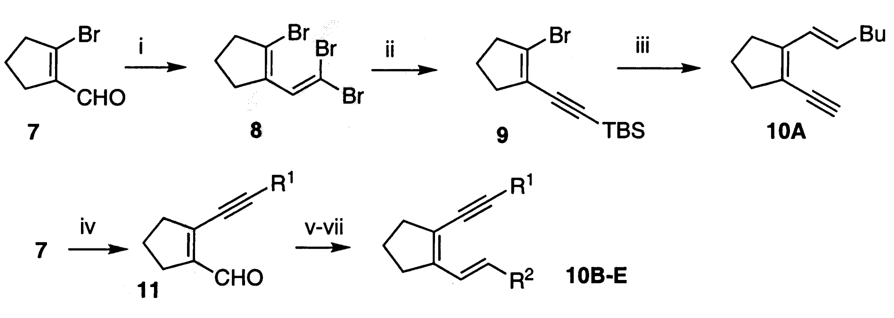
Dienylacetylenes **10A**–**E** (substituent letters for **10**, **12** correlate with Table 1 Entry letters) were prepared according to the synthetic routes in Scheme 2 using readily-available bromo-aldehyde derivative **7**.[9] Two general routes were employed, involving either direct palladium-catalyzed coupling of **7** with an alkyne, followed by Wittig reaction on enyne-aldehyde **11** or two-step conversion of **7** to bromoenyne **9**, followed by Suzuki coupling. The conversion of **8** to **9** was surprisingly efficient (91% yield) even in the presence of the extra bromine atom.

Table 1

Synthesis of benzofurans (**12**) via the coupling of dienylacetylenes (**10**) with carbene complex **1**



Entry	R^1	R^2	*Cis*/*trans*	Yield **12** (%)
A	H	Bu	*Trans*	71
B[8]	Bu	H	–	84
C	Bu	COOMe	*Trans*	61
D	Bu	Ph	*Trans*	81
E	Bu	Ph	*Cis*	63 (**12E** = **12D**)

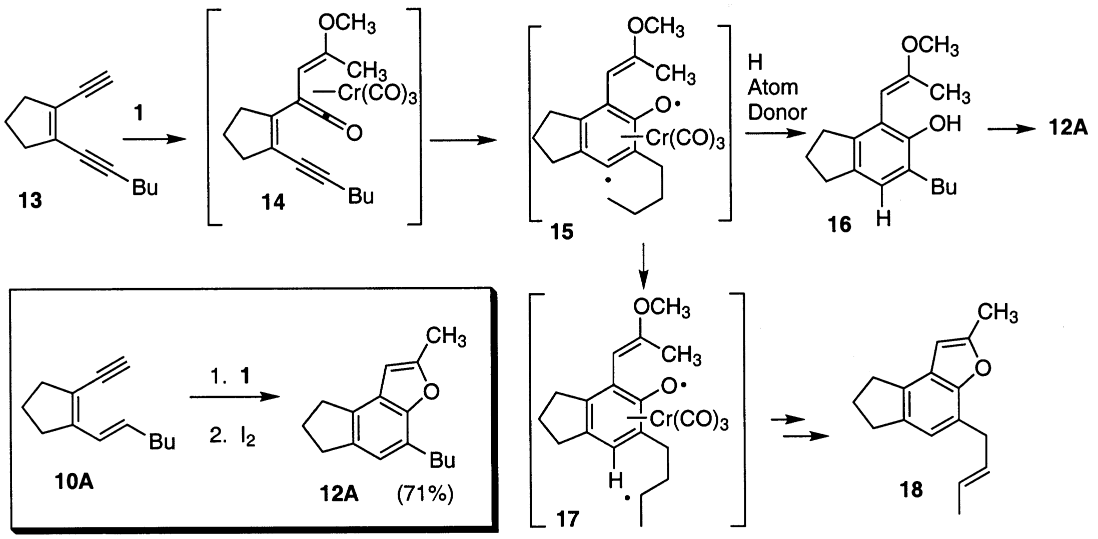


Scheme 2. (i) $CBr_4/PPh_3/Zn$ (83%). (ii) *n*-BuLi −78°C, then TBSCl (91%). (iii) $(HO)_2B–CH=CHBu/2\%\ (PPh_3)_2PdCl_2$, then Bu_4NF (95%). (iv) BuCCH or TMSCCH, 1–5% $PdCl_2$, $PPh_3/CuI/EtN(i\text{-}Pr)_2/DMF$. (v) For **10B**: $Ph_3P=CH_2$ (55%). (vi) For **10C**: $Ph_3P=CHCOOMe$ (81%). (vii) For **10D**,**E**: $Ph_3P=CHPh$ (85%), then Bu_4NF, then separate stereoisomers; **10D**–53%, **10E**–34%

The reaction of dienynes **10A–E** with Fischer carbene complex **1** afforded benzofuran derivatives (**12A–E**) in good-to-excellent yields (Table 1) in a very clean reaction. The highest yields of product were observed after treatment of the crude reaction mixtures with iodine. The proton NMR spectrum of the crude product prior to iodine treatment showed a complex reaction mixture consistent with the presence of arene–chromium complexes. Apparently the complex reaction mixture was converted to a single uncomplexed benzofuran derivative upon treatment with iodine.

The examples in Table 1 vary in the substitution pattern on the alkyne and the terminating alkene. The reaction process is tolerant of a variety of substitution patterns within the terminating alkene. Simple (Entries A and B), as well as further-conjugated systems (Entries C–E) are tolerated by the reaction. As noted in Entries D and E, the *trans* isomer provides a higher yield of benzofuran than the *cis* isomer. A possible problem with the *cis* isomer is failure to obtain the desired conformation (s-*cis*) for the electrocyclic ring closure.

In an earlier publication, an alternate but low-yielding synthesis of compound **12A** using enediyne **13** and carbene complex **1** was described (Scheme 3).[2] This product arises through Moore cyclization of intermediate vinylketene complex **14**,[10] followed by reduction of the resulting diradical **15** by hydrogen abstraction from dioxane, eventually affording **12A**. The major product of this reaction was however the unsaturated analog **18**, which arises through a series of intramolecular hydrogen atom transfers.[11] In order to compare the merits of the two methods for the synthesis of **12A**, the coupling of carbene complex **1** with enediyne **13** was attempted in the presence of the more efficient hydrogen atom donors 1,3-cyclohexadiene or terpinene.[12] Under the optimal conditions using 0.2 M cyclohexadiene in dioxane, compound **12A** was obtained in 67% yield accompanied by only trace amounts of unsaturated compound **18**; preparation of **12A** from **10A** (Scheme 3 inset and Table 1, Entry 1) proceeded in comparable (71%) yield. The less expensive hydrogen atom donor terpinene was also tested, however this compound was very difficult to separate from the product.



Scheme 3.

In summary, synthesis of benzofurans through the coupling of conjugated dienynes with Fischer carbene complexes has been demonstrated for a variety of dienynes. In all cases examined, formation of the benzofuran was the exclusive reaction pathway. The reaction process is synthetically equivalent to the coupling of Fischer carbene complexes with enediynes in the presence of hydrogen atom donors, which proceeds through diradical intermediates.

Acknowledgements

We thank the Petroleum Research Fund, Administered by the American Chemical Society, the National Science Foundation, and New Mexico State University for financial support. We thank Ms Caroline Ladd of the University of Maryland for acquisition of mass spectral data.

References

1. Herndon, J. W.; Hayford, A. *Organometallics* **1995**, *14*, 1556–1558.
2. Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4562–4563.
3. Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564–4565.
4. Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267–1269.
5. For the latest review of this chemistry, see Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187–198.
6. See: Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Bird, C. W., Eds.; Elsevier Science: Oxford, 1996; Vol. 2, Chapter 8.
7. See: Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Bird, C. W., Eds.; Elsevier Science: Oxford, 1996; Vol. 2, Chapter 7.
8. Sample procedure: A solution of methylcarbene complex **1** (0.212 g, 0.848 mmol) and dienyne **10B** (0.123 g, 0.7069 mmol) in dioxane (10 mL) was added dropwise to refluxing dioxane (20 mL) over a 2 h period. After the addition was complete, the mixture was refluxed for an additional 24 h. The reaction mixture was then allowed to cool to room temperature and then concentrated in vacuo. Hexane (30 mL) was added and the green chromium residue was filtered out over a bed of Celite. The solvent was removed on a rotary evaporator. The crude product was dissolved in chloroform (30 mL) and iodine (225 mg, 0.900 mmol) was added. The mixture was allowed to stir 12–24 h and the poured into an aqueous sodium thiosulfate solution in a separatory funnel. The chloroform layer was dried over sodium sulfate and the solvent was removed on a rotary evaporator. Final purification using flash column chromatography (silica gel/9:1 hexanes:ethyl acetate) yielded benzofuran **12B** (0.138 g, 0.6079 mmol) in 86% yield. IR ($CDCl_3$) 3020, 2955, 2930, 2857, 1733, 1628, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (1H, d, $J=8.2$ Hz), 7.07 (1H, d, $J=8.2$ Hz), 3.14 (2H, t, $J=7.3$ Hz), 2.93 (2H, t, $J=7.3$ Hz), 2.60 (2H, t, $J=7.3$ Hz), 2.34 (3H, s), 2.15 (2H, quintet, $J=7.3$ Hz), 1.2–1.6 (4H, m), 0.92 (3H, t, $J=7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 153.01, 150.50, 137.75, 134.85, 126.13, 118.75, 114.69, 108.15, 33.58, 32.12, 31.36, 25.79, 23.95, 22.38, 13.93, 11.85; MS (EI): 228 (M+, 88), 227 (39), 226 (11), 186 (24), 185 (100); HRMS calcd for $C_{16}H_{20}O$ 228.15141, found 228.15174.
9. Prepared in one step from the reaction of cyclopentanone with DMF/PBr_3. Wang, K. K.; Liu, B.; Lu, Y. *Tetrahedron Lett.* **1995**, *36*, 3785–3788.
10. This is a well-established reaction pathway for enyne-ketene derivatives. For a review, see: Moore, H. W.; Benjamin, R. Y. *Chemtracts Org. Chem.* **1992**, *5*, 273–313.
11. The formation of compound **18** proceeds with high selectivity if hydrogen atom donors are omitted from the reaction. Zhang, Y.; Herndon, J. W. *Tetrahedron* **2000**, *56*, 2175–2182.
12. Similar intermediates have been successfully trapped using this approach. Rahm, A.; Wulff, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 1807–1808.