Organic &
Biomolecular Chemistry

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COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c3ob40642c

Received 31st March 2013,
Accepted 19th May 2013

DOI: 10.1039/c3ob40642c

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Tandem nucleophilic addition–Oppenauer oxidation of aromatic aldehydes to aryl ketones with triorganoaluminium reagents†

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In the presence of pinacolone, the *in situ* prepared triorganoaluminium reagents reacted with aromatic aldehydes to give ketones in moderate to high yield. We propose that the products are formed *via* a tandem organoaluminium reagents addition–Oppenauer oxidation sequence.

Aryl ketones are the basic units in many natural products, pharmacologically important molecules[1] and many synthetic approaches have been developed in the past few decades for their synthesis. Besides the well known Friedel–Crafts acylation reaction (unreactive with electron-deficient arenes)[2] the direct conversions of aldehydes to ketones, such as the noble metal catalyzed acylation of aryl halides,[3] aryl boronic acids,[4] hydroacylation of olefins,[5] and arenes,[6] are convenient procedures for aryl ketone synthesis.

The tandem nucleophilic addition–Oppenauer oxidation of aldehydes to ketones provides another approach for the synthesis of variable ketones that can be prepared from the corresponding aldehydes in one step. The nucleophiles involved in such conversions are Grignard reagents,[7] organozirconium reagents,[8] allylchromium,[9] organoborates,[10] or organoindium reagents formed *in situ* in Barbier-type reactions.[11]

Based on our interests in the nucleophilic addition reaction of organozinc reagents towards carbonyl[12] and imino compounds,[13] we have found that Lewis acids can dramatically influence the reactivity of organometallic reagents. Recently, Zhang *et al.*[14] reported a novel olefination reaction of aromatic aldehydes with organozinc reagents (prepared by *in situ* transformation of Grignard reagents with $ZnCl_2$) in the presence of $AlCl_3$. We were interested in determining whether stilbenes could be formed *via* the reaction of benzyl magnesium halides with benzaldehyde in the presence of $AlCl_3$ (without the addition of $ZnCl_2$, as one can easily deduce the role of $ZnCl_2$ was to convert reactive benzylic Grignard reagents into less reactive benzylic zinc derivatives). Surprisingly, the desired stilbene was not formed; however, the corresponding secondary alcohol and an unexpected 1,2-diphenylethanone were obtained in 65% and 23% yield respectively.[15]

Although stilbene was not obtained, the appearance of significant amounts of ketone was exciting as this product appears to be produced *via* an *in situ* tandem organoaluminium addition–Oppenauer oxidation of aldehydes. To the best of our knowledge, the only similar report of such reactions involving an organoaluminium reagent appeared early in 1990 in which trimethyl aluminium was used as the nucleophile and the mechanism was not clear.[16] Combined with several excellent reports on the tandem Mg-Oppenauer oxidation of aldehydes[7] we considered it worthwhile to explore this reaction further.

Benzaldehyde was reported to be an excellent hydrogen acceptor in Oppenauer oxidations[7] but we do not think it is a good choice in the tandem organometallic reagent addition–Oppenauer oxidation of aldehydes. First of all, the R_f values of benzaldehyde and the ketone products are similar unless there are polar substituents in the benzene ring of the ketones. Thus the addition of large amounts of excess benzaldehyde may burden product purification. Second, as the mechanism of the magnesium-Oppenauer oxidation of aldehydes shows (Fig. 1), competitive reactions exist between the nucleophilic addition of the Grignard reagent to aldehyde (**I**) and Oppenauer oxidation of secondary alkoxide (**II**) by aldehyde (**I**) in the reaction system. To avoid the *in situ* Oppenauer oxidation, a low reaction temperature is thus required.[7a] Importantly the amount of Grignard reagent must be accurately titrated to ensure that all of the aromatic aldehyde (**I**) is fully consumed. If the amount of Grignard reagent is underestimated, the excess Grignard reagent would react with the formed ketone (**III**) or with the subsequently added benzaldehyde to give the phenyl magnesium alkoxide (**IV**) and then be oxidized to the ketone (**V**) by-product. On the other hand, should the amount of Grignard reagent be overestimated, then the aromatic

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob40642c

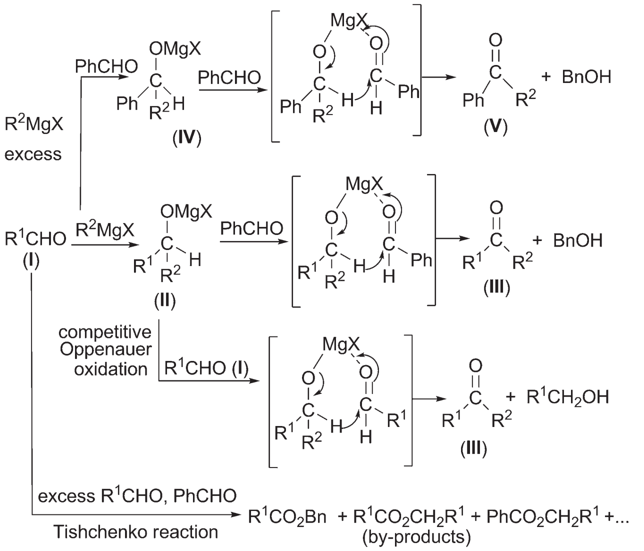
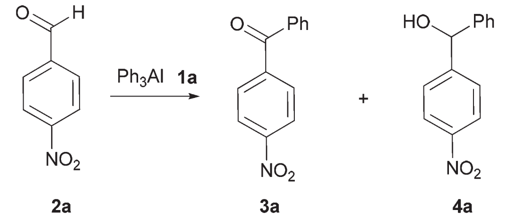


Fig. 1 Mechanism and side reactions of the tandem Grignard reagent addition–Oppenauer oxidation using benzaldehyde as a hydrogen acceptor.

Table 1 Optimization of the reaction conditions^a



Entry	Additive (equiv.)	Solvent	Yield of **3a**^{b} [%]
1	—	THF	18^a
2	—	THF	23^c
3	Acetone (2.0)	THF	56
4	Acetone (5.0)	THF	62
5	Acetophenone (2.0)	THF	54
6	Benzophenone (2.0)	THF	34
7	Benzoquinone (2.0)	THF	45
8	Pinacolone (2.0)	THF	67
9	Pinacolone (5.0)	THF	73
10		Pinacolone–THF	87^d
11	CF_3CO_2H (0.05)	Pinacolone–THF	92^d
12	Pinacolone (5.0)	Et_2O^e	25
13	Pinacolone (5.0)	Bu_2O^e	18
14		Pinacolone–THF	26^f
15		Pinacolone–THF	64^g

^{a} Reaction conditions: nitrobenzaldehyde **2a** (3.5 mmol) was treated with Ph_3Al **1a** (3.5 mmol) and ketone in THF (20 mL) at room temperature. ^{b} Isolated yields. ^{c} Two equiv. of aldehyde was added. ^{d} The reaction proceeded in 20 ml of pinacolone–THF (1 : 1). ^{e} The reaction mixture was not fully dissolved. ^{f} The reaction mixture was cooled in an ice-water bath for 12 hours. ^{g} The reaction mixture was heated at 50 °C for 12 hours.

aldehyde (**I**) would be in excess, and along with the added benzaldehyde, may proceed *via* a Tishchenko reaction to give esters as by-products.[17]

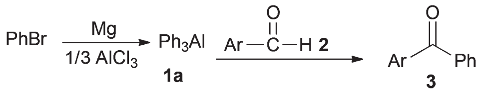
Ketones are also good hydrogen acceptors in the Oppenauer oxidation of primary and secondary alcohols.[18] We believe that in the tandem nucleophilic addition–Oppenauer oxidation reaction, ketones are better oxidants than benzaldehyde as ketones are less electrophilic than aldehydes and can be differentiated from aldehydes by weaker nucleophiles. Second, ketones do not react *via* the Tishchenko reaction, therefore eliminating a major side product in the Oppenauer oxidation reaction. Additionally, small ketones like acetone and their reduction products 2-propanol normally have lower boiling points and larger dipole moments, ensuring their easy removal by water washing or distillation.

To achieve the ketone mediated tandem organoaluminium reagent addition–Oppenauer oxidation of aldehydes, a variety of ketones were screened using triphenyl aluminium **1a**[19] and 4-nitrobenzaldehyde **2a** in a model reaction. The results illustrated in Table 1 indicate that **2a** is a weak oxidant, for when 1.0 equiv. of **2a** was added, the ketone **3a** was produced in only 18% yield, which increased a little when an additional equiv. of aldehyde **2a** was added (Table 1, entries 1 and 2). It was gratifying that when 2 equiv. of acetone were added, the yield of ketone **3a** increased to 56%. However, further additions of acetone did not affect the yield of ketone **3a** (Table 1, entries 3 and 4). Other ketones such as acetophenone, benzophenone, pinacolone, benzoquinone were then screened. Benzophenone and acetophenone gave lower yields of **3a** compared to acetone. Pinacolone was shown to be a better oxidant, as **3a** was obtained in 67% yield when 2 equiv. of pinacolone was added. The yield of **3a** was improved to 73% by the addition of 5 equiv. of pinacolone. We found that this reaction can be performed best using pinacolone–THF (1 : 1) as the solvent whereby the product **3a** was obtained in 87% yield after stirring at room temperature for two days. Only ketone **3a** and alcohol **4a** were produced. Neither the nucleophilic addition product of triphenyl aluminium reagent to pinacolone nor the aldol condensation product from pinacolone reacting with aromatic aldehyde **2a** was formed. The addition of CF_3CO_2H (0.05 equiv.) after complete consumption of aldehyde **2a** can further enhance the yield of **3a** to 92% (entries 10 and 11).

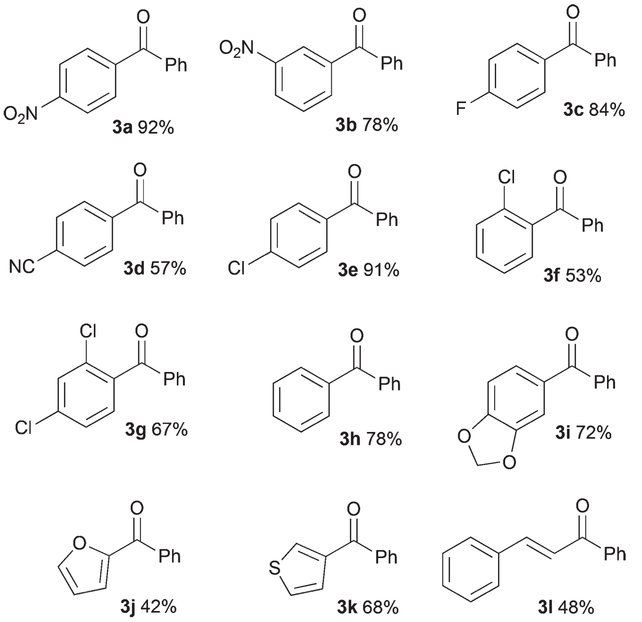
The solvents Et_2O and Bu_2O were unsuitable due to their limited solubility with 4-nitrobenzaldehyde and triphenyl aluminium (Table 1, entries 12 and 13). Conducting the reaction at room temperature was optimal; when the tandem addition–Oppenauer oxidation reaction was held at 0 °C or lower, little or no reaction occurred. Higher reaction temperatures led to lower yields and several by-products appeared (entries 14 and 15). The efficiency of pinacolone is attributed to its high oxidation potential.

With the optimized reaction conditions in hand, we then investigated the substrate scope of aromatic aldehydes with the triphenyl aluminium reagent **1a**. The results, summarized in Table 2, indicate that a range of aromatic aldehydes **2a–2l** were all efficiently transformed to their corresponding products **3a–3l** in fair to excellent yields. Various functional groups, such as chloro, fluoro, nitro and cyano, are well tolerated on the benzene rings of aromatic aldehydes. Sterically hindered 2-substituted aldehydes (**2f**, **2g**) can also be converted into corresponding ketones in acceptable yields (**3f**, **3g**).

Table 2 Reaction of triphenyl aluminium with aromatic aldehydes[a,b]

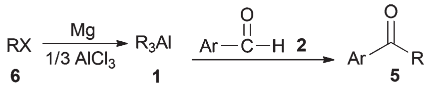


2a = 4-nitrobenzaldehyde
2b = 3-nitrobenzaldehyde
2c = 4-fluorobenzaldehyde
2d = 4-cyanobenzaldehyde
2e = 4-chlorobenzaldehyde
2f = 2-chlorobenzaldehyde
2g = 2,4-dichlorobenzaldehyde
2h = benzaldehyde
2i = piperonal
2j = furfuraldehyde
2k = 3-thiophenecarboxaldehyde
2l = cinnamaldehyde



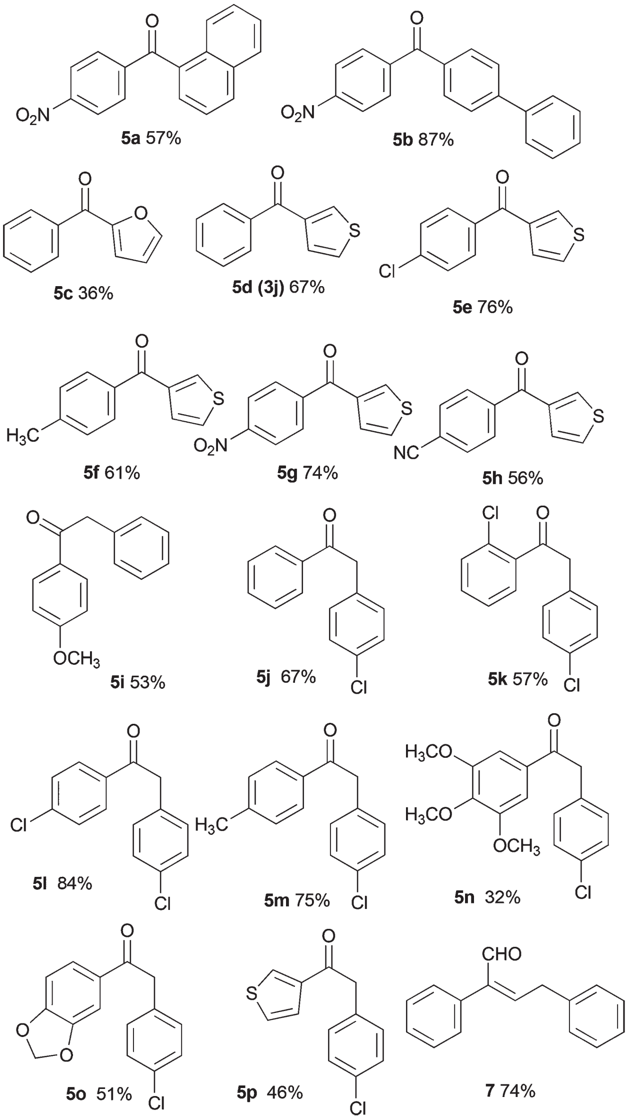
[a] Unless otherwise noted, the reactions were performed by employing Ph_3Al (3.5 mmol) and aryl aldehyde (3.5 mmol) in 20 ml of pinacolone–THF (1 : 1). [b] Isolated yield.

Table 3 Reaction of aryl aldehydes with triaryl aluminium reagents[a,b]



6a = α-bromonaphthalene
6b = 4-bromobiphenyl
6c : furan was used
6d = 3-bromothiophene
6e = benzyl chloride
6f = 4-chlorobenzyl chloride

2a = 4-nitrobenzaldehyde
2d = 4-cyanobenzaldehyde
2e = 4-chlorobenzaldehyde
2f = 2-chlorobenzaldehyde
2h = benzaldehyde
2i = piperonal
2k = 3-thiophenecarboxaldehyde
2m = 4-methyl benzaldehyde
2n = 4-anisaldehyde
2o = 3,4,5-trimethoxybenzaldehyde
2p = phenylacetaldehyde



[a] Unless otherwise stated, the reactions were performed by employing Ph_3Al (3.5 mmol) and aryl aldehyde (3.5 mmol) in 20 ml of pinacolone–THF (1 : 1). [b] Isolated yield.

Heteroaromatic carboxaldehydes, such as furfuraldehyde (**2j**) and 3-thiophenecarboxaldehyde (**2k**), gave the corresponding ketones (**3j** and **3k**) in lower yields than aromatic carboxaldehydes; probably because of either the instability of these heteroaromatic carboxaldehydes (especially furfuraldehyde) in this reaction system or the inert reactivity of these secondary alkoxides which bonded with a strong electron-donating heteroaromatic ring, they are inert substrates in the following Oppenauer oxidation. Cinnamaldehyde reacted with the triphenyl aluminium reagent regioselectively to give chalcone **3l** in 48% yield.

After screening the reactivity of aromatic aldehydes, the scope of other triorganoaluminium reagents was investigated. To our delight, triorganoaluminium reagents prepared by *in situ* reaction of various kinds of organo bromides or chlorides in the presence of magnesium (1.5 equiv.) and $AlCl_3$ (1/3 equiv.) reacted smoothly with aromatic aldehydes to give the corresponding ketones in moderate to good yields (Table 3). In this context, sterically hindered tri(α-naphthyl) aluminum reagent reacted with 4-nitrobenzaldehydes **2a** to give the ketone **5a** in 57% yield, whereas the less sterically hindered tribiphenyl aluminium **4b** gives ketone **5b** in 87% yield. Hetero aromatic aluminum reagents can also be applied here. Although the tri(2-furanyl) aluminium reagent, obtained by direct transmetalation of 2-furyllithium with one-third equivalent of aluminium chloride, reacted with benzaldehyde to give the corresponding ketone **5c** in low yield; the trithiophen-3-ylaluminium reagent was better and reacted with aromatic aldehyde to give the corresponding ketones in good yields (**5d–5h**).

Tribenzylic aluminium reagents can be easily prepared from benzylic Grignard reagents. However, the yields of benzyl ketones are lower than those from aromatic aluminium reagents, probably due to the enolizable nature of these benzyl ketones that may form condensation products with other carbonyl compounds in these reaction systems. Aromatic aldehydes bearing strong electron-donating/withdrawing groups reacted readily with tribenzylic aluminium reagents to furnish the corresponding ketones in high yields; however, the yields of ketones (**5n–5p**) were low. Neither prolonging the reaction time nor elevating the amount of pinacolone enhanced the ketone yields. When an enolizable aldehyde such as phenylacetaldehyde **2p** was treated with **1a**, the self-condensation product **7** was isolated. Fatty aldehydes reacted with the aluminium reagents produced by this method did not give ketones in acceptable yields, most likely due to the enolizable nature of the aldehydes or the ketone products. Attempts to use R_2AlCl and $RAlCl_2$ instead of R_3Al were less effective and the corresponding ketone was obtained in lower yields.

In conclusion, we have successfully developed a new and efficient tandem triorganoaluminium addition–Oppenauer oxidation of aromatic aldehydes to aryl ketones. The *in situ* prepared triorganoaluminium reagents are highly selective organometallic reagents that specifically react with aromatic aldehydes even with large amounts of ketones in the reaction system. Pinacolone was shown to be a potent oxidant in the tandem nucleophilic addition–Oppenauer oxidation of aromatic aldehydes.

Acknowledgements

The authors are grateful for financial support from the National Natural Science Foundation of China (No. 21262030 and 20962017) and the Natural Science Foundation of Gansu Province, China (No. 1107RJZA263).

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