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Note

A ruthenium-catalyzed one-pot method for α-alkylation of ketones with aldehydes

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Abstract

Ketones react with an array of aldehydes in dioxane at 80 °C in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ along with KOH to give the corresponding α-alkylated ketones in moderate to good yields. A reaction pathway involving base-catalyzed cross-aldol reaction between ketones and aldehydes to form α,β-unsaturated ketones and regioselective reduction of carbon–carbon double bond of α,β-unsaturated ketones is proposed for this catalytic process.

Keywords: Aldehydes; Aldol reaction; α-alkylation; Ketones; Reduction; Ruthenium catalyst

1. Introduction

Transition metal-catalyzed carbon–carbon bond forming reaction has been widely explored and used as a promising tool in synthetic organic chemistry [1]. In connection with this report, as part of our ongoing studies on ruthenium catalysis, we recently found an unusual type of ruthenium-catalyzed transfer hydrogenation between ketones **1** and primary alcohols **2** accompanied by carbon–carbon coupling under KOH, in which alkylated ketones **3** (Scheme 1, route a) [2] or unconventional transfer hydrogenated secondary alcohols **4** (Scheme 1, route b) [3] were preferentially formed according to the molar ratio of primary alcohols to ketones [4]. It was also disclosed that secondary alcohols **5** were found to be coupled with primary alcohols **2** in the presence of a ruthenium catalyst along with sacrificial hydrogen acceptor to give coupled secondary alcohols **4** (Scheme 1, route c) [5]. In closely related with our report shown in route a of Scheme 1, Ishii et al. have also reported an iridium-catalyzed α-alkylation of ketones with primary alcohols [6]. It was suggested by both groups that the α-alkylation of ketones with primary alcohols proceeds via an initial oxidation of the alcohol to aldehyde [2,6]. Under these circumstances [7], we have directed our attention to ruthenium-catalyzed α-alkylation of ketones with aldehydes [8]. Herein, this report describes a ruthenium-catalyzed one-pot method for α-alkylation of ketones with an array of aldehydes [9].

2. Results and discussion

First, several reactions between acetophenone (**1a**, **1**: R = Ph) and benzaldehyde (**6a**, **6**: R′ = Ph) were tried to optimize the reaction conditions and elucidate the feature of the present alkylation (Eq. (1)). When **1a** was treated with equimolar amount of **6a** in dioxane at 80 °C for 40 h in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ (2 mol%) along with KOH, the coupled ketone 1,3-diphenylpropan-1-one (**3a**, **3**: R = R′ = Ph) was formed in 71% isolated yield with concomitant formation of further hydrogenated coupled alcohol 1,3-diphenylpropan-1-ol (**4a**, **4**: R = R′ = Ph) (2% yield). Performing the reaction for a shorter time (26 h) was accompanied by a considerable

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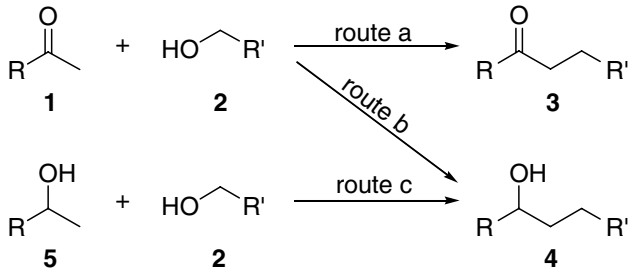
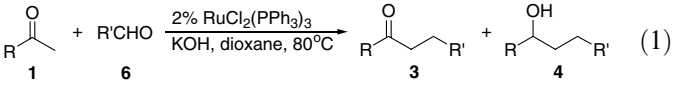


Scheme 1.

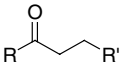
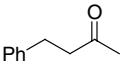
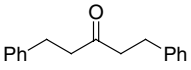
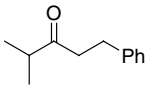
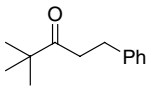
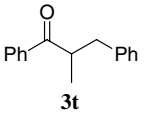
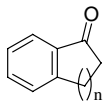
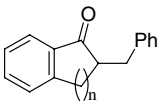
amount of initial cross-aldol product benzylideneacetophenone (12% yield) with lower yield of **3a** (36%). Equimolar amount of both substrates is desirable in atom economy point of view since the reaction under the molar ratio of [**6a**]/[**1a**] = 2 resulted in a slightly increased yield of **3a** (79%). As has been shown in our recent report [3], the reduction of initial benzylideneacetophenone to **3a** seems to be derived from solvent dioxane. Actually, in a separate experiment, we confirmed that benzylideneacetophenone was reduced to **3a** in 69% yield under $RuCl_2(PPh_3)_3$ (2 mol%)/KOH (1 equivalent)/dioxane (3 ml)/80 °C/40 h. This observation also indicates that the olefinic double bond of benzylideneacetophenone is more susceptible to reduction than the carbonyl group of that under the employed conditions.



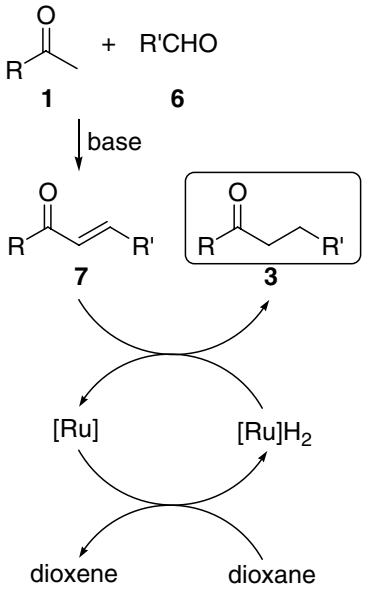
(1)

Having established reaction conditions, a series of ketones **1** and aldehydes **6** were screened in order to investigate the reaction scope, and several representative results are summarized in Table 1. The reaction of **1a** with several aromatic and heteroaromatic aldehydes (**6a**–**6e**) proceeds to give the corresponding coupled ketones **3a**–**3e** in 63–81% yields with the minimal formation of the further hydrogenated coupled secondary alcohols **4**. The product yield was not significantly affected by the electronic nature of the substituent on the aromatic ring of aldehydes. From the reaction between **1a** and ferrocenecarboxaldehyde (**6f**), the corresponding coupled ketone (**3f**) was also produced in 44% yield with a considerable amount of the initial cross-aldol product 3-ferrocenyl-1-phenylpropen-1-one (22%). The reaction proceeds likewise with aliphatic aldehyde **6g** to give the coupled ketone **3g**, however, the product yield was lower than that when aromatic aldehydes were used. In the reaction of aryl- and heteroaryl(methyl) ketones (**1b**–**1i**) with **6a**, the corresponding coupled ketones were also obtained in the range of 49–76% yields. As is the case for the reaction between **1a** and **6f**, the reaction of acetylferrocene (**1j**) with **6a**, besides the ususal coupled ketone **3p** (54% yield), resulted in a considerable yield of the initial aldol product cinnamoylferrocene (20%). With alkyl(methyl) ketones (**1k**–**1m**), the alkylation took place exclusively at less-hindered methyl position over α-methylene and -methine. Similar regioselectivity has been observed by our recent reports [2,5,10] and others [11]. In the case of propiophenone (**1n**) which has only methylene

Table 1
Ruthenium-catalyzed α-alkylation of ketones **1** with aldehydes **6**[a]

Ketones **1**	Aldehydes **6**	Products **3**	Yield (%)[b]
	R′CHO		
R = Ph (**1a**)	R′ = Ph (**6a**)	**3a**	71
	R′ = 4-MeC_6H_4 (**6b**)	**3b**	67
	R′ = 4-$MeOC_6H_4$ (**6c**)	**3c**	63
	R′ = 4-ClC_6H_4 (**6d**)	**3d**	64
	R′ = 2-furyl (**6e**)	**3e**	81
	R′ = ferrocenyl (**6f**)	**3f**	44[c]
	R′ = heptyl (**6g**)	**3g**	48
R = 2-HOC_6H_4 (**1b**)	**6a**	**3h**	49
R = 2-MeC_6H_4 (**1c**)	**6a**	**3i**	62
R = 3-MeC_6H_4 (**1d**)	**6a**	**3j**	76
R = 4-MeC_6H_4 (**1e**)	**6a**	**3k**	55
R = 4-$MeOC_6H_4$ (**1f**)	**6a**	**3l**	69
R = 4-FC_6H_4 (**1g**)	**6a**	**3m**	68
R = 2-thienyl (**1h**)	**6a**	**3n**	69
R = 2-naphthyl (**1i**)	**6a**	**3o**	54
R = ferrocenyl (**1j**)	**6a**	**3p**	54[d]
 **1k**	**6a**	 **3q**	34
 **1l**	**6a**	 **3r**	52
 **1m**	**6a**	 **3s**	73
 **1n**	**6a**	 **3t**	trace
			
n = 1 (**1o**)	**6a**	**3u**	45
n = 2 (**1p**)	**6a**	**3v**	75

[a] All reactions were carried out with **1** (1 mmol), **2** (1 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), and KOH (1 mmol) in dioxane (3 ml) at 80 °C for 40 h.
[b] Isolated yield.
[c] 3-Ferrocenyl-1-phenylpropen-1-one was also formed in 22% yield.
[d] Cinnamoylferrocene was also formed in 20% yield.



Scheme 2.

reaction site, the reaction did not proceed at all toward coupling. However, benzo-fused cyclic ketones such as 1-indanone (**1o**) and 1-tetralone (**1p**) which have only methylene reaction site were readily alkylated with **6a** to give the corresponding alkylated ketones **3u** and **3v**.

As to the reaction pathway, α,β-unsaturated ketones **7**, initially formed by base-catalyzed cross-aldol reaction between ketones **1** and aldehydes **6**, seem to be reduced to coupled ketones **3** or coupled secondary alcohols **4** by $[Ru]H_2$ derived from ruthenium catalyst and dioxane (Scheme 2). It is known that dioxane has been used as a hydrogen donor in transition metal-catalyzed transfer hydrogenation [12].

3. Conclusion

In summary, we have demonstrated that ketones react with an array of aldehydes in dioxane in the presence of a catalytic amount of a ruthenium catalyst together with KOH to give the corresponding α-alkylated ketones. To the best of our knowledge, this protocol is the first one-pot strategy for α-alkyaltion of ketones by aldehydes.

4. Experimental

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. Mass spectra were obtained using EI ionization at 70 eV. GLC analyses were carried out with a Shimadzu GC-17 A instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as carrier gas. The isolation of pure products was carried out via column chromatography (silica gel 60, 70–230 mesh, Merck) and thin layer chromatography (silica gel 60 GF_{254}, Merck). Commercially available organic and inorganic compounds were used without further purification.

4.1. Typical experimental procedure

A mixture of acetophenone (**1a**) (0.120 g, 1 mmol), benzaldehyde (**6a**) (0.106 g, 1 mmol), $RuCl_2(PPh_3)_3$ (0.019 g, 0.02 mmol), and KOH (0.056 g, 1 mmol) in dioxane (3 ml) was placed in a 5 ml screw-capped vial and allowed to react at 80 °C for 40 h. The reaction mixture was filtered through a short silica gel column ($CHCl_3$-ethyl acetate mixture) to eliminate inorganic salts. Removal of the solvent left an oil, which was purified by thin-layer chromatography (silica gel, ethyl acetate/hexane = 1/10) to give 1,3-diphenylpropan-1-one (**3a**) (0.150 g, 71%).

The compounds **3a** [2], **3f** [13], **3i**–**3m** [2], **3o** [2], and **3r**–**3v** [2] are noted in our recent report and identified by comparison with the prepared samples.

4.1.1. 3-(4-Methylphenyl)-1-phenylpropan-1-one (3b) [14]

Pale yellow oil; ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.02 (t, $J = 7.5$ Hz, 2H), 3.27 (t, $J = 7.5$ Hz, 2H), 7.09–7.15 (m, 4H), 7.41–7.45 (m, 2H), 7.52–7.56 (m, 1H), 7.93–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.9, 29.6, 40.5, 128.0, 128.2, 128.5, 129.1, 133.0, 135.5, 136.8, 138.1, 199.3.

4.1.2. 3-(4-Methoxyphenyl)-1-phenylpropan-1-one (3c) [14]

Pale yellow oil; ^1H NMR ($CDCl_3$): δ 3.01 (t, $J = 7.5$ Hz, 2H), 3.26 (t, $J = 7.5$ Hz, 2H), 3.78 (s, 3H), 6.84 (d, $J = 8.5$ Hz, 2H), 7.17 (d, $J = 8.5$ Hz, 2H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.94–7.96 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 29.7, 41.1, 55.7, 114.3, 128.4, 129.0, 129.8, 133.4, 133.7, 137.3, 158.4, 199.8.

4.1.3. 3-(4-Chlorophenyl)-1-phenylpropan-1-one (3d) [15]

Pale yellow oil; ^1H NMR ($CDCl_3$): δ 3.03 (t, $J = 7.5$ Hz, 2H), 3.27 (t, $J = 7.5$ Hz, 2H), 7.16–7.18 (m, 2H), 7.23–7.26 (m, 2H), 7.43–7.46 (m, 2H), 7.53–7.57 (m, 1H), 7.93–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 29.8, 40.5, 128.4, 128.9, 129.0, 130.2, 132.3, 133.6, 137.1, 140.1, 199.2.

4.1.4. 3-(2-Furanyl)-1-phenylpropan-1-one (3e) [16]

Pale yellow oil; ^1H NMR ($CDCl_3$): δ 3.09 (t, $J = 7.5$ Hz, 2H), 3.33 (t, $J = 7.5$ Hz, 2H), 6.04 (t, $J = 3.0$ Hz, 1H), 6.27 (d, $J = 3.0$ Hz, 1H), 7.25–7.30 (m, 1H), 7P.45 (t, $J = 7.5$ Hz, 1H), 7.54–7.57 (m, 1H), 7.95–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 22.5, 36.9, 105.3, 110.2, 128.0, 128.6, 133.1, 136.7, 141.0, 154.7, 198.6 (C=O).

4.1.5. 1-Phenyldecan-1-one (3g)

This compound is commercially available and identified by comparison with authentic sample.

4.1.6. 1-(2-Hydroxyphenyl)-3-phenylpropan-1-one (**3h**) [17]

Pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 3.05 (t, $J = 7.5$ Hz, 2H), 3.30 (t, $J = 7.5$ Hz, 2H), 6.85 (t, $J = 7.5$ Hz, 1H), 6.97 (d, $J = 8.6$ Hz, 1H), 7.19–7.31 (m, 5H), 7.41–7.45 (m, 1H), 7.70–7.72 (m, 1H), 12.30 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.9, 40.0, 118.5, 118.8, 119.2, 126.2, 128.3, 128.5, 129.8, 136.3, 140.6, 162.4, 205.3 (C=O).

4.1.7. 3-Phenyl-1-(2-thienyl)propan-1-one (**3n**) [18]

Pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 3.06 (t, $J = 7.8$ Hz, 2H), 3.22 (t, $J = 7.8$ Hz, 2H), 7.08–7.10 (m, 1H), 7.18–7.31 (m, 5H), 7.60 (dd, $J = 5.0$ and 1.0 Hz, 1H), 7.67 (dd, $J = 5.0$ and 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 30.3, 41.0, 126.1, 128.0, 128.4, 128.5, 131.8, 133.5, 140.9, 144.1, 192.1 (C=O).

4.1.8. 1-Ferrocenyl-3-phenylpropan-1-one (**3p**)

Reddish yellow solid, m.p. 78–79 °C (from hexane) (lit. [19] 79–81 °C); ^{1}H NMR ($CDCl_3$): δ 2.98–3.09 (m, 4H), 4.07 (s, 5H), 4.47 (t, $J = 2.0$ Hz, 2H), 4.76 (t, $J = 2.0$ Hz, 2H), 7.19–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 30.1, 41.5, 69.2, 69.6, 72.2, 78.9, 126.1, 128.5, 128.6, 141.6, 203.1 (C=O).

4.1.9. 1,5-Diphenylpentan-3-one (**3q**) [20]

Pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 2.69 (t, $J = 7.5$ Hz, 4H), 2.87 (t, $J = 7.8$ Hz, 4H), 7.11–7.31 (m, 10H); ^{13}C-NMR ($CDCl_3$): δ 29.7, 44.4, 126.0, 128.2, 128.4, 140.9, 209.0 (C=O); MS m/z (relative intensity): 238 (M^+, 72), 105 (100).

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References

[1] F. Diederich, P.J. Stang (Eds.), Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, Weinheim, 1995.
[2] C.S. Cho, B.T. Kim, T.-J. Kim, S.C. Shim, Tetrahedron Lett. 43 (2002) 7987.
[3] C.S. Cho, B.T. Kim, T.-J. Kim, S.C. Shim, J. Org. Chem. 66 (2001) 9020.
[4] For recent reviews on transition metal-catalyzed transfer hydrogention, see: (a) G. Zassinovich, G. Mestroni, S. Gladiali, Chem. Rev. 92 (1992) 1051;
(b) J.-E. Bäckvall, R.L. Chowdhury, U. Karlsson, G. Wang, in: A.F. Williams, C. Floriani, A.E. Merbach (Eds.), Perspectives in Coordination Chemistry, VCH, New York, 1992, pp. 463–486;
(c) R. Noyori, S. Hashiguchi, S. Acc. Chem. Res. 30 (1997) 97;
(d) T. Naota, H. Takaya, S.-I. Murahashi, Chem. Rev. 98 (1998) 2599;
(e) M. Palmer, M. Wills, Tetrahedron: Asymmetr. 10 (1999) 2045.
[5] C.S. Cho, B.T. Kim, H.-S. Kim, T.-J. Kim, S.C. Shim, Organometallics 22 (2003) 3608.
[6] K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, J. Am. Chem. Soc. 126 (2004) 72–73.
[7] These reactions could also be applied to ruthenium-catalyzed Friedlaender quinoline synthesis by oxidative cyclization of 2-aminobenzyl alcohol with ketones and secondary alcohols: (a) C.S. Cho, B.T. Kim, T.-J. Kim, S.C. Shim, Chem. Commun. (2001) 2576;
(b) C.S. Cho, B.T. Kim, H.-J. Choi, T.-J. Kim, S.C. Shim, Tetrahedron 59 (2003) 7997.
[8] Conventional α-alkylation of ketone is generally achieved by the coupling between nucleophilic enolates and electrophilic alkylating agents: J. d'Angelo, Tetrahedron 32 (1976) 2979.
[9] Although a ruthenium-catalyzed route for α-alkylation of ketones by primary alcohols reported in Ref. [2] is more useful than this method using aldehydes instead of primary alcohols as commented by a reviewer, the present one-pot procedure, in a sense of the efficiency of reaction, is also superior to conventional α-alkylation of ketones by aldehydes, which usually proceeds via separate step-by-step unit transformations such as aldol reaction and regioselective reduction.
[10] C.S. Cho, B.T. Kim, M.J. Lee, T.-J. Kim, S.C. Shim, Angew. Chem. Int. Ed. Engl. 40 (2001) 958.
[11] (a) M. Palucki, S.L. Buchwald, J. Am. Chem. Soc. 119 (1997) 11108;
(b) B.C. Hamann, J.F. Hartwig, J. Am. Chem. Soc. 119 (1997) 12382.
[12] (a) T. Nishiguchi, K. Tachi, K. Fukuzumi, J. Am. Chem. Soc. 94 (1972) 8916;
(b) T. Nishiguchi, K. Fukuzumi, J. Am. Chem. Soc. 96 (1974) 1893;
(c) H. Imai, T. Nishiguchi, K. Fukuzumi, J. Org. Chem. 41 (1976) 665.
[13] C.S. Cho, J.H. Park, B.T. Kim, T.-J. Kim, S.C. Shim, M.C. Kim, Bull. Korean Chem. Soc. 25 (2004) 423.
[14] V. Calo, A. Nacci, L. Lopez, A. Napola, Tetrahedron Lett. 42 (2001) 4701.
[15] K. Kokubo, M. Miura, M. Nomura, Organometallics 14 (1995) 4521.
[16] P. Canonne, M. Akssira, Tetrahedron Lett. 24 (1983) 5519.
[17] C. Cimarelli, G. Palmieri, Tetrahedron 54 (1998) 15711.
[18] L.J. Goossen, K. Ghosh, Eur. J. Org. Chem. 19 (2002) 3254.
[19] V.A. Darin, N.A. Federman, J. Miller, M.M. de Freitas Afonso, H.C. Fonsatti, A.D.L. Borges, J. Prakt. Chem. 341 (1999) 588.
[20] J.F. Hayes, M. Shipman, H. Twin, J. Org. Chem. 67 (2002) 935.