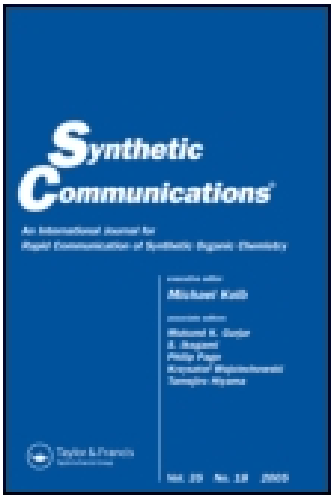


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Zirconium(IV) Chloride Catalyzed Cyclization of ortho-Allylphenols: Synthesis of 2-Methyl-2,3-dihydrobenzofurans

H. M. Meshram [a], K. Premalatha [a], K. Rameshbabu [a], B. Eeshwaraiah [a] & J. S. Yadav [a]
[a] Organic Division I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India
Published online: 10 Jan 2011.

To cite this article: H. M. Meshram, K. Premalatha, K. Rameshbabu, B. Eeshwaraiah & J. S. Yadav (2004) Zirconium(IV) Chloride Catalyzed Cyclization of ortho-Allylphenols: Synthesis of 2-Methyl-2,3-dihydrobenzofurans, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:17, 3091-3097, DOI: 10.1081/SCC-200028551

To link to this article: http://dx.doi.org/10.1081/SCC-200028551

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 17, pp. 3091–3097, 2004

Zirconium(IV) Chloride Catalyzed Cyclization of *ortho*-Allylphenols: Synthesis of 2-Methyl-2,3-dihydrobenzofurans

H. M. Meshram,* K. Premalatha, K. Rameshbabu, B. Eeshwaraiah, and J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad, India

ABSTRACT

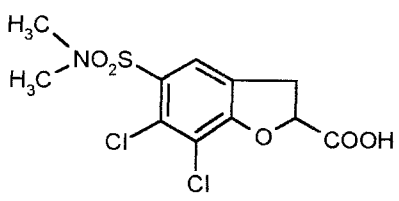
Intramolecular cyclization of *ortho*-allylphenols has been carried out using zirconium (IV) chloride in mild condition. This method avoids the use of expensive reagents and leads to highly functionalized dihydrobenzofurans.

Key Words: *ortho*-Allylphenols; Intramolecular cyclization; Zirconium (IV) chloride; Dihydrobenzofurans.

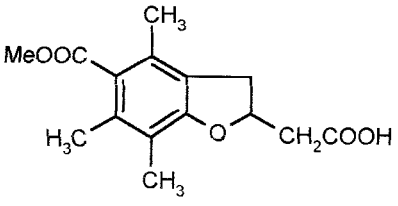
*Correspondence: H. M. Meshram, Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India; Fax: +091 40 7170512; E-mail: hmmeshram@yahoo.com.

DOI: 10.1081/SCC-200028551 0039-7911 (Print); 1532-2432 (Online)

2,3-Dihydrobenzofuran nuclei are found in a variety of bioactive natural products[1a–c] and therapeutic agents.[2] Particularly, carboxylic acid derivatives I and II show antiinflammatory and antioxidant activity.



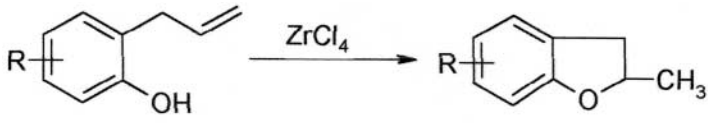
I



II

Generally, 2,3-dihydrobenzofuran systems are constructed by the cyclization of *ortho*-allylphenols. There are various methods[3–6] to accomplish this cyclization in different reacton conditions. However, most of the methods have the drawbacks of using harsh reaction conditions and expensive metal salts. So there is still need to develop a mild and simple procedure for the cyclization of *ortho*-allylphenols. Recently, zirconium (IV) chloride has attracted more attention because of its diverse application in organic synthesis.[7–13] Our involvement in metal catalyzed reactions[14] prompted us to perform zirconium (IV) chloride catalyzed cyclization of *ortho*-allylphenols, which leads to 2-methyl-2,3-dihydrobenzofuran containing ample functionality.

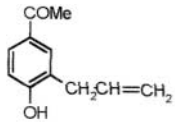
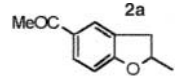
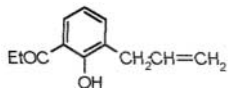
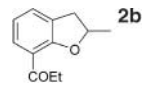
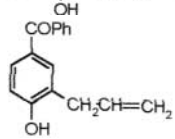
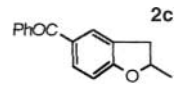
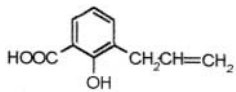
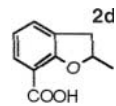
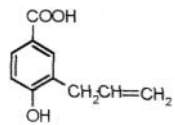
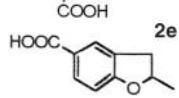
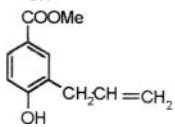
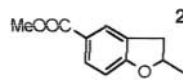
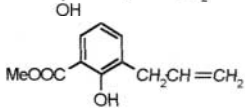
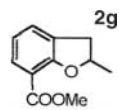
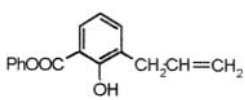
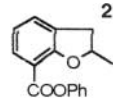
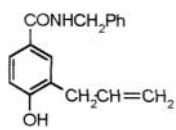
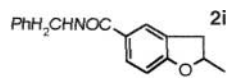
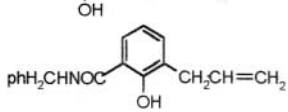
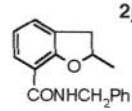
Thus zirconium (IV) chloride was added to *ortho*-allylphenol in dichloromethane at 0°C and stirred at room temperature (see Table 1) under nitrogen atmosphere. After work-up, 2-methyl-2,3-dihydrobenzofurans were isolated in good yield. The reaction proceeded with a stoichiometric (1 : 1) amount of zirconium (IV) chloride, but it could be accelerated by the addition of 1 : 1.2 equivalents of zirconium (IV) chloride. In case of allylphenol bearing alkyl keto subsistent (entry 1 and 2), the reaction proceedes with one equivalent of zirconium (IV) chloride with high yields. In case of aryl keto substituents (entry 3), the reactions were sluggiish. The reaction was also sluggish and incomplete with the substrate having free acid (entry 4 and 5). The rate



1 2

Scheme 1.

Table 1. Zirconium (IV) chloride catalyzed cyclization of *ortho*-allylphenols.

Entry	Substrate	Time (hours)	Product	Yield[a] (%)
1		12		70
2		10		71
3		15		60[b]
4		20		60[b]
5		20		60[b]
6		12		85
7		10		85
8		12		70
9		10		80
10		8		80

[a]Isolated yield.
[b]Remaining starting material recovered.

of reaction could be enhanced by using methyl ester (entry 6 and 7) and amide (entry 9 and 10) functionalities; however, aryl ester (entry 8) was found to suppress the reaction. We had examined the reaction in different solvents like dichloromethane, tetrahydrofuran, and acetonitrile, but dichloromethane gave better yields.

In conclusion, we have demonstrated a simple and mild method for the cyclization of *ortho*-allylphenols. This procedure is applicable for the synthesis of functionalized 2-methyl-2,3-dihydrobenzofurans, which may find applications in drug discovery.

EXPERIMENTAL PROCEDURE

Boiling points and melting points are uncorrected. Melting points were recorded on Buchi R535 apparatus. The infrared (IR) spectra were recorded on Nicole 740 FT IR spectrometer; ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on FT (200 and 300 MHz Gemini) spectrometer. Mass spectra were recorded on either Micromass 7070 h or Finnigan Mat 1020 B mass spectrometer operating at 70 eV. Thin layer chromatography was done on precoated silica gel 60f 254 (0.5 mm) glass plates.

Typical Experimental Procedure

The solution of *ortho*-allylphenol (10 mmol) in dichloromethane (40 mL) was cooled to 0°C and zirconium (IV) chloride (10 mmol) was added in portions. The stirring was continued for stipulated period of time (see Table 1). After completion, it was quenched with water and the organic layer separated. The aqueous layer was extracted with more dichloromethane. The combined organic phase was washed with water, dried over sodium sulfate, and concentrated to give the crude product, which was purified by silica gel column chromatography and characterized by mass and NMR spectral data.

SPECTRAL DATA FOR SELECTED COMPOUNDS

2a: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (d, $J = 8.43$ Hz, 3H), 2.52 (s, 3H), 2.82 (dd, $J = 6.5$ Hz, 12.8 Hz, 1H), 3.38 (dd, $J = 6.5$ Hz, 12.8 Hz, 1H), 4.9–5.05 (m, 1H), 6.7 (d, $J = 14.06$ Hz, 1H), 7.75 (d, $J = 14.24$ Hz, 2H). MS (m/z) (relative intensity) 176 (34), 161 (100), 43 (20). Anal. Calcd. for $C_{11}H_{11}O_2$: C, 74.98; H, 6.86; Found: C, 74.94; H, 6.80.%

2b: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.19 (t, $J = 8.16$ Hz, 3H), 1.55 (d, $J = 6.9$ Hz, 3H), 2.88 (dd, $J = 6.8$ Hz, 13.0 Hz, 1H), 2.98 (q $J = 7.9$ Hz, 2H), 3.32 (dd, $J = 6.8$ Hz, 13.0 Hz, 1H), 4.98–5.08 (m, 1H), 6.82 (t, $J = 7.4$ Hz, 1H), 7.22 (d, $J = 7.82$ Hz, 1H), 7.62 (d, $J = 9.56$ Hz, 1H). MS (m/z) (relative intensity) 190 (20), 161 (100), 105 (18). Anal. Calcd. for $C_{12}H_{13}O_2$: C, 75.76; H, 7.42; Found: C, 75.79; H, 7.39.%

2c: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.42 (d, $J = 8.3$ Hz, 3H), 2.76 (dd, $J = 6.9$ Hz, 12.9 Hz, 1H), 3.29 (dd, $J = 6.9$ Hz, 12.9 Hz, 1H), 4.94–4.99 (m, 1H), 6.62 (d, $J = 10$ Hz, 1H), 7.32–7.62 (m, 6H). MS (m/z) (relative intensity) 239 (50), 162 (100), 105 (40). Anal. Calcd. for $C_{16}H_{13}O_2$: C, 80.65; H, 5.92; Found: C, 80.69; H, 5.90%.

2d: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56 (d, $J = 7.14$ Hz, 3H), 2.85 (dd, $J = 6.5$ Hz, 12.7 Hz, 1H), 3.35 (dd, $J = 6.5$ Hz, 12.7 Hz, 1H), 4.95–5.85 (m, 1H), 6.8 (t, $J = 7.6$ Hz, 1H),7.25 (d, $J = 14.28$ Hz, 1H), 7.68 (d, $J = 13.98$ Hz, 1H). Anal. Calcd. for $C_{10}H_9O_3$: C, 67.41; H, 5.66; Found: C, 67.44; H, 5.68%.

2e: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (d, $J = 6.9$ Hz, 3H), 2.81 (dd, $J = 7.0$ Hz, 13.1 Hz, 1H), 3.32 (dd, $J = 7.0$ Hz, 13.1 Hz, 1H), 4.90–5.05 (m, 1H), 6.68 (d, $J = 7.69$ Hz, 1H), 7.8 (d, $J = 6.1$ Hz, 2H). Anal. Calcd. for $C_{10}H_9O_3$: C, 67.41; H, 5.66; Found: C, 67.46; H, 5.61%.

2g: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.55 (d, $J = 6.6$ Hz, 3H), 2.81 (dd, $J = 6.8$ Hz, 13.0 Hz, 1H), 3.32 (dd, $J = 6.8$ Hz, 13.0 Hz, 1H), 3.84 (s, 3H), 4.98–5.09 (m, 1H), 6.8 (t, $J = 7.5$ Hz, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 7.63 (d, $J = 7.5$ Hz, 1H). MS (m/z) (relative intensity) 192 (100), 161 (70), 105 (33). Anal. Calcd. for $C_{11}H_{11}O_3$: C, 68.74; H, 6.29; Found: C, 68.78; H, 6.32%.

2i: Solid mp: 89°C ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.58 (d, $J = 6.08$ Hz, 3H), 2.86 (dd, $J = 6.9$ Hz, 12.9 Hz, 1H), 3.4 (dd, $J = 6.92$ Hz, 12.9 Hz, 1H), 5.05–5.2 (m, 1H), 6.9 (t, $J = 7.82$ Hz, 1H), 7.2–7.42 (m, 6H), 7.92 (d, $J = 8.82$ Hz, 1H). Anal. Calcd. for $C_{17}H_{16}O_2N$: C, 73.38; H, 6.41; N, 5.24: Found: C, 73.40; H, 6.46; N, 5.21%.

2j: Liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.45 (s, 2H), δ 1.47 (d, $J = 5.06$, 3H), 2.91 (dd, $J = 6.1$ Hz, 12.3 Hz, 1H), 3.35 (dd, $J = 6.1$ Hz, 12.3 Hz, 1H), 4.95–5.1 (m, 1H), 6.92 (t, $J = 8.82$ Hz, 1H), 7.15–7.35 (m, 5H), 7.92 (d, $J = 8.84$ Hz, 1H). Anal. Calcd. for $C_{17}H_{16}O_2N$: C, 73.38; H, 6.41; N, 5.24; Found: C, 73.41; H, 6.42; N, 5.23%.

ACKNOWLEDGMENT

K. Premalatha is thankful to CSIR, New Delhi, for financial support in the form of fellowship.

REFERENCES

1. (a) Sih, C.J.; Ravikumar, P.R.; Huang, F.; Buckner, C.; Whitloc, H. Isolation and synthesis of pinoresinol diglucoside, a major antihypertensive principle of Tu Chung (*Eucommio uhnoides*, oliver). J. Am. Chem. Soc. **1976**, *98*, 5412; (b) Nagai, M.; Noguchi, M.; Iizuka, T.; Otani, K.; Kamata, K. Vascodilator effects of des(α-carboxy-3,4,dihydroxy phenethy) lithospermic acid (8-epiblechnic acid), a derivative of lithospermic acid in solviac Miltiorrhizae Radix. Biol. Pharm. Bull. **1996**, *19*, 228–232; (c) Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, H.; Nishibe, S.; Hisada, S. Chem. Pharm. Bull. **1981**, *29*, 3586–3592.
2. (a) Brufani, M.; Ceccarelli, S.; Giannetti, P.; Paesono, A.; Scuri, R.; Zanarella, S Br. Pat. 2221 463 **1990**; (b) Preparation of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, 2-(2,3-dihydro-5-acyloxy-4,6,7-trimethylbenzofuranyl) acetic acid and their esters. Antihypertensive drugs. Chem. Abstr. **1990**, *113*, 58915; (c) Brunmer, H. Euro. Pat. Offen. 2227423, s1972; (d) Chem. Abstr. **1973**, *78*, 62181.
3. (a) Maier, L. Organic phosphorus compounds 68. The direct synthesis of tri (alkyl and aryl seleno) phosphites and of tris(p-anisyltelluro) phosphite (1). Helv. Chim. Acta. **1976**, 252; (b) KaraKhanov, E.A.; Freger, A.A.; Viktorova, E.A. Mechanism of phenol synthesis during reactions of 2,3-dihydrobenzofurans on acid catalysts. Izv. Vyssh Vche Zagved Khim. Khim Tekhnol. **1973**, *16* (4), 586–588.
4. (a) Cho, J.Y.; Kyong, U.; Baik, K.U.; Yoo, E.S.; Yoshikawa, K.; Park, M.H. In vitro anti-inflammatory effects of neolignonan woorenosides from the rhizomes of *Coptis japanica*. J. Natl. Prod. **2000**, *63*, 1205–1209; (b) Laszlo, J.; Laszlo, K.; Sandor, A. Simple synthesis of benzofuranoid neolignane from *Myristica fragrans*. J. Natl. Prod. **2000**, *63*, 866–870.
5. Bergman, J.; Engman, L. Oxidatuve cyclization of some γ- and δ-hydroxy olefins indused by telurium dioxide. J. Am. Chem. Soc. **1981**, *103*, 5196–5200.
6. Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. Palladium-catalyzed carbonylative annulation of -o-alkynyl phenols: synthesis of 2- substitutes- 3-aroylbenzo(b) furans. J. Org. Chem. **2002**, *67*, 2365–2368.
7. Evans, D.A.; Chapman, K.T.; Bisaha, J. Asymmetric Diels–Alder cyclo addition reactions with chiral α,β-unsaturated N-acyloxazolidinones. Am. Chem. Soc. **1988**, *110*, 1238.
8. Yam, V.W.W.; Chong, S.H.F.; Chung, C.K.K. Synthesis and luminescence behaviour of rhenium(I) diynl complexes. X-ray crystal structures

of [Re(co)3(tBu2bpy)(C≡C—C≡C—H)] and [Re(Co)3(tBu2bpy)(C≡C—C≡C—ph)]. Chem. Commun. **1998**, *19*, 2121.

9. Phillipson, N.; Anson, M.S.; Montana, J.G.; Taylor, R.J.K. Ketone homologation to produce α-methoxy ketones: application to conduritol synthesis. J. Chem. Soc. Perkin. Trans. I **1997**, *19*, 2821.
10. Lenarsic, R.; Kocevar, M.; Polane, S. $ZrCl_4$-Mediated regioselective electrophilic amination of activated arenes with new alkyl aryl amino carbonyl diazene carboxylates: intermolecular and intramolecular reactions. J. Org. Chem. **1999**, *64*, 2558.
11. Caminade, A.-M.; Majorl, J.P; Joopknol; Ben, L.F. Phosphorhydrazide macrocycles and cryptands. Synlett. **1996**, *11*, 1025.
12. Harrowven, D.C.; Dainty, R.F. Zirconium tetrachloride as a mediator for ambient temperature ortho-Fries rearrangements. Tetrahedron Lett. **1996**, *37*, 7659.
13. Yadav, J.S.; Reddy, B.V.S.; Raj, K.S.; Reddy, K.B.; Prasad, A.R. Ze^{4+}-Catalyzed efficient synthesis of α-amino phosphonates. Synthesis **2001**, *15*, 2277.
14. (a) Yadav, J.S.; Reddy, G.S.; Meshram, H.M. Zinc promoted simple and convenient synthesis of carbomates: an easy access for amino group protection. Tetrahedron Lett. **1998**, *39*, 3259; (b) Meshram, H.M.; Reddy, G.S.; Reddy, M.M.; Yadav, J.S. Zinc mediated facile amide formation: application to alkyl, aryl, heterocyle, carbohydrate and amino acids. Tetrahedron Lett. **1998**, *39*, 4103.

Received May 13, 2004