Mannich-Type Reaction in Water in the Presence of a Surfactant

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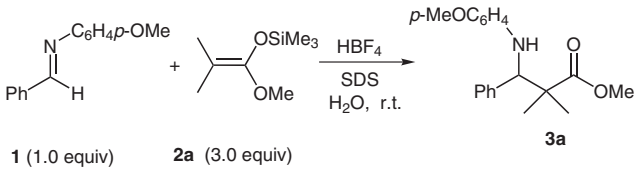
Abstract: The effect of sodium dodecyl sulfate (SDS) loading in fluoroboric acid catalyzed Mannich-type reactions of ketene silyl acetals with aldimines was studied. The reaction proceeded smoothly in the presence of 1 mol% of SDS. Formation of small particles was observed by transmission electron microscopy.

Key words: Mannich-type reaction, water, imine, surfactant, amino ester

The Mannich-type reaction of silyl enolates with aldimines constitutes an important method with which to prepare β-amino carbonyl intermediates that facilitate access to many biologically active nitrogen containing compounds.[1] A number of Lewis acid catalysts have been developed that promote such Mannich-type reactions,[2] and enantioselective versions have also recently been developed.[3,4,5] Organic reactions in aqueous media have attracted much attention from synthetic organic chemists lately, not only because water is the most abundant, cheapest and most environmentally friendly solvent, but also because water, when compared to conventional organic solvents, possesses many unique characteristics.[6] We have recently found that Mannich-type reactions take place smoothly under the influence of substoichiometric amounts of Brønsted acid, typically fluoroboric acid (HBF_4), to furnish the corresponding β-amino carbonyl compounds, in high yields, in aqueous organic solvents. Furthermore, the HBF_4-catalyzed Mannich-type reaction proceeded in the presence of sodium dodecyl sulfate (SDS) in water, under organic solvent-free conditions.[7] Aza Diels–Alder reactions in aqueous media have also been successfully achieved.[8] In the HBF_4-catalyzed Mannich-type reaction in water, we previously used 40 mol% of SDS to obtain the corresponding β-amino carbonyl compounds in high yields.[9] Addition of SDS resulted in the generation of small particles through the formation of micelles, thus increasing the solubility of the substrates in water and facilitating a smooth reaction. Unfortunately, normal phase separation during work-up was hampered by the formation of emulsions due to the presence of such large amounts of SDS. In order to overcome this difficulty, an anion-exchange resin was required which enabled the reaction mixture to be worked up more efficiently. We subsequently reinvestigated the loading of SDS and found that the amount could be significantly reduced when ketene silyl acetals were employed as a nucleophile. Herein we wish to report the results obtained using a Mannich-type reaction in water, in the presence of catalytic amounts of SDS.[10]

At the outset, loading of SDS was studied using the reaction of the ketene silyl acetal **2a** with aldimine **1** (Table 1). When standard reaction conditions (40 mol% of SDS)[7b,d] were employed, the β-amino ester **3a** was obtained quantitatively (entry 1). Interestingly, the Mannich-type reaction also proceeded smoothly in the presence of as low as 1 mol% of SDS (entry 3). Further decreases in the loading of SDS dropped the yield of **3a** significantly, though the reaction still proceeded, though sluggishly, in the absence of SDS (entry 4). An increase in the amount of HBF_4 to 30 mol% led to the slow formation of the adduct in good yield (entry 5). We thus selected two protocols with which to further investigate the modified Mannich-type reaction; Protocol 1: HBF_4 (10 mol%) with SDS (1 mol%) and Protocol 2: HBF_4 (30 mol%) in the absence of SDS.

Table 1 Effect of the Loading of HBF_4 and SDS



1 (1.0 equiv) **2a** (3.0 equiv) **3a**

Entry	SDS (mol%)	HBF_4 (mol%)	Time (h)	Yield (%)
1	40	10	0.5	100
2	10	10	0.5	99
3	1	10	1	94
4	0	10	4	20
5	0	30	4	81

The results of the Mannich-type reaction of silyl enol ethers and those of the ketene silyl acetals (3.0 equiv) obtained with Protocol 1 are shown in Table 2. The reaction of ketene silyl acetals (**2a**–**e**) and the ketene thio acetal **2f** generally proceeded smoothly in the presence of as low as 1 mol% of SDS. In contrast, the Mannich-type reaction of silyl enol ethers were not effective, with the exception of the silyl enol ether **2i**, derived from acetophenone. It should be noted that both silyl enol ethers and ketene silyl acetals reacted well when 40 mol% of SDS was employed. The use of anion-exchange resins could be avoid-

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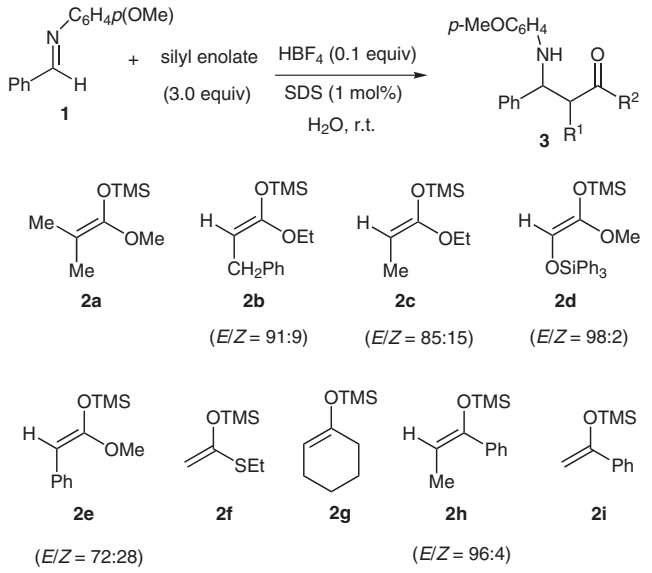
Table 2 Results of the Mannich-Type Reactions



Entry	Nu	Time (h)	Product	Yield (%)	*syn*:*anti*
1	**2a**	1	**3a**	94	–
2	**2b**	6	**3b**	100	19:81
3	**2c**	2	**3c**	97	70:30
4	**2d**	2	**3d**	91	85:15
5	**2e**	1	**3e**	93	16:84
6	**2f**	1	**3f**	99	–
7	**2g**	7	**3g**	13	38:62
8	**2h**	5	**3h**	0	–
9	**2i**	7	**3i**	89	–

ed using 1 mol% of SDS since, despite the formation of a turbid solution, clear phase separation was possible.

Three-component Mannich-type reactions[11] were also studied using protocols 1 and 2 (Table 3). Aliphatic aldehydes as well as aromatic aldehydes reacted smoothly to afford the corresponding β-amino esters in good to high yields.

The Mannich-type reaction in water, in the presence of SDS, is considered to proceed under micellar conditions. Transmission electron microscopic (TEM) observation of the reaction mixture in the presence of 40 mol% of SDS, both 10 minutes (left) and 30 minutes (right) after the reaction started, clearly showed the formation of small particles, thus demonstrating that the reaction proceeded under micellar conditions (Figure 1; top). The formation of similar, small particles was also observed even in the presence of just 1 mol% of SDS. In contrast, since the substrates are not soluble in water, particle formation was not observed by TEM in the absence of SDS. In this case, the reaction presumably proceeded at the boundary between substrates and water. Recently, Sharpless and co-workers reported on the rate acceleration of organic reactions on the water surface.[12] In the present case, the Mannich-type reaction is faster under micellar conditions than on the conventional water surface.

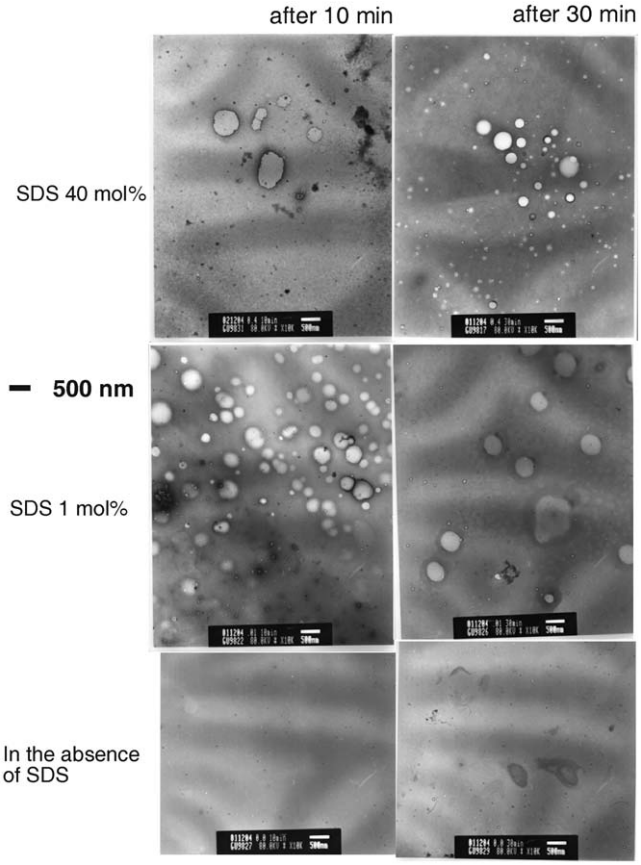
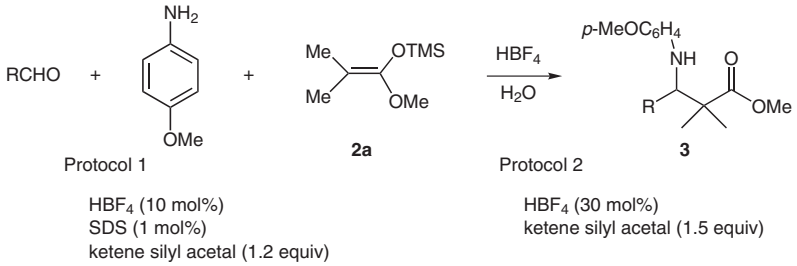


Figure 1 Transmission electron microscopy of the reaction mixture

Finally, the stability of the ketene silyl acetal in water was studied. As a model, the reaction of the ketene silyl acetal **2a** with the aldimine **4**, derived from pivalaldehyde, was investigated (Figure 2). Since **4** does not form the Mannich adduct owing to its steric hindrance, the stability of **2a** could be measured in the presence of **4**. The amount of **2a** was monitored by GC with dodecane as an internal standard. As can be seen in Figure 2, when imine **4** was absent, **2a** decomposed almost instantaneously in HBF_4 in the presence of SDS (Exp. 1). In the presence of the aldimine **4**, **2a** decomposed quickly in water when SDS was present (Exp. 2), whereas in the absence of SDS, **2a** survived for more than five hours (Exp. 3). These observations demonstrate that the Mannich-type reaction must proceed quite rapidly under micellar conditions since the stability of the ketene silyl acetal is lower under micellar conditions than in pure water, in which ketene silyl acetal is separated from the water phase.

Table 3 Results of the Three-Component Mannich-Type Reactions



Entry	Aldehyde	Product	Protocol 1		Protocol 2	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	C_6H_5CHO	**3a**	40 min	87	5	74
2	4-MeC_6H_4CHO	**3j**	3	92	5	73
3	2-furfural	**3k**	1	90	5	96
4	PhCOCHO[a]	**3l**	5	88	5	89
5	$BnOCH_2CHO$	**3m**	3	73	5	84
6	$PhCH_2CH_2CHO$	**3n**	3	53	5	86

[a] PhCOCHO·H_2O was employed.

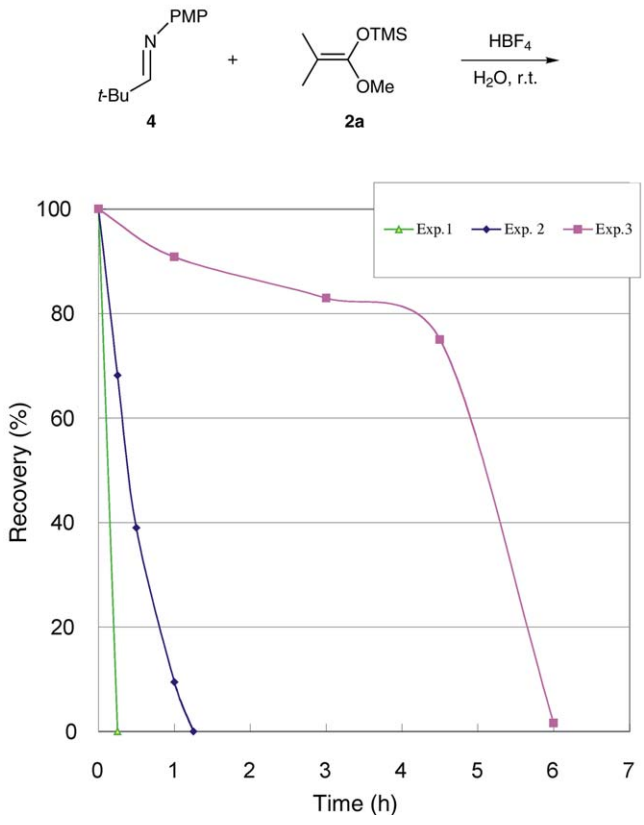


Figure 2 Stability of a ketene silyl acetal **2a** in various solvent systems; (Exp. 1) **2a**, HBF_4 (10 mol%), SDS (1 mol%), H_2O, r.t.; (Exp. 2) **4**, **2a** (3 equiv), HBF_4 (10 mol%), SDS (1 mol%), H_2O, r.t.; (Exp. 3) **4**, **2a** (3 equiv), HBF_4 (10 mol%), H_2O, r.t.

In conclusion, we have developed two methods for the Brønsted acid catalyzed Mannich-type reaction of ketene silyl acetals with aldimines, generated in situ from the corresponding aldehyde and amine, in water. This approach enables a simple work-up that does not require the addition of ion-exchange resin.

NMR spectra were measured with a Varian Unity-INOVA 400 spectrometer in $CDCl_3$. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. All solvents were purified according to standard procedures. Column chromatography (PSQ 60B, Fuji Silysia Chemical Ltd.) and preparative TLC (Wakogel B-5F, Wako Pure Chemical Industries) were conducted on silica gel.

Typical Procedure

An aq soln of HBF_4 (1.3598 M, 8 μL, 0.008 mmol) was added to a r.t. mixture of *N*-benzylidene-*p*-anisidine (**1**; 17 mg, 0.0805 mmol), ketene silyl acetal (**2a**; 48 μL, 0.241 mmol) and SDS (0.10027 M, 8 μL, 0.0008 mmol) in H_2O (0.5 mL). After being stirred at r.t. for 0.5 h, the reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to dryness. Purification of the crude mixture by preparative TLC (SiO_2, hexane–EtOAc, 10:1) gave **3a** (94%).

TEM Analysis

The sample was mounted on a grid with films of carbon-coated Parlodion by floating the grid on a drop of the reaction mixture. The sample side of the grid was washed with ion-exchanged H_2O and negatively stained with freshly prepared 2% uranyl acetate. The grid was examined with a JEOL JEM1010 transmission microscope at 80 kV.

Methyl 3-[*N*-(4-Methoxyphenylamino)]-2,2-dimethyl-3-phenylpropionate (3a)
R_f = 0.3 (hexane–EtOAc, 10:1).

IR ($CHCl_3$): 3422, 3015, 2953, 1724, 1514, 1236, 1138, 704, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.24 (s, 3 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 4.45 (s, 1 H), 4.45 (s, 1 H), 6.45 (d, *J* = 8.8 Hz, 2 H), 6.63 (d, *J* = 8.8 Hz, 2 H), 7.25–7.28 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 151.9, 141.2, 139.3, 128.3, 127.9, 127.3, 114.6, 114.6, 65.1, 55.6, 52.0, 47.1, 24.5, 20.4.

MS: *m*/*z* (%) = 313(3) [M^+], 212 (82), 196 (100), 167 (30), 77 (28), 41 (55).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.71; H, 7.25; N, 4.76.

Methyl 2-Benzyl-3-[*N*-(4-methoxyphenylamino)]-3-phenylpropionate (3b)
Mp 111.0–113.0 °C (EtOH); R_f = 0.3 (hexane–EtOAc, 10:1).

IR ($CHCl_3$): 3416, 3013, 2835, 1720, 1510, 1454, 1236, 1180, 1038, 820, 700, 519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.40 (m, 10 H), 6.65–6.74 (m, 2 H), 6.45–6.50 (m, 2 H), 4.62 (d, *J* = 5.5 Hz, 1 H, *anti*), 4.47 (d, *J* = 5.3 Hz, 1 H, *syn*), 4.35 (s, 1 H, *anti*), 4.36 (s, 1 H, *syn*), 4.36 (br s, 1 H), 3.90 (q, *J* = 7.1 Hz, 2 H, *anti*), 3.93 (q, *J* = 7.1 Hz, 2 H, *syn*), 3.69 (s, 3 H, *anti*), 3.68 (s, 3 H, *syn*), 3.00–3.14 (m, 2 H), 2.85–2.96 (m, 1 H), 0.97 (t, *J* = 7.1 Hz, 3 H, *anti*), 0.95 (t, *J* = 7.1 Hz, 3 H, *syn*).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*) = 173.1, 152.2, 141.2, 140.7, 139.3, 128.8, 128.5, 128.4, 127.5, 127.0, 126.3, 115.0, 114.7, 60.6, 60.5, 55.7, 54.6, 33.7, 13.9.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*) = 174.0, 151.8, 141.5, 141.0, 138.6, 128.9, 128.5, 128.4, 127.3, 126.7, 126.5, 114.7, 114.5, 60.5, 59.0, 55.7, 54.7, 36.4, 13.9.

MS: *m*/*z* (%) = 389 (6) [M^+], 213 (13), 212 (100), 196 (11), 91 (12).

Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.87; H, 6.71; N, 3.57.

Methyl 3-[*N*-(4-Methoxyphenylamino)]-2-methyl-3-phenylpropionate (3c)
Oil; R_f = 0.3 (hexane–EtOAc, 8:1).

IR ($CHCl_3$): 3420, 3032, 2835, 1724, 1510, 1244, 1182, 1040, 820, 702, 521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.32 (m, 5 H), 6.64–6.68 (m, 2 H), 6.46–6.50 (m, 2 H), 4.63 (d, *J* = 5.3 Hz, 1 H, *syn*), 4.41 (d, *J* = 7.7 Hz, 1 H, *anti*), 4.32 (br s, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H, *anti*), 4.06 (q, *J* = 7.1 Hz, 2 H, *syn*), 3.68 (s, 3 H, *anti*), 3.67 (s, 3 H, *syn*), 2.91 (dq, *J* = 7.1 Hz, 5.3 Hz, 1 H, *syn*), 2.80 (dq, *J* = 7.7 Hz, 7.0 Hz, 1 H, *anti*), 1.16 (t, *J* = 7.1 Hz, 3 H, *anti*), 1.15 (d, *J* = 7.7 Hz, 3 H, *syn*), 1.14 (t, *J* = 7.1 Hz, 3 H, *anti*), 1.13 (d, *J* = 7.0 Hz, 3 H, *anti*).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*) = 175.0, 152.0, 141.4, 141.1, 128.5, 127.3, 126.9, 114.8, 114.7, 61.7, 60.6, 55.6, 46.9, 15.2, 14.1.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*) = 174.3, 152.1, 141.3, 141.0, 128.4, 127.2, 126.9, 114.9, 114.7, 60.7, 60.5, 55.7, 46.2, 14.1, 11.9.

MS: *m*/*z* (%) = 313 (6) [M^+], 213 (15), 212 (100), 211 (16), 196 (19), 91 (6), 77 (7), 57 (8).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.67; H, 7.68; N, 4.67.

Methyl 3-[*N*-(4-Methoxyphenylamino)]-3-phenyl-2-triphenylsiloxypropionate (3d)
Mp 129.0–135.0 °C (MeOH); R_f = 0.3 (hexane–EtOAc, 10:1).

IR ($CHCl_3$): 3420, 3013, 2953, 1755, 1514, 1429, 1229, 1119, 739, 507 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.54 (m, 20 H), 6.64–6.67 (m, 2 H, *syn*), 6.63–6.66 (m, 2 H, *anti*), 6.45–6.48 (m, 2 H, *syn*), 6.36–6.38 (m, 2 H, *anti*), 4.84 (dd, *J* = 8.4 Hz, 2.5 Hz, 1 H, *syn*), 4.84 (dd, *J* = 8.1 Hz, 5.6 Hz, 1 H, *anti*), 4.71 (d, *J* = 8.4 Hz, 1 H, *syn*), 4.71 (d, *J* = 8.1 Hz, 1 H, *anti*), 4.66 (d, *J* = 5.6 Hz, 1 H, *anti*), 4.65 (d, *J* = 2.5 Hz, 1 H, *syn*), 3.67 (s, 3 H, *syn*), 3.67 (s, 3 H, *anti*), 3.35 (s, 3 H, *syn*) 3.32 (s, 3 H, *anti*).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*) = 171.5, 152.0, 140.8, 138.6, 135.5, 133.1, 130.0, 128.5, 127.7, 127.4, 127.4, 114.7, 114.7, 60.9, 60.4, 55.7, 51.8.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*) = 171.1, 152.2, 140.6, 138.7, 134.9, 133.1, 130.2, 128.3, 127.9, 127.4, 127.3, 115.1, 114.7, 61.7, 60.9, 55.6, 51.5.

MS: *m*/*z* (%) = 559 (2) [M^+], 271 (2), 270 (2), 256 (6), 213 (16), 212 (100), 199 (2), 197 (3), 196 (3), 183 (2), 181 (3), 180 (3), 168 (5), 134 (4), 105 (2), 77 (2).

Anal. Calcd for $C_{35}H_{33}NO_4Si$: C, 75.10; H, 5.94; N, 2.50. Found: C, 74.88; H, 5.73; N, 2.48.

Methyl 3-[*N*-(4-Methoxyphenylamino)]-2,3-diphenylpropionate (3e)
Mp 145.5–147.0 °C (MeOH); R_f = 0.3 (hexane–EtOAc, 8:1).

IR ($CHCl_3$): 3398, 3031, 2955, 2835, 1734, 1512, 1454, 1240, 1163, 1036, 822, 700, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.46 (m, 10 H), 6.62–6.67 (m, 2 H, *syn*), 6.56–6.60 (m, 2 H, *anti*), 6.52–6.55 (m, 2 H, *syn*), 6.31–6.35 (m, 2 H, *anti*), 4.87 (d, *J* = 8.6 Hz, 1 H, *syn*), 4.87 (d, *J* = 9.9 Hz, 1 H, *anti*), 3.93 (d, *J* = 8.6 Hz, 1 H, *syn*), 3.87 (d, *J* = 9.9 Hz, 1 H, *anti*), 3.63 (s, 3 H, *anti*), 3.63 (s, 3 H, *syn*), 3.44 (s, 3 H, *syn*), 3.44 (s, 3 H, *anti*).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*) = 171.9, 152.4, 141.7, 141.2, 135.1, 129.0, 128.8, 128.5, 128.2, 127.6, 127.3, 115.5, 114.5, 64.3, 60.0, 55.6, 51.9.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*) = 172.9, 152.3, 140.8, 140.6, 135.5, 128.8, 128.3, 128.3, 127.5, 127.2, 127.9, 115.6, 114.6, 62.4, 58.9, 55.6, 52.2.

MS: *m*/*z* (%) = 211 (82), 196 (100), 167 (25), 92 (11), 89 (12), 77 (20), 64 (17), 63 (18), 51 (16).

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.63; H, 6.63; N, 3.80.

Ethyl 3-[*N*-(4-Methoxyphenylamino)]-3-phenylpropanethioate (3f)
Mp 76.0–77.0 °C (EtOH); R_f = 0.4 (hexane–EtOAc, 8:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.42 (m, 5 H), 6.66–6.70 (m, 2 H), 6.48–6.52 (m, 2 H), 4.76 (t, *J* = 6.8 Hz, 1 H), 4.27 (br s, 1 H), 3.68 (s, 3 H), 2.96 (d, *J* = 6.8 Hz, 2 H), 2.85 (q, *J* = 7.5 Hz, 2 H), 1.19 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 152.3, 142.2, 140.9, 128.7, 127.44, 126.3, 115.1, 114.7, 56.6, 55.6, 51.6, 23.6, 14.5.

IR ($CHCl_3$): 3406, 3030, 2934, 1711, 1364, 665 cm^{-1}.

MS (DI): *m*/*z* (%) = 315 (15) [$M]^+$, 213 (12), 212 (100), 196 (16), 122 (6), 104 (5), 77 (7).

Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44; S, 10.17. Found: C, 68.82; H, 6.96; N, 4.51; S, 9.83.

2-[Phenyl-*N*-(4-methoxyphenylamino)methyl]cyclohexanone (3g)[13]

R_f = 0.2 (Hexane–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.49 (m, 5 H), 6.62–6.65 (m, 2 H), 6.46–6.50 (m, 2 H), 4.73 (d, *J* = 4.2 Hz, 1 H, *syn*), 4.54 (d, *J* = 7.3 Hz, 1 H, *anti*), 4.36 (br s, 1 H), 3.67 (s, 3 H, *syn*), 3.61 (s, 3 H, *anti*), 1.26–2.86 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.8, 211.4, 152.1, 152.1, 141.8, 141.7, 141.6, 141.4, 128.4, 128.3, 127.5, 127.3, 127.1, 126.9, 115.5, 115.1, 114.6, 114.6, 58.9, 58.2, 57.5, 56.7, 55.6, 55.6, 42.4, 41.7, 28.9, 28.4, 27.9, 27.0, 24.9, 23.6.

MS: *m*/*z* (%) = 211 (85), 196 (100), 167 (22), 141(7), 115 (8), 92 (8), 89 (9), 77 (13), 63 (12), 51 (10).

3-*N*-(4-Methoxyphenylamino)-1,3-diphenyl-1-propanone (3i)

R_f = 0.3 (hexane–EtOAc, 5:1).

IR ($CHCl_3$): 3412, 3022, 2934, 1686, 1512, 1238, 775, 667 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.92 (m, 2 H), 7.54–7.58 (m, 1 H), 7.42–7.46 (m, 4 H), 7.30–7.34 (m, 2 H), 7.21–7.25 (m, 1 H), 6.66–6.69 (m, 2 H), 6.51–6.54 (m, 2 H), 4.92 (dd, *J* = 5.1 Hz, 7.7 Hz, 1 H), 4.29 (br s, 1 H), 3.68 (s, 3 H), 3.49 (dd, *J* = 5.1 Hz, 16.1 Hz, 1 H), 3.40 (dd, *J* = 7.7 Hz, 16.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 152.4, 143.2, 141.2, 136.8, 133.4, 128.8, 128.7, 128.2, 127.3, 126.4, 115.4, 114.7, 55.7, 46.4.

MS: *m*/*z* (%) = 211 (80), 196 (100), 167 (24), 115 (10), 92 (10), 89 (11), 77 (16), 63 (16), 51 (14).

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.74; H, 6.66; N, 4.28.

Methyl 3-[*N*-(4-Methoxyphenylamino)]-2,2-dimethyl-3-(4-methylphenyl)propionate (3j)

Mp 110.5–111.0 °C (MeOH); R_f = 0.2 (hexane–EtOAc, 10:1).

IR ($CHCl_3$): 3422, 3026, 2953, 1724, 1512, 1236, 822 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, 2 H), 7.07 (d, 2 H), 6.61–6.65 (m, 2 H), 6.43–6.47 (m, 2 H), 4.42 (2 × s, 2 H), 3.65 (2 × s, 6 H), 2.29 (s, 3 H), 1.23 (s, 3 H), 1.15 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 151.8, 141.2, 136.9, 136.2, 128.7, 128.2, 114.7, 114.6, 64.8, 55.6, 52.0, 47.1, 24.4, 21.0, 20.4.

MS: *m*/*z* (%) = 327 (3) [M]$^+$, 226 (100), 210 (56), 181 (6), 134 (9), 91 (10), 77 (12), 59 (8), 41 (22).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.51; H, 7.63; N, 4.11.

Methyl 3-(2-Furyl)-3-[*N*-(4-methoxyphenylamino)]-2,2-dimethylpropionate (3k)

Mp 75.5–76.5 °C (EtOH); R_f = 0.7 (hexane–EtOAc, 3:1).

IR ($CHCl_3$): 3408, 3009, 2953, 1724, 1512, 1232, 1148, 673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.25 (s, 3 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 4.14 (br s, 1 H), 4.62 (s, 1 H), 6.12 (d, *J* = 3.1 Hz, 1 H), 6.25 (dd, *J* = 1.8 Hz, 3.1 Hz, 1 H), 6.58–6.60 (m, 2 H), 6.67–6.72 (m, 2 H), 7.30 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 153.5, 152.6, 141.6, 141.2, 115.6, 114.6, 110.1, 108.0, 59.9, 55.6, 52.0, 47.3, 23.5, 20.8.

MS: *m*/*z* (%) = 303 (5) [M]$^+$, 202 (95), 186 (15), 122 (20), 77 (22), 59 (23), 41 (100).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.27; H, 7.11; N, 4.65.

Methyl 3-[*N*-(4-Methoxyphenylamino)]-2,2-dimethyl-4-phenyl-4-oxobutanoate (3l)[14]

R_f = 0.5 (MeCN–toluene, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 3 H), 1.31 (s, 3 H), 3.56 (s, 3 H), 3.72 (s, 3 H), 4.49 (s, 1 H), 5.20 (s, 1 H), 6.73–6.75 (m, 4 H), 7.41–7.45 (m, 2 H), 7.52–7.56 (m, 1 H), 7.87–7.90 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 153.1, 141.4, 137.4, 133.3, 128.6, 128.3, 116.2, 144.9, 47.6, 55.7, 52.0, 46.5, 46.0, 23.0, 21.9.

IR ($CHCl_3$): 3528, 3381, 3030, 2953, 1732, 1682, 1514, 1240, 790, 716 cm^{-1}.

MS (DI): *m*/*z* (%) = 341 (7) [M]$^+$, 240 (12), 237 (15), 236 (100), 177 (12), 176 (61), 134 (17), 105 (15), 77 (23).

Methyl 4-Benzyloxy-3-[*N*-(4-methoxyphenylamino)]-2,2-dimethylbutanoate (3m)

R_f = 0.7 (hexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.37 (m, 5 H), 6.72–6.76 (m, 2 H), 6.60–6.64 (m, 2 H), 4.56 (d, *J* = 11.2 Hz, 1 H), 4.37 (d, *J* = 7.3 Hz, 1 H), 4.32 (d, *J* = 11.2 Hz, 1 H), 3.77 (dq, *J* = 6.2 Hz, 1 H), 3.73 (s, 3 H), 3.42 (d, *J* = 7.9 Hz, 1 H), 3.50 (s, 3 H), 1.27 (s, 3 H), 1.21 (s, 3 H), 1.17 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 151.4, 144.3, 138.3, 128.3, 127.9, 127.5, 114.9, 114.0, 74.4, 70.5, 65.4, 55.8, 51.6, 47.2, 24.0, 22.9, 17.9.

IR ($CHCl_3$): 3423, 3030, 2875, 1724, 1514, 1456, 1236, 1138, 793, 675 cm^{-1}.

MS (DI): *m*/*z* (%) = 371 (14) [M]$^+$, 270 (23), 237 (19), 236 (100), 176 (45), 162 (22), 134 (9), 91 (39), 77 (6), 65 (7).

Methyl 3-[*N*-(4-Methoxyphenylamino)]-2,2-dimethyl-5-phenylpentanoate (3n)

oil; R_f = 0.4 (hexane–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.27 (m, 2 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 6.72–6.76 (m, 2 H), 6.57–6.59 (m, 2 H), 3.75 (s, 3 H), 3.54 (s, 1 H), 3.43 (s, 1 H), 2.77–2.84 (m, 1 H), 2.51–2.59 (m, 1 H), 1.84–1.91 (m, 1 H), 1.55–1.60 (m, 1 H), 1.18 (s, 3 H), 1.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 151.5, 143.4, 141.8, 128.4, 128.2, 125.8, 114.8, 114.0, 60.1, 55.7, 51.6, 48.0, 35.0, 33.2, 22.5, 21.8.

IR ($CHCl_3$): 3530, 3425, 3013, 2835, 1724, 1506, 1456, 1215, 1040, 791, 719, 517 cm^{-1}.

MS (DI): *m*/*z* (%) = 341 (10) [M]$^+$, 240 (100), 149 (30), 134 (11), 91 (32).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.70; H, 7.89; N, 4.08.

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