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Solvent-free reaction on KF-alumina under microwave: serendipitous one-pot domino synthesis of new isobenzofuran-1(3H)-ones from alpha-hydroxyketones

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Abstract—The reaction of four α-hydroxyketones **1a–d** with a double equivalent of t-butyl acetylacetonate in the presence of KF-alumina under microwave irradiation afforded 6-acetyl-5-hydroxy-3,3-dialkyl-7-methyl isobenzofuran-1(3H)-ones **3a–d**.
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Butenolide heterocycles are widespread in nature and are present in numerous biologically important compounds.[1] The activity of these heterocycles has been attributed to the butenolide part. They can also be important starting materials for the total synthesis of various natural products as well as for the development of new asymmetric methodologies.[2] A general synthesis of butenolides consists in a base-catalyzed reaction of activated acetate with an α-hydroxyketone.[3] In particular, the acetylbutenolide has previously been obtained in the same manner using ethyl acetylacetonate in poor yields.[4]

The mechanism of the formation of butenolides was well studied in the case of ethyl malonate and ethyl cyanoacetate.[5] The formation of the butenolide is known to take place through a transesterification of the ester by the α-hydroxyketone in the presence of a basic catalyst, followed by an internal Knoevenagel reaction, favored by a gem-disubstituent effect of the gem-3,3-dialkyl group.[6,7]

For our part, we have already reported an improved synthesis of lactones by condensation of α-hydroxyketone **1** with ethyl cyanoacetate and diester malonate in the presence of a base under microwave irradiation.[5] We have subsequently described an efficient method for butenolide synthesis microwave irradiation using KF-alumina as base and in solvent-free conditions.[8] Using the same protocol, we decided to prepare acetylbutenolides **2** from t-butyl acetylacetonate according to the expected reaction as shown in Figure 1.

Surprisingly, the reaction of 3-hydroxy-3-methylbutan-2-one **1a** with 1 equiv of t-butyl acetylacetonate gave a poor yield of the expected butenolide (23%), along with a secondary product. The yield of the new product **3a** increased with the use of 2 equiv of t-butyl acetylacetonate.

We have shown that different hydroxyketones **1a–d** lead to similar products, all containing an aromatic substructure.

Studies by GC–MS spectroscopy, NMR (^{1}H, ^{13}C), and the IR spectroscopies allowed the clarification of these secondary products structures, as being 6-acetyl-5-hydroxy-3,3-dialkyl-7-methyl isobenzofuran-1(3H)-ones **3a–d**.
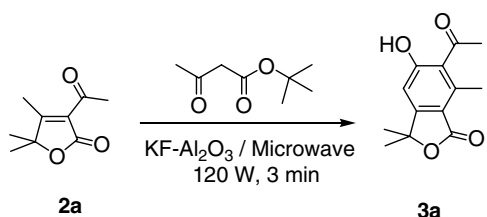
These new products result from the reaction of two molecules of acetylacetonate with one molecule of α-hydroxyketone on KF-alumina. The formation of this type of products is favored by increasing the KF-Al$_2$O$_3$ amount.

a $R_1 = R_2 = Me$; **b** $R_1 = Me$, $R_2 = Et$; **c** $R_1 = Me$, $R_2 = allyl$; **d** $R_1, R_2 = cyclohexyl$
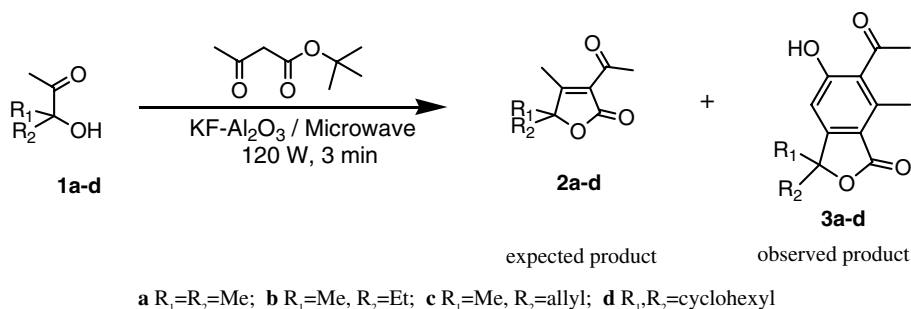
Figure 1. Formation of acetyl butenolide from α-hydroxyketone (expected product) and the isolated product.

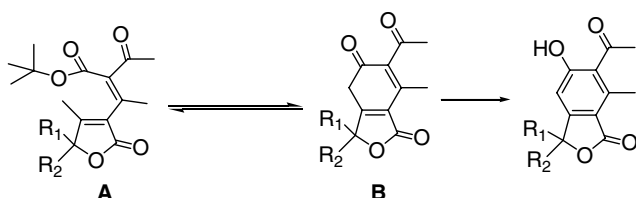
Figure 2. The observed reaction: formation of the isobenzofuranone.

The new 6-acetyl-5-hydroxy-3,3-dialkyl-7-methyl isobenzofuran-1(3H)-ones **3a**–**d**[9] result from the reaction of the acetylbutenolides **2a**–**d** with the second equivalent of *t*-butyl acetylacetonate (Fig. 2). This point was experimentally checked by the reaction of a sample of pure acetylbutenolide **2a** ($R_1 = R_2 = Me$) with *t*-butyl acetylacetonate in the presence of KF-alumina leading **3a** in a good yield (85%).

In fact, the formation of isobenzofuranones can be explained by a domino[10] one-pot reaction catalyzed by the base, KF-Al$_2$O$_3$.

The proposed cascade reaction consists of

(1) A base-catalyzed transesterification between **1a**–**d** and *t*-butyl acetylacetonate.
(2) A Knoevenagel base-catalyzed reaction with the formation of **2a**–**d**.
(3) A Knoevenagel condensation of the second equivalent of acetylacetonate on the butenolide **2a**–**d** with the formation of **A** (according to Fig. 3).
(4) A Claisen–Dieckmann reaction with the formation of **B** (according to Fig. 3).
(5) An aromatization reaction into **3** (according to Fig. 3).

The final step in the process, which is the driving force of this domino-reaction, is the irreversible aromatization of intermediate **B**, producing therefore the phenolate ion. This domino-reaction is in fact similar to the synthesis of aromatics observed in plants from polyketide products.[11]

In summary, we have reported a new and valuable method for functionalized isobenzofuran-1(3H)-ones synthesis by a one-pot cascade reaction of α-hydroxyketones with acetylacetonates. These obtained isobenzofuranones **3** are highly functionalized and hence represent versatile intermediate for organic synthesis.

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Figure 3. Cascade synthesis of 6-acetyl-5-hydroxy-3,3-dialkyl-7-methyl isobenzofuran-1(3H)-ones **3a**–**d**.

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9. In a typical experiment, a mixture of 3-hydroxy-3-methyl-butan-2-one (20 mmol) and *t*-butyl acetylacetonate (40 mmol) was adsorbed on KF-alumina (3 g) and then irradiated under a microwave (Synthewave 402, 2450 MHz, 120 W, 3 min). Aqueous HCl (18%, 15 mL) was added and the mixture was extracted with ether (3×50 mL). The combined organic layers were subsequently washed with water, dried, and concentrated. The obtained white solid was recrystallized in ethanol to provide the desired isobenzofuran-1-ones (**3a–d**) (yields 42–53%).

6-Acetyl-5-hydroxy-3,3,7-trimethyl-(3H)-isobenzofuran-1-one (**3a**). Yield 42%; mp 247–248 °C; IR v 3207, 1720, 1757 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 1.61 (s, 6H), 2.73 (s, 3H), 2.99 (s, 3H), 6.78 (s, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 17.17 (1C), 27.20 (2C), 33.55 (1C), 82.72 (1C), 108.03, 114.93, 123.45, 144.01, 160.71, 166.36 (6C), 169.21 (1C), 206.33 (1C); EIMS *m/z* (% relative intensity) 234 (M$^+$, 61), 219 (100), 201 (37) 191 (5), 175 (14); C$_{13}$H$_{14}$O$_4$ calcd (%): C, 66.66, H, 6.02. Found (%): C, 66.71, H, 6.10.

6-Acetyl-3-ethyl-5-hydroxy-3,7-dimethyl-(3H)-isobenzofuran-1-one (**3b**). Yield 53%; mp 180–184 °C; IR v 3268, 1722, 1761 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 0.75–0.85 (t, 3H), 1.60 (s, 3H), 1.76–2.10 (m, 2H), 2.74 (s, 3H), 2.99 (s, 3H), 6.74 (s, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 7.75 (1C), 17.26 (1C), 25.68 (1C), 33.62 (1C), 85.33 (1C), 108.29, 115.85, 123.23, 143.96, 160.52, 166.49 (6C), 169.52 (1C), 206.39 (1C); EIMS *m/z* (% relative intensity) 248 (M$^+$, 32), 233 (15), 220 (13), 219 (100), 201 (28), 176 (5); C$_{14}$H$_{16}$O$_4$ calcd (%): C, 67.73, H, 6.5. Found (%): C, 67.64, H, 6.46.

6-Acetyl-3-allyl-5-hydroxy-3,7-dimethyl-(3H)-isobenzofuran-1-one (**3c**). Yield 53%; mp 192–194 °C; IR v 3242, 1719, 1758 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 1.57 (s, 3H), 2.45–2.67 (d, 2H), 2.73 (s, 3H), 2.98 (s, 3H), 5.04–5.12 (d, 2H), 5.51–5.67 (m, 1H), 6.76 (s, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 17.22 (1C), 25.49 (1C), 33.60 (1C), 44.20 (1C) 84.18 (1C), 115.65 (1C), 130.67 (1C), 108.49, 120.49, 123.37, 143.93, 159.19, 166.33 (6C), 169.21 (1C), 206.36 (1C); EIMS *m/z* (% relative intensity) 261 (MH$^+$, 100), 243 (18), 217 (74), 199 (8), 175 (19); C$_{15}$H$_{16}$O$_4$ calcd (%): C, 69.22, H, 6.2. Found (%): C, 69.11, H, 6.05.

5′-Acetyl-6′-hydroxy-4′-methyl-[spirocyclohexane-1,1]-(3H)-isobenzofuran-3′-one (**3d**). Yield 50%; mp >250 °C; IR v 3206, 1711, 1753 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 1.70–1.90 (m, 10H), 2.73 (s, 3H), 2.99 (s, 3H), 6.77 (s, 1H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 7.75 (1C), 17.26 (1C), 25.68 (1C), 33.62 (1C), 85.33 (1C), 108.29, 115.85, 123.23, 143.96, 160.52, 166.49 (6C), 169.52 (1C), 206.39 (1C); EIMS *m/z* (% relative intensity) 274 (M$^+$, 100), 259 (17), 232 (13), 231 (63), 218 (25), 203 (39), 185 (11); C$_{16}$H$_{18}$O$_4$ calcd (%): C, 70.06, H, 6.61. Found (%): C, 69.97, H, 6.52.

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