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Radical promoted cyclizations of aromatic carbonyl compounds to benzopyrans using titanocene(III) chloride

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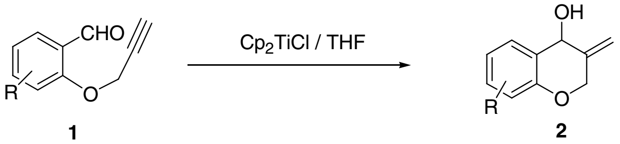
Abstract—Aromatic carbonyl compounds undergo smooth intramolecular radical cyclization with alkenes or alkynes using titanocene(III) chloride to furnish the corresponding benzopyrans. The radical initiator, Cp_2TiCl, was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF under argon.

Carbon–carbon bond formation either by ionic or radical pathways for the preparation of complicated organic molecules provides an important tool in organic synthesis.[1] Transition metal mediated reactions are one of the most attractive methods[2] for this purpose in synthetic organic chemistry. The intramolecular carbonyl-ene reaction is recognized[3] as a useful method for carbon–carbon bond formation and has been well studied. Various methods have been reported with most involving an oxacyclic ring formation through a C–C single bond via ionic reactions.[4] In the course of our research[5] to develop new methods for C–C bond formation using radical chemistry, we report a facile cyclization of aromatic carbonyl compounds containing an internal radical acceptor such as an alkene or an alkyne using titanium(III) chloride (Cp_2TiCl) to obtain substituted benzopyrans which constitute an important class of biologically active oxygen heterocycles.[6]

Titanocene(III) chloride is a well-known reagent[7] for generating carbon-centred radicals from epoxides. Very recently, diastereoselective inter- and intramolecular pinacol couplings of aldehydes have been reported[8] using a titanium(III) complex. Based on this observation, we performed a radical promoted cyclization of aromatic carbonyl compounds **1** containing an internal radical acceptor such as an alkene or an alkyne using Cp_2TiCl in THF under argon (Scheme 1). The radical initiator, Cp_2TiCl, was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF under argon. We observed that the intermolecular coupling product was the major product when Cp_2TiCl was added to compound **1** in the normal way. However, slow addition of carbonyl compound **1** to the reagent (Cp_2TiCl) yielded the cyclized product **2** in good yield without any of the coupling product.



Scheme 1.

Thus, a number of aromatic carbonyl compounds were subjected to radical cyclization reaction with titanocene(III) chloride and the results are summarized in Table 1.

It was found that the reaction was faster with aldehydes (observed by TLC) (Table 1, entries 1–4) compared to a ketone (Table 1, entry 5). Under optimum reaction conditions, a solution of the carbonyl compound in THF was slowly added to a solution of 2 equiv of titanocene(III) chloride in THF under argon.[9] It is noteworthy that 7-*endo* cyclization was unsuccessful for compound **1f**; only the self-coupling product was obtained in good yield (Table 1, entry 6). In the case of aliphatic aldehydes no desired product was obtained on radical cyclization; it is likely that the reduced product was obtained, however, which was not fully characterized.

Keywords: Radical cyclization; Aromatic carbonyls; Titanocene(III) chloride; Benzopyrans.

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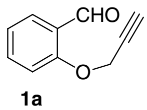
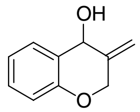
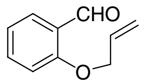
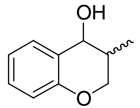
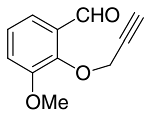
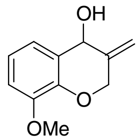
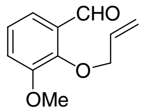
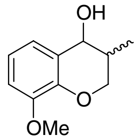
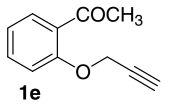
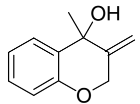
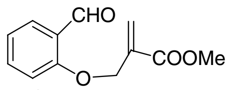
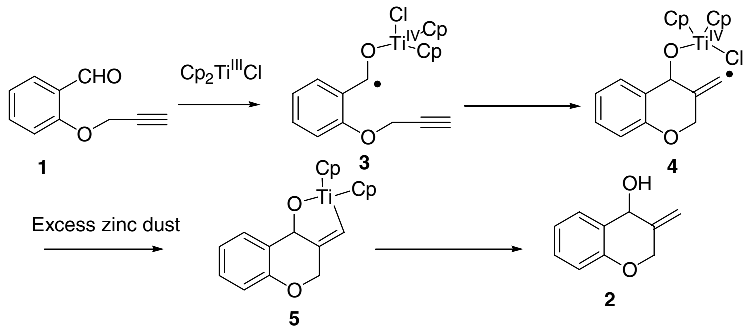
Table 1. Cyclization of carbonyl compounds using titanocene(III) chloride

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 **1a**	2.5	 **2a**	75
2	 **1b**	3	 **2b**	72[b]
3	 **1c**	2.5	 **2c**	70
4	 **1d**	3	 **2d**	68[b]
5	 **1e**	24	 **2e**	55
6	 **1f**		Only self-coupling product formed	80

[a] Yields refer to pure isolated products.

[b] Mixture of two isomers in a 2:1 ratio (determined from the ^{1}H NMR of the crude product).



Scheme 2.

In a separate experiment, it was observed for the first time that 1 equiv of Cp$_2$TiCl in the presence of excess zinc was sufficient for the entire consumption of the starting carbonyl compounds. A reasonable mechanistic pathway is proposed as depicted in Scheme 2.

Initially, titanocene(III) chloride will generate a benzyl radical at the carbonyl carbon of **3**, which reacts with the alkyne (or olefin) producing a new radical centre **4**. The resulting titanium(IV) species would then further be reduced by excess zinc dust present in the reaction medium to give the intramolecularly stabilized radical **5**. Finally, decomposition with saturated aqueous NaH$_2$PO$_4$ and work-up furnishes the product **2**. All new compounds were fully characterized by spectral and analytical data.

In conclusion, we have developed a method to synthesize benzopyrans by radical cyclization of aromatic carbonyl compounds using titanium(III) chloride as the radical initiator. To our knowledge, this is the first time that 1 equiv of a titanocene(III) reagent has been reported for complete conversion of aromatic carbonyls to the corresponding benzopyrans in the presence of excess zinc.

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References and notes

1. Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989.
2. Soderberg, B. C. G. *Coord. Chem. Rev.* **2003**, *241*, 147.
3. (a) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476; (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426; (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021; (d) *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press, 1991; Vol. 2, p 527.
4. (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092; (b) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693; (c) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739; (d) Davis, C. E.; Coates, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 491; (e) Lopez, F.; Castedo, L.; Mascarenas, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 4218; (f) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499.
5. (a) Roy, S. C.; Rana, K. K.; Guin, C. *J. Org. Chem.* **2002**, *67*, 3242; (b) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2004**, *45*, 6575; (c) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 1155; (d) Mandal, S. K.; Jana, S.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 6115, [Corrigendum: Mandal, S. K.; Jana, S.; Roy, S. C. *Tetrahedron Lett.* **2005**, *46*, 7463].
6. (a) Zhao, G.-L.; Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 4527; (b) Schweizer, E. E.; Meeder-Nycz, O. In *Chromenes, Chromanes, Chromones*; Ellis, G. P., Ed.; Wiley-Interscience: New York, 1997; p 11; (c) Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science* **1976**, *193*, 542; (d) Aleman, C.; Ishiki, H. M. *J. Org. Chem.* **1999**, *64*, 1768; (e) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1318; (f) Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 2760.
7. Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986, and references cited therein.
8. (a) Gansauer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070; (b) Yamamoto, Y.; Hattori, R.; Miwa, T.; Nakagai, Y.; Kubota, T.; Yamamoto, C.; Okamoto, Y.; Itoh, K. *J. Org. Chem.* **2001**, *66*, 3865.
9. Typical experimental procedure: A red solution of Cp_2TiCl_2 (249 mg, 1 mmol) in deoxygenated THF (12.5 mL) was stirred with activated zinc dust[5a] (130 mg, 2 mmol) under argon until it turned green. Then, a solution of carbonyl compound **1a** (160 mg, 1 mmol) in deoxygenated THF (12 mL) was added dropwise over 2.5 h at room temperature. The mixture was further stirred for an additional 5 min and then decomposed with saturated aqueous sodium dihydrogen phosphate solution (10 mL). Most of the THF was removed under reduced pressure and the resulting residue was extracted with diethyl ether (3×25 mL). The organic layer was washed successively with water (2×5 mL), brine (2×5 mL) and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material obtained was purified by column chromatography over silica gel (10% ethyl acetate in light petroleum) to furnish **2a** (120 mg, 75%) as a colourless oil. IR (neat): 3288, 2987, 2873, 1608, 1583, 1487, 1461, 1425, 1298, 1276, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.55 (d, $J = 12$ Hz, 1H), 4.71 (d, $J = 12$ Hz, 1H), 5.13 (s, 1H), 5.26 (d, $J = 0.9$ Hz, 1H), 5.38 (d, $J = 0.9$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.94 (m, 1H), 7.20 (m, 1H), 7.38 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 67.54, 67.79, 113.67, 116.79, 121.07, 124.68, 128.94, 129.64, 141.83, 154.27. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.10; H, 6.29.