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Bromodimethylsulfonium Bromide Catalyzed Three-Component Mannich-Type Reactions

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Keywords: β-Amino carbonyl compounds / Aldehydes / Amines / Bromodimethylsulfonium bromide

Bromodimethylsulfonium bromide catalyzes Mannich-type reactions of a variety of aldimines, generated in situ from aldehydes and anilines, with enolizable ketones or diethyl malonate in three-component reactions to afford the corresponding β-amino carbonyl compounds. The salient features of this protocol are: shorter reaction times, simplicity of the procedure, good to excellent yields, avoidance of aqueous workup and column-chromatographic separations, and high stereoselectivities.

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Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, as high degrees of molecular diversity can be introduced in these reactions in a very fast, efficient, and timesaving manner, and without the isolation of any intermediates. As a result, considerable attention has been paid to the development of new and improved one-pot multicomponent reactions in recent years.[1]

A Mannich-type reaction is a multicomponent reaction of a non-enolizable aldehyde, a primary or secondary amine, and an enolizable carbonyl compound to afford the corresponding β-amino carbonyl compound.[2] These β-amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals and natural products[3] and have found wide application in organic synthesis.

The classical Mannich reaction has some limitations, such as requirements for harsh reaction conditions and long reaction times. In addition, indirect-type[4] Mannich reactions using preformed electrophiles such as imines and stable nucleophiles such as enolates or enol ethers suffer from the drawback of the necessity for the isolation and purification of the preformed intermediates. Therefore, a modified and improved methodology, known as the direct-type Mannich reaction, in the presence of various catalysts and using directly carbonyl compounds as nucleophiles was introduced.

Owing to the importance of β-amino carbonyl compounds, numerous methods for the synthesis of these compounds either by indirect-type or direct-type Mannich reactions have been reported over the years. Recently, direct-type Mannich reactions of aldehydes, enolizable ketones or diethyl malonate, and arylamines in the presence of various catalysts such as $NbCl_5$,[5] $Zn(OTf)_2$,[6] silica sulfuric acid,[7] $Yb(OPf)_3$,[8] $[NaBAr^F{}_4]$,[9] $ZrOCl_2{\cdot}8H_2O$,[10] etc. have been reported. Although these methodologies are useful, most of the methods still encounter some limitations, such as requirements for expensive catalysts or longer reaction times. It is thus evident that there remains a wide scope for the development of clean and efficient methodologies for the preparation of β-amino carbonyl compounds through a convenient and environmentally friendly method.

Bromodimethylsulfonium bromide (BDMS) is a readily accessible, cheap, and highly effective reagent,[11] as well as a catalyst for various organic transformations.[12] Recently, Das et al. reported the efficiency of bromodimethylsulfonium bromide in one-pot multicomponent syntheses of homoallylic amines.[13] In addition, very recently we have demonstrated the virtue of this catalyst for Michael additions of amines to electron-deficient alkenes.[12a] In continuation of our work on the development of new synthetic methodologies,[14] we sought to explore the advantages of this reagent further for other important transformations. Here we report a simple and effective methodology for one-pot, three-component, Mannich-type reactions of aromatic aldehydes, aromatic amines, and enolizable ketones or diethyl malonates in the presence of BDMS as a catalyst as shown in Scheme 1.

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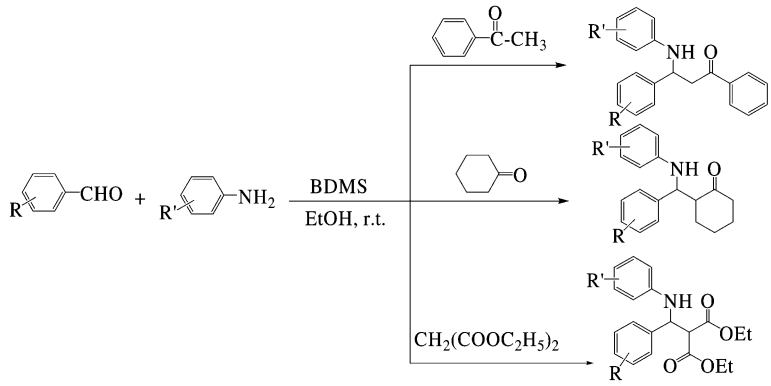

Scheme 1.

Results and Discussion

Initially, the three-component Mannich-type reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol), and acetophenone (2.0 mmol) in the presence of bromodimethylsulfonium bromide as a catalyst was examined. Interestingly, we observed that 10 mol-% of bromodimethylsulfonium bromide is sufficient to catalyze the three-component, one-pot reaction in a very good yield within 30 min. In the absence of the catalyst the reaction failed to provide the desired product even after 48 h of stirring. Interestingly, this protocol offers a wealth of advantages over the indirect methods, since there is no need for the preparation of silyl enol ethers or preformed imines. In the screening of different solvents to find the most suitable solvent for this transformation, ethanol was found to be superior to other solvents such as THF, toluene, 1,4-dioxane, and CH_2Cl_2 in terms both of reaction time and of yields obtained. Encouraged by this result, we examined the scope of this protocol by using various electron-withdrawing aromatic aldehydes and amines. It is interesting to note that the pure products of all these reactions can be obtained just by recrystallisation of the crude materials from ethanol, avoiding aqueous workup and tedious column-chromatographic separation.

Next, benzaldehyde was treated individually with a variety of aromatic amines such as 3-chloro-, 2-nitro-, or 4-nitroaniline in combination with acetophenone, which provided very good to excellent yields within 30 min to 1 h (Table 1, Entries 2–4). It is gratifying to mention that this method does not suffer from any steric effects for *ortho*-substituted amines such as 2-nitroaniline as reported for other recent methods.[5] Similarly 4-ethylaniline provided the desired β-amino ketone with good yields (Table 1, Entry 5).

Next, aldehydes substituted with electron-withdrawing groups, such as 3-bromo- and 4-chlorobenzaldehyde, were treated separately with a variety of aromatic amines in combination with acetophenone under the same experimental conditions, and the corresponding desired products were isolated in very good yields without any difficulty (Entries 6–13). It is worth mentioning that nitro aldehydes such as 4-nitrobenzaldehyde and 3-nitrobenzaldehyde provided the corresponding chalcones instead of the desired β-amino ketones on treatment with aniline and acetophenone separately under the same experimental conditions. We believe that the nitro-substituted aldehydes prefer the aldol reaction followed by subsequent dehydration rather than in situ aldimine formation and subsequent nucleophilic addition. Next, terephthalaldehyde was treated with 2 equiv. of aniline and acetophenone to afford a bis product as shown in Table 1 (Entry 14).

Next, to generalize the method, aliphatic aldehydes such as acetaldehyde were treated with aniline and acetophenone under the same experimental conditions. After 12 h of stirring, we were unable to obtain the desired Mannich products. Similarly, the combination of an aliphatic amine such as butylamine with benzaldehyde and acetophenone under the same experimental conditions was not successful even after prolonged stirring. Likewise, the reaction of an aliphatic ketone such as acetone was also not applicable for a Mannich-type reaction with benzaldehyde and aniline under the given experimental conditions. Next, in an attempt to check the applicability of benzylamine, we were unsuccessful in achieving the desired β-amino ketone. From these studies we have established that our new method is a selective procedure for Mannich-type reactions of aromatic aldehydes, amines, and ketones.

After that, to extend the preparative utility and generality of this multicomponent reaction, benzaldehyde and 4-chlorobenzaldehyde were treated individually with aniline and 3-chloroaniline in combination with other enolizable carbonyl compounds such as cyclohexanone or diethyl malonate under the same experimental conditions, as shown in Scheme 2.

The results are summarized in Table 2. Interestingly, the reactions of cyclohexanone with benzaldehyde or 4-chlorobenzaldehyde exhibit good diastereoselectivity and provide the *anti* isomers as the major products (Table 2, Entries 1–3). A similar diastereoselectivity was also observed by Hashemi and his group.[10] The *anti*/*syn* ratios were determined by ^{1}H NMR spectroscopy. To confirm the *anti* configurations of these products unambiguously, compound **5b** was recrystallised from ethanol and a single-crystal XRD was performed. The ORTEP plot of the product, showing the *anti* configuration, is depicted in Figure 1. The unit cell

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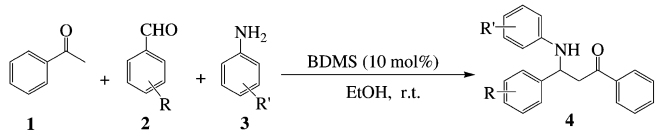
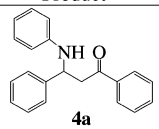
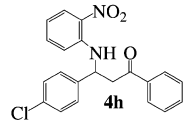
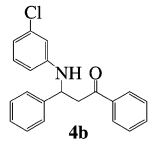
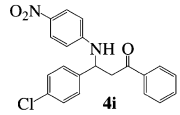
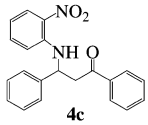
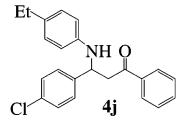
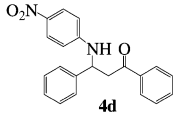
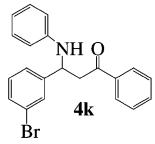
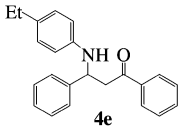
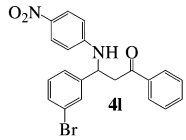
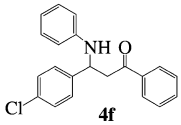
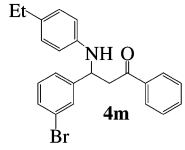
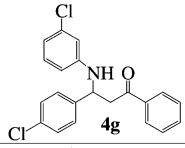
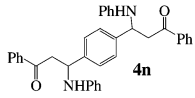
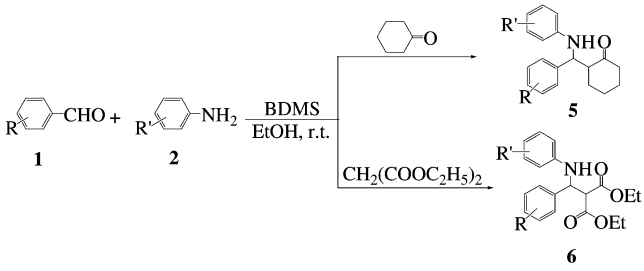
Table 1. Three-component bromodimethylsulfonium bromide catalyzed direct Mannich-type reactions of various aromatic aldehydes, amines, and ketones.



Entry	Product[a]	Time	Yield (%)[b]	Entry	Product[a]	Time	Yield (%)[b]
1	 **4a**	30 min	96[4]	8	 **4h**	2 h	87
2	 **4b**	30 min	98	9	 **4i**	40 min	97
3	 **4c**	1 h	88	10	 **4j**	4 h	95
4	 **4d**	30 min	95	11	 **4k**	3 h	90
5	 **4e**	1 h	97	12	 **4l**	1 h	89
6	 **4f**	40 min	97[4]	13	 **4m**	2 h	92
7	 **4g**	4 h	98	14	 **4n**	30 min	89

[a] All the products were fully characterized by the usual spectroscopic techniques. [b] Isolated yield.



Scheme 2.

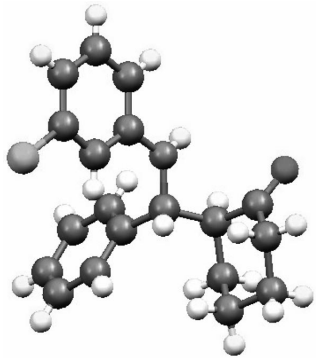


Figure 1. ORTEP plot of **5b** showing *anti* configuration.

consists of four molecules, and they exhibit intermolecular hydrogen bonding between the C=O group of one molecule and the N–H group of another.

Likewise, diethyl malonate also reacted under the same experimental conditions and provided the corresponding ethyl ester of the β-amino acid (Table 2, Entries 4–5) in good yields (Scheme 3).

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Table 2. BDMS-catalyzed multicomponent reactions of aromatic aldehydes, amines, and either cyclohexanone or diethyl malonate.

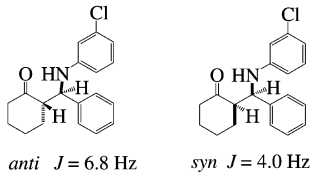
Entry	R	R′	Product[a]	Time	Yield[b] (%)	*anti*/*syn*[c]
1	H	H	**5a**	15 min	86[6]	98:2
2	H	3-Cl	**5b**	15 min	92[7]	98:2
3	4-Cl	3-Cl	**5c**	20 min	88	99:1
4	H	H	**6a**	6 h	92[6]	–
5	H	3-Cl	**6b**	7 h	94	–

[a] All the products were fully characterized by usual spectroscopic techniques. [b] Isolated yields. [c] Ratios were determined by ^{1}H NMR spectroscopy.

Table 3. Comparison of the catalytic activity of BDMS with those of different catalysts for the Mannich reaction of benzaldehyde, aniline, and acetophenone.

Run	Catalyst	Reaction conditions	Reaction time	Yield (%)[a]
1	no catalyst	EtOH, room temp.	48 h	n.r.
2	$FeCl_3$	EtOH, room temp.	24 h	n.r.[6]
3	$NbCl_5$	EtOH, room temp.	12 h	95[6]
4	$Yb(OPf)_3$	$PhCH_3/C_6F_5CF_3$	12 h	98[9]
5	silica sulfuric acid	EtOH, room temp.	12 h	92[8]
6	$[NaBAr^F{}_4]$	H_2O, 30 °C	48 h	81[10]
7	BDMS	EtOH, room temp.	30 min	96

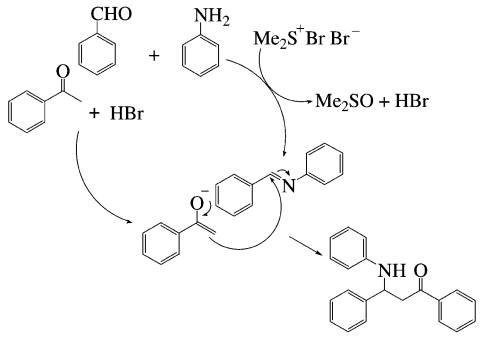
[a] Corresponding reference; n.r. = no reaction.



Scheme 3. *syn* and *anti* isomers of product **5b**.

It is worth mentioning that this method is faster, more cost-effective, and simpler than most of the existing methods. The efficacy and generality of the catalyst bromodimethylsulfonium bromide can be gauged by comparison (Table 3). For this comparison the reaction of acetophenone, benzaldehyde, and aniline was chosen as a model reaction, and comparison was carried out on the basis of reaction conditions, reaction time, and percentage yields obtained.

The catalyst bromodimethylsulfonium bromide is an inexpensive reagent. We believe that BDMS catalyzes these conversions through the rapid formation of imines, along with its simultaneous transformation into Me_2SO and HBr. The nucleophilic additions of enolizable ketones into these imines in the presence of HBr, followed by hydrolysis, afforded β-amino carbonyl compounds. The reaction between Me_2SO and HBr then regenerated the bromodimethylsulfonium bromide catalyst (Scheme 4).



Scheme 4. Plausible mechanistic illustration of BDMS-catalyzed Mannich-type reactions.

Conclusions

We have demonstrated the efficacy and generality of bromodimethylsulfonium bromide as a versatile catalyst for the synthesis of β-amino carbonyl compounds through the Mannich-type reactions of a variety of aldimines, generated in situ from aldehydes and anilines, with enolizable ketones or diethyl malonate. The salient features of this protocol are: (a) the simplicity of the procedure, (b) the ready accessibility of the catalyst and its cost effectiveness, (c) the avoidance of column chromatography, and (d) high yields and good diastereoselectivities.

Experimental Section

General: Melting points were recorded with a Büchi B-545 melting point apparatus. IR spectra were recorded in KBr with a Nicolet Impact 410 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 MHz spectrometer in $CDCl_3$ with TMS as internal reference. Elemental analyses were carried out with a Perkin–Elmer 2400 automatic C,H,N,S analyzer. The XRD was performed with a Bruker Nonius Smart Apex II single-crystal X-ray diffractometer. CCDC-665099 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of Bromodimethylsulfonium Bromide (BDMS):[15] Dimethyl sulfide (1.83 mL, 25 mmol) was added to dry dichloromethane (5 mL) in a 150 mL standard joint conical flask. Then, bromine

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(1.3 mL, 25 mmol) was dissolved in dry dichloromethane (5 mL) and added slowly to the above solution at ice-bath temperature over a period of 5 min. During the addition, light orange crystals of bromodimethylsulfonium bromide began to separate. After the addition of bromine was complete, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. The crystalline product (4.3 g) was obtained in 77% yield, m.p. 80 °C.

General Reaction Procedure: Bromodimethylsulfonium bromide (0.2 mmol) was added to a mixture of benzaldehyde (2 mmol), aniline (2 mmol), and acetophenone (2 mmol), and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude solid was just filtered off and washed with a hexane/ethanol (80:20) mixture. The solid residue was then dissolved in hot ethanol and was recrystallized to provide the pure product. The pure product was characterized by conventional spectroscopic methods, and its data were compared with those reported.[4]

3-[(3-Chlorophenyl)amino]-1,3-diphenylpropan-1-one (4b): Yield: 0.658 g, 98%. White solid, m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (dd, J = 7.2 Hz, J = 16.4 Hz, 1 H), 3.50 (dd, J = 4.8 Hz, J = 16.0 Hz, 1 H), 4.71 (br. s, 1 H), 4.97 (t, J = 6.0 Hz 1 H), 6.42 (d, J = 8.0 Hz, 1 H), 6.54 (s, 1 H), 6.62 (d, J = 7.6 Hz, 1 H), 6.98 (t, J = 8.0 Hz, 1 H), 7.27 (d, J = 7.2 Hz, 1 H), 7.34 (t, J = 7.2 Hz, 2 H), 7.41–7.47 (m, 4 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.90 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.9, 54.5, 111.8, 113.5, 117.5, 126.1, 127.4, 128.0, 128.6, 128.8, 129.9, 133.4, 134.6, 136.4, 142.1, 148.0, 197.9 ppm. IR (KBr): $\tilde{\nu}$ = 3372, 1686 cm^{-1}. $C_{21}H_{18}ClNO$ (335.83): C 75.11, H 5.40, N 4.17; found C 75.28, H 5.43, N 4.07.

1,3-Diphenyl-3-[(2-nitrophenyl)amino]propan-1-one (4c): Yield: 0.610 g, 88%. Yellow solid, m.p. 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (dd, J = 5.2 Hz, J = 17.2 Hz, 1 H), 3.66 (dd, J = 7.6 Hz, J = 17.2 Hz, 1 H), 5.33–5.39 (m, 1 H), 6.63 (t, J = 7.2 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 7.29–7.37 (m, 4 H), 7.43–7.48 (m, 4 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.92 (d, J = 7.2 Hz, 2 H), 8.16 (d, J = 7.2 Hz, 1 H), 8.63 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.2, 54.0, 115.5, 116.5, 126.8, 127.3, 128.3, 128.7, 129.3, 129.6, 133.0, 134.1, 136.7, 136.9, 142.0, 144.8, 197.2 ppm. IR (KBr): $\tilde{\nu}$ = 3370, 1685, 1592, 1352 cm^{-1}. $C_{21}H_{18}N_2O_3$ (346.38): C 72.82, H 5.24, N 8.09; found C 72.93, H 5.20, N 7.94.

1,3-Diphenyl-3-[(4-nitrophenyl)amino]propan-1-one (4d): Yield: 0.658 g, 95%. Yellow solid, m.p. 177–178 °C (ref.[16] m.p. 179–180 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (d, J = 6.8 Hz, 2 H), 5.10 (t, J = 6.0 Hz, 1 H), 5.58 (br. s, 1 H), 6.52 (d, J = 9.2 Hz, 2 H), 7.28 (d, J = 7.2 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 7.2 Hz, 3 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H), 8.00 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.0, 55.0, 101.9, 112.9, 126.7, 128.5, 128.7, 129.3, 129.7, 134.4, 136.9, 139.1, 141.6, 152.6, 198.4 ppm. IR (KBr): $\tilde{\nu}$ = 3371, 1685, 1590, 1350 cm^{-1}. $C_{21}H_{18}N_2O_3$ (346.38): C 72.82, H 5.24, N 8.09; found C 72.65, H 5.16, N 8.19.

3-[(4-Ethylphenyl)amino]-1,3-diphenylpropan-1-one (4e): Yield: 0.639 g, 97%. White solid, m.p. 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.6 Hz, 3 H), 2.48 (q, J = 7.6 Hz, 2 H), 3.42 (dd, J = 7.6 Hz, J = 16.4 Hz, 1 H), 3.51 (dd, J = 5.2 Hz, J = 16.4 Hz, 1 H), 4.60 (br. s,1 H), 4.97 (dd, J = 5.2 Hz, J = 7.6 Hz 1 H), 6.51 (d, J = 8.4 Hz, 2 H), 6.93 (d, J = 8.4 Hz, 2 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.32 (t, J = 7.2 Hz, 2 H), 7.42–7.46 (m, 4 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 28.0, 46.4, 55.2, 114.2, 126.6, 127.4, 128.3, 128.5, 128.8, 128.9, 133.5, 133.8, 136.7, 143.2, 144.9, 198.4 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 1679 cm^{-1}. $C_{23}H_{23}NO$ (329.44): C 83.86, H 7.04, N 4.25; found C 83.60, H 7.11, N 4.38.

3-(4-Chlorophenyl)-3-[(3-chlorophenyl)amino]-1-phenylpropan-1-one (4g): Yield: 0.726 g, 98%. White solid, m.p. 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42–3.46 (m, 2 H), 4.71 (br. s, 1 H), 4.93–4.96 (m, 1 H), 6.40 (d, J = 8.4 Hz, 1 H), 6.51 (s, 1 H), 6.64 (d, J = 8.0 Hz, 1 H), 6.99 (t, J = 8.4 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.58 (t, J = 8.4 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 46.4, 54.4, 112.4, 114.0, 118.4, 128.2, 128.6, 129.3, 129.5, 130.6, 133.6, 134.2, 135.3, 136.9, 141.4, 148.4, 198.2 ppm. IR (KBr): $\tilde{\nu}$ = 3376, 1684 cm^{-1}. $C_{21}H_{17}Cl_2NO$ (370.28): C 68.12, H 4.63, N 3.78; found C 67.90, H 4.57, N 3.69.

3-(4-Chlorophenyl)-3-[(2-nitrophenyl)amino]-1-phenylpropan-1-one (4h): Yield: 0.663 g, 87%. Yellow solid, m.p. 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (dd, J = 4.4 Hz, J = 16.8 Hz, 1 H), 3.62 (dd, J = 6.4 Hz, J = 16.4 Hz, 1 H), 5.29–5.33 (m, 1 H), 6.64 (t, J = 8.8 Hz, 1 H), 6.71 (d, J = 8.8 Hz, 1 H), 7.28–7.32 (m, 3 H), 7.36 (d, J = 7.6 Hz, 2 H), 7.44 (t, J = 8.0 Hz, 2 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H), 8.14 (d, J = 8.8 Hz, 1 H), 8.57 (d, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.7, 53.1, 115.0, 116.4, 127.0, 128.0, 128.3, 129.0, 129.4, 132.7, 133.7, 134.0, 136.4, 136.5, 140.3, 144.2, 196.5 ppm. IR (KBr): $\tilde{\nu}$ = 3376, 1685, 1591, 1297 cm^{-1}. $C_{21}H_{17}ClN_2O_3$ (380.83): C 66.23, H 4.50, N 7.36; found C 66.32, H 4.42, N 7.25.

3-(4-Chlorophenyl)-3-[(4-nitrophenyl)amino]-1-phenylpropan-1-one (4i): Yield: 0.739 g, 97%. Yellow solid, m.p. 150–151 °C (ref.[16] m.p. 149–150 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (d, J = 6.4 Hz, 2 H), 5.07 (q, J = 6.0 Hz, 1 H), 5.56 (d, J = 6.0 Hz, 1 H), 6.50 (d, J = 9.2 Hz, 2 H), 7.30–7.35 (m, 4 H), 7.47 (t, J = 8.0 Hz, 2 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.89 (d, J = 7.6 Hz, 2 H), 8.01 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.5, 53.7, 112.4, 126.4, 127.8, 128.3, 129.0, 129.4, 133.7, 134.1, 136.3, 138.6, 139.9, 152.2, 197.7 ppm. IR (KBr): $\tilde{\nu}$ = 3375, 1685, 1593, 1296 cm^{-1}. $C_{21}H_{17}ClN_2O_3$ (380.83): C 66.23, H 4.50, N 7.36; found C 66.31, H 4.46, N 7.27.

3-(4-Chlorophenyl)-3-[(4-ethylphenyl)amino]-1-phenylpropan-1-one (4j): Yield: 0.691 g, 95%. White solid, m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.6 Hz, 3 H), 2.47 (q, J = 7.6 Hz, 2 H), 3.47 (d, J = 7.2 Hz, 2 H), 4.71(br. s, 1 H), 4.92 (t, J = 6.8 Hz, 1 H), 6.51 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 2 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.88 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 28.1, 46.1, 55.2, 114.8, 128.2, 128.4, 128.7, 128.9, 129.1, 133.2, 133.8, 134.8, 136.6, 141.3, 143.9, 198.0 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 1680 cm^{-1}. $C_{23}H_{22}ClNO$ (363.89): C 75.92, H 6.09, N 3.85; found C 75.71, H 6.12, N 3.96.

3-(3-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4k): Yield: 0.685 g, 90%. Light blue solid, m.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.47–3.50 (m, 2 H), 4.68 (br. s, 1 H), 4.94–4.97 (m, 1 H), 6.58 (d, J = 7.6 Hz, 2 H), 6.72 (t, J = 7.2 Hz, 1 H), 7.11 (t, J = 7.2 Hz, 2 H), 7.19 (t, J = 7.6 Hz, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.41 (d, J = 7.6 Hz, 1 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.60 (s, 1 H), 7.91 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 46.2, 55.0, 114.4, 118.7, 123.2, 125.4, 128.4, 129.0, 129.4, 129.8, 130.6, 130.8, 133.8, 134.9, 145.4, 146.4, 197.9 ppm. IR (KBr): $\tilde{\nu}$ = 3380, 1681 cm^{-1}. $C_{21}H_{18}BrNO$ (380.28): C 66.33, H 4.77, N 3.68; found C 66.42, H 4.70, N 3.59.

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3-(3-Bromophenyl)-3-[(4-nitrophenyl)amino]-1-phenylpropan-1-one (4l): Yield: 0.757 g, 89%. Light yellow solid, m.p. 159–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (d, J = 6.0 Hz, 2 H), 5.02 (q, J = 6.0 Hz, 1 H), 5.48 (d, J = 6.4 Hz, 1 H), 6.48 (d, J = 9.2 Hz, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.51 (s, 1 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.87 (d, J = 7.2 Hz, 2 H), 7.99 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 45.5, 53.8, 112.3, 123.3, 125.0, 126.3, 128.2. 128.9, 129.3, 130.8, 131.2, 134.0, 136.1, 138.7, 143.8, 152.0, 197.4 ppm. IR (KBr): $\tilde{\nu}$ = 3380, 1685, 1598, 1337 cm^{-1}. $C_{21}H_{17}BrN_2O_3$ (425.28): C 59.31, H 4.03, N 6.59; found C 59.10, H 4.08, N 6.50.

3-(3-Bromophenyl)-3-[(4-ethylphenyl)amino]-1-phenylpropan-1-one (4m): Yield: 0.751 g, 92%. White solid, 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.6 Hz, 3 H), 2.46 (q, J = 7.6 Hz, 2 H), 3.35 (dd, J = 7.6 Hz, J = 16.4 Hz, 1 H), 3.44 (dd, J = 5.2 Hz, J = 16.0 Hz, 1 H), 4.40 (br. s, 1 H), 4.88 (dd, J = 5.2, J = 7.2 Hz, 1 H), 6.45 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8. 4 Hz, 2 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.32–7.36 (m, 2 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.57 (s, 1 H), 7.88 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 28.0, 46.4, 54.7, 114.1, 123.1, 125.3, 128.3, 128.6, 128.9, 129.6, 130.5, 130.6, 133.7, 134.0, 136.6, 144.8, 146.1, 197.9 ppm. IR (KBr): $\tilde{\nu}$ = 3401, 1680 cm^{-1}. $C_{23}H_{22}BrNO$ (408.34): C 67.65, H 5.43, N 3.43; found C 67.50, H 5.39, N 3.58.

1,4-Bis[3-oxo-3-phenyl-1-(phenylamino)propyl]benzene (4n): Yield: 0.934 g, 89%. Light green solid, m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (d, J = 6.0 Hz, 4 H), 4.70 (br. s, 2 H), 4.96 (t, J = 5.6 Hz, 2 H), 6.55 (d, J = 6.8 Hz, 4 H), 6.67 (t, J = 6.8 Hz, 2 H), 7.08 (t, J = 6.8 Hz, 4 H), 7.38 (s, 4 H), 7.42 (t, J = 7.2 Hz, 4 H), 7.53 (t, J = 8.0 Hz, 2 H), 7.87 (d, J = 7.2 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.1, 54.9, 114.2, 118.3, 121.2, 127.2, 128.4, 128.9, 129.3, 133.7, 136.8, 142.1, 143.8, 146.8, 198.6 ppm. IR (KBr): $\tilde{\nu}$ = 3447, 1680 cm^{-1}. $C_{36}H_{32}N_2O_2$ (524.66): C 82.41, H 6.15, N 5.34; found C 82.63, H 6.08, N 5.23.

2-{(4-Chlorophenyl)[(3-chlorophenyl)amino]methyl}cyclohexanone (5c): Yield: 0.613 g, 88%. Light brown solid, m.p. 154–155 °C. Data for the major isomer (*anti*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.79 (m, 3 H), 1.90–1.99 (m, 3 H), 2.31–2.41 (m, 2 H), 2.72–2.76 (m, 1 H), 4.52 (d, J = 6.0 Hz, 1 H), 4.90 (br. s, 1 H), 6.38 (d, J = 8.4 Hz, 1 H), 6.48 (s, 1 H), 6.61 (d, J = 7.2 Hz, 1 H), 6.97 (t, J = 8.0 Hz, 1 H), 7.29 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 28.0, 32.0, 42.4, 57.3, 57.7, 112.0, 113.5, 117.8, 128.7, 128.9, 130.3, 133.1, 135.0, 140.0, 148.4, 212.5 ppm. IR (KBr): $\tilde{\nu}$ = 3339, 1706 cm^{-1}. $C_{19}H_{19}Cl_2NO$ (348.27): C 65.53, H 5.50, N 4.02; found C 65.34, H 5.43, N 3.90.

Diethyl 2-{[(3-Chlorophenyl)amino](phenyl)methyl}malonate (6b): Yield: 0.707 g, 94%. White solid, m.p. 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.2 Hz, 3 H), 1.17 (t, J = 7.2 Hz, 3 H), 3.88 (d, J = 5.2 Hz, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.18 (d, J = 5.6 Hz, 1 H), 5.56 (br. s, 1 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.58 (s, 1 H), 6.62 (d, J = 8.8 Hz, 1 H), 6.99 (t, J = 8.8 Hz, 1 H), 7.26–7.35 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 13.9, 56.7, 57.8, 61.5, 61.9, 111.8, 113.3, 117.6, 126.5, 127.7, 128.6, 130.0, 134.9, 139.0, 147.8, 167.0, 168.0 ppm. IR (KBr): $\tilde{\nu}$ = 3370, 1752 cm^{-1}. $C_{20}H_{22}ClNO_4$ (375.85): C 63.91, H 5.90, N 3.73; found C 63.71, H 5.83, N 3.61.

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