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Synthesis of *ortho*-hydroxyacetophenone derivatives from Baylis–Hillman acetates

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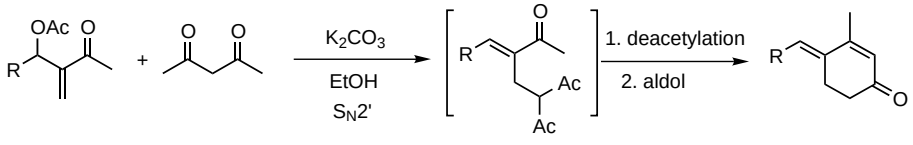
Abstract—Synthesis of *ortho*-hydroxyacetophenone derivatives **5** was carried out from the reaction of Baylis–Hillman acetates **1** and active methylene compounds **2** in *N*,*N*-dimethylformamide in the presence of K_2CO_3.

ortho-Hydroxyacetophenones are important synthetic intermediates for the synthesis of various useful compounds such as flavonols,[1a] lamellarin alkaloids,[1b] fluorescence 3-hydroxychromones[1c] and many other compounds.[1] *ortho*-Hydroxyacetophenones and related compounds can be prepared by the Fries type rearrangement most often[2a–c] or by other methods.[2d,e]

Recently, Chamakh and Amri have reported on the novel one-pot synthesis of (*E*)-4-alkylidene-2-cyclohexen-1-ones via a cross coupling of the Baylis–Hillman acetates **1** and aliphatic 1,3-diketones in the presence of potassium carbonate in absolute ethanol at reflux temperature (Scheme 1).[3] In the paper, they reported the mechanism as the tandem three-step reaction: S_N2' substitution–deacetylation–cyclization reactions.

We presumed that we could prepare the *ortho*-hydroxyacetophenone derivative **5a** if we protect the deacetylation step before the last intramolecular aldol condensation (Scheme 2). Deacetylation might occur effectively in the presence of nucleophilic species and a proton source.[4] We thought that deacetylation could be minimized in an aprotic and polar solvent such as *N*,*N*-dimethylformamide (DMF).[4] As expected the desired *ortho*-hydroxyacetophenone derivative **5a** was obtained in reasonable yield. Among the examined conditions the use of DMF and K_2CO_3 gave the best results. Similar systems such as KF/DMF, Cs_2CO_3/DMF or K_2CO_3/CH_3CN were found to be less effective.

As shown in Scheme 2, the reaction of the Baylis–Hillman acetate **1a** and 2,4-pentanedione (**2a**) in DMF gave the corresponding 2-hydroxy-4-methyl-5-benzylacetophenone (**5a**) in 71% isolated yield.[5,6] The plausible reaction mechanism is shown in Scheme 2. Initial S_N2' reaction between **1a** and **2a** gave the allylic substitution product **3**. This compound existed as a tautomeric keto–enol mixture (keto-form/enol-form, 5:2) in $CDCl_3$, whereas keto-form of **3** was observed as a sole tautomer in DMSO-d_6. Subsequent aldol condensation of **3**



Scheme 1.

Keywords: *ortho*-hydroxyacetophenones; Baylis–Hillman acetates; deacetylation; *N*,*N*-dimethylformamide.
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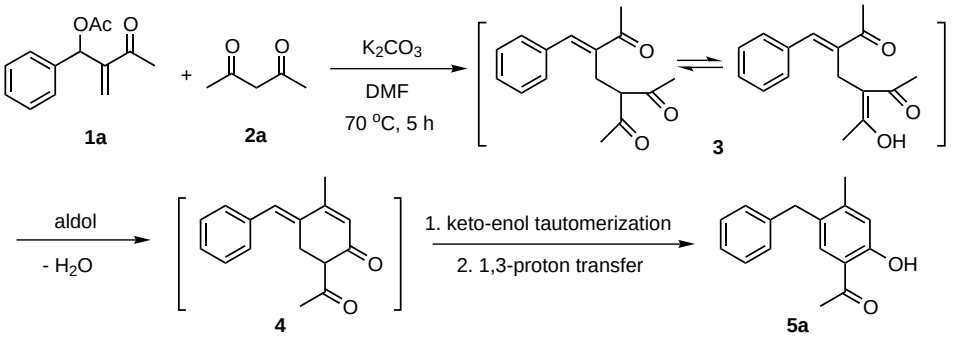


Scheme 2.

afforded **4**. Rapid keto–enol tautomerization and proton transfer gave **5a**. Trace amount of deacetylated compound **6** was observed on TLC (see Scheme 3). It is noteworthy to compare the results in ethanol with those of in DMF (Scheme 3). Under the reported Amri's conditions, small amount of **5a** (6%) and appreciable amounts of (*E*)-4-benzylidene-3-methyl-2-cyclohexen-1-one (**6**, 40%)[5] were isolated. In this case, unusual ethoxy compound **7** was isolated.[5] Similar results were observed in methanol solvent.[5]

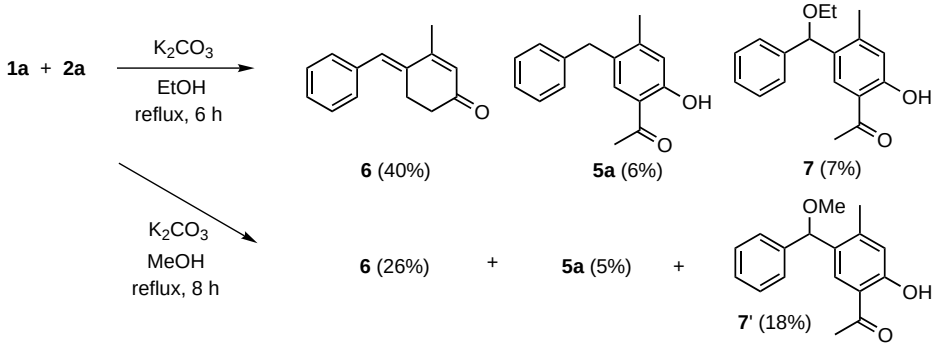
The reaction must be conducted under nitrogen atmosphere. Otherwise, severe decomposition of the generated product to intractable mixtures was observed. The major decomposition process could be thought as the air oxidation of the benzylic position followed by further oxidation toward quinone system.

With the optimized conditions (DMF, K_2CO_3, heating) for the synthesis of *ortho*-hydroxyacetophenone derivative **5a** in hand, we examined the reaction of some Baylis–Hillman acetates[7] with 2,4-pentanedione (**2a**), ethyl acetoacetate (**2b**), methanesulfonylacetone (**2c**) and 1-benzoylacetone (**2d**). The representative results are summarized in Table 1. Baylis–Hillman acetates **1b** and **1c** gave the corresponding *ortho*-hydroxyacetophenones **5b** and **5c**, respectively. From the Baylis–Hillman acetates **1d** and **1e**, which were derived from ethyl vinyl ketone, 4-hydroxyacetophenones were isolated together with 2-hydroxyacetophenones (entries 4 and 5). The 4-hydroxy compounds **5d′** and **5e′** were generated as shown in Scheme 4.

Similarly, the reaction with ethyl acetoacetate (**2b**) gave similar results (entries 6 and 7). However, in these cases **5f′** and **5g′** were isolated, which were formed via decarbethoxylation. It is interesting to note that (*E*)-4-benzylidene-2-cyclohexen-1-one derivatives, **5f′** and **5g′**, were isolated in appreciable amounts in the case of ethyl acetoacetate. These results imply decarbethoxylation is easier than the corresponding deacetylation. Besides **2a** and **2b**, other activated methylene compounds such as methanesulfonylacetone (**2c**) and 1-benzoylacetone (**2d**) gave similar results (entries 8 and 9).

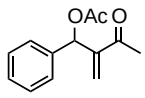
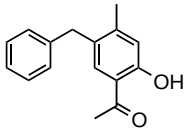
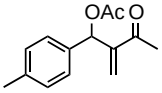
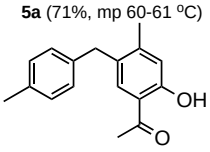
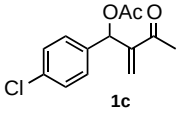
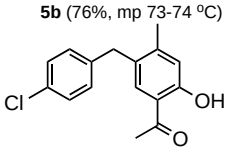
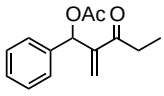
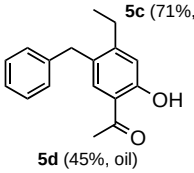
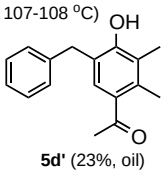
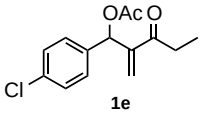
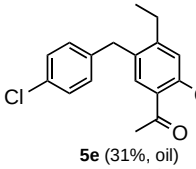
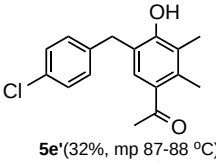
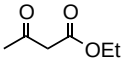
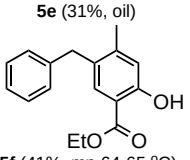
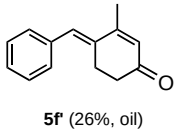
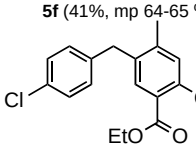
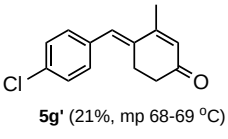
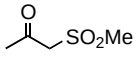
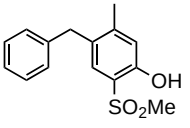
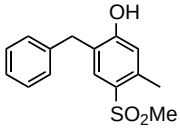
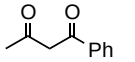
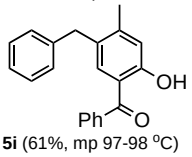
General procedure for the preparation of **5** is straightforward as follows: A stirred solution of **1** and active methylene compounds **2** (1.1 equiv.) in DMF in the presence of K_2CO_3 (1.1 equiv.) was heated to 70–90°C under N_2 for the time given in Table 1. After the usual work-up process and column chromatography (hexane/ether, 15:1) desired **5** was isolated in good to moderate yields.[5]

In conclusion, we have disclosed the facile synthesis of *ortho*-hydroxyacetophenones and related compounds. By changing the reaction conditions slightly,



Scheme 3.

Table 1. Synthesis of *o*-hydroxyacetophenone derivatives

entry	B-H acetate	1,3-diketone	conditions	product (% yield)
1	 **1a**	 **2a**	K_2CO_3, DMF 70 °C, 5 h	 **5a** (71%, mp 60-61 °C)
2	 **1b**	**2a**	K_2CO_3, DMF 70 °C, 5 h	 **5b** (76%, mp 73-74 °C)
3	 **1c**	**2a**	K_2CO_3, DMF 70 °C, 5 h	 **5c** (71%, mp 107-108 °C)
4	 **1d**	**2a**	K_2CO_3, DMF 80 °C, 5 h	 **5d** (45%, oil)  **5d'** (23%, oil)
5	 **1e**	**2a**	K_2CO_3, DMF 80 °C, 5 h	 **5e** (31%, oil)  **5e'**(32%, mp 87-88 °C)
6	**1a**	 **2b**	K_2CO_3, DMF 90 °C, 7 h	 **5f** (41%, mp 64-65 °C)  **5f'** (26%, oil)
7	**1c**	**2b**	K_2CO_3, DMF 90 °C, 7 h	 **5g** (41%, mp 73-74 °C)  **5g'** (21%, mp 68-69 °C)
8	**1a**	 **2c**	K_2CO_3, DMF 90 °C, 7 h	 **5h** (52%, mp 130-131 °C)  **5h'** (16%, oil)
9	**1a**	 **2d**	K_2CO_3, DMF 80 °C, 8 h	 **5i** (61%, mp 97-98 °C)

selective synthesis of different compounds could be achieved. By adopting the Amri's condition (use of ethanol solvent) 4-alkylidene-2-cyclohexen-1-ones could be synthesized. Whereas, when the solvent was replaced with DMF *ortho*-hydroxyacetophenone derivatives could be obtained.

Acknowledgements

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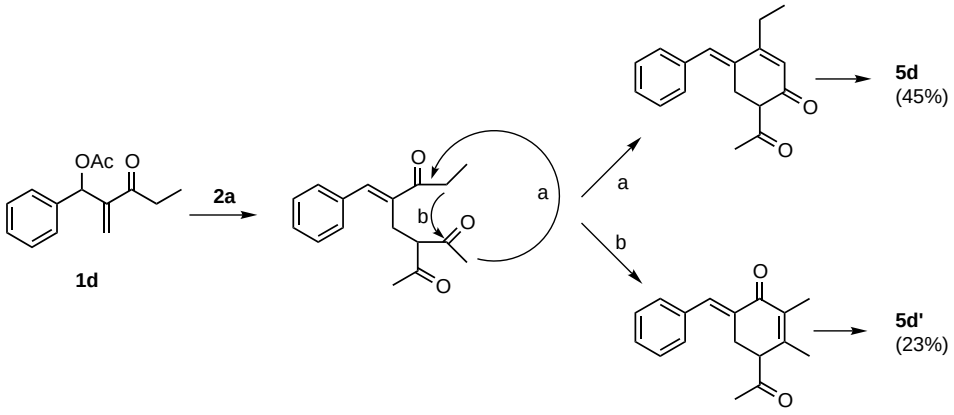

Scheme 4.

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2. (a) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Synlett* **1995**, 1153; (b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 2053 and references cited therein; (c) Crouse, D. J.; Hurlbut, S. L.; Wheeler, D. M. S. *J. Org. Chem.* **1981**, *46*, 374; (d) Zanatta, N.; Barichello, R.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **1999**, 765; (e) Cimarelli, C.; Palmieri, G. *Tetrahedron* **1998**, *54*, 15711.
3. Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375.
4. In order to confirm our assumption, we examined deacetylation of 3-benzyl-2,4-pentanedione. 4-Phenyl-2-butanone was obtained in 92% yield in refluxing ethanol in the presence of K_2CO_3. As expected, however, 3-benzyl-2,4-pentanedione was remained intact after 3–4 h in DMF at 70–80°C. For more general references regarding deacetylation and decarboalkoxylation, see: (a) Krapcho, A. P. *Synthesis* **1982**, 805; (b) Bauchat, P.; Le Rouille, E.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1991**, *128*, 267; (c) Beltaief, I.; Amri, H. *Synth. Commun.* **1995**, *25*, 2981; (d) Kroutil, W.; Osprian, I.; Mischitz, M.; Faber, K. *Synthesis* **1997**, 156; (e) Celli, A. M.; Lampariello, L. R.; Chimichi, S.; Nesi, R.; Scotton, M. *Can. J. Chem.* **1982**, *60*, 1327; (f) Hamed, A. A.; Salem, M. A. I.; Hataba, A. M.; Attia, I. A. *Pol. J. Chem.* **1985**, *59*, 1161.
5. Selected data for **5a**: white solid, mp 60–61°C; IR (KBr) 2917, 1638, 1491, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 2.54 (s, 3H), 3.95 (s, 2H), 6.80 (s, 1H), 7.09–7.29 (m, 5H), 7.42 (s, 1H), 12.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.35, 26.49, 38.65, 117.82, 119.63, 126.22, 128.45, 128.54, 129.76, 131.58, 139.94, 147.20, 161.03, 203.94; Mass (70 eV) m/z (rel. intensity) 43 (10), 91 (20), 197 (61), 225 (99), 240 (M^+, 100).
   Selected data for **6**: oil; IR (KBr) 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.47 (t, $J=6.9$ Hz, 2H), 2.99 (t, $J=6.9$ Hz, 2H), 5.99 (s, 1H), 6.94 (s, 1H), 7.28–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.85, 26.78, 37.10, 127.63, 127.73, 128.43, 129.18, 131.27, 135.80, 136.51, 155.69, 199.25; Mass (70 eV) m/z (rel. intensity) 91 (24), 115 (31), 141 (38), 155 (72), 183 (27), 198 (M^+, 100).
   Selected data for **7**: oil; IR (KBr) 3445, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, $J=6.9$ Hz, 3H), 2.26 (s, 3H), 2.53 (s, 3H), 3.54 (qd, $J=7.2$ and 1.5 Hz, 2H), 5.45 (s, 1H), 6.77 (s, 1H), 7.27–7.37 (m, 5H), 7.67 (s, 1H), 12.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.40 (CH_3), 19.92 (CH_3), 26.46 (CH_3), 64.79 (CH_2), 80.24 (CH), 117.66 (C), 119.82 (CH), 127.46 (CH), 127.69 (CH), 128.44 (CH), 129.36 (CH), 131.21 (C), 140.76 (C), 146.46 (C), 161.51 (C), 204.20 (C); Mass (70 eV) m/z (rel. intensity) 43 (17), 105 (22), 179 (44), 207 (85), 239 (100), 284 (M^+, 84).
   Selected data for **7′**: oil; IR (KBr) 3464, 1643, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H), 2.57 (s, 3H), 3.39 (s, 3H), 5.33 (s, 1H), 6.77 (s, 1H), 7.25–7.47 (m, 5H), 7.72 (s, 1H), 12.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.93, 26.52, 57.04, 82.04, 117.70, 119.85, 127.50, 127.79, 128.45, 129.08, 130.84, 140.34, 146.26, 161.52, 204.22; Mass (70 eV) m/z (rel. intensity) 43 (13), 105 (14), 193 (100), 239 (100), 270 (M^+, 90).
6. The structure of **5a** was confirmed further by NOE experiment. Irradiation of the benzylic proton ($\delta=3.95$ ppm) showed NOE increment (0.9%) of methyl proton at 4-position ($\delta=2.21$ ppm) and two aromatic protons (0.9 and 0.7%, respectively). From the NOE experiment we can exclude the regioisomeric structure, 2-methyl-4-hydroxy-5-benzylacetophenone.
7. We examined the reaction of Baylis–Hillman acetate derived from hexanal as an example of aliphatic aldehydes. However, intractable mixtures were formed due to many side reactions. Elimination of acetic acid and subsequent Diels–Alder reaction was one of the side reactions as reported in our previous paper, see: Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173.