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ARTICLE

Microwave-Assisted Dealkoxycarbonylation of α-Mono- and α,α-Disubstituted β-Keto- and α-Cyanoesters mediated by a Silica Gel Bed

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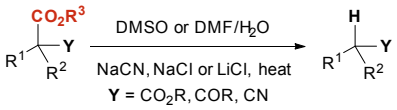
A new and alternative protocol for the classical Krapcho type reaction is reported here, involving a microwave-assisted method which replaced the typical aprotic polar solvent by a silica gel support with the adding of only few µL of DMF to improve the effect of the microwave irradiation. Such experimental procedure was successfully applied to several α-mono- and α,α-disubstituted β-ketoesters and α-cyanoalkylesters allowing the rapid isolation of the corresponding ketones and nitriles, with moderate to high yields, in short reaction time.

Introduction

Activated esters, among them, malonates, β-ketoesters and α-cyanoesters have been remarkably important in organic chemistry due to they are easily alkylated and transformed in diverse precursors for synthetic applications. The monoalkylation or dialkylation reactions over the mentioned substrates are typically followed by dealkoxycarbonylation (or decarboalkoxylation) processes.[1] In the last decade, three extensive reviews were published enclosing the countless synthetic applications of dealkoxycarbonylation of β-ketoesters, malonates, α-cyanoesters, etc. Reactions were mainly promoted by heating the starting material in wet (DMSO or DMF), in the presence of diverse salts like NaCN, NaCl or the more frequently used LiCl, as useful extensions of the well-known Krapcho reaction. (Scheme 1).[2]



Scheme 1 Experimental conditions previously used for the classical Krapcho reaction

Although, the above procedures continue being very useful, the long reaction time (in several cases), high temperatures, and several aqueous extractions to remove the aprotic solvent are required, which normally affects the reaction yields. In order to overcome these drawbacks, some researchers have used microwave irradiation (MWI) and other variants to the original Krapcho reaction in their dealkoxycarbonylation processes. In this direction, several examples have been reported applying MWI to perform the dealkoxycarbonylation under the classical Krapcho reaction. All of them limited to alkylated malonates or β-ketoesters.[3]

With other variants, Loupy *et al.*,[4] used MWI for dealkoxycarbonylation reactions on substituted 2-ethoxycarbonylcyclohexanones in the presence of LiBr and Bu_4NBr as a solid-liquid phase transfer catalyst (PTC) in solvent-free reaction conditions. In turn, Curran *et al.*[5] developed the dealkoxycarbonylation reaction of unsubstituted and α-monosubstituted malonates and β-ketoesters in MWI conditions, using simply wet DMF and without adding salts. Nevertheless, these reaction conditions were not effective for both α, α-disubstituted-β-keto and malonate esters. More recently, Murphree *et al.*[6] reported a study on this reaction with several α-monosubstituted malonate ethyl esters under MWI evaluating several lithium salts. The best results were obtained when lithium sulfate was used in the presence of water as solvent.

As part of our current research work on the synthesis of non-symmetric ketones mediated by β-ketoesters,[7] we are reporting here a general microwave-assisted dealkoxycarbonylation, of both, α-mono- and α,α-disubstituted methyl(ethyl) acetoacetates and α,α-disubstituted methyl 2-cyanoacetates by absorption of these reagents over silica gel.

Recently we required to synthesize several oxime ethers VI and **VII** from methyl acetoacetate (**I**) to furtherly be subjected to bicyclization reactions mediated by free radicals. As shown in Figure 1, a dealkoxycarbonylation process on esters **II/IV** was the key step in this retrosynthetic analysis.

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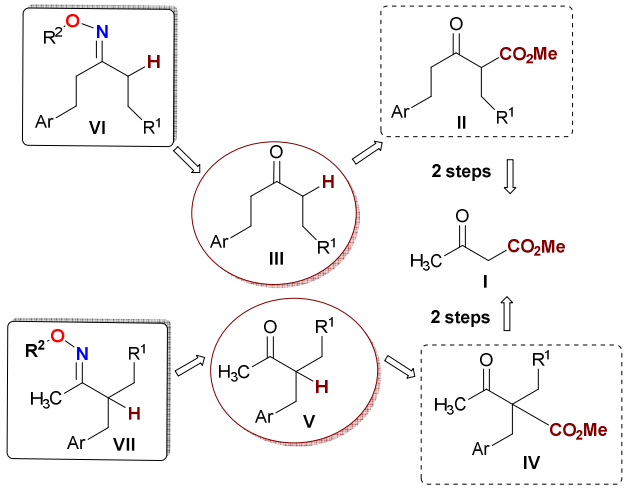
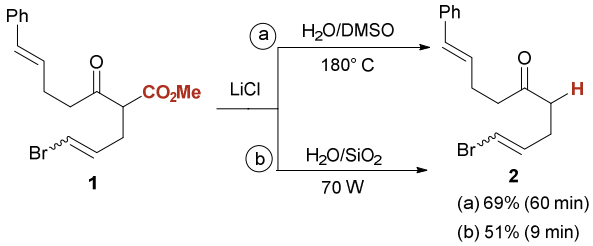


Fig. 1 Retrosynthetic analysis for the oxime ethers VI-VII synthetized from methyl acetoacetate

Results and Discussion

To start with our purposes, we attempted to obtain ketones type **III** and **V** through the dealkoxycarbonylation reaction of their corresponding β-ketoesters **II** and **IV**, respectively, *via* the classical Krapcho procedure. Thus, as a model reaction for α-monoalkylated β-ketoesters type II, a mixture of the methyl 2-(3-bromoallyl)-3-oxo-7-phenylhept-6-enoate (**1**) (0.72 g, 2.19 mmol), LiCl (0.18 g, 4.27 mmol), water (38 μL, 2.14 mmol) and DMSO (5 mL) was heated at 180 °C during 1 h. After reaction finished and the classical work up was performed, the expected 1-bromo-9-phenylnona-1,8-dien-5-one (**2**) was obtained in 69% yield, (approach (a), Scheme 2). In general, by following this procedure the desired ketones **III** and **V** were obtained just in low to acceptable yields (40-70%), in a temperature range of 110-180 °C, with a reaction time range of 1-5 h and after long time-consuming work up in all cases.[7]

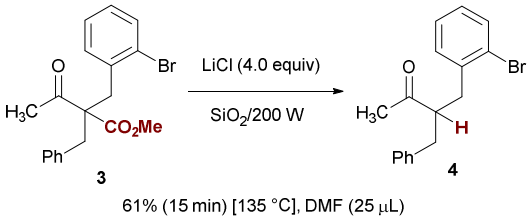
Looking for a more expeditious method, a variant of the classical Krapcho reaction was considered. Thus, based on previous reports,[3-6] the above reaction was repeated by absorbing on silica gel (70-230 mesh) of the ester **1** (0.35 g, 2.05 mmol), LiCl (0.36 g, 8.50 mmol), water (80 L, 4.40 mmol). Then, the reaction mixture was subjected to MWI at 70 W during 9 min leading the ketone **2** in 51% yield, (approach (b), Scheme 2).



Scheme 2 Comparative dealkoxycarbonylation reaction on the α-monosusbstituted methyl β-ketoesters **1**

Although compound **2** was isolated in relative less yield under MWI (approach (b)) in comparison with the classical Krapcho reaction carried out under conventional heating (approach (a)), this finding led us to reveal an alternative route for this reaction using silica gel as support material and MWI as heating source. Moreover, isolation of product **2** was simpler than that from the approach (a) with a significant shorter reaction time. From this approach ketone **2** was easily isolated and purified just by pouring the silica gel absorbed crude directly into the column chromatography containing 15 g of clean silica gel and using (7-9% ether/hexane, 1% gradient) as eluent. Hence, the aqueous extraction to eliminate part of the aprotic solvent was not required, as is usual in the original Krapcho procedure, as well as, in most of its variants.

With the above result in hand, as a further challenge, we tried to extend our previous MWI assisted method toward, hard to decarboxylate, α,α-disubstituted β-ketoesters.[2-8] In that sense, we chose the methyl 2-benzyl-2-(2-bromobenzyl)-3-oxobutanoate (**3**), as model precursor, to standardize and polish the reaction conditions. In a first assay (a), a mixture of ester **3** (0.090 g, 0.25 mmol), LiCl (0.040 g, 1.01 mmol) and water (75 μL) was absorbed in silica gel (0.01 g) and subjected to MWI in a CEM reactor. After 45 min of irradiation at 100 °C and 200 W, the thin layer chromatography (TLC) showed a complex mixture of products and unreacted starting material **3**. In a second assay (b), the same reaction was repeated but adding DMF (25 μL) instead of water, affording the expected 3-benzyl-4-(2-bromo-phenyl)butan-2-one (**4**) in 61% yield, after only 15 min of irradiation (Scheme 3). This ketone was isolated and purified, by following our easy work up, as described above.



Scheme 3 Dealkoxycarbonylation of the α,α-disubstituted β-ketoester 3 under the established reaction conditions

Aimed to explore a wider scope of this approach, a variety α,α-disubstituted-β-ketoesters, α-cyanoesters (Table 1), and α-monosubstituted β-ketoesters (Table 2) were subjected to our established MWI/Silica gel assisted reaction conditions in the range of 120-150 °C, obtaining the expected ketones **6a-c** or

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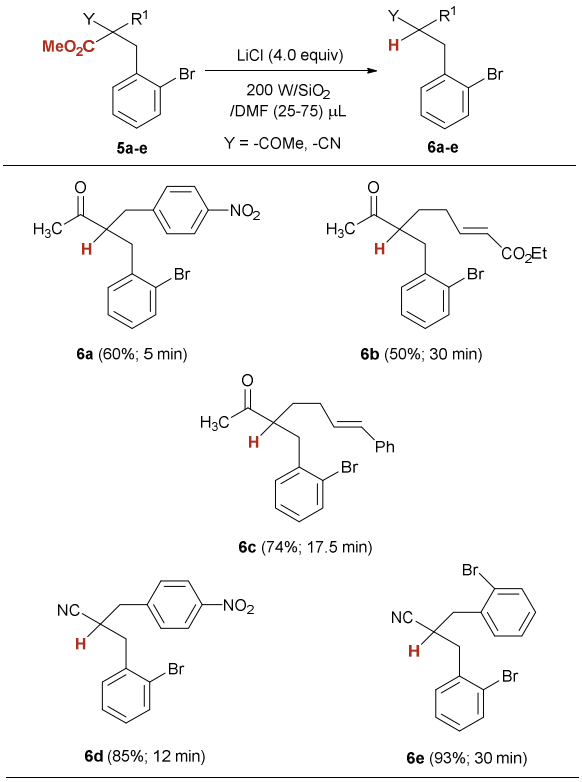
nitriles **6d-e** and also the ketones **8a-e**, respectively, in good to excellent isolated yields (50-93%).

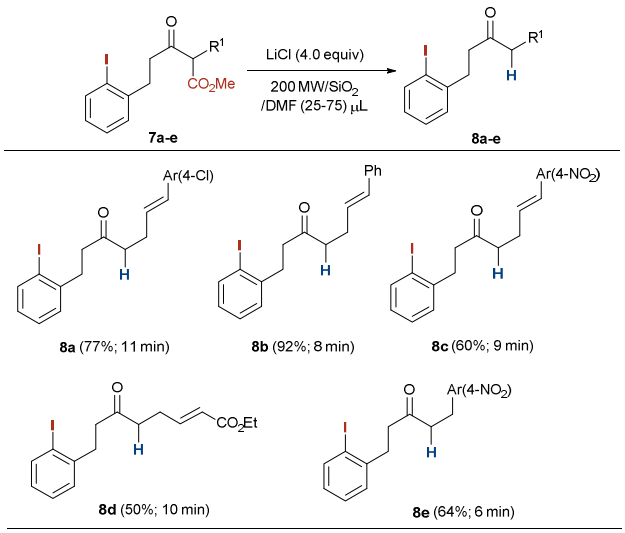
It is remarkable the fact that high yields of ketones **6c** (74%), **8a** (77%), **8b** (92%), **8c** (60%) were obtained from the dealkoxycarbonylation of their corresponding α,α-disubstituted and α-monosusbstituted methyl β-ketoesters bearing a cinnamyl moiety in their structures. In contrast, β-ketoesters with an alkenyl carboethoxy appendix showed modest yields, *i.e*. **6b** (50%) and **8d** (50%) in comparable reaction time. Besides, the disubstituted α-cyanoesters **5d** and **5e** afforded their respective nitriles **6d** and **6e** in very good 85% and 93% yields, respectively.

Table 1 Dealkoxycarbonylation reaction of α,α-disubstituted methyl β-ketoesters **5a-c** and α-cyanoesters **5d,e**



It is relevant to note, that when we tried to perform the dealkoxycarbonylation reaction of the α,α-disubstituted β-keto ester **3** absorbed on silica gel with LiCl and water (instead of DMF) (Scheme 3), such a reaction did not proceed fairly. Probably because, as it is well-known, the α,α-disubstituted β-ketoesters takes longer dealkoxycarbonylation time than α-monosubstituted derivatives.[2,8] Hence, in that assay, the added water probably evaporated rapidly before reaction was completed. Interestingly, the adding of DMF helped to solve the problem, which could be associated with both high boiling point (153 °C) and high dielectric constant (ε = 36.7) exhibited by this solvent. In consequence, DMF contains low volatile and polar molecules sensitive to external electric fields required to develop the microwave phenomenon.[9]

Table 2 Dealkoxycarbonylation reaction of α-monosusbstituted methyl β-ketoesters **7a-7e**



In our method, silica gel was chosen as solid support due to its resistant to the required temperatures for dealkoxycarbonylation reaction (~150 °C) and because of its high capability to absorb the starting materials.[10] It is presumed that the silanol groups (Si-OH) play an important role of retaining the required humidity for this process, but also acting as source of protons and providing a polar surface not only to change the spatial orientation of the reactants but also to facilitate the solvation of the lithium chloride and substrates through hydrogen bonds (Figure 2).

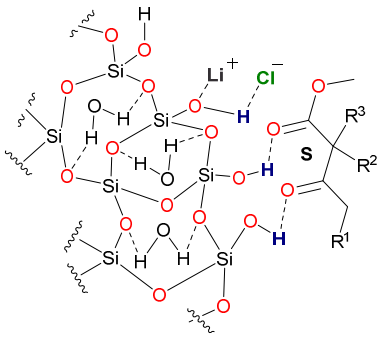


Fig. 2 Suggested interactions between substrate (**S**), H_2O, LiCl and the silica gel used as solid support in our established MWI procedure. Oxigen atoms in black color belong to abosorbed water molecules. Hydrogen atoms in bold and blue color represent hydrogen-bonding sites to activate both LiCl-catalyst and substrate (**S**)

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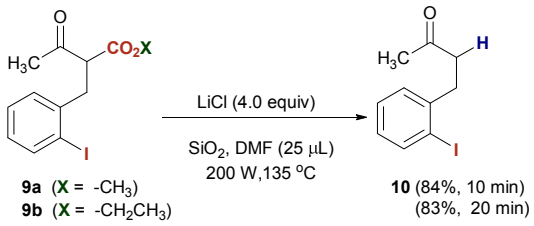
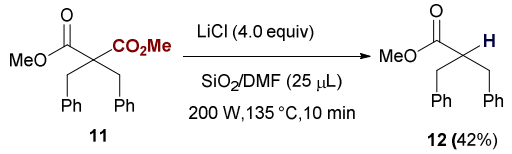
In order to evaluate the effect of the alkoxyl group on the alcoholic moiety, we also investigated and compared the efficiency of our method toward α-monosubstituted methyl- vs ethyl β-ketoesters. Thereby, methyl and ethyl esters **9a** and **9b**, respectively, were prepared and subsequently dealkoxycarbonylated under our established reaction conditions. The ethyl acetoacetate derivative **9b** required two-fold of time than its methyl analogue **9a** to afford product **10** in similar yields (Scheme 4). This finding is consistent with the literature reports, indicating that methyl esters are dealkoxycarbonylated faster than ethyl esters.[8]



Scheme 4 Comparative dealkoxycarbonylation reaction of α-monosubstituted methyl- vs ethyl β-ketoesters **9a** and **9b** respectively

Although in this research work we did not require dealkoxycarbonylate malonate methyl esters, we applied our established protocol to the dialkylated malonate derivative **11**. Reaction proceeded in similar way and product methyl 2-benzyl-3-phenylpropanoate (**12**) was obtained in an acceptable 42% yield (Scheme 5).



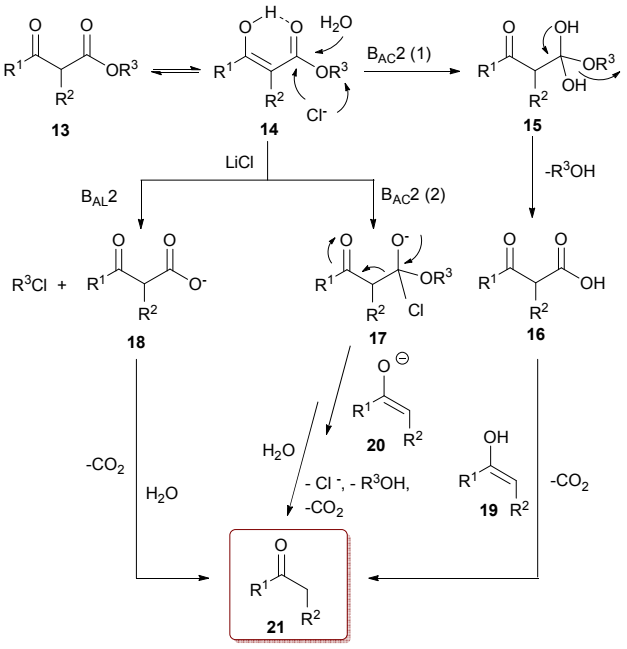
Scheme 5 Dealkoxycarbonylation reaction of 2,2-dimethyl diester dibenzylmalonate (**11**)

In a further experiment, the treatment under MWI (200 W, 135 °C, 8 min) of the α-monosubstituted β-ketoester **7b** adsorbed over silica gel, without adding lithium salt afforded ketone **8b** in 68%. As mentioned above, the same reaction performed under the presence of LiCl afforded **8b** in 92% yield (see Table 2). This finding indicates that LiCl, although, it is not strictly necessary to make reaction proceed, its presence is effectively convenient to improve the efficiency of this reaction. This result agree with the findings of Curran *et al.*,[5] in the dealkoxycarbonylation reaction of α-monosubstituted β-ketoesters under MWI in a mixture DMF/water without adding salts.

At this point, it is worth to recall the described mechanisms for dealkoxycarbonylation of α-monosusbstituted β-keto- and malonate esters to afford ketones type **21**, where the mechanistic behavior depends on the structure of the substrate and the reaction conditions. Moreover, it is recognized the formation of an enol species type **14** as the key intermediate in β-ketoesters for this process (Scheme 6).[5]

The dealkoxycarbonylation performed in wet DMF or DMSO (in absence of salts), for α-monosusbstituted β-ketoesters **13**, proceeds through a neutral hydrolysis (or its enolic **14** form), followed by decarboxylation of the acid **16**, and the subsequent enolic tautomerization process on **19** to afford the target ketone **21** (*i.e.* $B_{AC}2$ (**1**) pathway in Scheme 6).[5]

However, adding salts like (LiCl, NaCl, KCN, etc.) a nucleophilic attack occurs of their corresponding anions (*i.e.* Cl^-, CN^-, etc.) on the carbonyl group (*i.e.* nucleophilic catalysis), to form tetrahedral species **17**. These species breaks down to the enolate intermediate **20** which is subsequently protonated to lead ketone **21**. Alternatively, a nucleophilic attack of the corresponding anion (*i.e.* Cl^- when LiCl is used), on the alkyl group R^3 of the alcoholic moiety in **14** could occur (i.e. $B_{AL}2$ pathway, Scheme 6), to generate the carboxylate species **18**. Subsequently a water mediated decarboxylation process should lead the target ketone **21**.



Scheme 6 Competitive mechanisms for dealkoxycarbonylation of α-monosusbstituted β-ketoesters **13** under uncatalyzed and LiCl/H_2O catalyzed reaction conditions

On the other hand, it was mentioned above that the α,α-disubstituted β-ketoesters **22** are resistant to dealkoxycarbonylation reactions in absence of salts.[8] According to Schemes 6 and 7, this finding could be supported by the fact that esters **22** cannot be enolized like **13** for that

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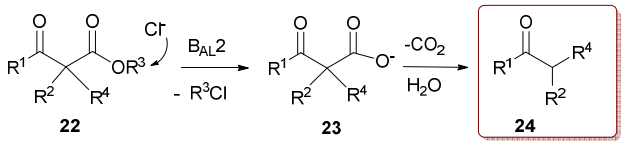
their carbonyl groups could not intramolecularly be activated as **14**. In consequence, the concurrence or synergism of the pathway type $B_{AC}2$ (**1**) is discarded for esters **22**, indeed, their ketonic products **24** could only be formed mediated by salts and predominantly via a $B_{AL}2$ pathway (Scheme 7),[8] which is reflected in a relatively time-consuming reaction in comparison with their α-monosusbstituted analogues **13**.



Scheme 7 Suggested mechanistic sequence for the LiCl/H_2O catalyzed dealkoxycarbonylation reaction of α,α-disubstituted β-keto esters **22**

At this stage, it is worth to highlight the versatility and advisability of our method for the dealkoxycarbonylation not only of α-monosubstituted β-keto esters but also α,α-disubstituted β-keto-, α-cyano- and malonate esters. This approach covers a broader scope of substrates in comparison with interesting previous MWI methods like reported by Curran *et al.,*[5] which was basically effective for α-monosubstituted malonates and β-ketoesters, but examples of α,α-disubstituted β-keto esters were not mentioned. In turn, Murphree *et al.*[6] also reported MWI assisted dealkoxycarbonylation reactions but only over monoalkylated malonates. To our knowledge, the current report is the first systematic and general work on dealkoxycarbonylation reaction of diversely α-mono- and α,α-disubstituted β-ketoesters supported over silica gel and mediated by microwave irradiation that have been made to date.

Conclusions

We have adapted the classical Krapcho type reaction to an alternative microwave-assisted method replacing the solvent by a silica gel support with the addition of only few μL of DMF. This experimental procedure was successfully applied to several α-mono- and α,α-disubstituted β-keto and α-cyanoalkylesters. Not only the reaction time could be substantially reduced, but also the purification process of the obtained products was simplified. Thus, this protocol is compatible with the green chemistry and potentially could be extended to synthetic chemistry when this type of reaction would be required.

Experimental Section

General Methods: Melting points were determined in open capillary tubes on Stuart SMP10. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck); the spots were visualized under UV light (254 nm). Column chromatography and flash column chromatography conducted under silica gel (Merck, 70-230 and 230-400 Mesh respectively). The chemical structures of intermediate and final products were elucidated by nuclear magnetic resonance spectra (1H NMR, 13C NMR) which were determined on a Bruker Avance II 400 MHz spectrometer. Chemical shifts reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as internal standard. Infrared spectra were determined on a SHIMADZU Spectrophotometer IR affinity-1 with ATR miracle pike. Elemental analysis was determined on a Thermo FlashEA 1112 series with CHN analyzer. High Resolution Mass Spectra (HRMS) were recorded on a JEOL JMS-AX505HA spectrometer with PEG-600 like standard. Reagents as methyl acetoacetate, diethyl malonate, aryl bromides, lithium chloride, potassium tert-butoxide, magnesium sulfate and solvents as THF (dried over Na-benzophenone) and DMF were purchased from commercial suppliers (Sigma-Aldrich Chemical Co., Acros Organics, etc.).

General procedure for the dealkoxycarbonylation reaction of α,α-disubstituted β-keto, α-cyanoesters, diethylmalonate and α-monosubstituted β-ketoesters.

A microwave tube was charged with β-ketoester (1.00 mmol), LiCl (4.00 mmol), silica gel (70-230 mesh, Merck, 0.40 g per 1.00 mmol of substrate), DMF (25-75 μL) and dichloromethane (3 mL). The mixture was stirred at room temperature until to get a homogeneous appearance and subsequently the excess of dichloromethane removed under vacuum. The tube was sealed with its plastic cup and heated without stirring in a CEM Discovery Microwave reactor (with dynamic method), until consumption of the substrate (monitored by TLC). The silica gel supported reaction mixture was cooled to room temperature and poured into a partially filled (with silica gel), column chromatography. Then, the product was isolated by using gradients of ethyl ether/hexane mixtures.

Ketones α,α-disubstituted

3-Benzyl-4-(2-bromophenyl) butan-2-one (**4**). Compound **4** was prepared according to the general procedure from β-keto ester **3** (0.095 g, 0.25 mmol), LiCl (0.044 g, 1.01 mmol), Silica gel (0.10 g) and DMF (25 μL). The vial was sealed and heated at 135 °C, 200 W by 15 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 7-9% ether/hexane, 1% gradient) to afford a colorless oil (0.048 g, 61%). Anal. calcd. for $C_{17}H_{17}BrO$: C, 64.37, H, 5.40; found: C, 64.36, H, 5.43. IR (ATR), (cm^{-1}): 3408; 3061, 2925, 2855, 1711 (C=O), 1601, 1565, 1494, 1445, 1359, 1328, 1161, 1107, 1026, 753, 526. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.79 (s, 3H), 2.77 (dd, *J* = 6.0, 13.0 Hz, 1H), 2.89 (dd, *J* = 6.0, 13.0 Hz, 1H), 2.95–3.07 (m, 2H), 3.33–3.41 (m, 1H), 7.08–7.12 (td, *J* = 2.0, 8.0 Hz, 1H,), 7.16–7.25 (m 5H), 7.27–7.31 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 31.8, 38.2, 38.4, 53.8, 124.4, 126.4, 127.5, 128.2, 128.5, 128.9, 131.6, 133.0, 138.7, 139.1, 211.8.

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3-(2-Bromobenzyl)-4-(4-nitrophenyl)butan-2-one (**6a**). Compound **6a** was prepared according to the general procedure from β-keto ester **5a** (0.10 g, 0.24 mmol), LiCl (0.042 g, 1.0 mmol), Silica gel (0.096 g) and DMF (25 µL). The vial was sealed and heated at 150 °C, 200 W by 5 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 1-6% ether/hexane, 1% gradient) to afford a yellow solid (0.048 g, 60%), Mp = 70.8-71.2 °C. IR (ATR) (cm^{-1}): 3400, 3078, 2848, 1705, 1328, 1275, 1020. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.87 (s, 3H), 2.78 - 2.89 (m, 2H), 2.08 (m, 2H), 3.36 – 3.43 (q, 1H), 7.13 (td, 1H, *J* = 8.0, 2.0 Hz), 7.17 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.25 (td, 1H, *J* = 8.0, 1.0 Hz), 7.31 (d, 2H, *J* = 9.0 Hz), 7.58 (d, 1H, *J* = 8.0, 1.0 Hz), 8.13 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 31.5, 37.2, 38.7, 53.3, 123.7, 124.4, 127.7, 128.6, 129.8, 131.6, 133.2, 137.9, 146.8, 147.1, 210.4. HRMS (DART): calcd for $C_{17}H_{16}BrNO_3$: 362.0392, found: 362.0394.

Ethyl (E)-5-(2-bromobenzyl)-6-oxohept-2-enoate (**6b**). Compound **6b** was prepared according to the general procedure from β-keto ester **5b** (0.094 g, 0.23 mmol), LiCl (0.041 g, 0.95 mmol), Silica gel (0.092 g) and DMF (25 µL). The vial was sealed and heated at 120 °C, 200 W by 30 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 1-2% ether/hexane, 1% gradient) to afford a yellow oil (0.039 g, 50%). Anal. calcd. for $C_{16}H_{19}BrO_3$: C, 56.65, H, 5.65, Found: C, 56.24, H, 5.52. IR (ATR), (cm^{-1}): 3059, 2982, 2953, 1713 (C=O, ketone), 1653, 1470, 1439, 1368, 1263, 1157, 1026, 976, 750, 660. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.30 (t, 3H, *J* = 7 Hz), 2.07 (s, 3H), 2.30 – 2.37 (m, 1H), 2.55 – 2.63 (m, 1H), 2.82 (dd, 1H, *J* = 14.0 Hz, *J* = 7 Hz), 3.04 – 3.09 (m, 1H), 3.15 – 3.22 (m, 1H), 4.19 (q, 2H, *J* = 7.0 Hz), 5.85 (d, 1H, *J* = 16.0 Hz), 6.82 – 6.90 (m, 1H), 6.82 – 6.90 (m, 1H), 7.14-7.22 (m, 2H), 7.58 (d, 1H, *J* = 8.0 Hz);^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 14.3, 30.7, 33.5, 38.0, 50.8, 60.3, 123.7, 124.5, 127.6, 128.5, 131.6, 133.2, 138.1, 145.1, 166.1, 210.2.

(E)-3-(2-Bromobenzyl)-6-phenylhex-5-en-2-one (**6c**). Compound **6c** was prepared according to the general procedure from β-keto ester **5c** (1.22 g, 3.04 mmol), LiCl (0.54 g, 12.73 mmol), Silica gel (1.22 g) and DMF (75 µL). The vial was sealed and heated at 150 °C, 200 W by 17.5 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 1-2% ether/hexane, 1% gradient) to afford a brown oil (0.77 g, 74%). Anal. calcd. for $C_{19}H_{19}BrO$: C, 66.48, H, 5.58; Found: C, 66.35, H, 5.50. IR (ATR), (cm^{-1}): 3058; 3026, 2930, 2845, 1711, 966, 745. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.03 (s, 3H), 2.34–2.41 (m, 1H), 2.52–2.59 (m, 1H), 2.87 (dd, *J* = 6.0, 14.0 Hz,1H), 3.01–3.07 (m, 1H), 3.15 (ddd, *J* = 6.0, 8.0, 14.0 Hz, 1H), 6.08–6.15 (m, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 7.07 (t, *J* = 7.0 Hz, 1H), 7.17–7.21 (m, 3H), 7.25–7.32 (m, 4H), 7.54 (d, *J* = 8.0 Hz,1H,); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 30.8, 34.9, 37.6, 52.0, 124.5, 126.1, 126.6, 127.3, 127.5, 128.2, 128.5, 131.7, 132.5, 133.0, 137.2, 138.8,211.2.

Nitriles α,α-disubstituted

2-(2-Bromobenzyl)-3-(4-nitrophenyl)propanenitrile (**6d**). Compound **6d** was prepared according to the general procedure from β-keto ester **5d** (0.086 g, 0.21 mmol), LiCl (0.037 g, 0,86 mmol), Silica gel (0.084 g) and DMF (25 µL). The vial was sealed and heated at 150 °C, 220 W by 12 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 14-20% ethyl acetate/hexane, 2% gradient) to afford a pale yellow solid (0.061g, 85%), Mp = 85-86 °C. Anal. calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.67, H, 3.80, N, 8.12; Found: C, 55.38, H, 3.74, N, 8.40. IR (ATR), (cm^{-1}): 3080, 2957, 2868, 2237, 1612, 1537, 1470, 1350, 1024, 852, 762; ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.99 (dd, *J*= 10.0, 14.0 Hz, 1H), 3.08 (d, *J* = 8.0 Hz, 2H), 3.11-3.15 (m, 1H), 3.21-3.28 (m, 1H), 7.14-7-19 (m, 1H), 7.27-7.33 (m, 2H), 7.44 (d, *J* = 9.0 Hz, 2H,), 7.56 (d, *J* = 8.0 Hz, 1H,), 8.20 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 33.7, 38.0, 38.6, 120.1, 124.0, 124.3, 128.0, 129.4, 130.0, 131.5, 133.2, 135.6, 144.0, 147.4.

2-(2-Bromobenzyl)-3-(2-bromophenyl)propanenitrile (**6e**). Compound **6e** was prepared according to the general procedure from β-keto ester **5e** (0.10 g, 0.24 mmol), LiCl (0.042 g, 0.98 mmol), Silica gel (0.096 g) and DMF (25 µL). The vial was sealed and heated at 150 °C, 220 W by 30 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 1-2% ether/hexane, 1% gradient) to afford a white solid (0.083 g, 93%), Mp = 82-83 °C. Anal. calcd. for $C_{16}H_{13}Br_2N$: C, 50.69, H, 3.46, N, 3.69; Found: C, 50.89, H, 3.45, N, 3.87. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.05 (dd, *J* = 13.9, 9.7 Hz, 2H), 3.20(dd, *J* = 13.6, 5.6 Hz, 2H), 3.41(tt, *J* = 9.8, 5.7 Hz, 1H) 7.16 (td, *J* = 7.7, 1.8 Hz, 2H), 7.32(td, *J* = 7.5, 1.3 Hz, 2H), 7.38(dd, *J* = 7.6, 1.8 Hz, 2H), 7.57(dd, *J* = 8.0, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 32.6, 38.6, 120.6, 124.5, 127.8, 129.2, 131.7, 133.1, 136.1.

Ester α,α-disubstituted

Methyl 2-benzyl-3-phenylpropanoate (**12**). Compound **12** was prepared according to the general procedure from malonate **11** (0.090 g, 0.29 mmol), LiCl (0.051 g, 1.19 mmol), Silica gel (0.11 g) and DMF (25 µL). The crude product was purified by column chromatography (Silica gel 70-230 mesh, (13-15% ethyl acetate/hexane, 1% gradient) to afford a colorless oil (0.030 g, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.83-2.88 (m, 2H), 3.00-3.05 (m, 3H), 3.55 (s, 3H), 7.19-7.34 (m, 10H). Other spectroscopic data for **12** were already reported in the literature.[11]

Ketones α-monosubstituted

(E)-7-(4-Chlorophenyl)-1-(2-iodophenyl)hept-6-en-3-one (**8a**). Compound **8a** was prepared according to the general procedure from β-keto ester **7a** (0.36 g, 0.74 mmol), LiCl (0.13 g, 3.01 mmol), Silica gel (0.30 g) and DMF (50 µL). The vial was sealed and heated at 135 °C, 200 W by 11 min. The crude product was purified by column chromatography (15% ethyl acetate/hexane) to afford a yellow oil (0.28 g, 90%). Anal. calcd. for $C_{19}H_{18}ClIO$: C, 53.73, H, 4.27; Found: C, 53.63, H, 4.19. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.51-2.55 (m, 2H), 2.63 (t, *J* = 7.0, 7.2 Hz, 2H), 2.78 (t, *J* = 7.6, 7.8 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 6.19 (dt, *J* = 6.8 Hz, 1H), 6.38 (d, *J*= 15.8 Hz, 1H,),

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6.89-6.94 (m, 1H), 7.25-7.35 (m, 7H), 7.83 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 27.1, 34.8, 42.2, 42.9, 100.2, 127.2, 128.1, 128.5, 128.47, 128.6, 129.5, 129.7, 132.7, 135.9, 139.6, 143.5, 208.5.

(E)-1-(2-Iodophenyl)-7-phenylhept-6-en-3-one (**8b**). Compound **8b** was prepared according to the general procedure from β-keto ester **7b** (0.90 g, 1.96 mmol), LiCl (0.35 g, 8.04 mmol), Silica gel (0.78 g) and DMF (50 µL). The vial was sealed and heated at 135 °C, 200 W by 8 min. The crude product was purified by column chromatography (12-14% ethyl acetate/hexane, 1% gradient) to afford a yellow solid (0.70 g, 92%), Mp = 62-64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.39-2.44 (m, 2H), 2.50-2.53 (m, 2H), 2.65-2.69 (m, 2H), 2.91-2.95 (m, 2H), 6.06-6.14 (m, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 6.78-6.82 (m, 1H), 7.05-7.25 (m, 7H), 7.70-7-76 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 27.2, 34.8, 42.4, 42.9, 100.2, 126.0, 127.1, 128.0, 128.5, 128.5, 128.8, 129.7, 130.9, 137.4, 139.6, 143.58, 208.61; HRMS (DART): calcd for $C_{19}H_{19}IO$: 391.0559, found: 391.0559.

(E)-1-(2-Iodophenyl)-7-(4-nitrophenyl)hept-6-en-3-one (**8c**). Compound **8c** was prepared according to the general procedure from β-keto ester **7c** (0.18 g, 0.36 mmol), LiCl (0.066 mg, 1.56 mmol), Silica gel (0.14 g) and DMF (25 µL). The vial was sealed and heated at 120 °C, 200 W by 9 min. The crude was purified by column chromatography (Silica gel 70-230 mesh, 80% dichloromethane/hexane) to afford a yellow solid (0.094 g, 60%), Mp = 62-64 °C. Anal. calcd. for $C_{19}H_{18}INO_3$: C, 52.43, H, 4.17, N, 3.22; Found: C, 52.33, H, 4.21, N, 3.12. IR (ATR), (cm^{-1}): 3459, 3115, 2936, 1707, 1512, 1344, 757. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.55-2.58 (m, 2H), 2.63 (d, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 7.7 Hz, 2H), 3.02 (t, *J* = 7.7 Hz, 2H), 6.39 (dt, *J* = 6.3 Hz, 1H), 6.47 (d, *J* = 16.1 Hz, 1H), 6.87-6.91 (m, 1H), 7.26 (d, *J* = 6.3 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 27.1, 34.8, 41.8, 42.8, 100.2, 123.6, 124.0, 126.5, 128.1, 128.5, 129.1, 129.7, 134.2, 139.6, 143.4, 143.8, 146.6, 208.1.

Ethyl (E)-8-(2-iodophenyl)-6-oxooct-2-enoate (**8d**). Compound **8d** was prepared according to the general procedure from β-keto ester **7d** (0.075 g, 0.17 mmol), LiCl (0.032 g, 0.74 mmol), Silica gel (0.068 g) and DMF (25 µL). The vial was sealed and heated at 120 °C, 200 W by 10 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, (11-14% ethyl acetate/hexane) to afford a yellow oil (0.038 g, 50%). Anal. calcd. for $C_{16}H_{19}IO_3$: C, 49.76, H, 4.96, Found: C, 50.11, H, 5.05. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.31 (t, *J* = 7.2 Hz, 3H, CH_3), 2.47 – 2.63 (m, 3H), 2.72 – 2.78 (m, 2H), 2.86 – 3.21 (m, 3H), 4.21 (q, *J* = 2.0 Hz, 2H, CH_2), 5.85 (d, *J* = 18.6 Hz, 1H, =CH), 6.84 – 6.98 (m, 2H), 7.24 – 7.31(m, 2H), 7.84 (d, *J* = 7.0 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 14.3, 26.0, 40.8, 42.8, 60.3, 100.2, 122.2, 128.2, 128.6, 129.7, 139.6, 143.4, 147.1, 166.4, 207.4.

1-(2-Iodophenyl)-5-(4-nitrophenyl)pentan-3-one (**8e**). Compound **8e** was prepared according to the general procedure from β-keto ester **7e** (0.29 g, 0.61 mmol), LiCl (0.11 g, 2.69 mmol), Silica gel (0.24 g) and DMF (25 µL). The vial was sealed and heated at 120 °C, 200 W by 6 min. The crude product was purified by column chromatography (Silica gel 70-230 mesh, 10-15% ethyl acetate/hexane, 1% gradient) to afford a pale yellow solid (0.16 g, 64%), Mp = 72.7-74.9 °C. Anal. calcd. for $C_{17}H_{16}INO_3$: C, 49.90, H, 3.94, N, 3.42; Found: C, 50.24, H, 4.05, N, 3.62. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.74 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 1H), 2.99 – 3.05 (m, 4H), 6.92 (td, *J* = 7.5 Hz, 1.6 Hz, 1H), 7.16 – 7.29 (m, 2H), 7.35 7.80 (d, *J* = 8.5 Hz, 2H). 7.82 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 29.4, 34.7, 42.9, 43.3, 100.1, 121.7, 128.5, 129.2, 129.7, 139.6, 143.5, 146.5, 148.8, 207.5.

4-(2-Bromophenyl)butan-2-one (**10**). Compound **10** was prepared according to the general procedure from β-keto ester **9a** (0.10 g, 0.34 mmol), LiCl (0.061 g, 1.41 mmol), Silica gel (0.14 g) and DMF (25 µL) or **9b** (0.13 g, 0.45 mmol), LiCl (0.084 g, 1.97 mmol), Silica gel (0.18 g) and DMF (25 µL). The vial was sealed and heated at 135 °C, 200 W by 10 min (from **9a**) and 20 min (from **9b**). The crude product was purified by column chromatography (Silica gel 70-230 mesh, 2-10% ethyl acetate/hexane, 2% gradient) to afford a colorless oil (0.065 g, 84% from **9a** and 84.4 mg, 83% from **9b**); ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.16 (s, 3H), 2.76-2.80 (m, 2H), 2.99-3.03 (m, 2H), 7.05-7.09 (m, 1H), 7.20-7.28 (m, 2H), 7.53 (d, *J* = 8.3 Hz, 1H). Other spectroscopic data were already reported in the literature.[12]

General procedure for the synthesis of α,α-disubstituted β-keto-, α-cyanoesters and methyl malonate

To a suspension (~ 0.33 M) of potassium *tert*-butoxide (1.00 equiv) in anhydrous THF, under inert atmosphere, it was added the α-monosubstituted β-keto or α-cyano ester (1.00 equiv) dropwise. The reaction mixture was stirred during 10 min, the alkyl bromide (1.05-2.00 equiv) was then added slowly and the stirring continued for 12h at room temperature. After this time (monitored by TLC), the reaction mixture was quenched with brine and extracted with ethyl acetate, the organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The product was isolated by column chromatography on silica gel.

α,α-Disubstituted β-ketoesters

Methyl 2-benzyl-2-(2-bromobenzyl)-3-oxobutanoate (**3**). Compound **3** was prepared according to the general procedure from methyl 2-(2-bromobenzyl)-3-oxobutanoate (**9a**) (0.42 g, 2.05 mmol), potassium *tert*-butoxide (0.26 g, 2.25 mmol), benzyl bromide (0.57 g, 2.25 mmol) and THF (7 mL). The crude product was purified by flash column chromatography (1% diethyl ether/hexanes) to afford a pale yellow solid (0.41 g, 54%), Mp = 52-54 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.98 (s, 3H), 3.33(dd, *J* = 14.0, 4.0 Hz, 2H), 3.49 (dd, *J* = 15.1, 4.3 Hz, 2H), 3.67 (s, 3H), 7.07-7.12 (m, 3H), 7.21-7.28 (m, 5H), 7.56 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.9, 38.7, 40.2, 52.2, 65.7, 126.1, 127.0, 127.3, 128.3, 128.3, 130.1, 131.2, 133.1, 136.2, 136.5, 172.0, 204.7; HRMS (DART): calcd for $C_{19}H_{19}BrO_3$: 401.0752, found: 401.0753.

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Methyl (E)-2-(3-(2-iodophenyl)propanoyl)-5-(4-nitrophenyl)pent-4-enoate (**5a**). Compound **5a** was prepared according to the general procedure from methyl 2-(2-bromobenzyl)-3-oxobutanoate (**9a**) (1.73 g, 6.07 mmol), potassium *tert*-butoxide (0.75 g, 6.33 mmol), *p*-nitrobenzyl bromide (1.39 g, 6.38 mmol) and 15 mL THF. The crude product was recrystallized from ether (5 mL) to afford a white solid (1.43 g, 56%), Mp = 105.1-106.5 °C. Anal**.** calcd. for $C_{19}H_{18}BrNO_5$: C, 54.30, H, 4.32, N, 3.33; Found: C, 54.59, H, 4.16, N, 3.40. IR (ATR), (cm^{-1}): 3067, 2952, 2932, 2844, 1741, 1707, 1559, 1342, 1242, 967, 745, 526. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.03 (s, 3H), 3.29 (d, *J*=14.0 Hz, 1H), 3.42–3.56 (m, 3H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.20 (ddd, *J* = 8.0, 2.0 Hz, 1H), 7.26 (m, 3H), 7.58 (ddd, *J* = 8.0, 1.0 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.8, 39.0, 39.3, 52.4, 65.7, 123.3, 126.15, 127.5, 128.8, 131.0, 131.1, 133.3, 135.6, 144.3, 147.1, 171.5, 204.0.

1-Ethyl 6-methyl (E)-5-acetyl-5-(2-bromobenzyl)hex-2-enedioate (**5b**). Compound **5b** was prepared according to the general procedure from methyl 2-(2-bromobenzyl)-3-oxobutanoate (**9a**) (0.30 g, 1.02 mmol), potassium *tert*-butoxide (0.12 g, 1.07 mmol), ethyl (*E*)-4-bromobut-2-enoate (0.29 g, 1.12 mmol) and 3.1 mL THF. The crude product was purified by flash column chromatography (18-24% ethyl acetate/hexanes, 2% gradient) to afford a yellow oil (0.23 g, 55%). Anal**.** calcd. for $C_{18}H_{21}BrO_5$: C, 54.42, H, 5.33. Found: C, 54.71, H, 5.28. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.27 (t, *J* = 7.02 Hz, 3H), 2.16 (s, 3H), 2.69-2.82 (m, 2H), 3.48 (dd, *J* = 14.6 Hz, 2H), 3.74 (s, 3H), 4.17 (q, *J* = 7.02 Hz, 2H), 5.82 (d, *J* = 15.4 Hz, 1H), 6.77-6.85 (m, 1H), 7.07-7.11 (m, 1H), 7.16-7.24 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$,100 MHz), δ (ppm): 14.2, 27.7, 35.3, 37.4, 52.6, 60.4, 64.3, 124.9, 126.0, 127.4, 128.7, 131.4, 133.2, 135.7, 142.5, 165.7, 171.5, 203.3.

Methyl (E)-2-acetyl-2-(2-bromobenzyl)-5-phenylpent-4-enoate (**5c**). Compound **5c** was prepared according to the general procedure from methyl 2-(2-bromobenzyl)-3-oxobutanoate (**9a**) (0.62 g, 2.2 mmol), potassium *tert*-butoxide (0.28 g, 2.4 mmol), 3-bromo-1-phenyl-1-propene (0.50 g, 2.4 mmol) and 4 mL THF. The crude product was purified by column chromatography (1-5% diethyl ether/hexanes, 1% gradient) to afford a yellow solid (0.49 g, 57%), Mp = 78.7 – 79.7 °C. **IR** (ATR), (cm^{-1})**:** 3061; 3023, 2950, 2918, 1745 (C=O, ester), 1712 (C=O, ketone),1432, 1355, 1275, 1217, 1196, 1180, 1039, 758, 736. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.15 (s, 3H), 2.73 – 2.84 (m, 2H), 3.46 – 3.56 (m, 2H), 3.71 (s, 3H), 6.06 – 6.14 (m, 1H), 6.41 (d, 1H), 7.06 – 7.09 (m, 1H),7.19 – 7.24 (m, 3H), 7.26 – 7.32 (m, 4H), 7.54 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 27.9, 36.4, 37.3, 52.4, 64.8, 124.0, 126.0, 126.2, 127.3, 127.4, 128.5, 128.5, 131.4, 133.1, 133.9, 136.3, 137.0,172.0, 204.1. HRMS (DART): calcd for $C_{21}H_{21}BrO_3$: 401.0752, found: 401.0753.

α,α-Disubstituted α-cyanoesters

Methyl 2-(2-bromobenzyl)-2-cyano-3-(4-nitrophenyl)-propanoate (**5d**). Compound **5d** was prepared according to the general procedure from methyl 3-(2-bromophenyl)-2-cyanopropanoate (0.3 g, 0.78 mmol), potassium *tert*-butoxide (0.090 g, 0.83 mmol), *p*-nitrobenzyl bromide (0.19 g, 0.90 mmol) and 2.4 mL THF. The crude product was purified by flash column chromatography (10-30% ethyl acetate/hexanes, 5% gradient) to afford a yellow solid (0.11 g, 36 %), Mp =129 – 131 °C. Anal**.** calcd. for $C_{18}H_{15}BrN_2O_4$: C, 53.62, H, 3.75, N, 6.95; Found: C, 53.87, H, 3.83, N, 6.68. IR (ATR), (cm^{-1}): 3111, 3082, 2959, 2924, 2855, 2250, 1748, 1605, 1514, 1346, 1229, 1057, 1045, 1024, 854, 840, 748, 702. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.14 (d, *J* = 13.5 Hz, 1H), 3.48-3.59 (m, 3H), 3.67 (s, 3H), 3.72 (s, 3H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 41.7, 41.8, 51.8, 53.7, 117.5, 123.7, 125.7, 127.8, 129., 131.1, 131.5, 133.5, 133.5, 141.4, 147.7, 168.0.

Methyl 2-(2-bromobenzyl)-3-(2-bromophenyl)-2-cyanopropanoate (**5e**). Compound **5d** was prepared according to the general procedure from methyl cyanoacetate (0.42g, 4.20 mmol), potassium *tert*-butoxide (0.48 g, 4.20 mmol), *p*-nitrobenzyl bromide (1.00 g, 4.00 mmol) and 16.8 mL THF. The crude product was purified by flash column chromatography (30-80% ethyl methylene chloride/hexanes, 10% gradient) to afford a white solid (0.45 g, 25%), Mp = 95- 96° C. Anal**.** calcd. for $C_{18}H_{15}Br_2NO_2$: C, 49.46, H, 3.46, N, 3.20; Found: C, 49.25, H, 3.38, N, 3.38. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.56 (q, *J* = 14.2 Hz, 4H), 3.76 (s, 3H), 7.17 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.6 Hz 2H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 40.9, 51.0, 53.8, 117.8, 125.9, 127.7, 129.5, 131.3, 133.3, 134.0, 168.5.

α,α-Disubstituted methyl malonate

Dimethyl 2,2-dibenzylmalonate (**11**). Compound **11** was prepared according to the general procedure using diethyl malonate (0.40 g, 3.03 mmol), potassium *tert*-butoxide (0.68 g, 6.06 mmol), benzyl bromide (1.20 g, 6.67 mmol) and 20.9 mL THF The crude product was purified by column chromatography (1-6% ethyl acetate/hexanes, 1% gradient) to afford white solid (0.60 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.29 (s, 4H), 3.69 (s, 6H), 7.21 (d, *J* = 7.4 Hz, 4H), 7.32 (m, 5H). Other spectroscopic data it was reported in literature.[13]

General procedure for the synthesis of α-mono- β-ketoesters

Method 1: To a suspension (~ 0.50 M) of sodium hydride (1.05 equiv) in anhydrous THF, under inert atmosphere, it was added the β-keto ester (1 equiv) dropwise. The reaction mixture was stirred by 10 min, next refluxed and then the alkyl bromide (1.05 equiv) was added slowly. The reaction mixture was stirred over night at 70° C. After this time, it was quenched with brine and extracted with ethyl acetate, the organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure.

Method 2: In the same way than the ***Method 1***, but in this case it was used potassium *tert*-butoxide as base and reaction mixture was stirred for 12 h at rt.

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Methyl (E)-5-(4-chlorophenyl)-2-(3-(2-iodophenyl)propanoyl) pent-4-enoate (**7a**). Compound **7a** was prepared according to ***Method 1*** from methyl 5-(2-iodophenyl)-3-oxopentanoate (618.4 mg, 1.84 mmol), sodium hydride (0.08 g, 1.94 mmol), *(E)*-1-chloro-4-(3-chloroprop-1-en-1-yl)benzene (0.37 g, 1.94 mmol) and 3.7 mL THF in reflux by 18 h. The crude product was purified by column chromatography (10-16% ethyl acetate/hexanes, 2% gradient), affording a yellow oil (0.46 g, 52%). Anal**.** calcd. for $C_{12}H_{13}BrO_3$: C, 52.25, H, 4.18; Found: C, 51.88, H, 4.08. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.79 (td, *J* = 7.2, 1.0 Hz, 2H), 2.82-2.88 (m, 1H), 2.96 (dd, *J* = 6.6, 6.4 Hz, 1H), 3.02-3.07 (m, 2H), 3.67 (t, *J* = 7.3 Hz, 1H), 3.74 (s, 3H), 6.11 (dt, *J* = 7.4, 7.2 Hz 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.90-6-94 (m, 1H), 7.24-7.31 (m, 6H), 7.83 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 31.5, 34.5, 42.5, 52.5, 58.4, 100.1, 126.3, 127.5, 128.2, 128.5, 128.7, 129.9, 131.7, 133.1, 133.5, 135.5, 139.6, 143.1, 169.4, 203.2.

Methyl (E)-2-(3-(2-iodophenyl)propanoyl)-5-phenylpent-4-enoate (**7b**). Compound **7b** was prepared according to ***Method 2*** from methyl (*E*)-3-oxo-7-phenylhept-6-enoate (0.19 g, 0.81 mmol), potassium *tert*-butoxide (0.11g, 0.89 mmol), 2-iodobenzyl bromide (0.27 g, 0.89 mmol) and 4 mL THF. Purification by column chromatography (10-14% ethyl acetate/hexanes, 1% gradient), afforded a yellow oil (0.27 g, 75%). ^{1}H NMR (400MHz, $CDCl_3$) δ(ppm) 2.43 (q, *J* = 6.9 Hz, 2H,), 2.45-2.53 (m, 1H), 2.69 (dt, *J* = 7.3 Hz, 1H), 3.20 (d, *J* = 7.5 Hz, 2H), 3.59 (s, 3H), 3.94 (t, *J* = 7.5 Hz, 1H), 6.08 (dt, *J* = 6.8 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H,), 6.8-6.8 (m, 1H), 7.10-7.21 (m, 7H), 7.72 (d, *J* = 8.0 Hz, 1H,); ^{13}C NMR ($CDCl_3$, 100 MHz), δ(ppm) 26.8, 38.7, 42.6, 52.5, 58.2, 100.0, 126.1, 127.2, 128.3, 128.5, 128.6, 128.7, 130.9, 131.1, 137.4, 139.7, 169.1, 203.4; HRMS (DART): calcd for $C_{21}H_{21}IO_3$: 449.0614, found: 449.0615.

Methyl (E)-2-(3-(2-iodophenyl)propanoyl)-5-(4-nitrophenyl)pent-4-enoate (**7c**). Compound **7c** was prepared according to ***Method 2*** from methyl 5-(2-iodophenyl)-3-oxopentanoate (0.49 g, 1.48 mmol), (*E*)-1-(3-bromoprop-1-en-1-yl)-4-nitrobenzene (0.39 g, 1.62 mmol), potassium *tert*-butoxide (0.20 g, 1.62 mmol) and 4.9 mL THF. Purification by column chromatography (silica gel 70-230 mesh, 20% ethyl acetate/hexane) afforded a yellow oil (0.25 g, 34%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.80-2.88 (m, 3H), 2.97 (dd, *J* = 6.02, 8.53 Hz, 1H), 3.02-3.06 (m, 2H), 3.69 (t, 7.4 Hz, 1H), 3.74 (s, 3H), 6.32 (dt, *J* = 7.37, 15.8, Hz, 1H,), 6.53 (d, *J* = 15.8 Hz, 1H,), 6.88-6.93 (m, 1H), 7.25-7.26 (m, 1H), 7.44 (d, *J* = 8.8 Hz, 2H,), 7.81 (d, *J* = 7.5 Hz, 1H,), 8.17 (d, *J* = 8.8 Hz, 2H,); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 31.5, 34.4, 42.4, 52.64, 58.0, 100.1, 123.9, 126.7, 128.5, 129.8, 130.9, 131.0, 139.5, 142.9, 143.3, 146.8, 169.1, 202.75; HRMS (DART): calcd for $C_{21}H_{20}INO_5$: 494.0464, found: 494.0470.

1-Ethyl 6-methyl (E)-5-(3-(2-iodophenyl)propanoyl)hex-2-enedioate (**7d**). Compound **7d** was prepared according to ***method 2*** from methyl 5-(2-iodophenyl)-3-oxopentanoate (0.25 g, 0.75 mmol), potassium *tert*-butoxide (0.09 g, 0.79 mmol), 3-bromo-1-phenyl-1-propene (0.21 g, 0.82 mmol) and 1.3 mL THF. The crude product purified by column chromatography (10-30% ethyl acetate/hexanes, 5% gradient) afforded a yellow oil (0.17 g, 57%). Anal. calcd. for $C_{18}H_{21}IO_5$: C, 48.66, H, 4.76, Found: C, 48.84, H, 4.83. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.30 (t, *J* = 7.2 Hz, 3H), 2.74–2.87 (m, 3H), 2.94 – 3.07 (m, 3H), 3.64 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 4.20 (q, *J* = 7.0 Hz, 2H), 5.88 (d, *J* = 15.6 Hz, 1H), 6.80-6.88 (m, 1H), 6.90–6.94 (m, 1H), 7.23–7.31 (m, 2H), 7.83 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 14.2, 30.2, 34.5, 42.3, 52.7, 57.2, 80.4, 100.0, 123.9, 128.2, 128.5, 129.8, 139.6, 142.9, 143.8, 165.9, 166.8, 202.2.

Methyl 5-(2-iodophenyl)-2-(4-nitrobenzyl)-3-oxopentanoate (**7e**). Compound **7e** was prepared according to ***Method 2*** from methyl 5-(2-iodophenyl)-3-oxopentanoate (0.55 g, 1.67 mmol), potassium *tert*-butoxide (0.26 g, 2.28 mmol), *p*-nitrobencyl bromide (0.26 g, 2.28 mmol) and 6.3 mL THF. The crude product was purified by column chromatography (1-5% diethyl ether/hexanes, 1% gradient) to afford a yellow oil (0.50 g, 65%). Anal. calcd. for $C_{19}H_{18}INO_5$: C, 48.84, H, 3.88, N, 3.00; Found: C, 49.20, H, 4.05, N, 3.11. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.64–2.73 (m, 1H), 2.89–3.01 (m, 3H), 3.23-3.35 (m, 2H), 3.69 (s, 3H,), 3.85 (t, *J* = 7.6 Hz, 1H), 6.91 (td, *J* = 7.5, 1.8 Hz, 1H), 7.19–7.34 (m, 4H), 7.80 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 33.5, 34.3, 42.8, 52.7, 59.5, 100.0, 123.8, 128.4, 129.7, 129.8, 139.5, 142.7, 145.7, 146.8, 166.6, 202.3.

Methyl 2-(2-bromobenzyl)-3-oxobutanoate (**9a**). Compound **9a** was prepared according to ***Method 2*** from methyl acetoacetate (1.00 g, 8.44 mmol), potassium *tert*-butoxide (1.00 g, 8.86 mmol), *o*-bromobenzyl bromide (2.40 g, 9.28 mmol) and 25 mL THF The crude product was purified by column chromatography (1-15% ethyl acetate/hexanes, 1% gradient) to afford yellow oil (2.10 g, 88%). Anal. calcd. for $C_{12}H_{13}BrO_3$: C, 50.55, H, 4.60; Found: C, 50.38, H, 4.42. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.27 (s, 3H), 2.32 (m, 2H), 3.73 (s, 3H), 4.03 (dd, *J* = 7.2 Hz, 1H), 7.11-7.15 (m, 1H), 7.23-7.31 (m, 2H), 7.57 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 29.8, 34.5, 58.7, 124.4, 127.6, 128.6, 131.7, 133.0, 137.4, 169.3, 202.2.

Ethyl 2-(2-bromobenzyl)-3-oxobutanoate (**9b**). Compound **9b** was prepared according to ***Method 2*** from ethyl acetoacetate (4.90 g, 39.0 mmol), potassium *tert*-butoxide (4.60 g, 39.0 mmol), *o*-bromobenzyl bromide (9.90 g, 39.0 mmol) and 130 mL THF. Crude product was purified by column chromatography (01-15% ethyl acetate/hexanes, 1% gradient) to afford yellow oil (9.60 g, 82%).); ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.19 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.25 (d, *J* = 7.4 Hz, 2H), 3.96 (t, *J* = 7.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 7.02-7.05 (m, 2H), 7.24 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 1H). Other spectroscopic data were already reported in the literature.[14]

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Table of contents Entry

An alternative microwave-assisted Krapcho type reaction of α-Mono- and α,α-Disubstituted β-Keto- and α-Cyanoesters was efficiently performed on a Silica Gel Bed.