

# Pinacol Synthesis in Aqueous Media

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Pinacol coupling of benzaldehyde in aqueous medium mediated by magnesium, zinc, iron, nickel, and tin was studied and effect of ultrasound on these reactions was examined. Magnesium-mediated pinacol coupling of various aromatic carbonyl compounds gave very good results and ultrasonic irradiation allows to shorten reaction time as well as to lower mole excess of the metal. Pinacol coupling proceeded well with zinc, too, but no reaction was observed with iron and some unexpected reaction (oxidation of benzaldehyde) was observed when nickel and tin were used as metals, respectively. The conversion of starting material as well as the proportion of a pinacol to a corresponding benzyl alcohol have strongly depended on the steric environment surrounding the carbonyl group.

The pinacol-coupling reactions are one of the frequently used methods for the formation of carbon—carbon bonds, which is documented in the recent reviews [1—3]. A lot of methods for pinacol coupling described previously claimed utilization of metals like sodium, lithium, Rieke's magnesium [4] or manganese [5], Al(Hg) [6] or chromonium(III) [7]. Anhydrous conditions and long reaction time were required to get satisfactory yields of the reaction products. On the other hand, some interesting papers describing the pinacol synthesis at environmentally friendly conditions in aqueous medium using aluminium powder [8, 9], indium [10] or samarium and iodine [11] were published recently.

A simple and effective method for pinacol coupling in water in the presence of small amount of ammonium chloride was published [12, 13] a few years ago. The yields of pinacols were 40—90 %, but the reaction time necessary to achieve such good yields was 12—24 h. The authors claimed that the pathways of pinacol coupling as well as reduction of carbonyl compounds to the corresponding alcohols involve the radical anion as the key intermediate. In all cases mentioned above reductions proceeded without any stereoselectivity and both *meso* and ( $\pm$ ) pinacols were formed in the ratio close to 50:50.

On the contrary, a highly stereoselective pinacolization of aromatic aldehydes was achieved using  $\text{TiCl}_4$ —Zn [14]. The yields of pinacolization were high, and ( $\pm$ ) isomers were the only products. The *meso* isomers were predominantly formed (*meso*—( $\pm$ ) ratio = 10—16:1) when copper(II) fluoride was used as the reactant [15].

A few attempts to improve pinacolization by sonication have been described recently. Aromatic carbonyl compounds pinacolize when sonicated with low-valent titanium in DME [16]. Aryl- or vinyl-substituted carbonyl compounds dimerize sonochemically in the presence of  $\text{TMSCl}$  and zinc in ethers. Pinacol disilyl ethers are obtained in yields higher than those of the silent reaction [17].

The main aim of this work was to examine a range of different metals (magnesium, zinc, iron, nickel, tin) as the mediators of the pinacol coupling and to find out if ultrasound can affect these reactions.

## EXPERIMENTAL

All chemical reagents were commercially available. The carbonyl compounds were purified (distilled and crystallized, respectively) before application in pinacol-coupling reactions. Magnesium turnings (98 %, for Grignard synthesis) and nickel powder (99 %, "100 mesh") were obtained from Aldrich. Zinc turnings, zinc powder, iron powder, magnesium powder, and tin turnings were obtained from Lachema.

The  $^1\text{H}$  NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in  $\text{CDCl}_3$  with tetramethylsilane as an internal standard. Conversion of starting material, ( $\pm$ )—*meso* ratio, and pinacol—alcohol ratio, respectively, were determined by  $^1\text{H}$  NMR based on the intensities of benzylic protons.

### Sonochemical Reactions [ ] ) ) ) ) ]

A suspension of a carbonyl compound (0.004 mol)

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**Table 1.** Influence of the Reaction Conditions on the Magnesium-Mediated Pinacol Coupling of Benzaldehyde; Benzaldehyde—Mg (Turnings) Mole Ratio 1:20 (if it is not stated otherwise)

Run	Reaction	Time	Conversion of Ia	w(Pinacol IIa)	w(Alcohol IIIa)
		min	%	%	%
1	))))	15	75	92	8
2	))))	30	84	93	7
3	))))	60	93	93	7
4	))))	90	100	95	5
5	silent	90	70	88	12
6	silent	180	99	93	7
7	)))) <sup>a</sup>	90	68	93	7
8	)))) <sup>b</sup>	90	35	82	18
9	)))) <sup>c</sup>	90	92	93	7
10	silent <sup>c</sup>	90	65	85	15
11	)))) <sup>d</sup>	90	95	87	13
12	)))) <sup>e</sup>	120	91	80 (64 <sup>f</sup> )	20
13	)))) <sup>d,e</sup>	120	93	78 (60 <sup>f</sup> )	22
14	silent <sup>g</sup>	90	72	85	15
15	silent <sup>h</sup>	12–24 h	88	99	1

a) Benzaldehyde—Mg mole ratio 1:10; b) benzaldehyde—Mg mole ratio 1:5; c) recovered Mg; d) reaction medium was pure water; e) 0.04 mol of benzaldehyde was used in reaction; f) yield of pinacol isolated after crystallization; g) reaction with sonochemically activated magnesium; h) data from Ref. [12].

and metal (0.08 mol) in 0.1 M aqueous ammonium chloride (20 cm<sup>3</sup>) was irradiated in a thermostated glass reactor fitted to an ultrasonic horn UUA 001 (Ultragen, Nitra, Slovakia) (20 kHz, 300 W) under pulsed conditions (pulse length: 4 s; 50 % duty) for 10 min (Mg powder), 15 min (Zn and Fe powders), and 90 min (Mg and Sn turnings), respectively, at room temperature under air atmosphere. The reaction was quenched with 3 M aqueous HCl (20 cm<sup>3</sup>) and extracted with ethyl acetate (3 × 50 cm<sup>3</sup>). The combined organic layers were washed with saturated aqueous KHCO<sub>3</sub> solution and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. Ethyl acetate was evaporated *in vacuo* and the crude product was analyzed by <sup>1</sup>H NMR spectroscopy or purified by crystallization from isohexane.

The energy emission of the reactor was measured by the Weissler test [18]: under the conditions used, sonication of aqueous KI (50 cm<sup>3</sup>, 1 mol dm<sup>-3</sup>) for 3 min gave 4.6 × 10<sup>-6</sup> mol dm<sup>-3</sup> of KI<sub>3</sub>.

### Silent Reactions

A suspension of a carbonyl compound (0.004 mol) and metal (0.08 mol) in 0.1 M aqueous ammonium chloride (20 cm<sup>3</sup>) was stirred vigorously for 10 min (Mg powder), 15 min (Zn and Fe powders) or 90 min (Mg and Sn turnings) at room temperature under air atmosphere. The reaction mixtures were processed as described above.

## RESULTS AND DISCUSSION

To start our study, we decided to make some preliminary survey of the pinacol coupling with benzaldehyde and compare our results with those described by

Zhang [12, 13].

From the results given in Table 1 it follows that 90 min sonication was sufficient to attain 100 % conversion of benzaldehyde. Silent reaction gave, at the same conditions, 70 % conversion only and the prolongation of the reaction time to 180 min was necessary to achieve 100 % conversion. We decided also to check if so big mole excess of magnesium is necessary for successful pinacol coupling, and found out that changing the benzaldehyde—magnesium ratio to 1:10 decreased the conversion to 67 %, and further lowering of the excess of magnesium substantially decreased benzaldehyde conversion. The magnesium turnings can be recovered easily and used in the next reaction without any significant effect on the reaction course (Table 1).

To check the synthetic utility of the procedure, an experiment with ten times the amount of the reactants (0.04 mol of benzaldehyde) was performed. Just minor lowering of the conversion was observed. Conversion of benzaldehyde was 91 % instead of complete conversion in the case of the reaction with 4 mmol of benzaldehyde. According to <sup>1</sup>H NMR analysis, there were 80 % of pinacol in the mixture of the products and 64 % of pinacol were isolated after crystallization.

We were curious also if the presence of NH<sub>4</sub>Cl is critical for the reaction. The experiments in pure water (without ammonium chloride) were performed and we found out that conversion of benzaldehyde in sonochemical reaction (90 min) was 95 % instead of 100 % in aqueous ammonium chloride. This finding is of interest especially from the environmental point of view.

Decreasing of the benzaldehyde conversion, observed when lower excess of magnesium turnings was used (Table 1), indicated that the course of the reaction could be dependent on the active surface of

**Table 2.** Influence of Quantity of Magnesium Powder [22] on Pinacol Coupling of Benzaldehyde in 0.1 M aq  $\text{NH}_4\text{Cl}$ ; Reaction Time 10 min

<i>Ia</i> —Mg mole ratio	Reaction	Conversion of <i>Ia</i>	<i>w</i> (Pinacol <i>IIa</i> )	<i>w</i> (Alcohol <i>IIIa</i> )
		%	%	%
1:20	silent	98	97	3
	))))	100	92	8
1:10	silent	97	83	17
	))))	100	89	11
1:5	silent	70	85	15
	))))	98	87	13
1:2	silent	60	82	18
	))))	90	85	15
1:1	silent	50	80	20
	))))	59	87	13
2:1	silent	6	80	20
	))))	44	100	0

**Table 3.** Influence of Quantity of Zinc Powder on Pinacol Coupling of Benzaldehyde in 0.1 M aq  $\text{NH}_4\text{Cl}$ ; Reaction Time 15 min

<i>Ia</i> —Zn mole ratio	Reaction	Conversion of <i>Ia</i>	<i>w</i> (Pinacol <i>IIa</i> )	<i>w</i> (Alcohol <i>IIIa</i> )
		%	%	%
1:20	silent	90	63	37
	))))	100	62	38
1:10	silent	84	80	20
	))))	92	86	14
1:5	silent	80	86	14
	))))	81	82	18
1:2	silent	35	90	10
	))))	50	90	10
1:1	silent	24	93	7
	))))	47	89	11
2:1	silent	28	94	6
	))))	42	93	7

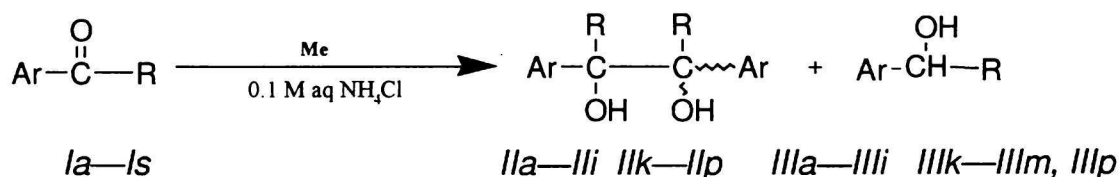
the metal. We therefore decided to use Mg powder instead of Mg turnings in the reactions. From the data given in Table 2 it follows that using the Mg powder accelerated the reaction very significantly. 100 % conversion of benzaldehyde was achieved in 10 min reaction time. Even more important is that decreasing of benzaldehyde—magnesium mole ratio from 1:20 to 1:10 had no influence on conversion either at sonochemical or at silent reaction. Further lowering of the mole ratio to 1:1 reduced the conversion of silent reaction to 50 % and the conversion of sonochemical reaction to 59 %. The effect of ultrasound was markedly manifested with a benzaldehyde—magnesium mole ratio 2:1. The silent reaction gave just 6 % conversion, while the sonochemical reaction gave 44 % of benzaldehyde conversion. The reproducibility of these reactions is very good. The experiments were repeated three or four times with very similar results.

It is possible to assume that the positive effect of ultrasonic irradiation is due to microstreaming, which accompanies implosions of microbubbles near the metal surface and provides an effective mass trans-

fer. The active surface of the metal is therefore considerably enlarged, which means that its activity is also enhanced. If this rate increase of the sonochemical pinacolizations would be due to the effective mass transfer only, as foreseen by *Kegelaers* [19] for heterogeneous reactions, the same effect on the reactions rate should be achieved by using efficient UltraTurax mixers.

To confirm or contradict this assumption we performed the following experiment. Magnesium turnings were irradiated in aqueous ammonium chloride for 90 min. Then the benzaldehyde was added and the pinacolization was performed under classical conditions (90 min) without ultrasound. Conversion of benzaldehyde was 72 %, which is very similar to that observed at the silent reaction. It means that the role of ultrasonic irradiation is not only in improving mass transfer or in enlarging metal surface, but it seems that the ultrasonic irradiation has a positive effect on an electron transfer from magnesium to the carbonyl compounds.

To improve the general applicability of this approach and find its limitation we performed some ad-



Me: Mg, Zn

<i>a</i>	R = H, Ar = C <sub>6</sub> H <sub>5</sub>	<i>k</i>	R = H, Ar = 2-ClC <sub>6</sub> H <sub>4</sub>
<i>b</i>	R = H, Ar = 2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>l</i>	R = H, Ar = 4-ClC <sub>6</sub> H <sub>4</sub>
<i>c</i>	R = H, Ar = 3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>m</i>	R = H, Ar = 4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
<i>d</i>	R = H, Ar = 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<i>n</i>	R = H, Ar = furan-2-yl
<i>e</i>	R = H, Ar = 2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<i>o</i>	R = H, Ar = thiophen-2-yl
<i>f</i>	R = H, Ar = 3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<i>p</i>	R = CH <sub>3</sub> , Ar = C <sub>6</sub> H <sub>5</sub>
<i>g</i>	R = H, Ar = 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<i>q</i>	R = H, Ar = ferrocenyl
<i>h</i>	R = H, Ar = 3,4-methylenedioxyphenyl	<i>r</i>	R = H, Ar = but-1-yl
<i>i</i>	R = H, Ar = 3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<i>s</i>	R = H, Ar = C <sub>6</sub> H <sub>5</sub> CH=CH—
<i>j</i>	R = H, Ar = 2,4,6-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>		

Scheme 1

ditional experiments with other metals (Zn, Fe, Ni). The results of the zinc-mediated reaction of benzaldehyde are given in Table 3. The values of the benzaldehyde conversion were similar to those observed at magnesium-mediated reactions. The only difference is in proportion of benzyl alcohol to pinacol in the reactions with benzaldehyde—zinc mole ratio 1:20. In contrary to the magnesium-mediated reactions, proportion of benzyl alcohol was 37—38 %. A more pronounced ultrasound effect was observed, like in the magnesium-mediated reactions, in the reactions with lower amount of zinc (benzaldehyde—zinc mole ratio = 1:2, 1:1, and 2:1, respectively). Zinc turnings cannot be used in pinacol coupling because after 90 min of the silent as well as sonochemical reaction with benzaldehyde—zinc mole ratio = 1:20 the starting material only was detected in the reaction mixture.

The reactions mediated by iron powder (benzaldehyde—iron mole ratio = 1:20) gave after 15 min stirring or sonication at room temperature just the traces of pinacol. Conversion of benzaldehyde was less than 1 % according to  $^1\text{H}$  NMR analyses.

Unexpected results were achieved at the reactions of benzaldehyde in aqueous ammonium chloride mediated by nickel powder (benzaldehyde—nickel powder mole ratio 1:20). Benzoic acid was the only product. Conversion of benzaldehyde was at sonochemical reaction (15 min) 100 %, at silent reaction (15 min) 30 %. To explain these results a silent reaction with nickel powder recovered from a previous silent reaction was performed. Oxidation ability of nickel was reduced. It indicates that nickel powder is covered by nickel peroxide that is probably responsible for this oxidation ability. Consumption of nickel peroxide from the nickel surface at the first silent reaction decreased the conversion of benzaldehyde at the second silent reaction from 30 % to 18 %. On the other hand, using nickel powder recovered from the second silent reac-

tion in sonochemical reaction increased its oxidation ability. Conversion of benzaldehyde was at the same conditions (15 min, room temperature) 42 % and benzoic acid was the only product. It is possible to assume that nickel peroxide can arise in aqueous medium in air atmosphere under ultrasonic irradiation. Oxidation ability of nickel peroxide is described in literature [20, 21].

The similar results were observed when tin turnings were used in the reactions. Sonochemical reaction with benzaldehyde and tin turnings (90 min) gave 50 % conversion of benzoic acid, silent reaction (90 min) gave 27 % conversion of benzoic acid. Benzaldehyde—tin turnings mole ratio was 1:20 in both cases. This observation is possible to explain by presentation of tin oxides that cover the metal surface.

It is possible to exclude oxidation of benzaldehyde to benzoic acid due to atmospheric oxygen, because benzaldehyde was the only compound detected by NMR spectroscopy in the reaction mixture at silent as well as at sonochemical reaction in aqueous ammonium chloride without metal.

The applicability of our procedure using magnesium turnings was checked on 19 different carbonyl derivatives (Scheme 1). As it is possible to see in Table 4, application of ultrasonic irradiation shortened the reaction time in all cases. This effect is more pronounced in the case of less reactive benzaldehydes. The conversion of the starting material as well as the yields of pinacols were higher at ultrasonic reactions than at silent reactions at the same time (90 min).

No clear-cut substituent effect was observed on the reaction course, which can be explained by some adsorption phenomena [13]. Most of the substituted benzaldehydes gave good yields of pinacols. 2-Furaldehyde (*In*) and 2-thiophenecarboxaldehyde (*Io*) underwent reaction smoothly and clean as no product

**Table 4.** Pinacol Coupling of Various Carbonyl Compounds Mediated by Magnesium (Turnings) in 0.1 M aq NH<sub>4</sub>Cl; Reaction Time 90 min, Substrate—Mg (Turnings) Mole Ratio 1:20

Substrate	Reaction	Conversion of Ia—Is	w(Pinacol IIa—IIs)	w(Alcohol IIIa—IIIs)
		%	%	%
Ia	))))	100	95	5
	silent	70	88	12
	silent <sup>a</sup>	88	99	1
Ib	))))	92	79	21
	silent	41	65	35
Ic	))))	98	87	13
	silent	64	86	14
Id	))))	94	81	19
	silent	86	85	15
	silent <sup>a</sup>	65	92	8
Ie	))))	88	52	48
	silent	58	50	50
If	))))	100	91	9
	silent	58	79	21
	silent <sup>a</sup>	78	100	0
Ig	))))	81	90	10
	silent	66	89	11
	silent <sup>a</sup>	96	100	0
Ih	))))	93	90	10
	silent	15	69	31
Ii	))))	80	81	19
	silent	51	82	18
Ij	))))	0	0	0
	silent	0	0	0
Ik	))))	90	65	35
	silent	16	13	87
	silent <sup>a</sup>	61	73	27
Il	))))	98	89	11
	silent	71	67	33
	silent <sup>a</sup>	90	93	7
Im	))))	60	84	16
	silent	55	86	14
In	))))	100	100	0
	silent	100	100	0
	silent <sup>a</sup>	100	100	0
Io	))))	100	100	0
	silent	79	100	0
Ip	))))	53	93	7
	silent	42	88	12
	silent <sup>a</sup>	66	92	8
Iq	))))	0	0	0
	silent	0	0	0
Ir	))))	0	0	0
	silent	0	0	0
	silent <sup>a</sup>	0	0	0
Is	))))	0	0	0
	silent	0	0	0

a) Data from Ref. [12], reaction time 12—24 h.

of competitive reduction (alcohol) was observed. On the other hand, we found that aliphatic aldehyde (*Ir*) as well as ferrocenecarboxaldehyde (*Iq*) and the cinnamaldehyde (*Is*) were inert. Just the starting material was detected at these reactions, both silent and ultrasonic. An aromatic ketone (*Ip*) underwent the reaction under these reaction conditions equally well as the aromatic aldehydes. We performed also an experiment with *p*-nitrobenzaldehyde, but a complicated mixture of the products was observed.

The pinacol—benzyl alcohol ratio is strongly affected by the steric effects of substituents on the aromatic rings [12, 13]. In the case of *ortho*-substituted benzaldehydes (*Ib*, *Ie*, *Ik*) we observed the increased formation of the corresponding alcohols, which is in contradiction to the *meta*- and *para*-substituted aldehydes. When two substituents were present in *ortho* positions no reaction products were obtained either at ultrasonic or at silent reactions (see *Ij*) and starting material only was detected in the reaction mix-

tures after the reactions. This result is in contradiction with the results published previously [12] where 1,6-dichlorobenzaldehyde gave 74 % of corresponding benzyl alcohol and no pinacol. Possible explanation is that methoxy group causes greater steric hindrance around the carbonyl group than chlorine atom.

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