SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 6, pp. 993–1000, 2004

Pinacol Coupling Reaction of Aromatic Aldehydes Mediated by Zn in Acid Aqueous Media Under Ultrasound Irradiation

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ABSTRACT

Pinacol coupling of aromatic aldehydes by Zn powder in aqueous H_2NSO_3H or H_3PO_4 under ultrasound irradiation can lead to the corresponding pinacols in 14–88% yields.

Key Words: Pinacol coupling; Acid aqueous media; Ultrasound irradiation.

1,2-Diols are very useful synthons for a variety of organic syntheses,[1] and which have been used as intermediates for the construction of biologically

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DOI: 10.1081/SCC-120028629 0039-7911 (Print); 1532-2432 (Online)

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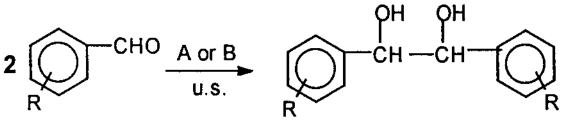
important natural product skeletons.[2] The formation of 1,2-diol has been attempted using a number of reagents such as Mg,[3] Mn,[4] Al,[5] In,[6] transition metal[7,8] and rare earth metal.[9] However, some of the reductants used are expensive or the reduction conditions are critical and these reactions are often associated with the toxic reagents and heavy metals, which would lead to economic and environmental concerns.

Organic reactions in water or aqueous media have attracted increasing interest currently because of the environmental issue and understanding biochemical processes. Water offers many practical and economic advantages as a reaction solvent, including low cost, safe handling and environmental compatibility. Recently, pinacol coupling reaction in aqueous media has been described in the literature;[3,5] however, these methods so far suffer from harsh reaction and workup conditions, using an excess amount of metal or have a long reaction time.

Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation.[10] Lim et al.[6] reported the reaction of aromatic aldehydes with indium in neutral aqueous media using sonication affording the corresponding diols in moderate to good yield; Basu et al.[7] reported the reduction of several aromatic ketones to diols by samarium in the presence of ammonium chloride under sonication at room temperature, and the reaction could be completed within 5 min; Mecarova and Toma[11] reported the pinacol coupling reaction in aqueous media under ultrasound irradiation and found that ultrasound considerably accelerates the benzaldehydes conversion. Our laboratory has also reported the pinacol coupling of aromatic aldehydes and ketones in aqueous media under ultrasound irradiation.[12–15] Herein, we wish to report the results of the pinacol coupling reaction of aromatic aldehydes by Zn in aqueous H_2NSO_3H (1N) or H_3PO_4 (3N) under ultrasound irradiation (Sch. 1).

When the substrate is $3\text{-}ClC_6H_4CHO$, we did the experiment using reaction system A: Zn (0.195 g, 3 mmol)/H_2NSO_3H (1N) and system B: Zn



Scheme 1. A: Zn (0.195 g, 3 mmol)/H_2NSO_3H (1N); B: Zn (0.195 g, 3 mmol)/H_3PO_4 (3N).

Table 1. Optimization of pinacol coupling of 3-ClC_6H_4CHO in acidic aqueous media under ultrasound irradiation.

Entry	Reaction system[a]	Ultrasound irradiation frequency (kHz)	Reaction time (h)	Isolated yield (%)
1	A	25	2.5	74
	B	25	2.5	88
2	A	40	2.5	72
	B	40	2.5	79
3	A	59	2.5	71
	B	59	2.5	64
4	B	25	2.0	73
5	B[b]	25	2.5	67
6	B[c]	25	2.5	81

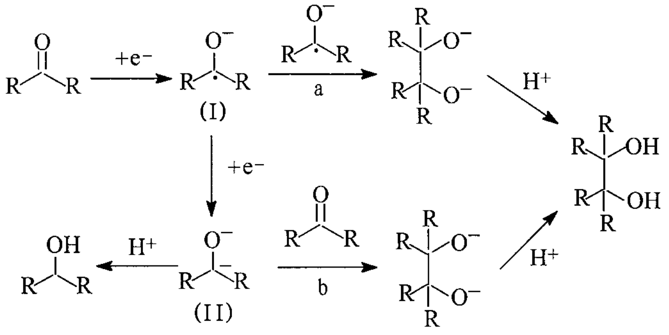
[a] A: Zn (0.195 g, 3 mmol)/H_2NSO_3H (1N); B: Zn (0.195 g, 3 mmol)/H_3PO_4 (3N).
[b] The amount of Zn is 0.13 g.
[c] The concentrate of H_3PO_4 is 2N.

(0.195 g, 3 mmol)/H_3PO_4 (3N). From the result in Table 1, we found that ultrasound irradiation frequency has little effect on the reaction yield (74%, 72% and 71%, respectively) for system A, but for B, the yield of pinacol (88%, 79% and 64%, respectively) significantly decreases following the enhancement of ultrasound irradiation frequency. From Table 1, we also found that for system B, prolonging the reaction time from 2.0 to 2.5 hr, the yield of pinacol increases from 73% (entry **4**) to 88% (entry **1**) under 25 kHz ultrasound irradiation. When lowering the amount of Zn (0.13 g) or the concentration of H_3PO_4 (2N) is lowered, the yield of pinacol decreased to 67% (entry **5**) and 81% (entry **6**) respectively, compared with that 88% (entry **1**).

An alternative and often competing reaction to pinacolization is reduction to the corresponding alcohol. In the present process, pinacol reaction was found mainly. Coupling is propagated by single-electron reduction of the carbonyl group to form a ketyl radical anion (**I**), which either undergoes radical–radical coupling (route a), or is further reduced to the corresponding dianion (**II**) and then nucleophilically attacks a second carbonyl group (route b), so leading to pinacol formation, while dianion (2) can be protonated by H^+ to generate minority of alcohol (Sch. 2).[2,7]

From the result in Table 1, the reaction conditions we choose are A: Zn (0.195 g, 3 mmol)/H_2NSO_3H (1N, 5 mL) and B: Zn (0.195 g, 3 mmol)/H_3PO_4 (3N, 5 mL). Using these two reaction systems, we did a series of experiments for pinacol coupling of aromatic aldehydes under ultrasound irradiation.

As shown in Table 2, some aromatic aldehydes *via* pinacol coupling can give pinacols in good yields in acidic aqueous media under ultrasound



Scheme 2.

irradiation. For system A, when the substrates are **1a**, **1b** and **1h**, the corresponding pinacol product was obtained in 74%, 70% and 63% yield respectively for 2.5 hr ultrasound irradiation; for system B, the yield of pinacol was 88%, 85% and 79% respectively, which also indicated that higher yield of

Table 2. Pinacol coupling of aromatic aldehydes in acidic aqueous media under ultrasound irradiation.

Entry	Substrates	Reaction system[a]	Isolated yield (%)	*dl*/*meso*[b]	R_f[c]
a	3-ClC_6H_4CHO	A	74	38/62	0.444
		B	88	46/54	
b	2-ClC_6H_4CHO	A	70	18/82	0.456
		B	85	24/76	
c	PhCHO	A	21	—	0.284
		B	45	—	
d	4-ClC_6H_4CHO	A	42	—	0.221
		B	34	—	
e	2,4-$Cl_2C_6H_3CHO$	A	54	—	0.448
		B	43	—	
f	4-$CH_3C_6H_4CHO$	A	23	—	0.294
		B	49	—	
g	3,4-$(OCH_2O)C_6H_3CHO$	A	14	—	0.222
		B	28	—	
h	3-BrC_6H_4CHO	A	63	33/67	0.500
		B	79	31/69	

[a] A: Zn (0.195 g, 3 mmol)/H_2NSO_3H (1N); B: Zn (0.195 g, 3 mmol)/H_3PO_4 (3N).
[b] Ratio of *dl*/*meso* was calculated by ^{1}HNMR.
[c] Eluant: petroleum ether/diethyl ether (V : V) = 1 : 1.

pinacols can be obtained under system B compared to system A. In contrast, electron-withdrawing groups in the aromatic ring of liquid aromatic aldehydes (entry **a**, **b**, **h**) increase the reactivity. Electron-withdrawing groups in the aromatic ring of solid aromatic aldehydes (entry **d**, **e**) and the aromatic aldehydes with electron donating group (entry **f**) show less reactivity. The steric hinderance around the carbonyl group (entry **e**, **g**) inhibits the coupling reaction.

The pinacol coupling reaction can form *dl* and *meso* stereoisomers; we easily found that in system A and system B, higher meso-stereoisomer was obtained except that the rate of *dl*/*meso* was nearly 1 : 1 (entry **a**).

In summary, ultrasound irradiation can efficiently prompt pinacol coupling of some aromatic aldehydes in acidic aqueous media. The main advantage of the present procedure is the milder reaction conditions, inexpensive reagent and operational simplicity.

EXPERIMENTAL

Liquid aldehydes were distilled before use. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). MS were determined on a VG-7070E spectrometer (El, 70 eV). ^{1}H NMR spectra was measured on Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40 kHz, 59 kHz and a nominal power 250 W; Shanghai Kudos Ultrasonic Instrument Co., Ltd.). The reaction flasks were located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from the ultrasonic bath.

General Procedure for the Pinacol Coupling of Aromatic Aldehydes in Acidic Media Under Ultrasound Irradiation

A 10 mL Pyrex flask was charged with the desired aldehyde (1 mmol), Zn powder (0.195 g, 3 mmol) and Zn/H_2NSO_3H (1N, 5 mL) or Zn/H_3PO_4 (3N, 5 mL). The mixture was irradiated in the water bath of an ultrasonic cleaner under an air conditions at 25–30°C for 2.5 hr. After the completion of the reaction, the resulting suspension was filtered to remove the Zn powder. The filtrate was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate for 12 hr and filtered. Ethyl acetate was evaporated under reduced pressure to give the crude product, which was separated by column chromatography on silica (200–300 mesh), eluted with petroleum ether or a mixture of petroleum ether and diethyl ether. All the products were confirmed by comparing their R_f value with that of the authentic samples, and IR, MS, ^1H NMR, spectral data.

2a. ^1H NMR: δ 3.29 (4H, b, OH), 4.56 (2H, s, CH, *dl*), 4.74 (2H, s, CH, *meso*), 6.87–7.36 (16H, m, Ph-H). m/z (%): 263 (1.2), 251 (1.6), 178 (4.6), 165 (4.6), 141 (100), 113 (23.8), 77 (71.0). IR (KBr) v: 3260–3318.

2b. ^1H NMR: δ 2.66 (2H, s, OH, *meso*), 2.76 (2H, s, OH, *dl*), 5.39 (2H, s, CH, *dl*), 5.63 (2H, s, CH, *meso*), 7.17–7.70 (16H, m, Ph-H). m/z (%): 282 (1), 165 (47), 141 (89), 113 (13), 107 (14), 77 (100), 51 (38). IR (KBr) v: 3100–3500.

2c. ^1H NMR: δ 2.20 (2H, s, OH, *meso*), 2.83 (2H, s, OH, *dl*), 4.72 (2H, s, CH, *dl*), 4.84 (2H, s, CH, *meso*), 7.14–7.32 (20H, m, Ph-H). m/z (%): 214 (1), 180 (7.6), 167 (12.5), 149 (6.0), 107 (93.8), 79 (100), 77 (73.8). IR (KBr) v: 3200–3480.

2d. ^1H NMR: δ 1.47 (6H, s, CH_3, *dl*), 1.54 (6H, s, CH_3, *meso*), 2.28 (2H, s, OH, *meso*), 2.57 (2H, s, OH, *dl*), 7.08–7.30 (16H, m, Ph-H). m/z (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) v: 3380–3420.

2e. ^1H NMR: δ 3.46 (4H, s, OH), 5.15 (2H, s, CH, *dl*), 5.47 (2H, s, CH, *meso*), 7.10–7.26 (12H, m, Ph-H). m/z (%): 352 (1), 305 (1.4), 233 (10), 175 (100), 145 (10), 111 (25), 77 (15). IR (KBr) v: 3320–3400.

2f. ^1H NMR: δ 2.06 (2H, s, OH, *meso*), 2.75 (2H, s, OH, *dl*), 4.68 (2H, s, CH, *dl*), 4.75 (2H, s, CH, *meso*) 7.04–7.26 (16H, m, Ph-H). m/z (%): 242 (1.2), 195 (6), 121 (100), 107 (12), 77 (13). IR (KBr) v: 3280–3450.

2g. ^1H NMR (DMSO as solvent): δ 4.44 (4H, s, OH), 5.14 (2H, s, CH, *dl*), 5.27 (2H, s, CH, *meso*), 5.96 (8H, s, CH_2), 6.52–6.82 (12H, m, Ph-H). m/z (%): 302 (1), 284 (2.5), 268 (5.0), 255 (11.8), 151 (100), 123 (32), 93 (77.1), 65 (39.0). IR (KBr) v: 3100–3600.

2h. ^1H NMR: δ 2.36 (2H, s, OH, *meso*), 2.93 (2H, s, OH, *dl*), 4.65 (2H, s, CH, *dl*), 4.81 (2H, s, CH, *meso*), 6.97–7.46 (16H, m, Ph-H). m/z (%): 325 (6), 186 (16), 157 (8), 107 (7), 77 (100), 51 (13). IR (KBr) v: 3200–3500.

ACKNOWLEDGMENTS

This project was supported by Educational Ministry of China, Educational Department of Hebei Province (2001104) and Natural Science Foundation of Hebei Province, China (203107).

REFERENCES

1. Ghribi, A.; Alexakis, A.; Normant, J.F. Asymmetric cleavage of chiral acetals by R_2CuLi, BF_3 reagents. Tetrahedron Lett. **1984**, *25*, 3083–3086.
2. Robertson, G.M. Pinacol coupling. In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, 563–611.
3. Zhang, W.C.; Li, C.J. Magnesium-mediated carbon-carbon bond formation in aqueous media: Barbier–Grignard allylation and pinacol coupling of aldehydes. J. Org. Chem. **1999**, *64*, 3230–3236.
4. Rieke, R.D.; Kim, S.H. New reagent for reductive coupling of carbonyl and imine compounds: Highly reactive manganese-mediated pinacol coupling of aryl aldehydes, aryl ketones, and aldimines. J. Org. Chem. **1998**, *63*, 5235–5239.
5. Khurana, J.M.; Sehgal, A. Rapid pinacolization of carbonyl compounds with aluminum-KOH. J. Chem. Soc., Chem. Commun. **1994**, *5*, 571.
6. Lim, H.J.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. Indium mediated pinacol coupling reaction of aromatic aldehydes in aqueous media. Tetrahedron Lett. **1998**, *39*, 4367–4368.
7. Basu, M.K.; Becker, F.F.; Banik, B.K. Ultrasound-promoted samarium/ammonium chloride mediated reductive coupling of aromatic ketones. J. Chem. Research (S), **2000**, 406–407.
8. Mukaiyama, T.; Yoshimura, N.; Igarashi, K.; Kagayama, A. Efficient diastereoselective pinacol coupling reaction of aliphatic and aromatic aldehydes by using newly utilized low valent titanium bromide and iodide species. Tetrahedron **2001**, *57*, 2499–2506.
9. Ogawa, A.; Takeuchi, H.; Hirao, T. Diastereoselective pinacol coupling of alkyl aryl ketones with rare earth metals in the presence of chlorosilanes. Tetrahedron Lett. **1999**, *40*, 7113–7114.
10. Li, J.T.; Han, J.F.; Yang, J.H.; Li, T.S. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation. Ultrasonics Sonochem. **2003**, *10*, 119–122.
11. Mečarová, M.; Toma, Ś. Optimization of pinacol coupling in aqueous media. Green Chem. **1999**, *1*, 257–259.
12. Li, J.T.; Bian, Y.J.; Zang, H.J.; Li, T.S. Pinacol coupling of aromatic aldehydes and ketones using magnesium in aqueous ammonium chloride under ultrasound. Synth. Commun. **2002**, *32*, 547–551.
13. Bian, Y.J.; Li, J.T.; Zang, H.J.; Li, T.S. Pinacol coupling of aromatic aldehydes and ketones using aluminum under ultrasound. Synth. Commun. **2002**, *32*, 1169–1174.

14. Zang, H.J.; Li, J.T.; Ning, N.; Wei, N.; Li, T.S. Pinacol coupling of aromatic aldehydes and ketones using Zn-$ZnCl_2$ under ultrasound. Indian J. Chem. **2002**, *41B*, 1078–1080.
15. Li, J.T.; Bian, Y.J.; Liu, S.M.; Li, T.S. Reductive coupling of aromatic aldehydes using manganese under ultrasound irradiation. Chin. J. Org. Chem. **2003**, *23*, 479–482.

Received in Japan July 25, 2003

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