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An efficient green MCR protocol for the stereoselective synthesis of β-acetamido ketones catalyzed by Selectfluor™

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ABSTRACT

An efficient, green, room temperature process for the stereoselective synthesis of β-amido ketones employing a one-pot multi-component reaction of aromatic aldehydes, α-substituted or α-unsubstituted ketones, an acid chloride, and a nitrile in presence of catalytic amount of Selectfluor™ is described. The process offers advantages such as high *anti*-selectivity, shorter reaction time, energy efficiency, and simple work-up.

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Fig. 1), commercially known as Selectfluor F-TEDA-BF_4, is a versatile reagent used for electrophilic fluorination of organic compounds.[1] Its stability, non-volatility, commercial availability, and user-friendliness make it as an ideal green reagent. Toxicology studies revealed that Selectfluor™ is relatively harmless and did not show any signs of mutagenic or carcinogenic activity.[1a] The ecological and environmental effects of Selectfluor™ such as its impact on algae growth, sewage-sludge respiration, and the toxicity on several species were found to be within the acceptable level.[1a] Intense research has generated applications of Selectfluor™ as a versatile mediator or catalyst for reactions[2] such as selective iodination, bromination, chlorination, nitration, thiocyanation, allylstannation of aldehydes and imines, cleavage of *p*-methoxybenzylidene (PMP), tetrahydropyranyl (THP), and 1,3-dithiane-protecting groups, and rearrangements of bicyclic iodides. Its efficiency as a catalyst is also demonstrated in the regioselective ring opening of epoxides and [4+2] cycloaddition reactions between imines and cyclic enol ethers.[2]

Devising reactions that achieve multi-bond formation in one-step operation is becoming one of the major challenges in step-economic synthesis. As an enabling technology, multi-component reactions (MCRs) make it possible to access target molecules with

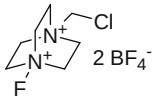

Figure 1. 1-Chloromethyl-4-fluoro-1, 4-diazoniabicyclo [2.2.2] octane bis (tetrafluoroborate) (Selectfluor™).

greater efficiency and atom economy.[3,4] β-Acetamido ketones are important building blocks for the synthesis of molecules such as 1,3-amino alcohols[5] and structural scaffolds found in natural nucleoside peptide antibiotics such as nikkomycins or neopolyoxins.[6] Recently it is reported that β-acetamido ketones can act as α-glucosidase inhibitors.[7] Its structural and bioactive properties led to the generation of a variety of processes employing different catalyst systems and reaction conditions.[8] In continuation of our efforts in introducing green methodologies for the synthesis of small drug-like molecules with several degrees of structural diversity, one of us had earlier reported the use of Mont. K10 for the stereoselective synthesis of β-acetamido ketones.[8a] Encouraged by the literature reports on the emergence of Selectfluor™ as a green catalyst for core organic transformations,[9] we proposed to examine the use of Selectfluor™ in the stereoselective synthesis of β-acetamido ketones following the procedure reported in our Mont K10 process[8a] (Scheme 1).

As an initial screen, we have employed 5 mol % of Selectfluor™ and the reaction was done at the reflux temperature of acetonitrile, which resulted in the formation of the corresponding β-acetamido ketone. The yield was disappointing because it was significantly

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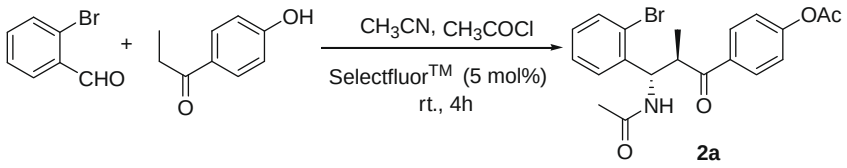


Scheme 1.

Table 1
Selectfluor™-catalyzed one-pot multi-component synthesis of β-acetamido ketones

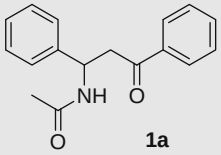
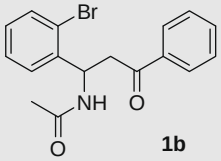
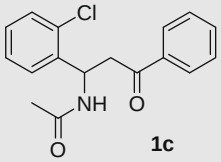
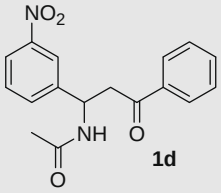
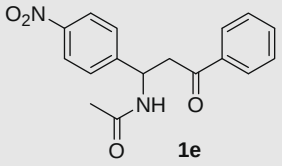
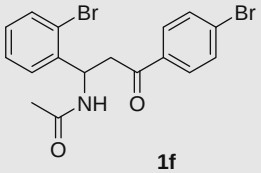
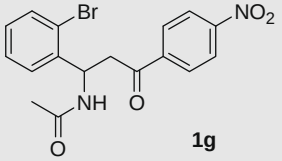
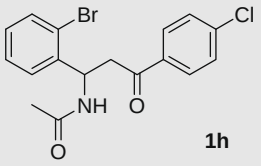
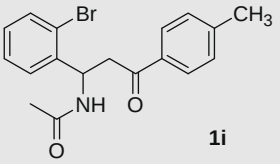
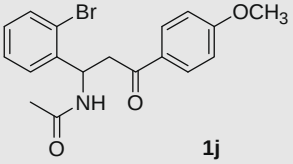
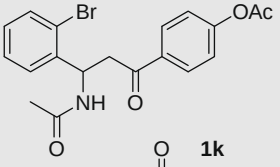
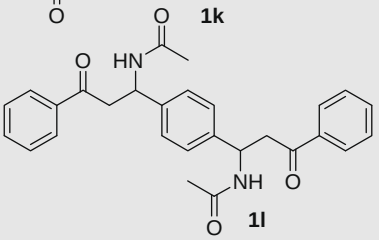
Entry	β-Acetamido ketone	% Yield[a]
1	 **1a**	74
2	 **1b**	85
3	 **1c**	79
4	 **1d**	71
5	 **1e**	75
6	 **1f**	85
7	 **1g**	89
8	 **1h**	87

Table 1 (*continued*)

Entry	β-Acetamido ketone	% Yield[a]
9	 **1i**	77
10	 **1j**	90
11	 **1k**	88
12	 **1l**	75

[a] Based on the weight of the isolated pure products.

low compared to that reported in the previous paper.[8a] We had then carried out the same reaction at room temperature and observed that the desired reaction had taken place to form the corresponding β-acetamido ketones in very good yield. By optimizing the reaction conditions, it was found that 5 mol % of Selectfluor™ was enough for the completion of the reaction with less reaction time (2–4 h). We have explored the generality of this Selectfluor™-mediated β-acetamido ketone synthesis with various substrates. Table 1 lists several of the β-acetamido ketones prepared. All the reactions afforded the corresponding β-acetamido ketone in good to excellent yields irrespective of the position of the substituents present in aldehyde or ketone. Work-up was simple and for all the substrates, the following procedure was adopted. Once the reaction was deemed complete (no further conversion in TLC), the reaction mixture was diluted with water and the precipitated β-acetamido ketone was collected by filtration. In all cases, simple washing with water delivered the desired product in very pure form.[10,11]

Given the successful development of this new procedure, we were prompted to study the stereochemical outcome of the product formation with α-substituted ketones. As shown in Table 2, reactions of α-substituted ketones such as 2-hydroxy propiophenone, 4-hydroxy propiophenone, ethyl methyl ketone, cyclohexanone, and acetyl acetone with various substituted aldehydes in

Table 2
Selectfluor™-catalyzed one-pot multi-component synthesis of β-acetamido ketones from α-substituted ketones

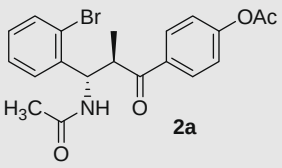
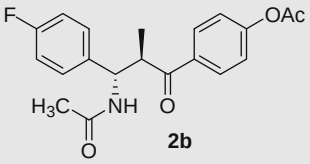
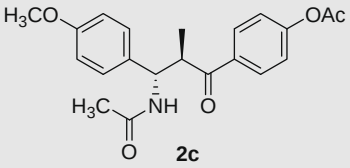
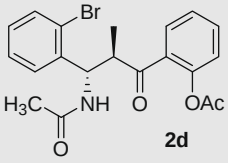
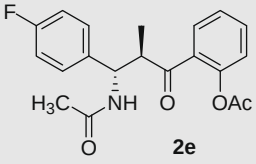
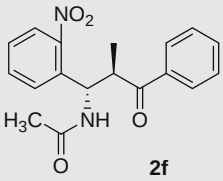
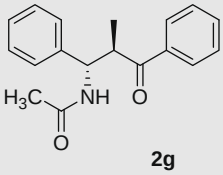
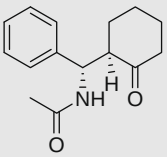
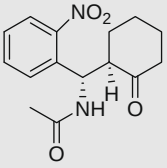
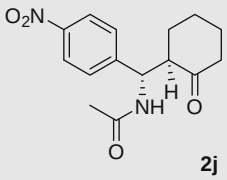
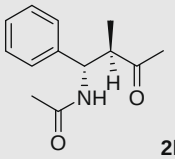
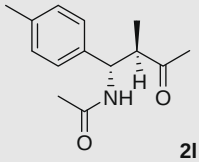
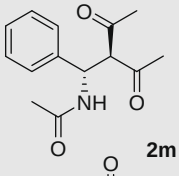
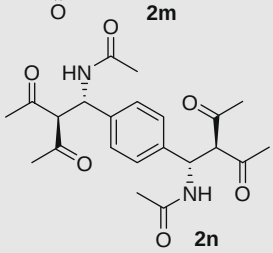
Entry	β-Acetamido ketone	% Yield[a] (*syn*:*anti*)[b]
1	 **2a**	72 (10:90)
2	 **2b**	68 (13:87)
3	 **2c**	71 (12:88)
4	 **2d**	73 (10:90)
5	 **2e**	69 (13:87)
6	 **2f**	74 (13:87)
7	 **2g**	60 (16:84)
8	 **2h**	60 (14:86)
9	 **2i**	69 (17:87)

Table 2 (*continued*)

Entry	β-Acetamido ketone	% Yield[a] (*syn*:*anti*)[b]
10	 **2j**	55 (11:89)
11	 **2k**	68 (12:88)
12	 **2l**	73 (13:87)
13	 **2m**	71 (38:62)
14	 **2n**	62 (15:85)

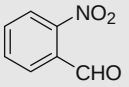
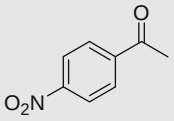
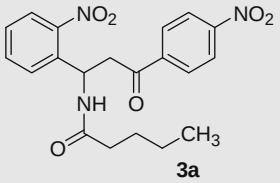
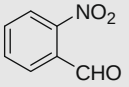
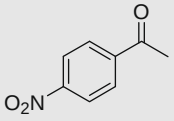
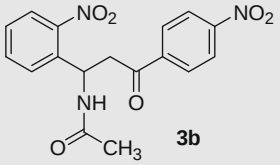
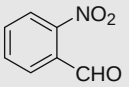
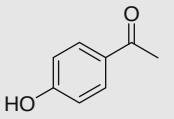
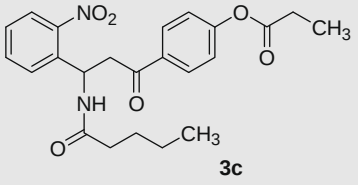
[a] Based on the isolated amount of the *anti*-diastereomer. Stereochemistry assigned based on the coupling constant for the methine proton as well as on the comparison with the previously reported spectral data.[8a]
[b] *Syn*/*anti* ratio determined from ^{1}H NMR of the crude mixture.

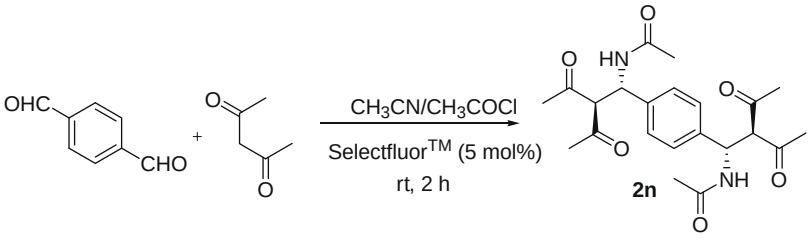
presence of Selectfluor™ as catalyst resulted in the selective formation of the *anti*-diastereomers in moderate to good yield. The isolation of the products was done by aqueous work-up followed by silica gel chromatography using petroleum ether/ ethyl acetate in the ratio 2:1.[12,13]

The application of this new synthetic protocol was extended to the reactions of di-aldehydes with α-unsubstituted ketones (Table 1, entry 12) and α-substituted ketones (Table 2, entry 14) under the same conditions. The reaction proceeded smoothly under room temperature and the corresponding bi-condensation products were isolated in comparable yield. The reactions of terephthalaldehyde with acetyl acetone yielded the *anti*-diastereomer of a bi-condensed β-acetamido ketone (Scheme 2, Table 2, entry 14). The work-up procedure was easier since no column purification was required. Here the precipitate obtained after the aqueous work-up on washing with diethyl ether yielded analytically pure products.[14]

The scope of the reaction was also investigated with aliphatic aldehydes and α,β-unsaturated aldehydes. All our attempts with aliphatic aldehydes such as formaldehyde, acetaldehyde, butyraldehyde, and 2-methylpropionaldehyde, and α,β-unsaturated

Table 3
Selectfluor™-catalyzed one-pot multi-component synthesis of β-acetamido or amido ketones with propionyl chloride and valeronitrile[16]

Entry	Aldehyde	Ketone	Acid chloride	Nitrile	β-Acetamido ketone	Yield
1			CH_3COCl	$CH_3(CH_2)_3CN$	 **3a**	81
2			CH_3CH_2COCl	CH_3CN	 **3b**	84
3			CH_3CH_2COCl	$CH_3(CH_2)_3CN$	 **3c**	81



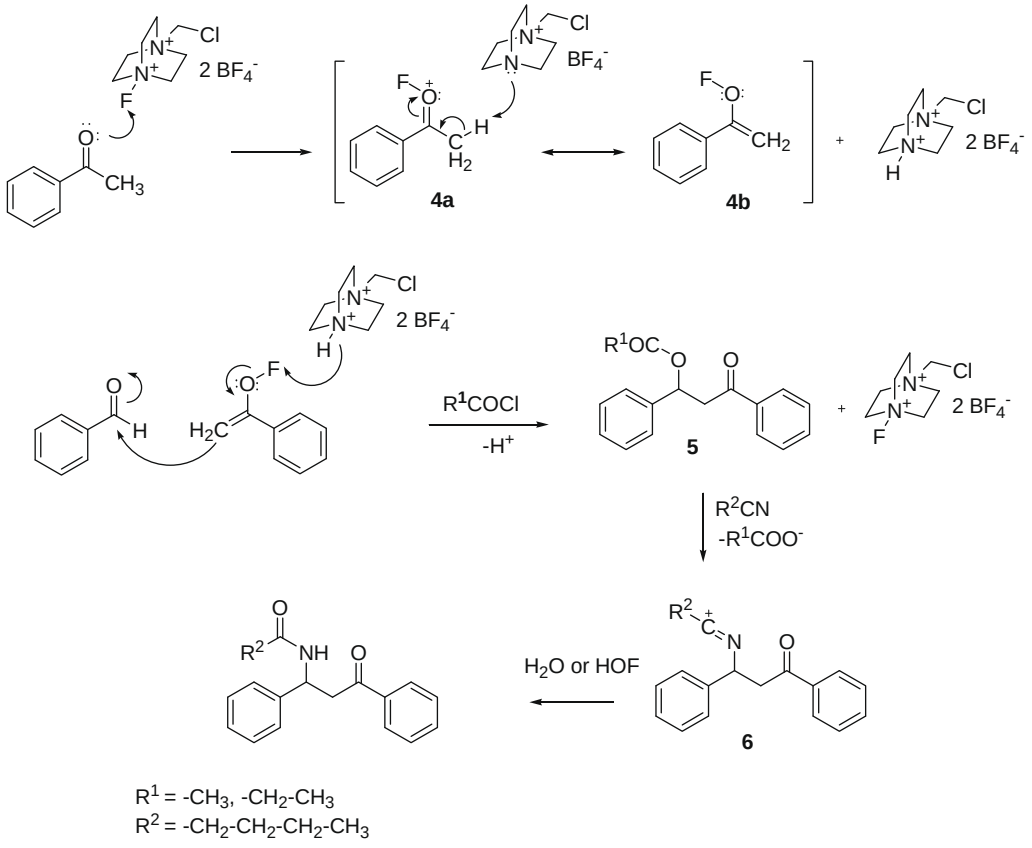
Scheme 2.

aldehydes such as crotonaldehyde and α-methylcinnamaldehyde failed to yield the corresponding β-acetamido or amido ketones.[15]

To elucidate the roles of acid chloride and nitrile in the reaction and for guaranteeing broad substrate scope, we further examined this reaction with different nitriles and acid chlorides. As shown in Table 3, Selectfluor™ is also extremely effective for β-amido ketone synthesis with nitriles and acid chlorides other than acetonitrile and acetyl chloride. The reaction of 2-nitrobenzaldehyde and 4-nitroacetophenone in valeronitrile in presence of acetyl chloride and Selectfluor™ at room temperature afforded the β-valeramido ketone (**3a)** in 81% yield**.** The same reaction when carried out with propionyl chloride and acetonitrile afforded β-acetamido ketone (**3b**) in 84% yield. Similarly, the reaction of 2-nitrobenzaldehyde with 4-hydroxy-acetophenone in valeronitrile in presence of propionyl chloride and Selectfluor™ afforded the β-valeramido ketoester (**3c)** in 81% yield.

Based on the observations presented above, a plausible mechanism as shown in Scheme 3 is put forward to explain the formation of β-acetamido or amido ketones under the catalysis of Selectfluor™. It is proposed that Selectfluor™ is acting as a Lewis acid for this reaction as in the case of the cleavage of *p*-methoxybenzylidene (PMP), tetrahydropyranyl (THP), and 1,3-dithiane-protecting groups by Selectfluor™ reported by Wong et al.[9a] Fluorine present in the $\equiv N^+F$ group may initiate the formation of a fluoro derivative of an enol **4b** in accordance with the mechanism of acid-catalyzed enol formation. Subsequent reactions of this fluoroenol with aldehyde and acid chloride may generate a β-acyloxy ketone **5**. The acyloxy group of **5** is then displaced by the nucleophilic nitrogen of the nitrile to provide a stable cation intermediate **6**, which on further reaction with water[8g] or other reactive species such as HOF[9a] formed during the reaction may lead to the formation of β-acetamido or amido ketones.

In conclusion, we have developed an efficient protocol for the stereoselective synthesis of β-acetamido ketones under very mild conditions using Selectfluor™ as catalyst. The amount of Selectfluor™ used for this reaction is truly catalytic (5 mol %), which is very less compared to the procedures documented in the literature. Because of the high solubility of Selectfluor™ in water, a simple aqueous work-up is enough to obtain most of the β-acetamido ketones in analytically pure form. The origin of diastereoselectivity is currently under investigation.



Scheme 3. Plausible mechanism for Selectfluor™ catalysis in the synthesis of β-acetamido or amido-ketones.

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Supplementary data

Supplementary data (spectral data of the new compounds, ^{1}H NMR spectrum of all new compounds, ^{13}C NMR spectrum for compounds **1g–i**, **2d–e**, **2n,** and **3a–c,** FT-IR spectrum for compounds **1b**, **1f–j**, **1l**, **2a–e**, **2m–n,** and **3a–c**, MS spectrum for compounds **1b**, **1f–i**, **1k–l**, **2n,** and **3a–c**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.022.

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10. *Typical experimental procedure for the β-acetamido ketone from α-unsubstituted ketones* (**1b**): A 100 mL two-necked round-bottomed flask was charged with anhydrous acetonitrile (25 mL), 2-bromobenzaldehyde (0.185 mg, 1 mmol),

acetophenone (0.120 mg, 1 mmol), acetyl chloride (0.5 mL), and Selectfluor™ (0.018 g, 5 mol % by weight of 2-bromobenzaldehyde) under constant stirring at room temperature. The reaction was monitored by TLC and was found to be complete after 4 h. The reaction mixture was then poured into distilled water and kept for 1 h. The precipitated colorless solid was collected on a filter, washed with distilled water (3 × 25 mL), and dried under vacuum. The vacuum-dried solid was then washed with anhydrous diethyl ether (2 × 15 mL) and air dried to yield pure β-acetamido ketone derivative. Mp 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91–7.88 (d, J = 7.38 Hz, 2H), 7.58–7.56 (d, J = 7.38 and 13.59 Hz, 2H), 7.45–7.41 (t, 3H), 7.1 (s, 3H), 7.08–6.99 (m, 2H), 5.79–5.73 (dd, J = 5.67 and 13.24 Hz, 1H), 3.81–3.73 (dd, J = 5.84 and 16.68 Hz, 1H), 3.48–3.40 (dd, J = 5.37 and 16.68 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 169.7, 133.48, 129.39, 129.22, 128.4, 127.7, 123.91, 50.18, 42.3, 23.43; FT-IR (KBr) γ_{max} 3283.9, 1679.5, 1646.4, 1533.59, 1474, 1401.1, 1361.33, 1256.25, 1228.13, 990.06, 758.01, 691.71, 645.3 cm^{-1}; MS m/z 266 (M+1−Br), 207, 184, 146, 105, 77, 43.

11. The spectral data for the compounds **1a**, **1c–e,** and **2f–l** are reported previously, see Ref. 8a. The values are well in agreement with the same obtained by the synthesis of these compounds following the new procedure.
12. *Typical experimental procedure for the β-acetamido ketone from α-substituted ketones* (**2m**): To a solution of benzaldehyde (0.212 g, 2 mmol), acetyl acetone (0.200 g, 2 mmol), and acetyl chloride (1 mL) in anhydrous acetonitrile (25 mL), Selectfluor™ (0.036 g, 5 mol %) was added and stirred for 2 h at room temperature (completion of the reaction was monitored by TLC). It was then poured into crushed ice and the residue obtained was filtered, washed with water (3 × 25 mL), and dried under vacuum. The dried residue obtained was then purified by column chromatography on silica gel with petroleum ether–ethyl acetate (2:1). The solid obtained was crystallized from ethyl acetate–petroleum ether (1:2) to yield the β-acetamido ketone. Mp 124–125 °C; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 7.22–7.30 (5H, m), 6.97–6.94 (d, J = 9.21 Hz, 1H), 5.88–5.83 (dd, J = 5.59, 9.36 Hz, 1H), 4.29–4.27 (d, J = 5.43 Hz, 1H), 2.27 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H); FT-IR (KBr) γ_{max} 3355, 1697, 1643, 1527, 1411, 1365, 1195, 1103, 756, 709, 671, 578, 532, 462 cm^{-1}; MS m/z 248 (M+1), 204, 170, 154, 148, 136, 106.
13. The spectral data for the compounds **2f–l** are reported previously, see Ref. [8a]. The values are well in agreement with the same obtained by the synthesis of these compounds following the new procedure.
14. *Typical experimental procedure for the synthesis of β-acetamido ketones from di-aldehyde* (**1l**): To a solution of terephthalaldehyde (0.084 g, 0.63 mmol), acetophenone (0.150 g, 1.26 mmol, two equivalents), and acetyl chloride (1 mL) in acetonitrile (20 mL), Selectfluor™ (0.022 g, 0.063 mmol, 5 mol % by weight of acetophenone) was added and stirred at room temperature for 2 h. Then the mixture was poured into crushed ice and stirred for 30 min. The precipitate formed was filtered, washed with water (3 × 25 mL), and dried under vacuum. The solid obtained was then washed with anhydrous diethyl ether (3 × 15 mL) to yield pure β-acetamido ketone. Mp 190–191 °C; ^{1}H NMR, (300 MHz, DMSO-d_6) δ 8.30–8.27 (d, J = 7.85 Hz, 2H), 7.96–7.94 (d, J = 7.40 Hz, 2H), 7.66–7.61 (t, 4H), 7.54–7.49 (t, 2H), 7.29 (s, 4H), 5.35–5.33 (d, J = 5.75 Hz, 2H), 3.56–3.48 (dd, J = 8.6 Hz and 17.20 Hz, 2H), 3.41–3.39 (d, J = 5.52 Hz, 2H), 2.08 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.05, 168.22, 141.55, 136.50, 133.20, 128.69, 127.98, 126.51, 48.56, 44.48, 30.66, 22.59; MS m/z 457 (M+1), 337, 279, 237, 157, 105; FT-IR (KBr) γ_{max} 3251, 1686, 1644, 1596, 1547, 1449, 1408, 1363, 1307, 1266, 1208, 1121, 1094, 1000, 836, 768, 692, 636, 607, 579, 556 cm^{-1}.
15. The mixture obtained from the reactions using aliphatic aldehydes upon aqueous work-up followed by silica gel chromatography afforded the starting aldehydes and ketones. The aqueous work-up of the mixture obtained from the reaction of α-methylcinnamaldehyde with 4-nitroacetophenone afforded a product with m/z 222.2 which corresponds to the addition of acetyl chloride to the aldehyde.
16. *Spectral data for* **3a**: ^{1}H NMR, (400 MHz, $CDCl_3$) δ 8.31–8.28 (d, J = 8.88 Hz, 2H), 8.11–8.09 (d, J = 8.88 Hz, 2H), 7.95–7.93 (t, 1H), 7.70–7.68 (d, J = 7.2 Hz, 1H), 7.61–7.58 (t, 1H), 7.45–7.43 (t, 1H), 6.9 (s, 1H), 5.95–5.93 (d, J = 6.4 Hz, 1H), 3.76–3.660(m,, 2H), 2.21–2.17 (t, 2H), 1.59–1.52 (m, 2H), 1.31–1.25 (m, 2H), 0.89–0.86 (t, 3H); ^{13}C NMR (400 MHz,, $CDCl_3$) δ 196.63, 172.93, 150.64, 148.40, 140.45, 136.04, 133.684, 129.82, 129.43, 128.75, 125.18, 123.99, 47.32, 43.13, 36.16, 27.50, 22.248, 13.69; MS m/z 402 (M+2), 401; FT-IR (KBr) γ_{max} 3329, 2956, 1689, 1645, 1603, 1521, 1406, 1348, 1236, 1192, 995, 850, 786, 689 cm^{-1}. *Spectral data for* **3b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54–8.52 (d, J = 7.2 Hz, 1H), 8.36–8.33 (m, 2H), 8.24–8.21 (m, 2H), 7.95–7.93 (dd, 1H), 7.77–7.69 (m, 2H), 7.54–7.50 (m, 1H) 5.76–5.71 (m,1H), 3.77–3.70 (dd, J = 10 Hz, 1H), 3.52–3.47 (dd, 1H), 1.76 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 195.44, 168.73, 150.01, 148.03, 140.80, 138.05, 133.64, 129.49, 128.54, 128.26, 124.07, 123.81, 44.57, 44.83, 22.36; FT-IR (KBr) γ_{max} 3327.21, 3113.11, 1689.64, 1643.35, 1602.85, 1519.91, 1444.68, 1348.24, 1294.24, 1228.66, 1112.93, 995.27, 850.61, 744.52, 709.8, 405.05 cm^{-1}; MS m/z 359 (M+2), 358, 299. *Spectral data for* **3c**: ^{1}H NMR, (400 MHz, $CDCl_3$) δ 7.97–7.91 (m, 3H), 7.68–7.66 (d, J = 8.0 Hz, 1H), 7.57–7.54 (m, 1H), 7.40–7.36 (t, 1H), 7.19–7.17 (d, J = 8.8 Hz, 2H), 7.01–7.699 (d, J = 7.2 Hz, 1H), 5.95–5.90 (q, J = 6.8 and 19.2 Hz, 1H), 3.72–3.57 (m, 2H), 2.63–2.57 (q, 2H), 2.21–2.17(2, 2H) 1.60–1.53 (m, 2H), 1.34–1.26 (m, 5H,), 0.90–0.86 (t, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 197.33, 172.57, 172.22, 155.07, 148.41, 136.72, 133.70, 133.45, 129.94, 129.67, 128.39, 125.05, 121.99, 47.31, 42.19, 36.28, 27.75, 27.50, 22.29, 13.72, 8.; MS m/z 428 (M+2), 427; FT-IR (KBr) γ_{max} 3266, 3070.68, 2953.02, 2927.94, 2864.29, 2360.87, 2335.8, 1762.94, 1683.86, 1643.35, 1598.99, 1523.76, 1409.96, 1338.6, 1141.86. 894.97, 742.59 cm^{-1}.