

The remarkable role of water during the chemoselective reduction of ketones mediated by metallic aluminium

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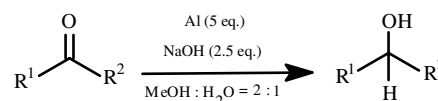
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Abstract—Diaryl ketones are reduced selectively to the corresponding benzhydrols in good yield by aluminium powder in the presence of sodium hydroxide in the solvent system MeOH:H₂O = 2:1 whereas dialkyl ketones, α -tetralone, aryl alkyl ketones and cycloalkanones remain mostly unaffected. Interestingly, diaryl ketones remain totally unchanged by the present reagent combination in the absence of water, that is in anhydrous methanol.

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The selective manipulation of one functional group in the presence of other(s) using nontoxic chemicals in economically viable and environmentally benign conditions is a formidable task for synthetic organic chemists.¹ There is a growing interest in carrying out important synthetic transformations in aqueous media.² There are reports³ of organic reactions where surprisingly beneficial effects of stoichiometric and sub-stoichiometric amounts of water have been elegantly demonstrated. The chemoselective reduction of ketones in the presence of other reducible functional groups is an important synthetic transformation.⁴ Many methods^{4,5} have been developed for this purpose including catalytic hydrogenation, hydride transfer, dissolving metal reduction, reduction using low-valent cationic reagents, Meerwein–Ponndorf–Verley reduction and photochemical and electrochemical reductions. There are also reports⁶ on the reduction of diaryl ketones in preference to other types of ketonic functionality. However, many of these reactions involve the use of costly and toxic substances, are difficult to carry out and the reaction products are complicated by side reactions. We report herein a simple and mild procedure for the reduction of diaryl ketones (Scheme 1) using aluminium powder and sodium hydroxide in aqueous methanol (MeOH:H₂O = 2:1), where excellent discrimination be-



Scheme 1.

tween various types of carbonyl functionality has been observed. The results are shown in Table 1.

As shown in Table 1, various diaryl ketones underwent smooth reduction to the corresponding benzhydrols (Table 1, entries 1–4) in good yields and high purities using this reagent system as depicted in Scheme 1. Diaryl ketones, aryl alkyl ketones and aryl aldehydes have been reported to undergo pinacol coupling with Al/Hg in dichloromethane^{7a} albeit in poor yield accompanied by by-products. However, the same compounds along with cycloalkanones are found to be reduced to the corresponding alcohols with Al/Hg in aqueous THF (THF:H₂O = 9:1).^{7b} Cycloalkanones and aliphatic acyclic ketones have been found to give complex mixtures of unidentified products during aluminium-mediated reduction^{7c} in dry methanol in the presence of excess KOH having reagent combination substrate: Al:KOH = 1:3:9. During dissolving metal reductions of ketones to the corresponding alcohols it has been frequently observed^{5b,8} that diaryl ketones and α -tetralone are converted to the corresponding hydrocarbons by over-reduction. In contrast, in the present aluminium-mediated method in aqueous methanol (MeOH:H₂O = 2:1) using the reagent combination substrate:Al:NaOH = 1:5:2.5 (which involves less alkali

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Table 1. Aluminium-mediated reduction of different types of carbonyl compounds in the presence of sodium hydroxide in aqueous methanol (methanol–water = 2:1)

Entry	Substrate	Product	Time (h)	Yield (%) ^a
1			2	85
2			3	79
3			3	71
4			2	92
5			4	93
6			4	19
7			5	92
8			4	23
9			3	36 ^b
10			2	89 (1:1) ^c

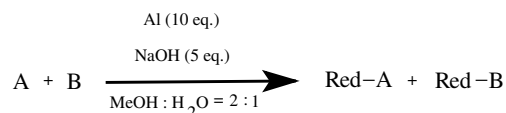
^a Yields refer to those of isolated pure products, fully characterized chemically and spectroscopically.

^b % of conversion as measured by ¹H NMR, remainder being starting material.

^c *dl:meso* by ¹H NMR.

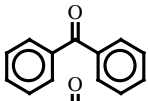

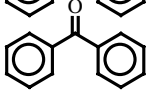
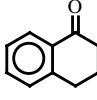
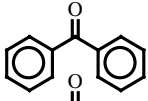
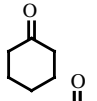
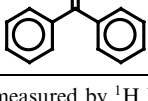
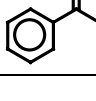
compared to the analogous method in anhydrous methanol^{7c}), α -tetralone (Table 1, entry 5) and dialkyl ketones (Table 1, entry 7) remain mostly unaffected; cycloalkanones (Table 1, entry 6), phenyl ethyl ketone (Table 1, entry 8) and 4-methoxyacetophenone (Table 1, entry 9) respond sluggishly. Therefore, the present aluminium-mediated method⁹ in an aqueous medium offers excellent chemoselectivity towards the reduction of diaryl ketones in the presence of other types of ketonic functionalities. This is supported by compatibility studies where binary mixtures of different types of ketones in equimolar amounts have been subjected to reduction in the presence of an excess of the reagents (Scheme 2, Table 2).

Intramolecular chemoselectivity of the present aluminium-mediated protocol is demonstrated in Scheme 3 where a diaryl ketone is reduced selectively to the corresponding 2° alcohol leaving the benzo-fused cyclic ketone intact.

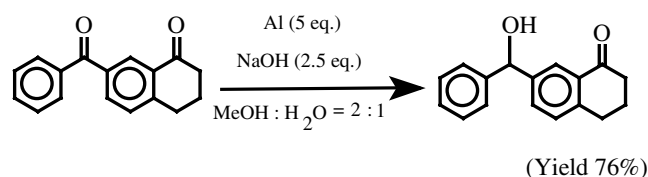
**Scheme 2.**

Although the mechanism of these aluminium-mediated chemoselective reductions is not clear it seems to be dependent on the reduction potentials of the carbonyl functionalities, where a functional group with a less negative reduction potential (i.e., a diaryl ketone) is reduced more readily. This transformation also depends on the amount of water present in the medium. It has been observed that benzophenone yields benzopinacol as the major product when the reaction is carried out in MeOH:H₂O = 1:2 whereas benzhydrol is obtained as the major product in MeOH:H₂O = 2:1. In MeOH:H₂O = 1:1 a mixture of benzhydrol and benzopinacol were obtained. It is interesting to observe that the sub-

Table 2. Intermolecular competition during aluminium-mediated reduction between different ketones in aqueous methanol (methanol–water = 2:1)

Entry	Substrate (A)	Substrate (B)	Time (h)	%-Reduction ^a of A	%-Reduction ^a of B
1			4	>95	<5
2			4	>95	<5
3			4	>95	25
4			4	>95	30

^a% of reduction measured by ¹H NMR.

**Scheme 3.**

strate (benzophenone) is recovered unchanged when the reaction is carried out in anhydrous methanol using the present reagent combination (substrate:Al:NaOH = 1:5:2.5). This indicates that the presence of water in the reaction medium is essential to bring about this reduction. Water in the reaction medium also seems to attenuate the reactivity of the present reagent system and plays an important role in imparting selectivity. This was not observed in the analogous aluminium-mediated processes⁷ reported earlier.

In conclusion, this aluminium-mediated reaction in aqueous methanol can serve as an efficient procedure for the chemoselective reduction of diaryl ketones in the presence of other types of ketonic functionality in relatively mild conditions and using less toxic and easily available reagents. Further investigations on mechanistic aspects and synthetic applications of this reaction are currently underway.

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9. Typical experimental procedure: Aluminium powder (135 mg, 5 mmol) was added to a solution of benzophenone (182 mg, 1 mmol) in methanol (3 mL) followed by a solution of sodium hydroxide (100 mg, 2.5 mmol) in water (1.5 mL) with stirring. Stirring was continued until the completion of the reaction as monitored by TLC. The reaction mixture was diluted with water, dichloromethane was added and the mixture was filtered. The residue was repeatedly washed with dichloromethane and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with water, dried and solvent was evaporated to furnish practically pure benzhydrol (156 mg, 85%).