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$[Ru(DMSO)_4]Cl_2$ catalyzes the α-alkylation of ketones by alcohols

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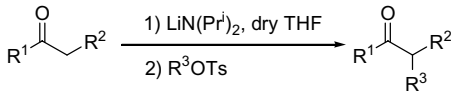
Abstract—The electrophilic α-alkylation of ketones with alcohols was accomplished by a $[Ru(DMSO)_4]Cl_2$ catalyzed process, water being the only wasted material. The reaction can be successfully governed to produce either the expected ketones or their related alcohols only by changing the reaction conditions. When 2-aminobenzyl alcohol was used, a cyclization process took place to yield 2,3-disubstituted quinolines.

The carbon–carbon bond formation is placed, without any doubt, as the pivotal method in organic synthesis,[1] especially, the α-alkylation of carbonyl compounds with different electrophiles (e.g., alkyl halides).[2] However, the classical protocols of this reaction create some problems (e.g., LDA, dry THF, alkyl tosylate, etc., Scheme 1), not only from a synthetic but also from an economic and an environmental point of view. Among them, one of the major drawbacks is the low atom economy or efficiency,[3] due to the use of strong bases with high molecular weight and the loss of the leaving group of the electrophile.

On the other hand, the problems with the waste and, of course, with the unavoidable inorganic salts derived from the living group and base sometimes make the classical alkylation methods not very practical for industrial use.



$$\text{Atom Efficiency} = \frac{\text{Mw of final Product}}{\sum_i (\text{Mw of all reagents})_i}$$

Scheme 1.

In the recent past, the realm of transition metal organic chemistry has provided us with excellent reagents able to overcome these classical problems. The ruthenium kingdom is one of them. Its chemistry has a variety of useful characteristics including high electron transfer ability, high coordination levels, Lewis acid activity and low redox potentials. Consequently, a large number of novel and useful reactions are beginning to be developed using both stoichiometric and catalytic amounts of different complexes.[4] Moreover, the relative low toxicity of ruthenium salts,[5] when they are compared with other heavy metal salts,[6] has permitted their use for the catalytic elimination of organic toxics[7] and as drugs for the treatment of cancer.[8] All these facts explain the great interest of the organic chemistry community for ruthenium chemistry.

We present in this letter the use of $[Ru(DMSO)_4]Cl_2$[9] as an efficient catalyst for the α-alkylation of ketones using alcohols as electrophiles. The alcohols are generally not used as electrophilic alkylating agents due to the high energy of C–O bond (≈90 kcal/mol). Moreover, under the normal basic reaction conditions employed in enolate alkylations, alcohols are transformed into alkoxide reducing the normal poor leaving group character of the oxygen. However, alcohols can be converted into electrophilic systems by their transformation into the corresponding sulfonic esters or halides.[10] Another possibility is their transformation into the corresponding

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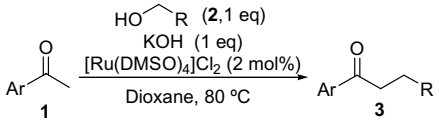
aldehydes, which have a clear electrophilic character. With these considerations in mind, we mixed equimolecular amounts of acetophenone, benzyl alcohol and KOH in the presence of a catalytic amount of $[Ru(DMSO)_4]Cl_2$[11] (2%) with the hope that ruthenium species would oxidize the alcohol to the corresponding electrophilic aldehyde[12] and it could condense with the ketone under the reaction conditions. To our delight, after a few hours at dioxane reflux, the MS–GC analysis of reaction mixture showed the presence of expected 1,3-diphenyl-1-propanone (**3a**), as well as the other by-products in different amounts, such as 1,3-diphenyl-1-propanol, benzaldehyde, 1-phenylethanol and chalcone.

The optimization of reaction conditions for the preparation of ketone **3a**, such as base (KOH, CsOH, Et_3N, none), solvent (1,4-dioxane, THF, water, MeCN, DMF, CH_2Cl_2), extra ligand (pyridinedicarboxylic acid) and temperature showed a maximum under the conditions depicted in Table 1. Other reaction conditions either gave a very low yield or failed.

The reaction gave excellent results for methyl aryl ketones **1** and arylmethanol derivatives **2**, the corresponding alkylated ketone **3** being in some cases the only product detected. The results were very homogeneous independently on functionalities on the aromatic ring. In the case of using *p*-trifluoromethylacetophenone (Table 1, entry 8), instead of obtaining the expected ketone, the main product isolated (48%) was the corresponding alcohol arising from the reduction of the expected ketone **3**, probably due to the higher electrophilic character of this electron-withdrawing substituted ketone. For this reason, the reaction was repeated with a double amount of alcohol (which is at the same time the source of reducing agents and the electrophile) giving the alcohol coming from the reduction of **3h** with good yield.

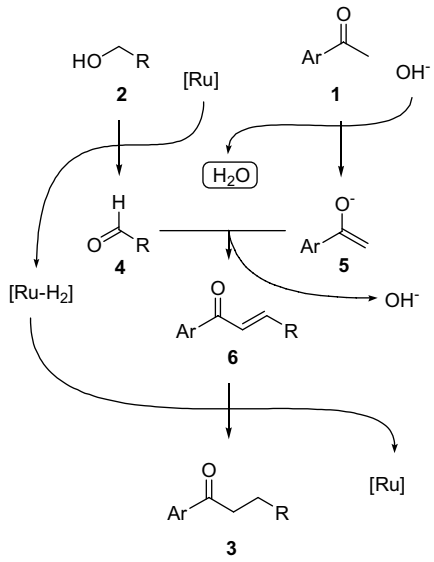
Table 1. Electrophilic α-alkylation of methyl aryl ketones using alcohols



Entry	Ketone **3**			
	No.	Ar	R	% Yield[a]
1	**a**	Ph	Ph	72
2	**b**	Ph	2-BrC_6H_4	93
3	**c**	Ph	3-$BnOC_6H_4$	86
4	**d**	4-MeC_6H_4	4-$MeOC_6H_4$	93
5	**e**	4-MeC_6H_4	4-ClC_6H_4	85
6	**f**	4-MeC_6H_4	2-ClC_6H_4	92
7	**g**	4-MeC_6H_4	3,4-$(MeO)_2C_6H_4$	69
8	**h**	4-$(F_3C)C_6H_4$	Ph	89[b]
9	**i**	2-$C_{10}H_8$	Ph	87
10	**j**	2-Thiophene	Ph	45
11	**k**	2-Thiophene	2-BrC_6H_4	41

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).

[b] Yield of the related alcohol when the reaction was performed using 2 equiv of benzyl alcohol.



Scheme 2.

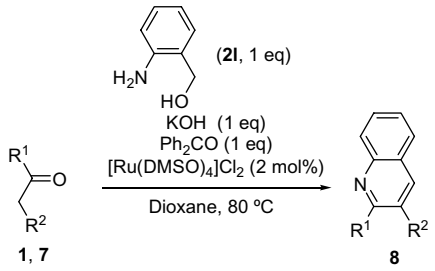
The only by-product detected in the case of thiophene derivatives **3j**,**k** was the related alcohol coming from the reduction of starting ketone **1**.

All the above results, together with the observation of different by-products of the reaction, drove us to propose the mechanism pathway depicted in Scheme 2, in which the ruthenium species are able to oxidize the alcohol **2** to the corresponding aldehyde **4**, yielding a hypothetical ruthenium hydride. The aldol condensation between this aldehyde and the enolate of ketone **5** (obtained in turn by deprotonation of the ketone **1** by the base or by reaction with the ruthenium hydride complex)[13] gave the α,β-unsaturated ketone **6**, which is finally reduced by the ruthenium hydride to yield alkylated ketone **3**, regenerating the starting ruthenium catalytic species, which can start a new catalytic cycle. According to this mechanistic pathway, the amount of KOH used could be catalytic. However, when the reaction was performed with lower amounts of base the yield dropped drastically, showing that the base plays an extra unknown role, probably, deprotonating the alcohol and/or forcing the formation of alkoxy-ruthenium complex.

It should be pointed out that the waste material of the reaction is water, which is a clear environmental friendly compound and with a very low molecular weight. This last fact makes the atom efficiency very high compared with any other method of electrophilic alkylation, anticipating a very promising future for this strategy.[14,15]

Another interesting point of this reaction appeared when it was performed using 2-aminobenzyl alcohol (**2l**). In this case, instead of the corresponding ketone of type **3** quinolines **8** were isolated, which formally arise from the internal condensation of the amine with the carbonyl compound in the intermediate of type **6**. The first trial was performed using acetophenone and alcohol **2l**, yielding the quinoline **8b** in 70% yield. The

Table 2. Synthesis of quinolines **8** by condensation of ketones and alochol **2l**



Entry	Quinoline **8**			
	No.	R^1	R^2	% Yield[a]
1	**a**	–$(CH_2)_4$–		88
2	**b**	Ph	H	94
3	**c**	Ph	Me	81
4	**d**	Ph	Et	67
5	**e**	4-MeC_6H_4	H	96
6	**f**	2-Furan	H	89
7	**g**	2-Thiophene	H	96

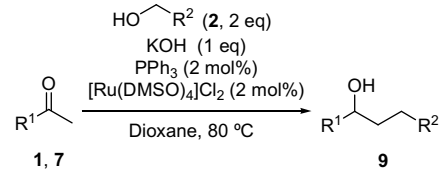
[a] Isolated yields after acid/base extraction.

analysis of the crude mixture showed the presence of 1-phenylethanol, indicating that the in situ formed ruthenium hydride is partially unable to restart the catalytic cycle and should be oxidized. Different hydrogen scavenger systems, such as the own starting ketone, 1-hexene or benzophenone were tested for avoiding this inconvenience. Similar results were obtained either using one equivalent of benzophenone or a double amount of the starting ketone, adopting the former scavenger (Table 2).

The isolation of pure quinolines was very easy only through an acid/base extraction. Under these new conditions not only alkyl aryl ketones **1** but also a dialkyl ketone **7** could be successfully used. Moreover, the reaction can be performed with ketones with longer substituent than methyl, which could be evidence that the condensation between the carbonyl group of the ketone and the amine to form the corresponding imine takes place prior to the aldol condensation and therefore favouring it.

Finally, it should be pointed out that the reaction can be forced to obtain the alcohols of type **9**, only by changing the reaction conditions. Thus, when the reaction was performed using a double amount of the corresponding alcohol under an argon atmosphere and in a pressure tube, while keeping the same conditions, the main product was the alcohol, which arises from the above described α-alkylated ketone reaction followed by a Meerwein–Ponndorf–Verley reduction process.[16] The optimization of reaction conditions, such as base (KOH, CsOH, Et_3N, none), solvent (1,4-dioxane, THF, water, MeCN, DMF, CH_2Cl_2), source of ruthenium {$RuCl_3$, $RuH(CO)(PPh_3)_3$, [Ru(DMSO)]Cl_2} and extra ligands (PPh_3, TMEDA, DIPHOS, *n*-Bu_4NBr) showed the best results using the conditions described in Table 3.

Table 3. Sequential electrophilic α-alkylation and reduction of ketones using alcohols



Entry	Alcohols **9**			
	No.	R^1	R^2	% Yield[a]
1	**a**	Bu^t	Ph	25
2	**b**	*n*-C_5H_{11}	Ph	35
3	**c**	Ph	Pr^i	45
4	**d**	Ph	Ph	78

[a] Isolated yields after column chromatography (silica gel: hexane/ethyl acetate).

In this case, all kind of ketones can be used, although the best results were obtained for alkyl aryl ketones, as well as benzylic alcohols, yields are in general modest.

In summary, the [Ru(DMSO)$_4$]Cl_2 is a very cheap, safe and efficient catalyst to promote the unusual α-alkylation of ketones. This process constitutes a good example of a very high atom efficiency reaction and provides an alternative entry to the synthesis of quinolines.

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