J Mater Sci (2008) 43:2254–2257
DOI 10.1007/s10853-007-2107-7

Synthesis of benzhydrol derivatives by metal imidozalen catalysed electrophilic addition of aromatic aldehyde to hydrocarbons under solvothermal condition

K. Jailakshmi · K. M. Lokanatha Rai · K. Byrappa

Received: 6 November 2006 / Accepted: 13 August 2007 / Published online: 21 February 2008

Abstract Salen metal complexes act as good catalysts for reactions in homogenised, heterogenised and heterogenised-homogeneous conditions. A simple method for the synthesis of benzhydrol derivatives is proposed using anisole and substituted benzaldehydes in the presence of a salen metal catalyst at high temperature and pressure using Morey autoclave. The compounds were isolated in good yield and were characterized by spectral and analytical methods.

Introduction

Benzhydrol is used as an intermediate in pharmaceuticals (including antihistamines), agrochemicals and other organic compounds. It is used as a fixative in perfumery and as a terminating group in polymerisations. It also finds use in many organic syntheses. Usual synthesis of benzhydrol involves the reduction of benzophenone using reducing agents like $NaBH_4$ or $LiBH_4$, besides, nucleophilic addition of organometallic reagents to aromatic aldehydes also produces benzhydrol in quantitative yield. Only few references are available for the direct synthesis of benzhydrol via the addition of aldehydes to aromatic hydrocarbon [1].

K. Jailakshmi · K. M. L. Rai (✉)
Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India
e-mail: kmlrai@yahoo.com

K. Byrappa
Department of Geology, University of Mysore, Manasagangotri, Mysore 570 006, India

Investigation of a number of different organometallic species indicated that dalkylmagnesium reagents yield the highest optical purities (Fig. 1).

The less known chiral diamines (**1**) and (**2**) Fig. 2, are reported to mediate the reactions between aryl Grignards and aldehydes [2]. The alcohols produced in all such cases range in optical purity from 40 to 75%ee; selectivites increase with the bulkiness of the aldehyde substituent [3].

Benzaldehyde and *n*-heptanal were found to react at −90 °C in less than 10 min with lithium dimethylcuprate to afford the corresponding alcohols in good yields [4] (Fig. 3).

A series of glycosylated derivatives[5] of benzophenone, benzhydrol, and benzhydril has been synthesized and evaluated for potential activity as venous antithrombotic agents. Studies on structure activity relationships revealed that compounds having an electron-withdrawing group in the benzhydril or benzhydrol moiety, and specifically those having the β-D-xylopyranosylstructure in the sugar moiety, were good antithrombotic agents in a rat model of venous thrombosis.

The chemistry of solvothermal reactions involves two major factors namely, high temperature and pressure. "Solvothermal reactions can be defined as reaction or a transformation of reactive in a closed system, in the presence of a solvent at a temperature higher than its boiling point. Consequently these reactions can be developed in supercritical or in sub critical conditions". Some of the reactions, which proceed at slow rates under normal pressure can be enhanced by increasing the pressure. This can be achieved by heating the reaction mixture under sealed condition. The development of solvothermal reaction is of interest because they offer the possibility of environmentally benign reaction conditions by reducing the burden of organic solvent disposal. Solvothermal process involve the

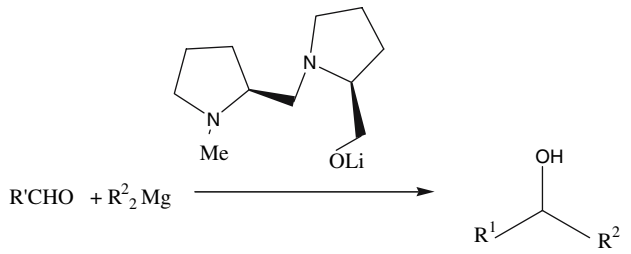


Fig. 1 Reaction of dialkylmagnesium with aldehyde

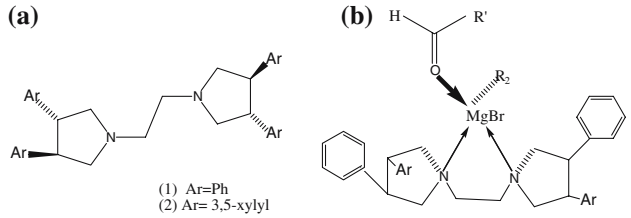


Fig. 2 Ethylene diamine ligand (**a**) and magnesium complex (**b**)

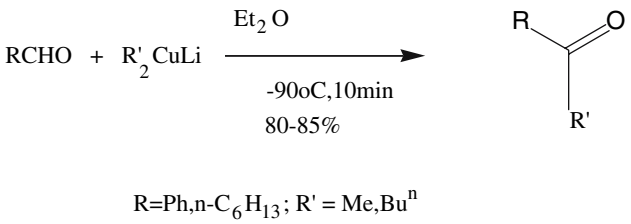


Fig. 3 Reaction of Gillman reagent

heterogeneous chemical reaction, which occur at solid-liquid or solid-liquid-gas interfaces under high temperature and high pressure.

Rai and Linganna successively used thiourea as thionating agent for (i) the conversion of 1,3,4-oxadiazole to 1,3,4-thiadiazole under solvothermal condition [6] by heating in a sealed tube at 100 °C. (ii) the conversion of esters to thioesters under solvothermal conditions using Morey's autoclave [7]. Besides this, Rai et al [8] successfully converted aldehyde semicarbazones to bishydrazones by thermolysis under pressure using ethanol as solvent in a sealed tube. These facts prompted us to use this technology to add aromatic aldehyde to aromatic hydrocarbon via solvothermal mode.

Further, "Salen" ligand, the condensation product of salicylaldehyde and ethylene diammine forms a variety of complexes with almost all kinds of metals, which have a wide range of applications in different spheres of chemistry [9–13]. Literature data shows that salen metal complexes are used in organic synthesis such as aziridination or epoxidation or cyclopropanation of alkenes, epoxide deoxygenation, hydrogenation of alkenes, addition of HCN to imines, asymmetric reduction of ketones, etc. On the other hand, imidazole and its derivatives have many applications since the imidazole ring is a good leaving group and it has been extensively utilised in synthetic chemistry. Imidazole is a protonated five-membered ring, which promotes the chemical reactions depending on the specific physical conditions at enzyme catalytic sites [14]. Prompted by the wide applicability of imidazole derivatives as well as salen complexes, we synthesised complexes with salen type ligand [15] called "Imidozalen", derived from 2*n*-butyl-4-chloro-5-formyl imidazole with ethylene diamine. The structure of the ligand was studied by X-ray crystal studies [16]. Later this ligand was complexed with metal moiety and the obtained complex was utilized in the electrophilic addition reaction.

In a typical synthesis, mixture of benzaldehyde, anisole and Mn(III)imidozalen complex were taken in the in a stainless steel SS316 Morey type of autoclave (fabricated at the Dept. of Geology, University of Mysore, India) provided with a Teflon liner of 30 mL capacity. Autoclave was then kept in an oven at 120 °C for 48 h. After the reaction, usual work up gave *p*-methoxybenzhydrol as white crystalline compound in 62% yield. IR, ^{1}H NMR spectral analysis and elemental analyses confirmed structural formula for the *p*-methoxybenzhydrol.

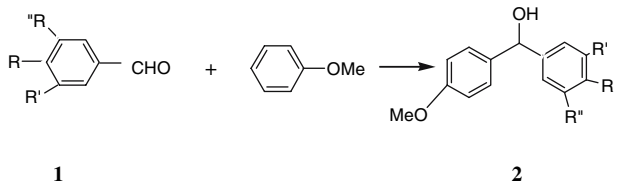
Experimental section

Melting points were recorded in open capillaries using Thomus Hoover apparatus and were uncorrected. TLC using silica gel-G as adsorbent routinely checked the compounds for their purity. IR spectra were recorded on Shimadzu FT 8300 spectrometer. ^{1}H NMR spectra were recorded on a Jeol 60 MHz FT NMR spectrometer using $CDCl_3$ as solvent and again reconfirmed on AMX400NMR, 400 MHz.

General procedure for the preparation of benzhydrol derivatives (Fig. 4)

A typical procedure for the synthesis of 4′-chloro, 4-methoxybenzhydrol (2a)

A mixture of Anisole (1.08 g,), 4-chlorobenzaldehyde [1.4 g] and approximately 0.5 g of the manganese (III) imidozalen complex was loaded in to the Teflon liner, the lid was closed and liner was placed in the autoclaves, the plates were kept on the liner and autoclave was closed and was tightened and was kept in oven for about 48 h. The autoclave was then opened and the product was extracted into ether, washed thoroughly with water to remove unreacted substances and other side products. Then, it was dried over anhydrous sodium sulphate and the solvent was removed by distillation in the water bath, yields a solid



1 2

a. R =Cl, R'= R" = H b. R = R' = OMe,R' = H

c. R = R' = R" = OMe d. R = $N(Me)_2$, R" = R '= H

e. R=R'=R" = H

Fig. 4 Reaction scheme for benzhydrol formation

mass, which shows one major spot in TLC. The product TLC shows a down spot, which is different from the starting material. After purification over a column chromatographically yield the required product in 62% (0.153 g); mp 107–109 °C; IR [KBr]: 3,565 cm^{-1}: ^1H NMR ($CDCl_3$): δ 7.58 (dd, 2H, ArH), 7.35 (dd, 2H, ArH), 7.30 (dd, 2H, ArH), 7.10 (dd, 2H, ArH), 5.79 (methine), 3.73 (s, 3H, OCH_3) Anal. Calcd. for $C_{14}H_{13}O_2Cl$; C, 61.28.; H,5.27; Found: C, 61.21; H, 5.31.

3′,4′,4-trimethoxybenzhydrol (2b)

Obtained from anisole (1.00 g) and veratraldehyde (1.67 g) as white crystalline compound in 42% (1.14 g) yield; m.p 175–180 °C; IR [KBr]: 3,565 cm^{-1}: ^1H NMR ($CDCl_3$): δ 7.30 (dd, 2H, ArH), 7.10 (dd, 2H, ArH), 6.35 (s, 2H, ArH), 5.79 (methine), 3.85 (bs, 6H, OCH_3), 3.80 (bs, 6H, OCH_3) Anal. Calcd. for $C_{16}H_{18}O_4$; C, 70.06; H, 6.61; Found: C, 70.11; H, 6.58.

3′,4′,5′,4-tetramethoxybenzhydrol (2c)

Obtained from anisole (1.00 g) and 3,4,5-trimethoxybenzaldehyde (1.95 g) as white crystalline compound in 51% (1.51 g) yield; m.p 180–187 °C; IR [KBr]: 3,565 cm^{-1}: ^1H NMR ($CDCl_3$): δ 7.30 (dd, 2H, ArH), 7.10 (dd, 2H, ArH), 6.82–6.99 (bd, 2H, ArH), 6.62 (s, 1H, ArH), 5.79 (methine), 3.76 (bs, 9H, OCH_3) Anal. Calcd. for $C_{17}H_{20}O_5$; C, 67.08; H, 5.51; Found: C, 67.12; H, 5.48.

4′-nitro-4-methoxybenzhydrol (2d)

Obtained from anisole (1.00 g) and 4-nitrobenzaldehyde (1.51 g) as pale yellow crystalline compound in 30% (0.78 g) yield; m.p 200–204 °C; IR [KBr]: 3,555 cm^{-1}: ^1H NMR ($CDCl_3$): δ 7.30 (dd, 2H, ArH), 7.26 (dd, 2H, ArH), 7.10 (dd, 2H, ArH), 7.02 (dd, 2H, ArH), 5.79 (methine), 3.70 (s, 3H, OCH_3). Anal. Calcd. for $C_{14}H_{13}NO_4$; C, 64.86; H, 5.06, N, 5.40; Found: C, 64.81; H, 5.00; N, 5.48.

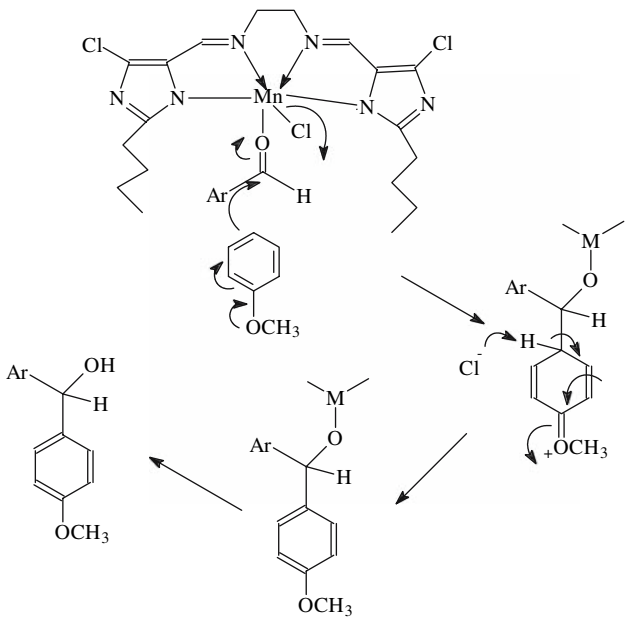
4-methoxybenzhydrol (2e)

Obtained from anisole (1.00 g) and 4-nitrobenzaldehyde (1.00 g) as white crystalline compound in 62.20% (1.27 g) yield; m.p 90–94 °C; IR [KBr]: 3,555 cm^{-1}: ^1H NMR ($CDCl_3$): δ 7.30 (dd, 2H, ArH), 7.20 (m, 5H, ArH), 7.10 (dd, 2H, ArH), 5.79 (methine), 3.70 (s, 3H, OCH_3). Anal. Calcd. for $C_{14}H_{14}O_2$; C, 78.46; H, 6.58; Found: C, 78.51; H, 6.53.

Discussion

The synthetic route is represented in Scheme 1. Here the use of the catalyst provides a suitable binding site which performs the function of a platform for the reactants to undergo the process of bond breaking and bond making and meanwhile the product leaves the site making it available for other molecules to undergo reaction. The probable mechanism is outlined below.

The mechanism involves the initial attack of the aldehyde at the central metal atom of the complex and assisted by the carbonyl oxygen atom. Further an electrophilic attack leads to the formation of an intermediate which leads to the formation of the resultant alcohol. The idea is to provide a novel synthetic route, which is simple, environmentally friendly and easy to handle. We have made an attempt to synthesize alcohols using the salen type imidozalen catalyst that acts as a good binding site. The reaction was carried out separately, using 4-chlorobenzaldehyde, 3,4-dimethoxyamino benzaldehyde, 3,4,5-trimethoxybenzaldehyde, 4-nitro benzaldehyde (Table 1).



Scheme 1 Mechanism for the formation of benzhydrol

Table 1 Addition of aldehydes to anisole

Entry	Aldehyde	Product/ Alcohol	Melting point (°C)	Yield (%)
1	4-chlorobenzaldehyde	2a	107–109	62
2	3,4-dimethoxy amino benzaldehyde	2b	175–180	42
3	3,4,5-trimethoxybenzaldehyde	2c	180–187	51
4	4-nitro benzaldehyde	2d	200–204	30
5	benzaldehyde	2e	90–94	62

The product obtained contained impurities and was purified using a silica gel/$CHCl_3$ column and the fractions collected were spotted and pooled to get different sub fractions, which were identified, by NMR and IR studies.

Conclusion

Scope of present work is that it is highly efficient and novel procedure. Involves a very simple reaction set up and is environment friendly. It is easy to handle. We have demonstrated how various alcohols can be prepared starting from corresponding aldehydes and anisole using salen type-imidozalen catalyst.

Acknowledgements One of the author (KJ) wishes to thank the Department of studies in Chemistry, University of Mysore for providing IR and elemental analyses facilities.

References

1. (a) Soai K, Mukaiyama T (1978) Chem Lett 491; (b) Mukaiyama T, Soai K, Sato T, Shimizu H, Suzuki K (1979) J Am Chem Soc 101:1455
2. Tomioko K, Nakajima M, Koga K (1987) Chem Lett 65
3. Tomioko K, Nakajima M, Koga K (1987) Tetrahedron Lett 28:1291
4. Lipshutz BH (1991) In: Comprehensive organic synthesis, vol 1. Pergamon Press, p 108
5. Bellamy F, Horton D, Millet J, Picart F, Samreth S, Chazan JB (1993) J Med Chem 36:898
6. Linganna N, Rai KML (1998) Synth Commun 28:4611
7. Aparna E, Rai KML, Byrappa K, Sureshbabu M, Jagadish RL, Gaonkar SL (2006) J Mater Sci 41:1391
8. Linganna N, Rai KML, Shashikanth S (1999) Indian J Chem Sect B 38B:1126
9. Ayala V, Corma A, Iglesias M, Sanchez F (2004) J Mol Catal A: Chem 221:201
10. Hamdan H, Navijanti V, Nur H, Nazian Mohd Muhid M (2005) Solid State Sci 7:239
11. Kerrigan NJ, Muller-Bunz H, Gilheany DG (2005) J Mol Catal A: Chem 227:163
12. Silva AR, Freire C, De Castro B (2004) New J Chem 2:253
13. Uchida T, Irie R, Katsuki T (2000) Tetrahedron 56:3501
14. Voet DZ, Voet G (1995) Biochemistry, 2nd edn. Wiley, New York, p 378
15. Jailakshmi K, Ph.D thesis, University of Mysore, Mysore
16. Yathirajan HS, Raju CR, Rai KML, Jailakshmi K, Nagaraja P, Palani K, Ponnuswamy MN, Nethaji M (2005) J Chem Crysta 35:211