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Synthesis of 1-aryl-2-propanones

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Abstract A new convenient synthesis of a series of 1-aryl-2-propanones using aromatic amines as precursors, *via* diazo-reaction and improved Meerwein arylation reaction under mild conditions, was achieved. In addition, 1-[3,5-bis(trifluoromethyl)phenyl]-2-propanone is a new compound among the synthesized compounds. This approach is an efficient synthetic method for the aryl-propanones with different substituting groups.

Keywords 1-aryl-2-propanone, aromatic amine, improved Meerwein arylation reaction, diazonium tetrafluoroborate

Aryl propanones are key intermediates for the synthesis of many organic molecules, particularly for the synthesis of pharmaceutically important compounds [1–3]. For example, 1-[3-(trifluoromethyl)phenyl]-2-propanone is an intermediate for the synthesis of Benfluorex and its analogues, an ideal emaciated agent [4–7], and 1-(1,3-benzodioxol-5-yl)-2-propanone is an intermediate for the synthesis of L- α -methyl-dopa or the like, which has antihypertensive functions [8–10]. 1-Phenyl-2-propanone is a precursor for the synthesis of prenylamine lactic acid, being used as anti-anginals, as well as for the synthesis of phenylisopropylamine, a precursor of a pseudo adrenal gland agent [11–13]. Several methods have been developed for the synthesis of 1-aryl-2-propanones due to their wide applications. Referring to Meerwein arylation reaction, we provide herewith a new route to produce aryl propanones using aromatic amines as the precursors *via* diazo reaction and improved Meerwein arylation reaction. At the same time, the influences of substituted groups of the aromatic rings on the reactions were discussed, including the influences of electron-withdrawing, electron-releasing, and sterically hindered groups. The reaction conditions

were optimized, giving satisfactory results. In comparison to what described in the literatures [14–23], this synthetic strategy is superior in its simple synthetic steps, mild reaction conditions and good yields.

1 Results and discussion

Aromatic amines were utilized as the precursors and through a diazo-reaction, diazonium tetrafluoroborates were prepared. Addition of the aryl diazonium tetrafluoroborate with isopropenyl acetate, in the presence of cuprous oxide as the catalyst and anhydrous sodium acetate as the buffer reagent, yielded a series of 1-aryl-2-propanones (see Fig. 1 and Table 1).

In general, the yields of Meerwein adducts were only in 30%–50%. When the water solution of diazonium salts (usually diazonium chlorides) reacted with unsaturated compounds using cupric salt as the catalyst, the yields of the Meerwein arylation reaction of aromatic ring with electron-withdrawing groups (such as NO₂, CF₃, Cl, F and so on) were considerably lower. Although, a new procedure was developed by Raucher [24,25] using diazonium bisulfates instead of the corresponding diazonium chlorides, the yields of the Meerwein adducts were still around 70% because the reactions were carried out in two separated phases (organic and aqueous). In order to circumvent the difficulty, not only were the corresponding diazonium tetrafluoroborates prepared in the present research, but the reactions were also carried out in a homogeneous organic phase since the reagent isopropenyl acetate was used as the solvent. Based on the improved conditions, the yields of Meerwein adducts were notably increased. This procedure was particularly well suited for the preparation of aryl propanones with electron-withdrawing groups and the yields exceeded 90% (see Table 1).

During the experiment, we found that the electronic effect of substituted group on the aromatic ring affected the Meerwein arylation reaction directly. Meerwein arylation reaction was easily carried out when the substituted groups were electron-withdrawing groups (such as NO₂, CF₃, Cl, F). The ketone with CF₃ (**1a**) was prepared at room temperature in a high yield (95%). Likewise,

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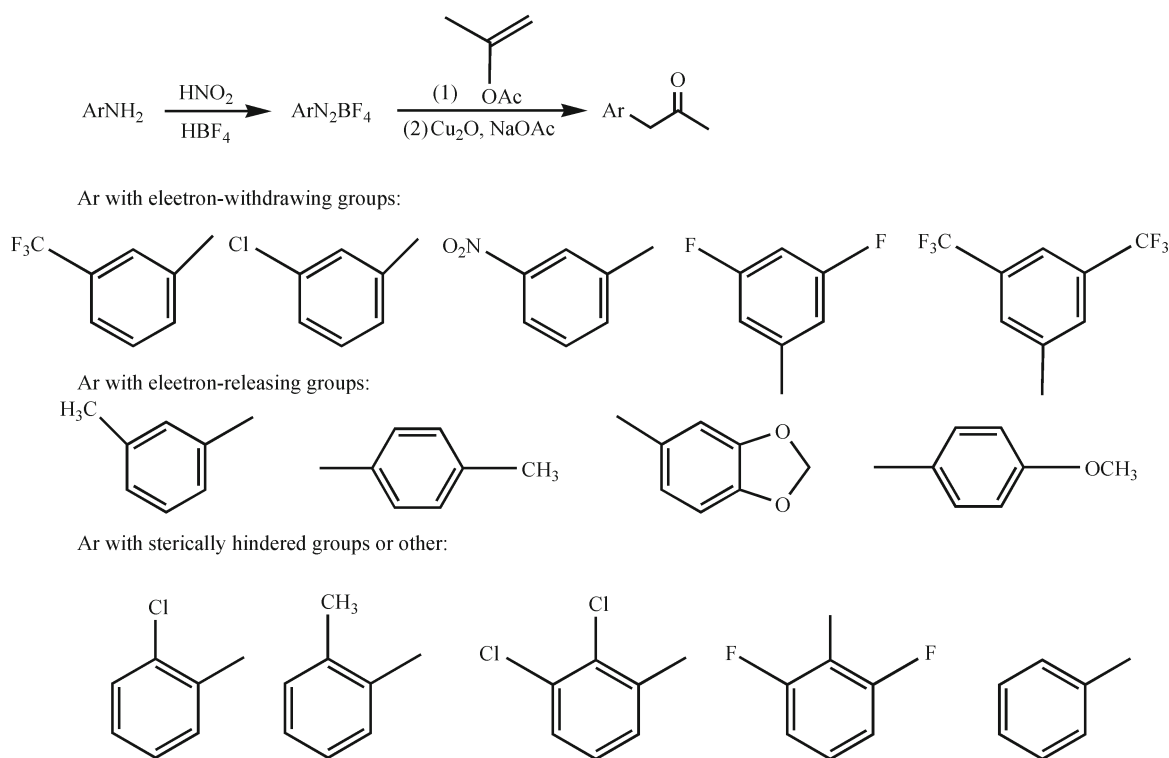
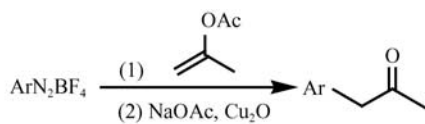


Fig. 1 Synthesis of 1-aryl-2-propanones

Table 1 Synthesis of 1-aryl-2-propanones



entry	substrate	product	yield/%	entry	substrate	product	yield/%
1			1a 95	8			2c 76
2			1b ^a 93	9			2d 61
3			1c 92	10			3a 60
4			1d 93	11			3b 75
5			1e 91	12			3c 70
6			2a 80	13			3d 50
7			2b 73	14			3e 90

^aNew compound

aromatic amines with F, Cl, NO₂ on the aromatic ring were also easily converted to their corresponding aryl propanones under mild conditions in excellent yields (above 90%). In contrast, Meerwein arylation reaction was not easily carried out when the substituted groups were OCH₃ or CH₃. Only the temperature was raised to 40°C–50°C and the reaction could be carried out. When the electron-releasing effects increased, for instance for compound **2d**, Meerwein arylation reaction was carried out at higher temperature (70°C–80°C) in lower yields (61%). In addition, the influence of steric hindrance is also a key factor to Meerwein arylation reaction. The amounts of undesired byproducts increased when diazonium tetrafluoroborates of *o*-aminochlorobenzene, *o*-toluidine, 2,6-difluorobenzeneamine, and 2,6-dichlorobenzeneamine were converted to their corresponding aryl propanones. Meerwein reaction was considered to be a radical mechanism in earlier studies [26,27]. The yields of Meerwein adducts with electron-releasing groups are lower than those with electron-withdrawing groups. This coincides with the character of dize salts [28], as also noted with our experimental results.

At the same time, with the synthesis of compound **3e** as an example, the influences of the catalyst, catalyst amount and reaction time to the yields of Meerwein arylation were studied as indicated below.

1.1 Effect of catalyst on the yield

Catalyst (0.0016 mol), 3.6 g of anhydrous sodium acetate and 10 mL of isopropenyl acetate were charged in a three-necked flask. Then, diazonium tetrafluoroborate (3 g, 0.016 mol) was added slowly at room temperature. The reaction mixture was stirred at 35°C–40°C for 6 h. The mixture was filtered and washed with ether. The solution was collected and concentrated to give the crude product which was analyzed by gas chromatography. Results were given in Table 2.

Table 2 Effect of catalyst on the yield

catalyst	CuCl	Cu ₂ O	CuCl ₂	CuO
yield /%	80	90	56	62

As outlined in Table 2, cuprous oxide is better than others. This may be caused by two factors. First, cuprous ion has a strong capacity for coordination and is easy to form the transition state of the metal complex. Second, by-product of nucleophilic substitution reaction was reduced because of the absence of a negative ion (Cl⁻).

1.2 Effect of catalyst amount on the yield

A certain amount of cuprous oxide, 3.6 g of anhydrous sodium acetate and 10 mL of isopropenyl acetate were

charged in a three-necked flask. Then, diazonium tetrafluoroborate (3 g, 0.016 mol) was slowly added at room temperature. The reaction mixture was stirred at 35°C–40°C for 6 h. The mixture was filtered and washed with ether. The solution was collected and concentrated to give the crude product which was analyzed by gas chromatography. The results were given in Table 3.

Table 3 Effect of catalyst amount on the yield

catalyst amount /mol	0.00016	0.0008	0.0016	0.0024	0.0032
yield /%	62	63	90	77	68

As shown in Table 3, a suitable catalyst amount is n (diazonium tetrafluoroborate): n (cuprous oxide) = 10 : 1.

1.3 Effect of time on the yield

Catalyst (0.0016 mol), 3.6 g of anhydrous sodium acetate and 10 mL of isopropenyl acetate were charged in a three-necked flask, then diazonium tetrafluoroborate (3 g, 0.016 mol) was slowly added at room temperature. The reaction mixture was stirred at 35°C–40°C for 2 h, 4 h, 6 h and 8 h, respectively. The mixture was filtered and washed with ether. The solution was collected and concentrated to give the crude product which was analyzed by gas chromatography. The results were given in Table 4.

Table 4 Effect of time on the yield

time/h	2	4	6	8
crude product/g	3.7	4.2	4.5	4.0
yield /%	75	87	90	85

As outlined in Table 4, a better reaction time is 6 h.

In conclusion, a facile synthesis of **3e** by the improved Meerwein arylation reaction is achieved with isopropenyl acetate as the solvent, cuprous oxide as the catalyst and the ratio of n (diazonium tetrafluoroborate): n (cuprous oxide) = 10:1, at 35°C–40°C for 6 h, giving 90% yield. Other compounds **1a–1e**, **2a–2d** and **3a–3d** were prepared under the same conditions (except for reaction time).

In addition, **1b** is a new compound among the synthesized fourteen compounds.

2 Experimental

2.1 Instruments and materials

Infrared spectra were determined on a FTS-40 spectrometer. MS measurements were performed on an ESI-MS spectrometer. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker AM-400 instrument. Chemical shifts refer to TMS on the δ scale. Gas chromatographic

analyses were carried out on a HP-5890 gas chromatograph. Melting points were measured on a Kofler apparatus and were uncorrected. Diopters were determined on a WRS-2S instrument.

Aromatic amines were used as chemical grade, and were distilled with zinc dust. Other reagents were used as analytical grade. 2,6-Difluorophenyl diazonium tetrafluoroborate was prepared by the method of Ref. [29].

2.2 Preparation of diazonium tetrafluoroborates

Concentrated hydrochloric acid (19 mL) and water (27.5 mL) were charged in a 100 mL three-necked flask fitted with mechanical stirrer and 0.075 mol of aromatic amine was slowly added with stirring. The reaction mixture was cooled to -5°C in an ice-salt bath and a cold solution of 5.3 g of sodium nitrite in 7 mL of water was added with stirring, while the temperature was held below -5°C . The reaction mixture was stirred for an additional 40 min. Then the mixture was transported to a plastic beaker (800 mL) cooled in an ice-salt bath and a cold solution of 6.02 g of boric acid in 19.5 mL of 40% hydrofluoric acid was added within 10 min with stirring. The reaction mixture was stirred for an additional 0.5 h. After an additional 2 h, the mixture was filtered and the solid was washed successively with 15 mL of fluoroboric acid, 15 mL of 50% ethanol, 15 mL of 95% ethanol and 15×2 mL of ethoxyethane to give the product that was dried in vacuum shelf dryer. This compound was directly used in the next step.

2.3 Preparation of 1-aryl-2-propanones

Anhydrous sodium acetate (6.2 g), 0.4 g of cuprous oxide, and 21 mL of isopropenyl acetate were charged in a 50 mL three-necked flask equipped with mechanical stirrer, and stirred at room temperature. Then 0.027 mol of diazonium tetrafluoroborate was added slowly at room temperature. The reaction mixture was stirred for an additional 6 h at 20°C – 80°C (**1a**–**1e**, **3a**, **3b**, **3d**: 20°C – 25°C ; **2a**–**2c**, **3c**, **3e**: 40°C – 50°C ; **2d**: 70°C – 80°C). The mixture was filtered and washed with dichloromethane. The solution was collected and concentrated under vacuum to give the crude product (or, purification by flash column chromatography gave the product).

1a: Yellow-green clear liquid, 95% yield, b.p. 98°C – $100^{\circ}\text{C}/267$ Pa (Ref. [30] 97°C – $99^{\circ}\text{C}/267$ Pa), n_{D}^{20} 1.4596 (Ref. [31] n_{D}^{20} 1.4596), purity 99.1%; $^1\text{H-NMR}$ (CDCl_3) δ : 2.21 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 7.39 (d, $J = 8.0$ Hz, 1H, PhH), 7.47 (d, $J = 12.0$ Hz, 2H, PhH), 7.54 (d, $J = 8.0$ Hz, 1H, PhH); $^{13}\text{C NMR}$ (CDCl_3) δ : 29.59 (CH_3), 50.31 (CH_2), 204.98 (CO), 131.1 (CF_3), 135.03, 132.91, 129.14, 126.21, 125.39, 124.01; IR (neat) ν : 1722 (C=O), 1494, 1452, 1332, 1163, 1124, 1075, 903, 809, 787, 703 cm^{-1} .

1b: White needles (recrystallized from petroleum ether), 93% yield, m.p. 52°C – 53°C ; $^1\text{H NMR}$ (CDCl_3) δ : 2.27 (s, 3H, CH_3), 3.88 (s, 2H, CH_2), 7.80 (s, 1H, PhH), 7.64 (s, 2H, PhH); $^{13}\text{C-NMR}$ (CDCl_3) δ : 29.88 (CH_3), 49.60 (CH_2), 203.53 (CO), 136.28, 131.89, 129.82, 121.89, 121.19; IR (KBr) ν : 1717 (C=O), 1624, 1381, 1292, 1116, 1022, 991, 924, 900, 851, 823, 735, 705, 685, 673, 533 cm^{-1} ; ESI-MS m/z : 269.2[M-H] $^+$. Anal. calcd. for $\text{C}_{11}\text{H}_8\text{F}_6\text{O}$: C 48.90, H 2.98, F 42.19; found: C 49.01, H 3.01, F 42.06.

1c: Yellow-green clear liquid, 92% yield, b.p. 66 – $68/400$ Pa (Ref. [31] $191.5^{\circ}\text{C}/101\text{kPa}$); $^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 6.74–6.70 (m, 3H, PhH); $^{13}\text{C NMR}$ (CDCl_3) δ : 29.55 (CH_3), 50.13 (CH_2), 204.50 (CO), 137.66, 164.37, 112.49, 102.70; IR (neat) ν : 1720 (C=O), 1596, 1460, 1476, 1359, 1161, 1028, 981, 859, 703, 662 cm^{-1} .

1d: Yellow clear liquid, 93% yield, b.p. 106°C – $108^{\circ}\text{C}/267$ Pa (Ref. [31] 121°C – $122^{\circ}\text{C}/400$ Pa), purity 99.0%; $^1\text{H-NMR}$ (CDCl_3) δ : 2.17 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 7.28–7.08 (m, 4H, PhH); $^{13}\text{C NMR}$ (CDCl_3) δ : 29.45 (CH_3), 50.31 (CH_2), 205.30 (CO), 136.07, 134.52, 130.60, 129.76, 128.67, 127.47; IR (neat) ν : 1721 (C=O), 1598, 1574, 1476, 1359, 1159, 1081, 903, 881, 772, 704, 683 cm^{-1} .

1e: Light yellow solid (recrystallized from petroleum ether-ethoxyethane), 92% yield, m.p. 59°C – 60°C (Ref. [32] 62°C – 65°C); $^1\text{H-NMR}$ (CDCl_3) δ : 2.25 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 7.52 (d, $J = 8.0$ Hz, 2H, PhH), 8.07 (s, 1H, PhH), 8.14 (t, $J = 4.0$ Hz, 1H, PhH); $^{13}\text{C NMR}$ (CDCl_3) δ : 29.74 (CH_3), 49.69 (CH_2), 204.14 (CO), 148.41, 135.92, 135.72, 129.45, 124.47, 122.14; IR (KBr) ν : 1714 (C=O), 1527, 1350, 1213, 1162, 1081, 984, 907, 834, 817, 731, 691, 631, 518 cm^{-1} .

2a: Yellow-green clear liquid, 80% yield, b.p. 90°C – $92^{\circ}\text{C}/267$ Pa (Ref. [31] 296 – $297^{\circ}\text{C}/101$ kPa); $^1\text{H-NMR}$ (CDCl_3) δ : 2.14 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 2.34 (s, 3H, PhCH_3), 7.22 (t, $J = 8.0$ Hz, 1H, PhH), 7.08 (d, $J = 7.4$ Hz, 1H, PhH), 7.0 (d, $J = 8.4$ Hz, 2H, PhH); $^{13}\text{C NMR}$ (CDCl_3) δ : 29.21 (CH_3), 51.04 (CH_2), 206.62 (CO), 21.34 (PhCH_3), 138.44, 134.18, 130.14, 128.67, 127.84, 126.42; IR (neat) ν : 1713 (C=O), 3019, 2921, 1608, 1489, 1423, 1357, 1327, 1224, 1157, 1095, 1022, 774, 738, 698 cm^{-1} .

2b: Light yellow liquid, 73% yield, b.p. 94°C – $96^{\circ}\text{C}/533$ Pa (Ref. [32] 108 – $111^{\circ}\text{C}/1.30$ kPa); $^1\text{H-NMR}$ (CDCl_3) δ : 2.09 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 2.30 (s, 3H, PhCH_3), 7.16 (s, 1H, PhH), 7.14 (s, 1H, PhH), 7.10 (s, 1H, PhH), 7.08 (s, 1H, PhH); $^{13}\text{C NMR}$ (CDCl_3) δ : 29.13 (CH_3), 50.67 (CH_2), 206.76 (CO), 21.18 (PhCH_3), 136.71, 131.21, 130.22, 129.72; IR (neat) ν : 1712 (C=O), 2923, 1905, 1610, 1514, 1419, 1358, 1230, 1159, 1108, 1022, 822, 786, 758 cm^{-1} .

2c: Light yellow-green liquid, 76% yield, b.p. 266°C – 268°C (Ref. [33] 142°C – $145^{\circ}\text{C}/2.13$ kPa); $^1\text{H-NMR}$ (CDCl_3) δ : 2.09 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 3.79 (s,

3H, PhOCH₃), 7.12 (d, *J* = 8.0 Hz, 2H, PhH), 6.87 (d, *J* = 8.0 Hz, 2H, PhH); ¹³C NMR (CDCl₃) δ: 29.09 (CH₃), 50.17 (CH₂), 206.75 (CO), 55.29 (PhOCH₃), 158.78, 130.41, 126.38, 114.27; IR (neat) ν: 1712 (C=O), 2936, 2839, 1602, 1512, 1464, 1358, 1249, 1161, 1109, 1032, 835 cm⁻¹.

2d: Yellow thick liquid, 61% yield, b.p. 141°C–143°C/267 Pa (Ref. [8] 142°C/347 Pa); ¹H-NMR (CDCl₃) δ: 2.15 (s, 3H, CH₃), 3.60 (s, 2H, CH₂), 5.94 (s, 2H, CH₂O), 6.77 (d, *J* = 8.0 Hz, 1H, PhH), 6.68 (d, *J* = 1.2 Hz, 1H, PhH), 6.65 (d, *J* = 4.0 Hz, 1H, PhH); ¹³C NMR (CDCl₃) δ: 29.10 (CH₃), 50.59 (CH₂), 206.45 (CO), 101.07 (OCH₂O), 147.96, 146.74, 127.86, 122.52, 109.77, 108.50; IR (neat) ν: 1712 (C=O), 2902, 1604, 1489, 1445, 1357, 1249, 1099, 1039, 926, 869, 813 cm⁻¹.

3a: White needles (recrystallized from petroleum ether), 60% yield, m.p. 42°C–43°C (Ref. [34] 45°C–47°C); ¹H-NMR (CDCl₃) δ: 2.23 (s, 3H, CH₃), 3.89 (s, 2H, CH₂), 7.40 (d, *J* = 8.0 Hz, 1H, PhH), 7.19–7.11 (m, 2H, PhH); ¹³C-NMR (CDCl₃) δ: 29.72 (CH₃), 49.08 (CH₂), 204.09 (CO), 135.29, 133.47, 132.84, 129.82, 129.52, 127.35; IR (KBr) ν: 1715 (C=O), 1624, 2910, 1939, 1871, 1587, 1568, 1491, 1454, 1428, 1402, 1359, 1322, 1251, 1198, 11623, 1051, 1018, 985, 891, 828, 771, 741, 711, 652, 577, 552, 518 cm⁻¹; ESI-MS *m/z*: 202.9 [M-H]⁺, 220.2[M+H₂O], 279.2 [M+2Cl], 301.3 [M+2Cl +Na], 318.2[M+2Cl+Na+H₂O].

3b: Light yellow liquid, 75% yield, b.p. 95°C–97°C/267 Pa (Ref. [35] 103°C–104°C/800 Pa); ¹H-NMR (CDCl₃) δ: 2.21 (s, 3H, CH₃), 3.85 (s, 2H, CH₂), 7.40–7.38 (m, 1H, PhH), 7.25–7.20 (m, 3H, PhH); ¹³C-NMR (CDCl₃) δ: 29.61 (CH₃), 48.37 (CH₂), 204.96 (CO), 134.46, 132.96, 131.66, 129.62, 128.70, 127.06; IR (neat) ν: 1725 (C=O), 1593, 1573, 1475, 1445, 1358, 1325, 1161, 1054, 750, 717, 683 cm⁻¹.

3c: Light yellow clear liquid, 70% yield, b.p. 89°C–91°C/533 Pa (Ref. [32] 108°C–110°C/933 Pa); ¹H-NMR (CDCl₃) δ: 2.14 (s, 3H, CH₃), 3.71 (s, 2H, CH₂), 2.24 (s, 3H, PhCH₃), 7.19–7.14 (m, 4H, PhH); ¹³C-NMR (CDCl₃) δ: 29.23 (CH₃), 49.16 (CH₂), 206.34 (CO), 19.61 (PhCH₃), 136.85, 133.19, 130.52, 130.38, 127.41, 126.30; IR (neat) ν: 1713 (C=O), 3019, 2924, 1604, 1496, 1463, 1423, 1357, 1325, 1228, 1159, 1112, 1053, 759, 741 cm⁻¹.

3d: Yellow liquid, 50% yield, b.p. 105°C–110°C/133 Pa (Ref. [31] 63°C–73°C/13–20 Pa); ¹H-NMR (CDCl₃) δ: 2.25 (s, 3H, CH₃), 3.78 (s, 2H, CH₂), 7.26–7.20 (m, 1H, PhH), 6.92–6.88 (m, 2H, PhH); ¹³C NMR (CDCl₃) δ: 29.26 (CH₃), 37.12 (CH₂), 203.18 (CO), 162.67, 160.21, 130.26, 111.18; IR (neat) ν: 1723 (C=O), 1769, 1667, 1621, 1469, 1434, 11371, 1206, 1050, 965, 905, 874, 782, 753, 690 cm⁻¹.

3e: Yellow clear liquid, 90% yield, b.p. 70°C–72°C/267 Pa (Ref. [36] 109°C–112°C/3.20 kPa); ¹H-NMR (CDCl₃) δ: 2.14 (s, 3H, CH₃), 3.69 (s, 2H, CH₂), 7.35–7.20 (m, 5H, PhH); ¹³C-NMR (CDCl₃) δ: 29.23 (CH₃), 51.05 (CH₂), 206.36 (CO), 134.31, 129.41, 128.76, 127.08; IR (neat) ν:

1712 (C=O), 3063, 3030, 1602, 1496, 1454, 1421, 1357, 1228, 1158, 1078, 1030, 913, 789, 735, 699, 632 cm⁻¹.

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