Pergamon

Tetrahedron Letters 42 (2001) 777–779

TETRAHEDRON
LETTERS

Synthesis of furano[2,3-*c*]-pyran-3-one and thieno[2,3-*c*]-pyran-3-one derivatives through the coupling of 3-alkynyl-2-heteroaromatic carboxaldehydes with Fischer carbene complexes

Yanshi Zhang and James W. Herndon*

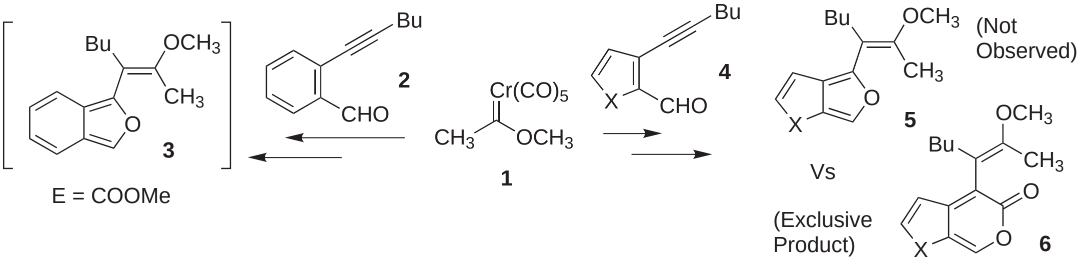
Department of Chemistry & Biochemistry, New Mexico State University, MSC 3C, Las Cruces, NM 88003, USA

Received 24 October 2000; accepted 20 November 2000

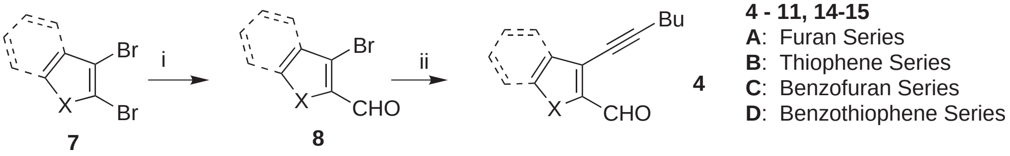
Abstract—The coupling of Fischer carbene complexes with 3-alkynyl-2-heteroaromatic carboxaldehyde derivatives has been examined. The reaction affords pyrones fused to furans or thiophenes in a single step. The compounds are stable enough for isolation. If the carbene complex features a remote alkene substituent, a subsequent Diels–Alder reaction can occur. © 2001 Elsevier Science Ltd. All rights reserved.

In a recent publication, the generation of isobenzofuran intermediates (e.g. **3**, Scheme 1) through the coupling of Fischer carbene complexes (e.g. **1**) with *o*-alkynylbenzoyl derivatives **2** was demonstrated.[1] In this manuscript the focus is on extension of this process to heteroaromatic analogs (**4**, X=O or S), which unexpectedly lead to isolable *o*-quinoidalpyrone derivatives **6**[2] and not *o*-quinoidalfuran derivatives **5**.[3] This manuscript will focus on the preparation and subsequent Diels–Alder cycloaddition reactions of derivatives of **6**.

Requisite alkyne-aldehydes **4A**–**D** were prepared from the corresponding commercially available (2,3-dibromothiophene) or known[4] dibromo compounds **7** according to the sequence of reactions in Scheme 2. Coupling of carbene complex **1** with furancarboxaldehyde **4A** afforded a moderately stable compound



Scheme 1.



Scheme 2.

---

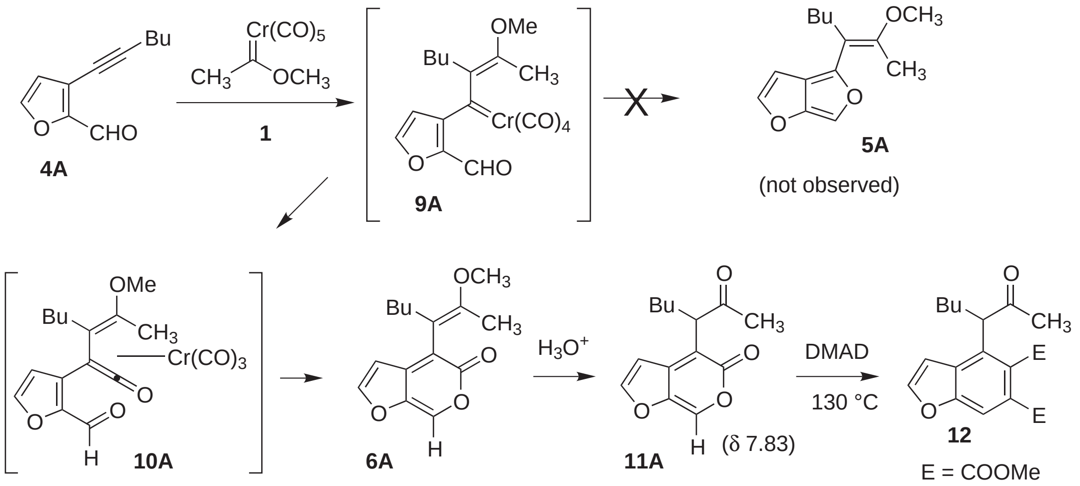
* Corresponding author.

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)02123-7

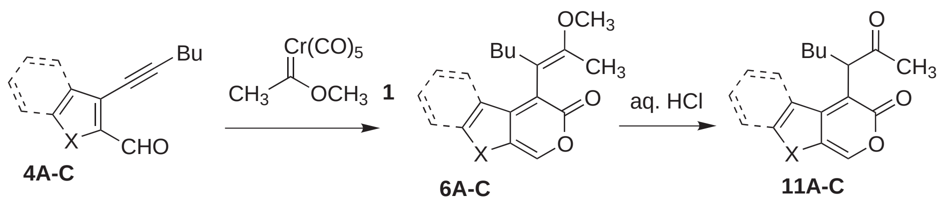
assigned as furanopyrone structure **6A** (Scheme 3). Hydrolysis afforded ketone **11A**, which was more stable and used for characterization purposes. Based on previous work,[1,5] compound **5A** was anticipated, however the chemical shift of the original aldehyde proton (δ 7.83) of **11A** was very different from the analogous proton in a known analog of **5A** (δ 7.45).[3] Furthermore, compound **11A** was unreactive to dimethyl acetylenedicarboxylate (DMAD) at room temperature, as expected for **5A**.[2] The Diels–Alder reaction with DMAD required refluxing chlorobenzene, and afforded benzofuran derivative **12**.[2] Based on these observations, the most likely structure for the carbene–alkyne coupling is the pyrone structure **6A** and not the furan structure **5A**. Further spectral analysis (^{13}C NMR, IR, mass spectroscopy) all support the pyrone structure. Although this ring system is unknown,[6] sulfur analogs of **6A** are known[2] and undergo the Diels–Alder reaction with DMAD under comparable conditions, affording the aromatic rings after thermal elimination of carbon dioxide.[7] The optimal conditions for the synthesis of pyrone derivative **6A** is refluxing a 1:1:1 mixture of carbene complex, alkyne, and triphenylphosphine in dioxane, which led to **7A** in 72% yield.

The formation of a pyrone derivative from this reaction was not initially expected based on the formation of isobenzofuran **3** in Scheme 1. Since CO insertion processes are suppressed for electron-rich metal–carbene species,[8] CO insertion should be less likely in the thiophene and furan systems **4** than in the relatively electron-poor benzene analog **2** of Scheme 1. The formation of pyrones in these studies might be attributed to the greater ring strain in derivatives such as **5**, and thus the ring-closure step in these systems is less favorable.[9] The generality of the pyrone-forming reaction was tested for various heteroaromatic carboxaldehyde derivatives; the results are presented in Scheme 4. The yields of the hydrolysis product are quite good. In all cases the fused pyrone derivative is the exclusive reaction product.

In the reaction of furan-aldehyde **4B** with butenylcarbene complex **13** (Scheme 5), the initially-formed pyrone derivative **14B** undergoes an intramolecular Diels–Alder reaction to afford lactone derivative **15B** as a single diastereomer.[10] The stereochemistry has been assigned as the depicted *endo* isomer since the coupling between H_B and H_D (8.9 Hz) is greater than H_C and H_D (4.8 Hz); similar values have been reported for related compounds.[11] A similar reaction pathway was observed for the reaction of complexes **4C** or **4D** with carbene complex **13**. The same yield and stereoselectivity was observed in refluxing THF. Only alkynes had previously been utilized as dienophiles for intramolecular Diels–Alder reactions with related thienopyrone ring systems;[10] this reaction required 156°C and proceeded with loss of CO_2. The reactions in Scheme 5 proceed at 65°C and retain the stereochemistry established in the Diels–Alder step. Variable degrees of stereoselectivity were reported for the intermolecular Diels–Alder reactions involving simple pyrones and unactivated alkenes.[12]

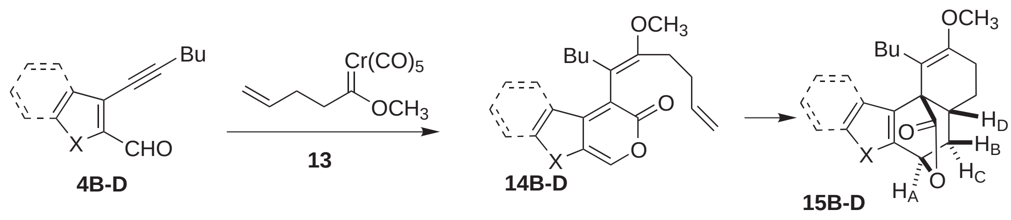


Scheme 3.



4A → **11A** (furano): 72%; **4B** → **11B** (thiopheno): 75%; **4C** → **11C** (benzofurano): 70%

Scheme 4.



4B → **15B** (thiopheno): 44%; **4C** → **15C** (benzofurano): 46%; **4D** → **15D** (benzothiopheno): 48%

Scheme 5.

In summary, we have shown a new and general route to the title ring systems and are further exploring the synthesis and reactivity of these unusual pyrone derivatives. Rapid molecular complexity is achieved in a single step through this tandem pyrone formation–intramolecular Diels–Alder reaction sequence, which involves a stereoselective formation of four carbon–carbon bonds and one carbon–oxygen bond.

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. Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267–1269.
2. For analogs where X = S, see: Jackson, M. P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 680–687.
3. Eberbach, W.; Laber, N.; Bussenius, J.; Fritz, H.; Rihs, G. *Chem. Ber.* **1993**, *126*, 975–995.
4. (a) 2,3-Dibromofuran: Gronowitz, S.; Michael, U. *Ark. Kemi.* **1970**, *32*, 283–294; (b) 2,3-Dibromobenzofuran: Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244–6251; (c) 2,3-Dibromobenzothiophene: Chippendale, K. E.; Iddon, B.; Suschitzky, H.; Taylor, D. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1168–72.
5. Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564–4565.
6. A computer substructure search turned up one literature citation; however, no compound featuring this ring system is contained in the article. Calvey, E. M.; Page, S. W.; Taylor, L. T. *J. Supercrit. Fluids* **1990**, *3*, 115–120.
7. For a review of pyrone Diels–Alder reactions, see: Afarinkia, K. A.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *42*, 9111–9171.
8. (a) Grotjahn, D. B.; Kroll, F. E. K.; Schäfer, T.; Harms, K.; Dötz, K. H. *Organometallics* **1992**, *11*, 298–310; (b) Barluenga, J.; Lopez, L. A.; Martínez, S.; Tomás, M. *J. Org. Chem.* **1998**, *63*, 7588–7589; (c) For a universal discussion of electronic effects in carbene–alkyne couplings, see: Waters, M. A.; Brandvold, T. A.; Isaacs, L.; Wulff, W. D.; Rheingold, A. L. *Organometallics* **1998**, *17*, 4298–4308.
9. For another example where a CO insertion process occurs due to ring strain, see: Barluenga, J.; Aznar, F.; Palomero, M. A.; Barluenga, S. *Org. Lett.* **1999**, *1*, 541–543.
10. Intramolecular reactions of thieno[2,3-*c*]-pyran-3-ones and unactivated terminal alkynes have been reported: Jackson, P. M.; Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2909–2918.
11. Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.* **1992**, *53*, 7839–7842.
12. (a) Posner, G. H.; Hutchings, R. H.; Woodard, B. T. *Synlett* **1997**, 432–435; (b) Afarinkia, K.; Daly, N. T.; Gomez-Farnos, S.; Joshi, S. *Tetrahedron Lett.* **2000**, *41*, 4955–4958.