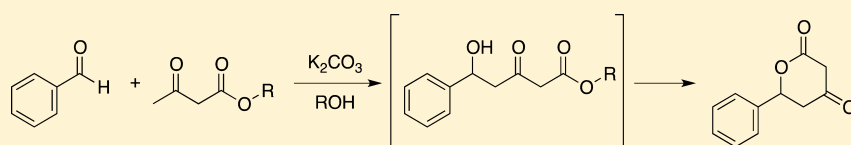


Investigation of the Mechanism for the Preparation of 6-Phenyl-2,4-dioxotetrahydropyrans by the Potassium Carbonate Promoted Condensation between Acetoacetate Esters and Benzaldehyde

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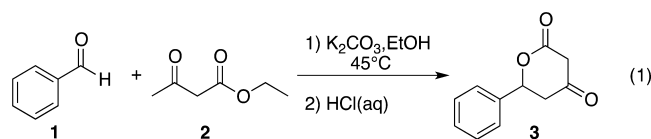
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S Supporting Information



ABSTRACT: Treatment of benzaldehyde and an acetoacetate ester with potassium carbonate in an alcohol solvent proceeds via γ -C-alkylation rather than α -C-alkylation resulting in the formation of 6-phenyl-2,4-dioxotetrahydropyran. Based upon results from deuterium exchange experiments, carbon-13 labeling experiments, ^1H NMR monitoring studies, and reactivity studies, our proposed mechanism for this reaction involves deprotonation at the α -carbon, intramolecular proton transfer to form a γ -anion, addition of the resulting γ -anion to the carbonyl carbon of benzaldehyde, and intramolecular transesterification.

It is well-known that the dianion of an acetoacetate ester undergoes alkylation or acylation at the γ -position.¹ Generation of the dianion is usually achieved by treating an acetoacetate ester with a strong base such as LDA,¹ potassium or sodium amide,² or NaH followed by *n*-BuLi.¹ We have reported that potassium carbonate in absolute ethanol promotes an unusual reaction between ethyl acetoacetate and benzaldehyde yielding 6-phenyl-2,4-dioxotetrahydropyran (eq 1).³



The outcome of this reaction is surprising because reactions between aromatic aldehydes and active methylene compounds typically yield Knoevenagel condensation products (α -alkylation)⁴ when carbonate bases are used. For example, Jimenez has found that both potassium and cesium carbonate catalyze the Knoevenagel condensation reaction between benzaldehyde and malononitrile in 1,4-dioxane.⁵ Catalytic iodine and potassium carbonate in ethanol have been used by Cai for Knoevenagel condensation reactions between substituted benzaldehydes and either malononitrile or ethyl cyanoacetate.⁶ Potassium carbonate was used as the base for microwave assisted Knoevenagel condensation reactions between benzaldehyde and ethyl cyanoacetate or diethyl malonate in the ionic liquid methylimidazolium.⁷ Cao has used potassium carbonate and PEG400,⁸ and Siebenhaar used sodium carbonate and 4 Å molecular sieves⁹ to catalyze solvent-free Knoevenagel condensation reactions

between aldehydes or ketones and malononitrile, ethyl cyanoacetate, diethyl malonate, or ethyl acetoacetate.

The reaction pathway that is most commonly used for preparing 6-aryl-2,4-dioxotetrahydropyrans, a group of compounds with diverse biological activities,¹⁰ involves trapping the preformed dianion of an acetoacetate ester with a carbonyl compound followed by treatment of the resulting hydroxyketoester with hydroxide and then acid.¹¹ The method that we have discovered is greener (ethanol and potassium carbonate versus tetrahydrofuran and *n*-butyl lithium), and it is procedurally less complex. In our original studies, 2.0 equiv of potassium carbonate were used; however, the reaction yields the desired lactones in comparable yields even when 1.2 equiv of potassium carbonate is used. Yields for this reaction with substituted benzaldehydes are between 56% and 93%, and no general trend has been observed for the yield variations.³ In this paper, we describe a set of experiments that provide evidence for the mechanism for this unexpected reaction.

Our initial work on this reaction focused on the use of ethyl acetoacetate and potassium carbonate in anhydrous ethanol (eq 1).³ To determine if the counterion of the carbonate base influenced the outcome of the reaction, the reaction was repeated using lithium, sodium, cesium, magnesium, calcium, and barium carbonate, while keeping all other variables constant. With lithium, sodium, and barium carbonate, no reaction occurred, and the use of magnesium and calcium carbonate led to the formation of a complex mixture with significant benzaldehyde and ethyl

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acetoacetate remaining. Only the reaction with cesium carbonate generated lactone **3**. Given that none of the carbonate salts, including K_2CO_3 , completely dissolve in the volume of solvent that is used for this reaction, the differences in carbonate reactivity may be related to the solubility of the solid carbonates. The solubility of solid carbonates in methanol increases as the ionic radius of the metal increases within a group, and group 1 carbonates are more soluble in methanol than group 2 carbonates.¹² Although the reaction works just as well when cesium carbonate is used, we have continued to primarily use potassium carbonate. We have also found that the reaction proceeds cleanly with ethyl, methyl, and *tert*-butyl acetoacetate esters in ethanol or methanol.

Before carbon-13 labeling experiments were performed, ^{13}C NMR signal assignments were determined using the heteronuclear multiple quantum correlation (HMQC) spectrum of **3** (see Supporting Information). To prove that the γ -carbon of the acetoacetate ester had added to the carbonyl carbon of the aldehyde, the reaction with benzaldehyde was repeated using ethyl acetoacetate with ^{13}C labels in positions 3 and 4. In the ^{13}C NMR spectrum of the product (**4**) (Figure 1), the labeled

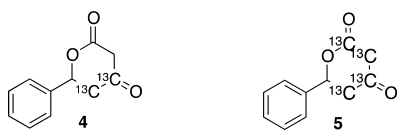


Figure 1. Carbon-13 labeled 6-phenyl-2,4-dioxotetrahydropyrans.

carbons were observed at 199.5 and 45.3 ppm, indicating that the γ -carbon of ethyl acetoacetate is bound to what was benzaldehyde's carbonyl carbon. Ethyl acetoacetate, which was labeled in the 1, 2, 3, and 4 positions, was also treated with benzaldehyde under our reaction conditions. The results for this experiment show that all four carbons of the acetoacetate ester backbone are incorporated into the product (**5**).

1H NMR was used to monitor the reaction between benzaldehyde, methyl acetoacetate, and K_2CO_3 in methanol-D4 at 45 °C, to determine whether the cyclization occurred before or after the $HCl(aq)$ quench. No methyl acetoacetate signals were observed 131 min after the potassium carbonate was added to the reaction, but benzaldehyde was still present. In addition, several new signals were observed: a singlet at 3.35 ppm, which corresponds to methanol, a singlet at 5.34 ppm, and two multiplets (7.32 and 7.45 ppm). The intensity of the singlet at 5.34 ppm and the multiplets increased as the reaction proceeded. After 16.3 h, the reaction was quenched with 1 M $HCl(aq)$. When K_2CO_3 was added to a methanol-D4 solution of the material from the acidic workup, and the temperature was increased to 45 °C to match the reaction conditions, the 1H NMR signals for the product from the workup were identical to the signals that developed as the reaction proceeded. This implies that $HCl(aq)$ is not catalyzing lactone formation; rather, it is only necessary for protonating the conjugate base of the product. Based upon this finding, an alternative workup was developed that yields the product in high purity, making it unnecessary to perform column chromatography. Quenching the reaction with water, followed by extraction with diethyl ether removes most of the impurities. Acidification of the water layer then generates compound **3**.

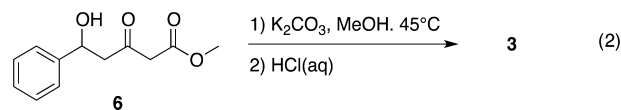
In an effort to understand why the 1H NMR signals for methyl acetoacetate had disappeared before the benzaldehyde had completely reacted, the 1H NMR monitoring study was

repeated without benzaldehyde. By the time the first spectrum was collected (7.4 min after K_2CO_3 addition), the methylene hydrogens (α -carbon) had undergone deuterium exchange with methanol-D4. Subsequent spectra showed that the hydrogens on the γ -carbon were also undergoing exchange and that the intensity of the signal for the methyl ester was decreasing, while the intensity of the signal due to the methyl group of methanol was increasing. After 2 h, only the signal for the methyl group of methanol was observed. Similarly, when ethyl acetoacetate was treated with K_2CO_3 in methanol-D4 at 45 °C, ethanol was detected by 1H NMR.

The disappearance of the methyl ester signal could be due to ester hydrolysis or transesterification with methanol-D4. However, when acetoacetic acid, the potential hydrolysis product, was treated with benzaldehyde under our normal reaction conditions, lactone **3** did not form. Therefore, it is unlikely that hydrolysis of the ester is occurring, and it is more likely that transesterification with methanol-D4 is causing the methyl ester signal to disappear.

To determine if potassium carbonate was necessary for the deuterium exchange to occur on the γ -carbon, methyl acetoacetate in methanol-D4, without potassium carbonate, was heated at 45 °C in the NMR probe, and spectra were collected every 15 min for 2 h. Only the methylene hydrogens underwent complete deuterium exchange. Because no signal for methanol was detected and because the integration values for the two methyl signals are similar, it appears that no other deuterium exchange has occurred. Because deuterium exchange at the γ -carbon only occurred when a base was present, it is likely that deprotonation at the γ -carbon is occurring under our normal reaction conditions.

If deprotonation at the γ -carbon of the acetoacetate ester is occurring and the γ -carbon is adding to the carbonyl carbon of benzaldehyde, it follows that compound **6** is most likely an intermediate for this transformation. To determine if compound **6** was capable of cyclizing under our reaction conditions, it was prepared using the dianion of methyl acetoacetate.^{11b} Previous reports dealing with the generation of δ -lactones from esters such as compound **6** used aqueous hydroxide followed by aqueous acid for the transformation. It has been suggested that the reaction occurs via base promoted hydrolysis followed by acid catalyzed esterification.^{11a,c} When compound **6** was treated with K_2CO_3 in absolute methanol (1 M) at 45 °C for 2 h followed by an acid workup, lactone **3** was generated in near-quantitative yield (eq 2). Therefore, hydroxyketoester **6** may be an intermediate for the lactone formation.



This reaction (eq 2) was also monitored using 1H NMR (0.1 M in methanol-D4 at 45 °C). As the reaction proceeded, the intensity of the signal for the methyl ester decreased, but it did not disappear until the reaction was complete (12.3 h). Surprisingly, only the methylene protons between the two carbonyl carbons of compound **6** underwent deuterium exchange. However, the 1H NMR spectrum of the product after workup in methanol-D4 with K_2CO_3 at 45 °C was identical to the spectra that were collected for the reaction and the spectrum of compound **3** in methanol-D4 with K_2CO_3 at 45 °C. This provides additional evidence for the conclusion that lactone formation occurs before the $HCl(aq)$ quench.

It should also be noted that when KOH was used in place of K_2CO_3 for the reaction shown in eq 2, the reaction was complete before the first spectrum could be collected, and again the spectra from before and after workup were identical. This result implies that lactone formation occurs before acid is added which contradicts the previously suggested mechanism of hydrolysis followed by acid catalyzed lactone formation.^{11a,c} Although KOH was a highly effective base for promoting the cyclization of hydroxyketoester **6**, the yield for the reaction between benzaldehyde and ethyl acetoacetate (eq 1) with KOH as the base was lower than what was observed when K_2CO_3 was used.

Unfortunately, we were unable to isolate compound **6**, the potential intermediate from the benzaldehyde and methyl acetoacetate reaction, when conventional heating methods were used. When the reaction was quenched with 1 M HCl(aq) before all of the benzaldehyde was consumed, only compound **3**, benzaldehyde, and methyl acetoacetate were identified. However, when the reaction was irradiated in a household microwave for 3 min, both compounds **6** and **3** were isolated from the reaction mixture in 8.6% and 14% yield respectively.

Despite finding evidence for the pathway by which compound **3** forms under our reaction conditions, several questions remain. Although K_2CO_3 has been used as a base for aldol reactions,¹³ it is surprising that K_2CO_3 generates either the dianion or the less stable conjugate base of the acetoacetate ester. While studying the solubility of K_2CO_3 in methanol, Platonov found that potassium methoxide (KOMe) was in higher concentration than potassium carbonate in solution.¹⁴ Accordingly, potassium ethoxide (KOEt) was used in place of K_2CO_3 , which resulted in the formation of compound **3** in similar yields (74–88%) to what had been observed when K_2CO_3 was used. This implies that the alkoxide ion could be the effective base for the K_2CO_3 promoted reaction rather than K_2CO_3 . We also found that only 1 equiv of KOEt was necessary for this transformation.

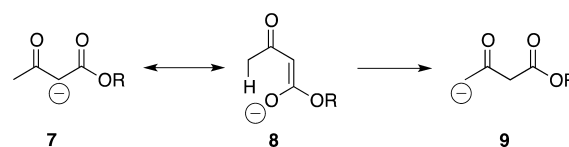
Because the protons on the α -carbon of an acetoacetate ester are more acidic than the protons on the γ -carbon, it would be expected that deprotonation would occur only at the α -carbon of ethyl acetoacetate when 1 equiv of KOEt is used. However, γ -alkylation is still observed. Lactone **3** was also obtained in 70–80% yield when the commercially available sodium salt of methyl acetoacetate was used with no additional base present.

Given that γ -alkylation still occurs when only 1 equiv of an alkoxide base is used or when the monosodium salt of methyl acetoacetate is used, it is unlikely that a dianion is forming. It is also unlikely that deprotonation at the γ -carbon is occurring via an intermolecular pathway because ethyl 2,2-dimethylacetoacetate does not react with benzaldehyde under our normal reaction conditions. Both K_2CO_3 and group 1 alkoxides have been used for aldol condensations¹³ for decades, so if the mechanism involves intermolecular deprotonation at the γ -carbon followed by an aldol addition, then ethyl 2,2-dimethylacetoacetate should react.

The lack of reactivity of ethyl 2,2-dimethylacetoacetate implies that α -ion formation is necessary for γ -alkylation to occur under our reaction conditions. Therefore, if γ -anion **9** is an intermediate in the reaction, it is possible that it forms via an intramolecular proton-transfer mechanism via a six-atom transition state involving direct removal of a proton from the γ -carbon (Scheme 1).

It was also observed that hydrogen–deuterium exchange did not occur at the γ -carbon when the reaction between

Scheme 1. Possible Intramolecular Proton-Transfer Mechanism



compound **3** and K_2CO_3 in methanol- D_4 was monitored by 1H NMR at 45 °C for 72 h. This result provides further evidence that intermolecular deprotonation is not occurring at the γ -carbon in these reactions. It also provides indirect support for intramolecular deprotonation, because deprotonation at the γ -carbon could not occur via intermediate **10** (the equivalent to **8**) because the ester oxygen is 4.4 Å away from the protons on the γ -carbon (Figure 2). The fact that compound **3** does

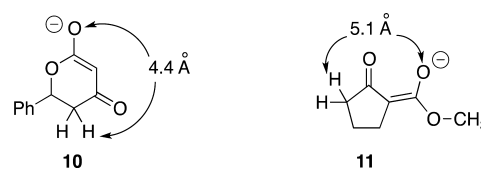
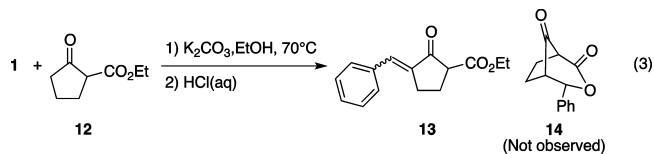


Figure 2. Calculated distances between the ester oxygen and protons on the γ -carbon.

not undergo deprotonation at the γ -carbon would also explain why it does not undergo further γ -C-alkylation even when excess benzaldehyde is used for this methodology. If deprotonation is occurring via a six-atom transition state, ethyl 2-oxocyclopentanecarboxylate, a conformationally constrained β -ketoester, should also not react with benzaldehyde because the calculated distance between the ester oxygen and the proton on the γ -carbon for anion **11** is 5.1 Å, which is too large for proton transfer to occur through the proposed six-atom transition state (see Figure 2).

When ethyl 2-oxocyclopentanecarboxylate (**12**) was treated with K_2CO_3 in the presence of benzaldehyde at 45 °C, a mixture of products including enone **13** was obtained. When the reaction was repeated at 70 °C (eq 3), enone **13** was the



major product (81% isolated yield). This result implies that the reaction is not proceeding through the proposed six-atom transition state because the distance is too large for this to occur.

If the mechanism is proceeding via a hydroxyketoester intermediate, the conformational constraints within this system may preclude lactone **14** from forming. Although not definitive evidence because the reaction at 45 °C generated a mixture, the absence of **14** also provides evidence against intermolecular transesterification of the hydrate of benzaldehyde followed by an intramolecular ring closure.

The results from the reaction with β -ketoester **12** suggest that if intramolecular proton transfer is occurring, it is more likely to proceed through enol **15** rather than through direct removal of a proton from the γ -carbon (Figure 3). This is further supported by the fact that acetoacetate esters with α -protons

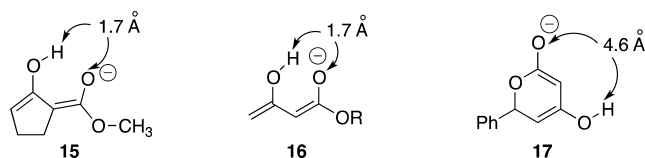


Figure 3. Possible enol intermediates.

react with benzaldehyde, but compound **3** does not. Proton transfer could readily occur with enol **15** (from compound **12**), and enol **16** (from an acetoacetate ester), but it could not occur with enol **17** (from **3**) because the distance is too great.

Based upon our findings, our proposed mechanism for the potassium carbonate induced condensation between benzaldehyde and an acetoacetate ester involves (1) deprotonation at the α -carbon, (2) rearrangement of the α -anion to form a γ -anion, (3) addition of the resulting γ -anion to the carbonyl carbon forming a hydroxyketoester, and then (4) intramolecular transesterification (see Scheme 2).

EXPERIMENTAL SECTION

General Experimental. Acetoacetic acid¹⁵ and compound **6**^{11b} were synthesized using known methods, and the ¹H NMR spectra for these compounds were compared to previously published ¹H NMR spectra (acetoacetic acid¹⁶ and **6**¹⁷). Benzaldehyde, ethyl acetoacetate, methyl acetoacetate sodium salt, ethyl acetoacetate-3,4-¹³C₂, ethyl acetoacetate-1,2,3,4-¹³C₄, ethyl 2-oxocyclopentane-carboxylate, potassium carbonate, potassium ethoxide, and methanol-D₄ were purchased and used without further purification. Ethanol and methanol were distilled under nitrogen from sodium. NMR spectra were collected on a 300 MHz spectrometer. IR spectra were collected using ATR (diamond crystal). Mass spectra were collected on a double-focusing sector mass spectrometer (70 eV). Distance calculations were performed using Parallel Quantum Solutions (PQS) software, version 4.0 (Parallel Quantum Solutions, Fayetteville, AR, USA).

General Procedure for the Preparation of Compounds **3, **4**, **5**, and **13**.** To a flame-dried screw-capped test tube¹⁸ under nitrogen was added benzaldehyde (1.0 equiv), the alcohol solvent (1.0 mL per mmol of benzaldehyde) (distilled from sodium and stored over activated 3 Å sieves), the acetoacetate ester (1.0 equiv), and the base (2.0 equiv of potassium carbonate or 1.0 equiv of potassium ethoxide). The septa and the nitrogen filled balloon were replaced with a screw cap, and the mixture (heterogeneous with K₂CO₃ and homogeneous with alkoxide bases) was stirred overnight (16–24 h) at the described temperature. The reaction mixture was then transferred to a separatory funnel using diethyl ether, and the product was extracted with water (2 times). The organic layer was discarded, and the combined aqueous layers were acidified with 6 M HCl and extracted with three portions of ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered, concentrated, and purified by flash chromatography or trituration with diethyl ether.^{10a}

6-Phenyldihydro-2H-pyran-2,4(3H)-dione-4,5-¹³C₂ (4**).** Using the standard procedure (0.52 mmol scale, 45 °C) and trituration with

diethyl ether afforded **4** (0.037 g, 37%)¹⁹ as a white solid; mp = 127–131 °C; ¹H NMR (CDCl₃) δ 7.43 (m, 5H), 5.71 (m, 1H), 3.69 (dd, J = 19.23, 7.44 Hz, 1H), 3.52 (ddd, J = 18.96, 6.03, 1.65 Hz, 1H), 2.96 (ddd J = 132.7, 4.1, 6.3 Hz, 1H), 2.14 (ddd J = 130.2, 6.0, 9.9 Hz, 1H); ¹³C NMR (CDCl₃, 50 scans) δ 199.5, 45.3; IR (ATR) 3037, 2921, 2899, 1731, 1682, 1280, 1238, 1049, 1000, 944, 892, 754, 694, 659 cm⁻¹; HRMS (EI) calcd for C₉H₁₀O₃¹³C₂ 192.06971, found 192.06978.

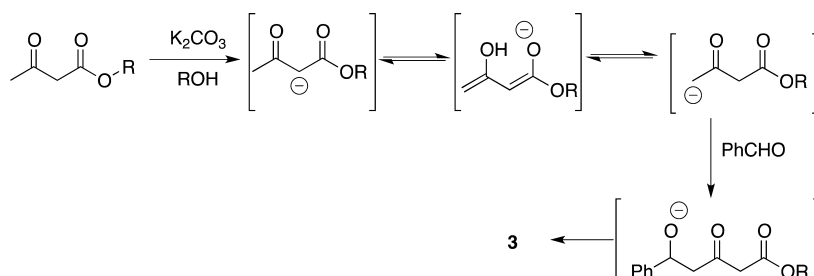
6-Phenyldihydro-2H-pyran-2,4(3H)-dione-2,3,4,5-¹³C₄ (5**).** Using the standard procedure (0.60 mmol scale, 45 °C) and trituration with diethyl ether afforded **5** (0.046 g, 39%)¹⁹ as a white solid; mp = 130–133 °C; ¹H NMR (CDCl₃) δ 7.43 (m, 5H), 5.71 (m, 1H), 3.81 (m, 1H), 3.32 (m, 2H), 2.71 ppm (m, 1H); ¹³C NMR (CDCl₃, 50 scans) δ 199.5, 167.0, 47.1, 45.2 ppm; IR (ATR) 3037, 2964, 2890, 1702, 1671, 1260, 1247, 1047, 997, 935, 888, 752, 694, 652 cm⁻¹; HRMS (EI) calcd for C₇H₁₀O₃¹³C₄ 194.07642, found 194.07647.

Methyl 3-(Hydroxy(phenyl)methyl)-2-oxocyclopentane-carboxylate (13**).** Using the standard procedure (2.0 mmol scale, 70 °C) and flash chromatography on silica gel (16–20% EtOAc/hexanes) afforded **13** (0.395g, 81%) as a yellow oil. A pale yellow solid (0.342 g, 70%) was obtained after trituration with Et₂O; mp = 90–93 °C; ¹H NMR (CDCl₃) δ 10.27 (s, 1H), 7.40 (m, 4H), 6.92 (t, J = 2.46, 2.46 Hz, 1H), 4.29 (q, J = 7.14, 0.14, 7.14 Hz, 2H), 2.90 (m, 2H), 2.67 (m, 2H), 1.34 (t, J = 7.14, 7.14 Hz, 3H); ¹³C (CDCl₃) (Mixture of keto and enol forms) δ 201.0, 170.0, 169.7, 169.5, 138.3, 136.7, 135.1, 134.7, 134.6, 130.7, 129.8, 129.2, 128.8, 128.6, 128.3, 127.5, 124.0, 106.1, 61.5, 60.2, 54.3, 26.3, 25.2, 24.4, 14.4, 14.2; IR (ATR) 3020, 2978, 2921, 1638, 1600, 1234, 1169, 1094, 770, 751, 723, 686, 634 cm⁻¹; HRMS (EI) calcd for C₁₅H₁₆O₃ 244.10995, found 244.10911.

General Procedure for NMR Monitoring Studies. To a flame-dried 5 mm screw-capped NMR tube under nitrogen were added benzaldehyde (0.10 mmol), 1.0 mL of methanol-D₄ with TMS, the acetoacetate ester (0.10 mmol), and potassium carbonate (0.20 mmol). The septa and the nitrogen filled balloon were replaced with the NMR cap. A timer was started immediately after the potassium carbonate was added. The sample was warmed to 45 °C in the NMR probe, and then the magnetic field was shimmed and locked on the sample. Eight scans of the heterogeneous mixture were collected every 60 min for 16 h. The reaction was worked up using the procedure described above.

Procedure for Microwave Experiment. To a small test tube were added benzaldehyde (0.10 mL, 0.99 mmol), 1.0 mL of ethanol, ethyl acetoacetate (0.13 mL, 1.03 mmol), and potassium carbonate (0.279 g, 2.02 mmol). The mixture was irradiated in a 1080 W household microwave at 50% power for 3 min. After the tube was cooled to room temperature, the reaction mixture was transferred to a separatory funnel using 15 mL of ethyl acetate and then 10 mL of 1 M HCl(aq) were slowly added. The aqueous layer was extracted with two additional portions (2 × 15 mL) of ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered, concentrated, and purified by flash chromatography (30%–60% EtOAc/hexanes) yielding compounds **6** (0.019g, 8.6%) and **3** (0.027g, 14%). Compound **6** R_f = 0.25 (30% EtOAc/hexanes); Compound **3** R_f = 0.27 (67% EtOAc/hexanes).

Scheme 2. Proposed Mechanism for the Potassium Carbonate Promoted Condensation between Benzaldehyde and an Acetoacetate Ester



■ ASSOCIATED CONTENT

● Supporting Information

Spectra from the NMR monitoring experiments, the HMQC spectrum for compound **3**, spectra data for all previously unpublished compounds (**4**, **5**, and **13**), and the *x,y,z* coordinates from computational studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (18) Although the work described in this paper was completed using screw-capped tubes, the reaction can also be performed using a reaction flask bearing a condenser.
- (19) The isolated yields for compounds **4** and **5** were low because the products were purified using trituration from ether. As previously published, the isolated yield for compound **3** (equivalent to **4** and **5** without carbon-13 labels) was 88% when column chromatography was used to isolate the product. However, the material obtained from the column did not have a well-defined melting point.