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Solvent-Promoted and -Controlled Aza-Michael Reaction with Aromatic Amines

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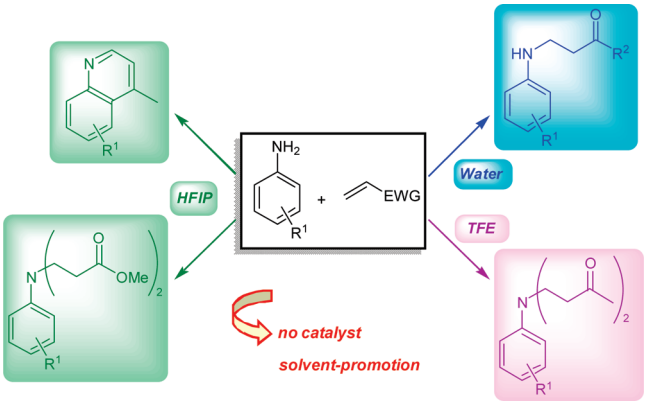

1,4-Addition of anilines onto Michael acceptors proceeds easily in specific polar protic solvents, without any promoting agent. According to the solvent and to the electrophile, the selectivity of the reaction can be finely tuned. With methyl acrylate as electrophile, only monoaddition takes place in water, while the diadduct is yielded in hexafluoroisopropyl alcohol (HFIP). The use of methyl vinyl ketone as a partner affords the monoadduct in water, the diadduct in trifluoroethanol (TFE), and the quinoline in HFIP.

Introduction

Anilines are poor nucleophiles with regard to aliphatic amines;[1] as a consequence, their addition onto electrophiles is very sluggish and requires the assistance of powerful promoters. However, it seems that the nucleophilicity of aromatic amines is highly solvent dependent, as exemplified by Mayr's nucleophilic scale of amines, where aniline is reported to react two times faster in water than in acetonitrile.[2] As a comparison, this "unexpected high nucleophilicity" of aniline in water is close to that of ethyl- and benzylamine.[2] Following from this, the 1,4-addition between aromatic amines and Michael acceptors proved to be highly challenging[3] until the recent breakthrough by the introduction of aqueous media with promoting agents (e.g., metal catalyst, surfactant).[3b,e,i] Still, examples are scarce, and most of the methods provide only access to the monoaddition products. We demonstrate herein that the highly polar protic solvents water, trifluoroethanol (TFE), and hexafluoroisopropyl alcohol (HFIP) are able to promote the 1,4-addition of aromatic amines onto Michael acceptors (methyl acrylate, methyl vinyl ketone) and that the selectivity of the reaction is under exclusive solvent control, affording thus monoadducts, diadducts, or even cyclialkylation products.

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(1) Lee, I.; Sung, D. D. In *Chemistry of Anilines*; Rappoport, Z., Ed.; Wiley: Chichester, 2007; pp 537−581.
(2) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688.
(3) (a) Banushali, M. J.; Nandurkar, N. S.; Jagtap, S. R.; Bhanage, B. M. *Catal. Commun.* **2008**, *9*, 1189–1195. (b) Chen, X.; She, J.; Shang, Z.; Wu, J.; Zhang, P. *Synthesis* **2008**, *24*, 3931–3936. (c) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal. A: Chem.* **2006**, *252*, 150–155. (d) Fetterly, B. M.; Jana, N. K.; Verkade, J. G. *Tetrahedron* **2006**, *62*, 440–456. (e) Surendra, K.; Krishnaveni, N. S.; Sridhar, R.; Rao, K. R. *Tetrahedron Lett.* **2006**, *47*, 2125–2128. (f) Karodia, N.; Liu, X.; Ludley, P.; Pletsas, D.; Stevenson, G. *Tetrahedron* **2006**, *62*, 11039–11043. (g) Yang, L.; Xu, L.-W.; Zhou, W.; Li, L.; Xia, C.-G. *Tetrahedron Lett.* **2006**, *47*, 7723–7726. (h) Duan, Z.; Xuan, X.; Li, T.; Yang, C.; Wu, Y. *Tetrahedron Lett.* **2006**, *47*, 5433–5436. (i) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. *Adv. Synth. Catal.* **2005**, *347*, 655–661. (j) Vicario, J.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2009**, *74*, 452–455. (k) Reboule, I.; Gil, R.; Collin, J. *Eur. J. Org. Chem.* **2008**, 532–539. (l) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639. (m) Xu, L.-W.; Xia, C.-G. *Helv. Chim. Acta* **2004**, *87*, 1522–1526. (n) Xu, L.-W.; Li, J.-W.; Xia, C.-G.; Zhou, S.-L.; Hu, X.-X. *Synlett* **2003**, 2425–2427.

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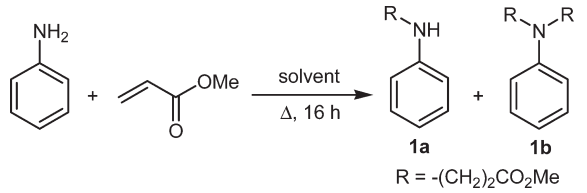
TABLE 1. Aza-Michael Reaction between Aniline and Methyl Acrylate in Various Solvents[a]



entry	solvent	methyl acrylate (equiv)	T (°C)	conv[b] (%)	**1a**/**1b**[c]
1	water	1.0	80	15	100:0
2	**water**	**3.0**	**80**	**40**	**100:0**
3[d]	**water/TFE**	**3.0**	**80**	**100**	**94:6**
4	TFE	1.0	80	50	80:20
5	TFE	3.0	80	77	71:29
6	HFIP	1.0	58	50	37:63
7	**HFIP**	**3.0**	**58**	**95**	**4:96**
8	CH_2Cl_2	1−3.0	40	0	
9	ethanol	1−3.0	78	0	

[a]Reactions conditions: aromatic amine (1.5 mmol), Michael acceptor (4.5 mmol) in solvent (1.5 mL). [b]Conversion was measured by GC. [c]Ratio was determined by ^{1}H NMR from the crude product. [d]2 equiv of TFE (0.17 mL) was used.

Results

The monoaddition of aniline onto methyl acrylate has been reported to proceed in water in the presence of tungstophosphoric acid[3b] or β-cyclodextrin,[3e] within 8−40 h at room temperature. In this connection, our first experiments were performed by reacting aniline and methyl acrylate in neat water at 80 °C (Table 1). While with 1 equiv of the electrophile only 15% conversion occurred after 16 h (entry 1), we were pleased to observe that with 3 equiv a reasonable 40% conversion took place to afford the β-amino monoester **1a** as sole product (entry 2). Apart from water, the fluorous alcohols TFE and HFIP have also been shown to be excellent solvents for other nucleophilic reactions with anilines, as exemplified by the opening of epoxides.[4−6] Thus, the aza-Michael addition was conducted again in water at 80 °C, but with TFE as a cosolvent (entry 3); this resulted in a full conversion of the starting material in 16 h, to yield **1a** (94%), along with traces of diaddition product **1b** (6%). However, the use of neat TFE as the reaction medium had a negative impact on the reaction course with a lower conversion rate (< 80%) and a lower selectivity (**1a**/**1b**, 70:30; entry 5). Unfortunately, this latter reaction could not be improved with a lower amount of methyl acrylate (with 1 equiv: 80:20; entry 4). In contrast, with 3 equiv of the Michael acceptor, the reaction performed in HFIP at reflux (58 °C) afforded an excellent 95% conversion within 16 h (entry 7). Moreover, in this solvent the reaction underwent a surprising complete switch of selectivity: the diaddition product **1b** was obtained as almost a single product (96%; entry 6). For comparison, the same reaction was performed in refluxing dichloromethane (40 °C) and ethanol (78 °C; entries 8 and 9, respectively). In these solvents, no reaction occurred revealing the unique role of water and fluoro alcohols in the promotion and the selectivity of the reaction.

Following the optimized reaction conditions reported in Table 1, various aromatic amines were assessed with methyl acrylate (3 equiv) in water, water/TFE, and HFIP under heating (Table 2). In water, while with simple aniline the reaction afforded **1a** with only 34% yield after 16 h (entry 1), the presence of electron-donating substituents (methyl, methoxy) on the arene ring allowed the reaction to afford the monoaddition products **2a** and **3a** in satisfying yields (52% and 62%, respectively; entries 2 and 3). Conversely, the presence of an electron-withdrawing group is detrimental, as exemplified by the lack of reaction with 4-chloroaniline as the substrate (entry 4). According to our preliminary experiments, the addition of TFE to water proved to be effective for the addition of simple aniline with 85% yield for **1a** toward 34% without TFE (entries 1 and 5). However, with 4-anisidine the conversion was complete but the reaction yielded mixtures of mono- and disubstituted adducts (entry 6), while with 4-chloroaniline only poor conversion was obtained (entry 7). Conversely, switching to HFIP as solvent gave excellent results to yield almost exclusively the product stemming from a double addition, accompanied by less than 5% of the monoaddition adduct. Yields of products were good to excellent for aniline and the electron-rich 4-toluidine and 4-anisidine (75−95% yields; entries 8−10); even 4-chloroaniline also reacted satisfyingly (66% yield, entry 11). However, with 4-nitroaniline no product was obtained (entry 12).

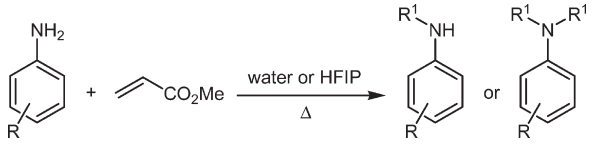
The 1,4-addition of aromatic amines with methyl vinyl ketone (MVK) as Michael acceptor has been previously reported.[3d−g] As for methyl acrylate, most of the reports describe the monoaddition onto the electrophile. However, according to our observations described above, the solvent could also influence the course of the reaction with this partner (Table 3). Indeed, in water as the medium, the reaction proceeded smoothly at room temperature within short reaction times, less than 4 h for electron-rich arenes and 6 h for 4-chloroaniline, and all products were obtained in good to high yields (65−83% yield, entries 1−7). Moreover, the use of TFE also allowed a complete consumption of starting materials at room temperature to lead exclusively to the diaddition adducts, here also in good yields (70−80%; entries 8−14). Furthermore, even with the poor nucleophile 4-nitroaniline, the reaction took place nicely in 24 h (70% yield). Surprisingly, under the same conditions (with 3 equiv of MVK at room temperature), the reaction performed in HFIP also afforded the amino diketone **6b**, albeit

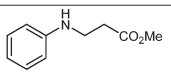
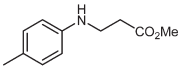
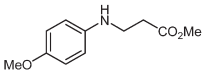
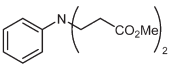
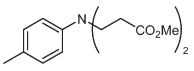
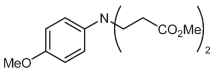
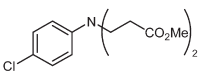
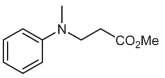
(4) Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2000**, *65*, 6749–6751.

(5) For reviews on fluorous alcohols, see: (a) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925–2943. (b) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29. (c) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 341−350.

(6) For recent contributions on reactions in fluorous alcohols, see: (a) Willot, M.; Chen, J. C.; Zhu, J. *Synlett* **2009**, 577–580. (b) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9739–9742. (c) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523–3529. (d) De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron* **2008**, *64*, 10497–10500. (e) Westermaier, M.; Mayr, H. *Chem.—Eur. J.* **2008**, *14*, 1638–1647. (f) Heydari, A.; Khaksar, S.; Tajbakhsh, M. *Synthesis* **2008**, 3126–3130. (g) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224–1226. (h) Hata, K.; Hamamoto, H.; Shiozaki, Y.; Cämmerer, S. B.; Kita, Y. *Tetrahedron* **2007**, *63*, 4052–4060. (i) Dubrovina, N. V.; Shuklov, I. A.; Birkholz, M.-N.; Michalik, D.; Paciello, R.; Börner, A. *Adv. Synth. Catal.* **2007**, *349*, 2183–2187. (j) Yagi, H.; Jerina, D. M. *J. Org. Chem.* **2007**, *72*, 9983–9990. (k) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553–2556. (l) Legros, J.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899–1902. (m) Di Salvo, A.; David, M.; Crousse, B.; Bonnet-Delpon, D. *Adv. Synth. Catal.* **2006**, *348*, 118–124.

TABLE 2. Aza-Michael Reaction of Aromatic Amines with Methyl Acrylate in Water and HFIP[a]



Entry	R	Solvent	Time [h]	Product[b]	Yield [%][c]
1	H	water	16	 **1a**	34
2	4-Me	water	16	 **2a**	52
3	4-MeO	water	16	 **3a**	62
4	4-Cl	water	16	–	–
5	H	water/TFE	16	**1a**	85
6	4-MeO	water/TFE	16	**3a**/**3b** (63:37)	100% conv.[d]
7	4-Cl	water/TFE	16	**4a**/**4b** (100:0)	20% conv.[d]
8	H	HFIP	12	 **1b**	75
9	4-Me	HFIP	12	 **2b**	80
10	4-MeO	HFIP	7	 **3b**	95
11	4-Cl	HFIP	12	 **4b**	66
12	4-NO_2	HFIP	–	–	–
13	*N*-Me	HFIP	2.5	 **5**	96

[a]Reaction conditions: aromatic amine (1.5 mmol), Michael acceptor (4.5 mmol) in water (1.5 mL; 80 °C) or HFIP (1.5 mL; 58 °C). [b]In HFIP, diaddition product was >95%. In water, only monoaddition product was afforded. [c]Isolated yields of the major product. [d]Not isolated.

accompanied by notable amounts of quinoline **18**. Notably, performing the same reaction at reflux in HFIP allowed us to obtain **18** in 56% yield, without any traces of diadduct **6b** (entry 15). Clearly, the quinoline derivative **18** comes from the conjugate addition of the amine to MVK, followed by cyclization and aromatization under air.[7] The synthesis of quinolines via a tandem aza-Michael reaction/cyclialkylation/oxidation process from aromatic amines and acrolein is well-known as the Skraup−Doebner−von Miller reaction, which takes place generally under harsh conditions (acidic medium, strong heating).[8] To our knowledge, there is only one study involving methyl vinyl ketone as a partner for this purpose: a reaction which proceeds with silica-supported $InCl_3$ under microwave irradiation.[9] In this context, the scope of the reaction between aniline and MVK in HFIP was extended to other aromatic amines (entries 16−20). It emerges that the process is quite general with electron-rich anilines: 4-toluidine, 4-anisidine, 3-toluidine, 3-anisidine, and 3,4-dimethoxy aniline also affording the corresponding quinoline derivatives in satisfactory yields (50−60%). However, in the presence of an electron-withdrawing 4-nitro group on the arene ring, monoaddition occurs but the product did not undergo subsequent cyclization, and instead, a second addition of the electrophile gave **17b** (80% yield; entry 21).

From a mechanistic standpoint, the solvent effect on the reaction depicted herein is rather intriguing. Nevertheless, one can notice that TFE and HFIP seem to share more features with water than with ethanol, as the first three solvents are able to promote the addition of aniline onto methyl acrylate. Moreover, water, TFE, and HFIP are highly polar and protogenic solvents, which could be key factors.[10] Indeed, it is commonly admitted that fluorous alcohols can activate protophilic electrophiles through hydrogen bonds (e.g., epoxides, esters, etc.).[10b,11] Thus, TFE and HFIP are both able to promote the first 1,4-addition of aniline onto a conjugated carbonyl compound to yield the corresponding product. Knowing that hydrogen bond donation ability of HFIP is much stronger than that of TFE, it is not surprising that HFIP is able to promote "further" transformation compared to TFE (diaddition with methyl acrylate, cyclialkylation with MVK). However, in the case of water the promotion of the reaction cannot be attributed to hydrogen bond donation only. Indeed, the high nucleophilicity of aniline in water, as described by Mayr, is based on the kinetics of reactions between benzhydrylium ions and amines, which does not take into account this effect. Thus, even if it is too early at this stage to get a deeper insight on the solvent effects, a reasonable hypothesis could be that water mainly "activates" the nucleophile, while the fluoro alcohols act more on the electrophile.

(7) HFIP has already been shown to promote internal electrophilic addition of aniline derivatives onto electron-poor ketones: Rodrigues, I.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2001**, *66*, 2098–2103.

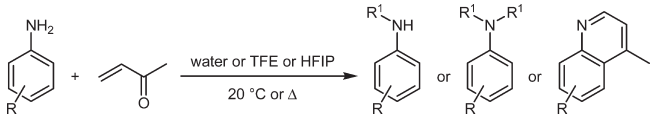
(8) *Name Reactions*, 2nd ed.; Li, J. J., Ed.; Springer: Berlin, 2003; pp 117−118 and 378−379.

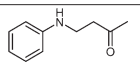
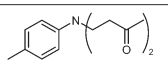
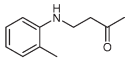
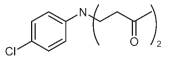
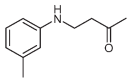
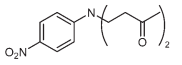
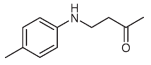
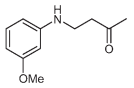
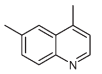
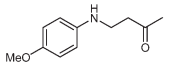
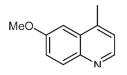
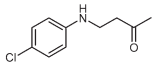
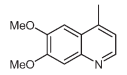
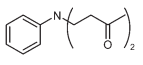
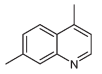
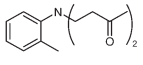
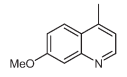
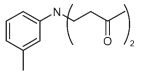
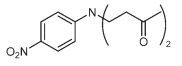
(9) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531–533.

(10) (a) Polarity parameter E_N^T for EtOH, 0.654; TFE, 0.898; HFIP, 1.068; H_2O, 1.000. Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319–2358. (b) Hydrogen bond donation parameter AN for EtOH, 37.1; TFE, 53.8; HFIP, 66.7; H_2O, 54.8. Eberson, L.; Hartshorn, M. P.; Persson, O.; Radner, F. *Chem. Commun.* **1996**, 2105–2112.

(11) For applications and studies on the hydrogen bond ability of fluorous alcohols, see: (a) Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Chem. Commun.* **2008**, 4954–4955. (b) Berrien, J.-F.; Ourévitch, M.; Morgant, G.; Ghermani, N. E.; Crousse, B.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2007**, *128*, 839–843. (c) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426.

TABLE 3. Aza-Michael Reaction of Anilines with MVK in Water, TFE, or HFIP[a]



Entry	R	Solvent	Time [h]	Product	Yield [%]	Entry	R	Solvent	Time [h]	Product	Yield [%]
1	H	water	2	 **6a**	80	11	4-Me	TFE	6	 **9b**	80
2	2-Me	water	4	 **7a**	70	13	4-Cl	TFE	12	 **12b**	74
3	3-Me	water	2	 **8a**	78	14	4-NO_2	TFE	24	 **13b**	70
4	4-Me	water	3	 **9a**	81	15	H	HFIP	6	 **14**	56
5	3-MeO	water	3	 **10a**	65	16	4-Me	HFIP	6	 **15**	53
6	4-MeO	water	2	 **11a**	83	17	4-MeO	HFIP	6	 **16**	50
7	4-Cl	water	6	 **12a**	77	18	3,4-$(MeO)_2$	HFIP	6	 **17**	56
8	H	TFE	6	 **6b**	80	19	3-Me	HFIP	6	 **18**	50
9	2-Me	TFE	6	 **7b**	75	20	3-MeO	HFIP	6	 **19**	62
10	3-Me	TFE	6	 **8b**	77	21	4-NO_2	HFIP	12	 **13b**	77

[a]Reactions conditions: aromatic amine (1.5 mmol), Michael acceptor (2.3−4.5 mmol) in water (1.5 mL; 20 °C) or TFE (1.5 mL, 20 °C) or HFIP (1.5 mL; 58 °C).

Conclusion

In conclusion, the Michael addition of anilines onto electron-deficient olefins proceeds easily in water, trifluoroethanol and hexafluoroisopropanol without any assisting agent. Moreover, according to the nature of the solvent and of the electrophile, the selectivity of the reaction can be finely tuned to afford mono- or diaddition products, or even quinolines, in a one-pot fashion.[12] Additional efforts involving the extension of the methodology to other electrophiles and an in-depth study for the solvent effect comprehension are underway.

Experimental Section

General Procedure for the Aza-Michael Addition of Aromatic Amines to Electron-Deficient Alkene in Water. A mixture of aromatic amine (1.5 mmol) and alkene (methyl acrylate,

(12) Note that on a large scale the fluoro alcohol can be easily recovered by simple distillation.

4.5 mmol; MVK, 2.3 mmol) in water (1.5 mL) was stirred at room temperature under air. After completion of the reaction (TLC monitoring), dichloromethane (30 mL) was added and the reaction mixture was transferred into a separating funnel. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2×30 mL). The combined organic layers were dried over anhyd $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The product was isolated in pure form after column chromatography (cyclohexane/AcOEt, 90:10).

General Procedure for the Aza-Michael Addition of Aromatic Amines to MVK in TFE. A mixture of aromatic amine (1.5 mmol) and MVK (4.5 mmol) in TFE (1.5 mL) was stirred at room temperature under air. After completion of the reaction (TLC monitoring), TFE was evaporated under vacuum and the product was purified by column chromatography on silica gel (cyclohexane/AcOEt 90:10).

General Procedure for the Aza-Michael Addition of Aromatic Amines to Electron-Deficient Alkene in HFIP. A mixture of aromatic amine (1.5 mmol) and alkene (4.5 mmol) in HFIP (1.5 mL) was heated at reflux (60 °C) under stirring. After completion of the reaction (TLC monitoring), HFIP was evaporated under vacuum and the product was purified by column chromatography on silica gel (cyclohexane/AcOEt 90:10).

General Procedure for the One-Pot Synthesis of Quinolines in HFIP. In a sealed tube, a solution of the aromatic amine (1.5 mmol) and MVK (4.5 mmol) in HFIP (1.5 mL) was heated at reflux (60 °C) under stirring. After completion of the reaction (TLC monitoring), HFIP was evaporated under vacuum and the product was purified by column chromatography on silica gel (cyclohexane/AcOEt 50:50).

Methyl 3-(phenylamino)propanoate (1a):[3a] white solid, 90 mg, 34% yield; mp 38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (t, J = 6.3 Hz, 2H), 3.30 (t, J = 6.3 Hz, 2H), 3.55 (s, 3H), 3.88 (bs, 1H), 6.46−6.49 (d, J = 8.6 Hz, 2H), 6.55−6.60 (t, J = 7.3 Hz, 1H), 7.01−7.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 33.7, 39.4, 51.8, 113.0, 117.7, 129.3, 147.6, 172.8. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.54; H, 7.26; N, 7.65.

Methyl 3-(4-methylphenylamino)propanoate (2a):[3a] white solid, 150 mg, 52% yield; mp 60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.63 (t, J = 6.4 Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 3.71 (s, 3H), 3.89 (bs, 1H), 6.57 (d, J = 8.5, 2H), 7.01 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.4, 33.7, 39.8, 51.7, 113.3, 127.0, 129.8, 145.3, 172.9. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.32; H, 7.49; N, 7.08.

Methyl 3-(4-methoxyphenylamino)propanoate (3a): yellow oil, 275 mg, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (t, J = 6.4 Hz, 2H), 3.4 (t, J = 6.4 Hz, 2H), 3.69 (s, 3H), 3.74 (s, 3H), 6.61 (d, J = 8.9, 2H), 6.77 (d, J = 8.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 33.7, 40.5, 51.7, 55.8, 114.6, 114.9, 141.7, 152.4, 172.9. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.82; H, 7.03; N, 6.53.

Methyl 3-[(2-methoxycarbonylethyl)phenylamino]propanoate (1b): yellow oil, 199 mg, 75% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (t, J = 7.2 Hz, 4H), 3.71 (t, J = 7.2 Hz, 4H), 3.73 (s, 6H), 6.74−6.80 (m, 3H), 7.26−7.32(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3, 47.0, 51.8, 112.6, 117.1, 129.5, 146.7, 172.5. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.37; H, 7.11; N, 5.31.

Methyl 3-[(2-methoxycarbonylethyl)-4-methylphenylamino]propanoate (2b): orange oil, 335 mg, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.47 (t, J = 6.9 Hz, 4H), 3.52 (t, J = 6.9 Hz, 4H), 3.57 (s, 6H), 6.55 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 32.1, 47.0, 51.4, 113.2, 126.4,29.8, 144.5, 172.4. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.56; H, 7.41; N, 5.06.

Methyl 3-[(2-methoxycarbonylethyl)-4-methoxyphenylamino]propanoate (3b): orange solid, 420 mg, 95% yield; mp 36 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (t, J = 6.9 Hz, 4H), 3.57 (t, J = 7.2 Hz, 4H), 3.70 (s, 6H), 3.79 (s, 3H), 6.77 (d, J = 9.3 Hz, 2H), 6.87 (d, J = 9.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 48.1, 51.6, 55.6, 114.9, 116.4, 141.4, 152.7, 172.6. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.98; H, 7.46; N, 4.90.

Methyl 3-[(2-methoxycarbonylethyl)-4-chlorophenylamino]propanoate (4b): yellow oil, 265 mg, 66% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (t, J = 7.2 Hz, 4H), 3.62 (t, J = 7.2 Hz, 4H), 3.67 (s, 6H), 6.61 (d, J = 9.0 Hz, 2H), 7.16 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 47.0, 51.8, 113.8, 122.0, 129.2, 145.3, 172.3. Anal. Calcd for $C_{14}H_{18}NClO_4$: C, 56.10; H, 6.05; N, 4.67. Found: C, 56.22; H, 5.88; N, 5.24.

Methyl 3-(*N*-methyl-*N*-phenylamino)propanoate (5): yellow oil, 280 mg, 96% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (t, J = 7.2 Hz, 2H), 3.0 (s, 3H), 3.73, (s, 3H), 3.74 (t, J = 7.2 Hz, 2H), 6.76−6.81 (m, 3H), 7.30−7.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 38.3, 48.7, 51.8, 112.6, 116.9, 129.3, 148.6, 172.8. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 63.37; H, 7.82; N, 7.25. Found: C, 68.19; H, 7.82; N, 7.29.

4-Phenylaminobutan-2-one (6a): white solid, 198 mg, 80% yield; mp 38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.75 (t, J = 6.1 Hz, 2H), 3.42 (t, J = 6.1 Hz, 2H), 3.99 (bs, 1H), 6.62 (d, J = 8.6 Hz, 2H), 6.72 (t, J = 7.3 Hz, 1H), 7.12- 7.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 38.4, 42.6, 113.0, 117.6, 129.3, 147.7, 208.1. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.46; H, 7.92; N, 8.50.

4-(2-Methylphenylamino)butan-2-one (7a): brown oil, 186 mg, 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.19 (s, 3H), 2.80 (t, J = 6.0 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 3.92 (bs, 1H), 6.64−6.73 (m, 2H), 7.07−7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 30.3, 38.4, 42.6, 109.7, 117.2, 122.6, 127.1, 130.3, 145.7, 208.3. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.51; H, 8.31; N, 8.12.

4-(3-Methylphenylamino)butan-2-one (8a): orange oil, 192 mg, 72% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.30 (s, 3H), 2.74 (t, J = 6.3 Hz, 2H), 3.42 (t, J = 6.3 Hz, 2H), 3.93 (bs, 1H), 6.42−6.45 (m, 2H), 6.56 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.7 Hz 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 30.3, 38.4, 42.7, 110.2, 113.8, 118.6, 129.2, 139.1, 147.8, 208.1. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.97; H, 8.51; N, 7.83.

4-(4-Methylphenylamino)butan-2-one (9a). yellow solid, 200 mg, 80%; mp 37 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.25 (s, 3H), 2.73 (t, J = 6.3 Hz, 2H), 3.40 (t, J = 6.3 Hz, 2H), 3.81 (bs, 1H), 6.54 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 30.3, 38.8, 42.6, 113.3, 127.0, 129.8, 145.4, 208.1. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.49; H, 8.41; N, 7.92.

4-(3-Methoxyphenylamino)butan-2-one (10a): orange oil, 188 mg, 65% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.73 (t, J = 6.1 Hz, 2H), 3.39 (t, J = 6.0 Hz, 2H), 3.76 (s, 3H), 4.02 (bs, 1H), 6.15 (t, J = 2.4 Hz 1H), 6.22 (dd, J = 2.4, 8.1 Hz, 1H), 6.28 (dd, J = 2.4, 8.1 Hz, 1H), 7.07 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 38.3, 42.6, 55.1, 99.0, 102.7, 106.1, 130.1, 149.1, 160.9, 208.1. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.48; H, 7.70; N, 7.23.

4-(4-Methoxyphenylamino)butan-2-one (11a): orange oil, 230 mg, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.69 (t, J = 6.1 Hz, 2H), 3.33 (t, J = 6.0 Hz, 2H), 3.71 (bs, 1H), 3.72 (s, 3H), 6.56 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 39.5, 42.7, 55.7, 114.6 (2C), 114.9 (2C) 141.9, 152.3, 208.2. Anal. Calcd for $C_{11}H_{15}NO$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.30; H, 7.60; N, 7.35.

4-(4-Chlorophenylamino)butan-2-one (12a): white solid, 230 mg, 77%; mp 71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.71 (t, J = 6.0 Hz, 2H), 3.36 (t, J = 6.0 Hz, 2H), 4.02 (s, 3H), 6.51 (d, J = 9.0 Hz, 2H), 7.10(d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 38.5, 42.4, 114.1, 122.1, 129.1, 146.3, 208.0. Anal.

Calcd for $C_{10}H_{12}NClO$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.85; H, 5.78; N, 6.85.

4-[(3-Oxobutyl)phenylamino]butan-2-one (6b): yellow oil, 290 mg, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 6H), 2.63 (t, J = 6.0 Hz, 4H), 3.50 (t, J = 6.0 Hz, 4H), 6.58 (d, J = 8.1 Hz, 2H), 6.64 (t, J = 7.3 Hz, 1H) 7.12−7.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.5, 41.2, 45.8, 112.7, 116.9, 129.5, 147.0, 207.7. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.93; H, 8.27; N, 5.90.

4-[(3-Oxobutyl)-2-methylphenylamino]butan-2-one (7b): orange oil, 286 mg, 75%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 6H), 2.22 (s, 3H), 2.51 (t, J = 6.0 Hz, 4H), 3.23 (t, J = 6.0 Hz, 4H), 7.0−7.19 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 30.3, 41.3, 48.8, 122.5, 124.3, 126.4, 131.2, 135.5, 148.2, 208.0. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 6.00. Found: C, 72.72; H, 8.48; N, 6.11.

4-[(3-Oxobutyl)-3-methylphenylamino]butan-2-one (8b): yellow oil, 295 mg, 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 6H), 2.31 (s, 3H), 2.71 (t, J = 6.0 Hz, 4H), 3.57 (t, J = 6.0 Hz, 4H), 6.44−6.51 (m, 2H), 6.56 (d, J = 7.3 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 30.5, 41.2, 45.7, 110.0, 113.5, 117.9, 129.3, 139.2, 147.1, 207.8. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.71; H, 8.57; N, 5.82.

4-[(3-Oxobutyl)-4-methylphenylamino]butan-2-one (9b): yellow oil, 305 mg, 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 6H), 2.25 (s, 3H), 2.69 (t, J = 6.0 Hz, 4H), 3.54 (t, J = 6.0 Hz, 4H), 6.61 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 30.6, 41.1, 46.1, 113.5, 126.5, 130.0, 145.0, 208.0. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.05; H, 8.70; N, 5.93.

4-[(3-Oxobutyl)-4-chlorophenylamino]butan-2-one (12b): white solid, 300 mg, 74% yield; mp 60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 6H), 2.68 (t, J = 6.0 Hz, 4H), 3.54 (t, J = 6.0 Hz, 4H), 6.56 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6, 40.9, 45.8, 113.8, 121.7, 129.2, 145.6, 207.5. Anal. Calcd for $C_{14}H_{18}NClO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.68; H, 6.76; N, 5.22.

4-[(3-Oxobutyl)-4-nitrophenylamino]butan-2-one (13b): yellow solid, 293 mg, 70% yield; mp 165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 6H), 2.77 (t, J = 6.9 Hz, 4H), 3.71 (t, J = 6.9 Hz, 4H), 6.56 (d, J = 9.6 Hz, 2H), 8.10 (d, J = 9.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.5, 40.8, 45.6, 110.4, 126.4, 137.3, 151.6, 206.6. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.36; H, 6.57; N, 10.07.

4-Methylquinoline (14): yellow oil, 120 mg, 56% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 3H), 7.25 (d, J = 4.3 Hz, 1H), 7.59 (t, J = 8.2 Hz, 1H), 7.74 (t, J = 8.2, 1H), 8.02 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.80 (d, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 18.7, 121.9, 123.9, 126.3, 128.3, 129.2, 130.0, 144.4, 148.0, 150.2; ESI m/z (rel int) 144 $[M + H]^+$ (100). Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.50; H, 6.28; N, 9.89.

4,6-Dimethylquinoline (15): yellow oil, 125 mg, 53% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 2.69 (s, 3H), 7.16 (dd, J = 4.3 Hz, 1H), 7.52 (dd, J = 1.7, 8.5 Hz, 1H), 7.72 (m, 1H), 7.99 (d, J = 8.6 Hz, 1H), 8.69 (d, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 21.8, 121.8, 122.7, 128.2, 129.6, 131.3, 136.0, 143.5, 146.4, 149.2; ESI m/z (rel int) 158 $[M + H]^+$(100). Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.70; H, 6.98; N, 8.96.

6-Methoxy-4-methylquinoline (16):[13] brown oil, 130 mg, 50% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.93 (s, 3H), 7.15−7.18 (m, 2H), 7.35 (dd, J = 2.7, 9 Hz, 1H), 8.0 (d, J = 9.3 Hz, 1H), 8.61 (d, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 55.5, 101.9, 121.4, 122.1, 129.2, 131.4, 142.7, 144.0, 147.6, 157.6; ESI m/z (rel int) 174 $[M + H]^+$ (100).

6,7-Dimethoxy-4-methylquinoline (17):[14] orange solid, 171 mg, 56% yield; mp 108 °C (lit.[14] mp 112.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 4.02 (s, 6H), 7.08 (s, 1H), 7.12 (s, 1H), 7.32 (s, 1H), 8.48 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 55.9, 56.0, 101.4, 108.4, 120.4, 123.4, 142.2, 145.0, 147.9, 149.3, 152.0; ESI m/z (rel int) 204 $[M + H]^+$ (100).

4,7-Dimethylquinoline (18):[15] orange oil, 118 mg, 50% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.64 (s, 3H), 7.14 (d, J = 4.5 Hz, 1H), 7.38 (dd, J = 1.3, 8.6 Hz, 1H), 7.87 (m, 2H), 8.71 (d, J = 4.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 21.7, 121.1, 123.5, 126.3, 128.5, 128.8, 139.3, 144.1, 148.1, 150.0; ESI m/z (rel int) 158 $[M + H]^+$ (100).

7-Methoxy-4-methylquinoline (19): orange oil, 161 mg, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.92 (s, 3H), 7.05 (d, J = 4.5 Hz, 1H), 7.18 (dd, J = 2.7, 9.0 Hz, 1H), 7.40 (d, J = 2.4 Hz,1H), 7.84 (d, J = 9.3 Hz,1H), 8.65 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 55.4, 107.8, 119.2, 120.0, 123.3, 125.0, 144.2, 150.0, 150.4, 160.3; ESI m/z (rel int) 174 $[M + H]^+$(100).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017–3035.

(14) Roberts, D.; Joule, J. A.; Bros, M. A.; Alvarez, M. *J. Org. Chem.* **1997**, *62*, 568–577.

(15) Osborne, A. G. *Tetrahedron* **1983**, *39*, 2831–2841.