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Titanocene(III) mediated radical cyclization of α-bromo carbonyl compounds: synthesis of tri-substituted tetrahydrofurans

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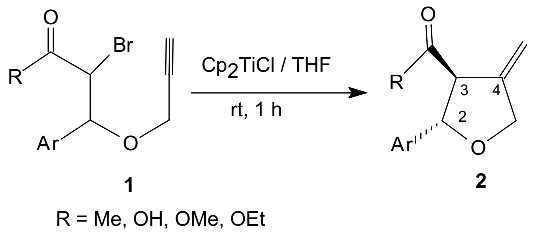
Abstract—A novel and efficient methodology has been developed for the construction of synthetically important tri-substituted tetrahydrofuran derivatives from bromo-alkenes and bromo-alkynes by radical cyclization reactions using the radical initiator Cp_2TiCl, generated in situ from commercially available titanocene dichloride and Zn dust in tetrahydrofuran under argon.

The use of radical reactions in organic synthesis have increased over the last two decades.[1] Intramolecular radical cyclization is an especially useful synthetic protocol for the construction of five- and six-membered carbocyclic and heterocyclic rings.[2] The classical method for carbon–carbon bond formation involving radical chemistry consists of the reactions of bromo-olefinic compounds in the presence of tributyltin hydride and AIBN. Disadvantages of using tin hydrides have led to other reagents being used in recent years.[3] Although silanes,[4] germanes[5] and other metal hydrides are good alternatives to tin hydrides, some of these suffer from limitations such as high cost, poor yields, toxicity and cumbersome reaction conditions. Moreover, radicals α to carbonyl groups have been considered unsuitable for carbon–carbon bond formation using tin hydrides due to the stabilized nature of the radical that favours its reduction.[6] Hence, an efficient and convenient synthetic methodology to accomplish carbon–carbon bond formation using a radical α to a carbonyl group is desirable. In continuation of our studies[7] towards the total synthesis of natural products by radical cyclization using Cp_2TiCl as the radical initiator, we report here for the first time a mild and efficient methodology for the preparation of tri-substituted tetrahydrofurans in good yields by intramolecular radical cyclizations of α-bromo carbonyl compounds in the presence of Cp_2TiCl. Tetrahydrofuran derivatives are versatile precursors for the synthesis of naturally occurring cytotoxic or anti-tumour agents[8] and also for the construction of a variety of sesquiterpenes and other natural products.[9] A report on the generation of radicals from α-bromo carbonyl compounds in the presence of Cp_2TiCl and their use in Reformatsky reactions appeared recently.[10] More recently, and when we were almost at the end this work, Bennett and co-workers reported[11] the titanocene(III) mediated reduction of organic halides under photoirradiation conditions.

The bromo-compounds **1** on radical cyclization using Cp_2TiCl in THF under argon for 1 h afforded[12] the cyclized products **2** in good to excellent yields (Scheme 1). The radical initiator Cp_2TiCl was generated[13] in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and Zn dust in tetrahydrofuran under an argon.

A series of bromo-alkynes **1a**–**g** and the bromo-alkene **1h** were subjected to radical cyclization reaction and the results are summarized in Table 1. The stereochemistry of the cyclized products **2a**–**h** was established by comparison with those prepared in our earlier work.[14] Compound **2h** was found to be an inseparable mixture



Scheme 1.

Keywords: Titanocene(III); Radical cyclization; Bromo-alkenes and alkynes.

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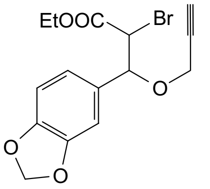
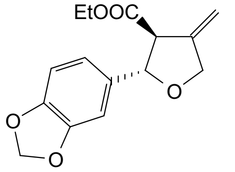
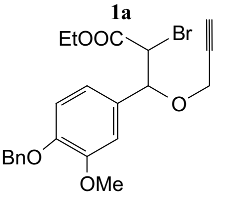
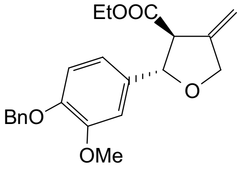
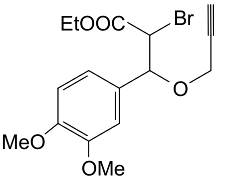
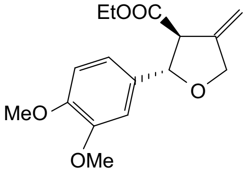
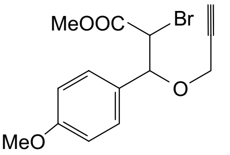
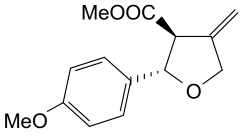
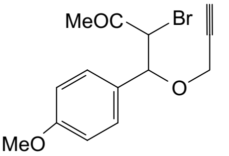
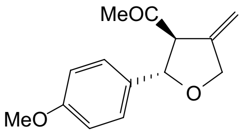
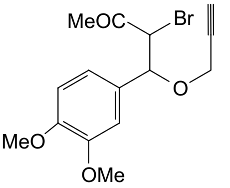
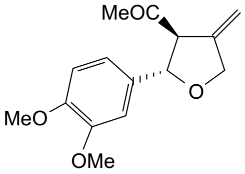
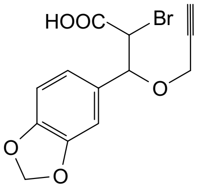
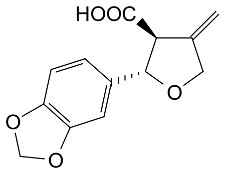
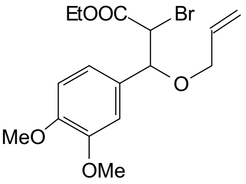
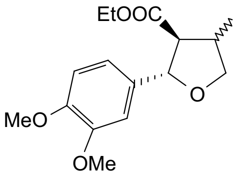
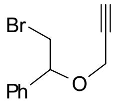
Table 1. Titanocene(III)-mediated cyclization of bromo-alkynes and alkenes

Entry	Substrate	Product[a]	Yield[b] (%)
1	 **1a**	 **2a**	80
2	 **1b**	 **2b**	82
3	 **1c**	 **2c**	81
4	 **1d**	 **2d**	85
5	 **1e**	 **2e**	70
6	 **1f**	 **2f**	75
7	 **1g**	 **2g**	66
8	 **1h**	 **2h**	80

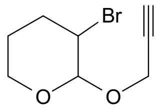
[a] Products were characterized by IR and NMR analysis and were compared with the spectra of authentic samples.

[b] Yields refer to pure isolated products.

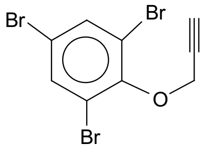
of two isomers in a ratio of 1:1 with respect to the C-4-Me. The starting bromo-ethers were prepared from the corresponding cinnamyl esters or acids by reaction with NBS in the presence of the appropriate alcohol following the standard procedure.[8,9,15] The α-bromo acid **1g** also underwent radical cyclization smoothly using three equivalents of Cp$_2$TiCl under the same reaction conditions but in slightly poorer yield. It is noteworthy that the generation of radicals from **1** by Cp$_2$TiCl is very selective as revealed by the fact that treatment of compounds **3**, **4** and **5** separately with Cp$_2$TiCl under the same reaction conditions did not produce radicals at all and left the starting compounds unchanged. Thus, it can be concluded that Cp$_2$TiCl generates radicals selectively and very efficiently from α-bromo carbonyl compounds.



3



4



5

In conclusion, a mild and efficient methodology for the construction of synthetically important tri-substituted tetrahydrofurans from bromo-alkynes and a bromo-alkene has been successfully developed by way of radical cyclizations using Cp$_2$TiCl as the radical initiator. The ring closure of precursors which would give 2-alkyl analogues of **2** has not been attempted.

Acknowledgements

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References and notes

1. (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072–3082; (b) Hirao, T. *Synlett* **1999**, 175–181; (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674–686.
2. (a) Ghosh, A. K.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2747–2755; (b) For bibliography see: Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286; (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, 1991.
3. (a) Mikamai, S.; Fujita, K.; Nakamura, T.; Yorinitsu, H.; Shinokubo, H.; Seijiro, M.; Oshima, K. *Org. Lett.* **2001**, *3*, 1853–1855; (b) Studer, A.; Amrein, S. *Synthesis* **2002**, 835–849; (c) Ingham, R. K.; Rosenberg, S. D.; Gilman, H. *Chem. Rev.* **1960**, *60*, 459–539; (d) Boyer, I. J. *Toxicity* **1989**, *55*, 253–298.
4. (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194; (b) Chatgilialoglu, C.; Guerrini, A.; Seconi, G. *Synlett* **1990**, 219–220; (c) Chatgilialoglu, C.; Guerrini, A.; Lucarini, M. *J. Org. Chem.* **1992**, *57*, 3405–3409; (d) Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103–112; (e) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Synlett* **1991**, 435–438; (f) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 4681–4684.
5. (a) Pike, P.; Hershberger, S.; Hershberger, J. *Tetrahedron* **1988**, *42*, 6295–6304; (b) Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, *34*, 591–594; (c) Chatgiliaoglu, C.; Ballestri, M. *Organometallics* **1995**, *14*, 5017–5018; (d) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1415–1416.
6. Hanessian, S.; Fabio, R. D.; Marcoux, J. F.; Prudhomme, M. *J. Org. Chem.* **1990**, *55*, 3436–3438.
7. (a) Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829–2834; (b) Roy, S. C.; Rana, K. K.; Guin, C. *J. Org. Chem.* **2002**, *67*, 3242–3248.
8. Dulcere, J. P.; Mihoubi, M. N.; Rodriguez, J. *J. Org. Chem.* **1993**, *58*, 5709–5716.
9. Okabe, M.; Abe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 1775–1777.
10. Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615–3617.
11. Hersant, G.; Ferjani, M. B. S.; Bennett, S. M. *Tetrahedron Lett.* **2004**, *45*, 8123–8126.
12. *Typical procedure*: a solution of titanocene dichloride (250 mg, 2 mmol) in dry THF (15 mL) was stirred with activated[7b] zinc dust (7 mmol) for 1 h under argon. The resulting green solution was then added dropwise to a stirred solution of the bromo-alkyne **1c** (370 mg, 1 mmol) in dry THF (5 mL) at room temperature over 30 min. The reaction mixture was stirred for an additional 0.5 h and decomposed with saturated aqueous sodium dihydrogen phosphate (5 mL). Most of the volatiles were removed under reduced pressure and the residue was extracted with diethyl ether (4 × 25 mL). The combined ether extracts were washed successively with water (2 × 10 mL), brine (2 × 10 mL) and finally dried over sodium sulfate. After removal of solvent the crude residue obtained was purified by column chromatography over silica gel (10% ethyl acetate in petroleum ether) to afford the tri-substituted tetrahydrofuran derivative **2c** (236 mg, 81%). IR (neat): 2935, 2837, 1732, 1608, 1593, 1517, 1463, 1371, 1263 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.28 (t, $J = 7.2$ Hz, 3H), 3.48 (dd, $J = 8.7, 2.7$ Hz, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 4.13–4.29 (m, 2H), 4.56 (AB$_q$, $J = 13.2$ Hz, two peaks further split into doublet, $J = 2.4$ Hz, 2H), 5.18 (d, $J = 9.3$ Hz, 1H), 5.08–5.19 (m, 2H), 6.82–6.94 (m, 3H); ^{13}C NMR (CDCl$_3$): δ 14.6, 56.2, 57.4, 61.5, 71.9, 83.8, 106.7, 109.3, 111.3, 119.0, 132.7, 146.9, 149.2, 149.4, 171.1.
13. Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–987, and references cited therein.
14. Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron* **2002**, *58*, 2435–2439.
15. Dulcere, J. P.; Rodriguez, J.; Santelli, M.; Zahra, J. P. *Tetrahedron Lett.* **1987**, *28*, 2009–2012.