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Benefits of a Dual Chemical and Physical Activation: Direct aza-Michael Addition of Anilines Promoted by Solvent Effect under High Pressure

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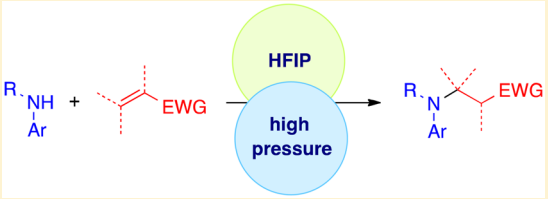
Supporting Information

ABSTRACT: The unique combination of hexafluoroisopropanol (HFIP) employed as solvent and hyperbaric conditions (10−15 kbar) allows unprecedented 1,4-addition of poor nucleophiles, such as aromatic amines, onto sluggish (cumbersome) Michael acceptors without any promoter or workup.



Solvents often play a prominent role in the behavior of a reaction due to specific solute/solvent interactions susceptible to acting at various stages of a chemical transformation.[1] Therefore, it is possible to modulate the reactivity of chemical compounds, and thus to promote a reaction and/or to orientate its outcome through simple solvent tuning and with no energy expense. Among solvents, water and the polyfluorinated alcohols trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) exhibit unique properties being at the top of Reichardt's polarity scale E_T (30) and H-bonding donation scale α_1.[2] A notable difference between water and polyfluorinated alcohols relies on the significant Brønsted acidity and poorer H-bonding acceptance β_1 of TFE and HFIP (Table 1).[3] As reaction media, these highly polar protic solvents have been shown to have a dramatically positive impact on aromatic amines, which are generally viewed as much poorer nucleophiles than their aliphatic counterparts.[4] For example, two of us reported that primary anilines add smoothly onto Michael acceptors, without any external promoter, on the condition to perform the reaction in water, TFE, or HFIP as solvent because no conversion was observed in any other solvent.[4a] Moreover, the selectivity was also under solvent control: monoaddition took place in water, whereas bis-adducts were obtained in fluorinated alcohols. Unfortunately, this 1,4-addition of anilines was strictly limited to simple, β-unsubstituted electrophilic partners, namely, methyl vinyl ketone or methyl acrylate, and failed with substituted Michael acceptors, thus restricting broad applications.

In this context, hyperbaric conditions (>5 kbar) have been shown to dramatically accelerate aza-Michael reactions, which are well-known to suffer from sharp steric issues.[5−10] This technique has the benefit of being cost-effective because the energy input is limited to the initial compression step in contrast with classical heating that requires continuous energy consumption during the entire reaction course. Thus, challenging nucleophiles/electrophiles, such as cumbersome aliphatic amines, secondary amines, or amides toward α- or β-substituted Michael acceptors, become reactive under high pressure,[5−9] whereas a single report described a sluggish addition of aniline onto an α-acrylate derivative (34% yield after 24 h at 15 kbar and 25 °C in THF).[5h] Although these reactions are commonly performed in organic solvents (such as THF and EtOH), the 1,4-addition of aliphatic amines onto acrylates[6] and that of azoles onto enones[7] have been described in water at 3−6 kbars. However, the improvement brought by water is either modest when compared to classical solvents[7] or unpredictable[6] due to the poor solubility of many chemicals in this solvent and the absence of stirring means in high pressure devices. Moreover, it should be noted that water freezes at 27 °C at approximately 10 kbar.[11] We thus imagined that combining the unique promoter effect of an adequate polyfluorinated alcohol to hyperbaric activation could facilitate the reaction between anilines and cumbersome Michael acceptors. The results below show that we have been nicely rewarded.

Investigations began with *N*-methylaniline **1a** and methyl crotonate **2a** in various solvents at room temperature and under 10 kbar (Table 1). In aprotic solvents (CH_2Cl_2, THF, MeCN), no conversion was observed after 24 h, and starting material was recovered unchanged (entries 1−3). The use of isopropyl

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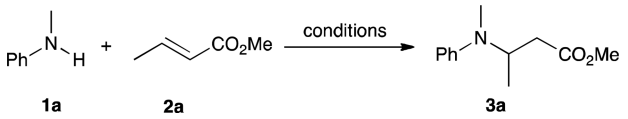
Table 1. Solvent-Promoted aza-Michael Addition between *N*-Methylaniline 1a and Methyl Crotonate 2a under High Pressure[a,b]



1a **2a** **3a**

entry	solvent	E_T (30)	pK_a[c]	α_1	β_1	P (kbar)	time (h)	conversion (%)[d]
1	CH_2Cl_2	40.7		0.10	0.00	10	24	0
2	THF	37.4		0.00	0.58	10	24	0
3	MeCN	45.6		0.23	0.37	10	24	0
4	*i*PrOH	48.4	16.5	0.53	0.68	10	24	0
5[e]	EtOH	51.8	15.9	0.75	0.62	10	24	9
6	MeOH	55.4	15.5	1.00	0.54	10	24	12
7	TCE	54.1	12.2	0.92	0.20	10	24	40
8	TFE	59.8	12.5	1.36	0.23	10	24	55
9	H_2O	63.1	15.7	1.54	0.37	5	24	0
10	HFIP	65.3	9.3	1.86	0.16	5	24	73
11	HFIP					10	24	90
12[f]	HFIP/CH_2Cl_2					10	24	20
13[g]	HFIP					14	17	100
14	HFIP					0.5	24	8
15[h]	HFIP					1×10^{-3}	17	18

[a]Reaction conditions: **1a** (1 mmol) and **2a** (2 mmol) in the solvent (0.5−1.5 mL) at rt. [b]Physicochemical values (at atmospheric pressure) taken from refs 2a, b, 3a, b, and 12. [c]Values in H_2O. [d]Conversion based on ^{1}H NMR; only Michael adduct was observed. [e]Performed with ethyl crotonate. [f]HFIP/CH_2Cl_2 1:1 (V/V) [g]Isolated yield: 81%. [h]Reaction performed at 58 °C.

alcohol was also unsuccessful (entry 4), whereas small conversion to expected adduct **3a** was observed in ethanol and methanol (9% and 12%; entries 5 and 6). The use of halogenated analogues of ethanol allowed fair conversion: 40% in trichloroethanol (TCE) and 55% in TFE (entries 7 and 8).

Water was also tested under high pressure; however, at 5 kbar, chemicals were insoluble and no conversion could be detected. In contrast, HFIP gave excellent results under pressure: 73% at 5 kbar and 90% at 10 kbar (entries 10 and 11). It must be mentioned that HFIP has to be used as solvent because halving its quantity (by performing the reaction in a 1:1 mixture of HFIP/CH_2Cl_2) induced only moderate activation with low conversion (20%) at 10 kbar (entry 12). Full conversion was attained at 14 kbar after 17 h, and product **3a** was obtained in 81% yield (entry 13). Because of the absence of any external promoter, the pure product was recovered by simple removal of the volatiles: HFIP (bp 58 °C) and methyl crotonate (bp 120 °C) can be recovered and recycled. To assess the promotion potency of the HFIP/high pressure combination, we performed two test reactions (entries 14 and 15). In the first attempt, a moderate pressure of 0.5 kbar was exerted, and only 8% conversion was reached after 24 h (entry 14). Another experiment was performed at atmospheric pressure in refluxing HFIP (58 °C), affording only 18% conversion after 17 h heating (entry 15). These experiments highlight the outstanding effect of HFIP when under hyperbaric conditions.[13] It is very important to note that, in contrast to regular alcohols, no transesterification occurs with the *β*-aminoester when HFIP is used as the reaction medium, and no *β*-elimination is observed that could reverse the reaction.

From a mechanistic standpoint, a plain correlation between physicochemical parameters of the alcohol solvents (*i*PrOH, EtOH, MeOH, TCE, TFE, and HFIP) and conversions obtained at 10 kbar clearly highlight the role of Brønsted acidity (or H-bond donation ability) with a correlation factor R^2 = 0.966 (Figure 1). Thus, the acidity of HFIP seems to stand at the appropriate point where it is sufficient to activate the

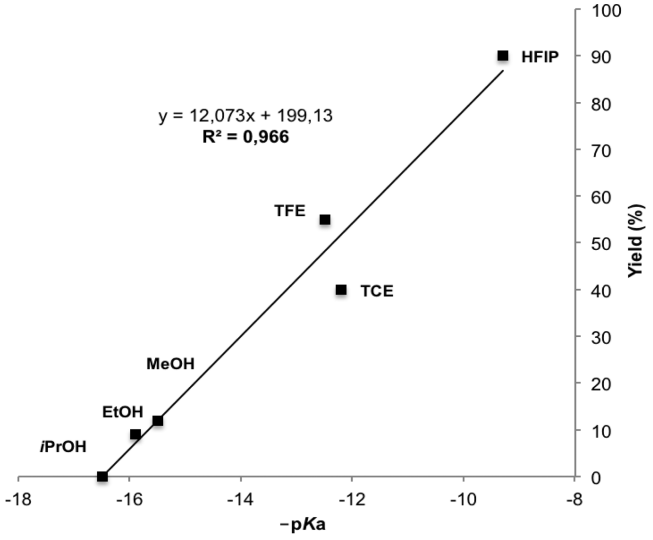


Figure 1. Yield (%) of the addition product of *N*-methylaniline onto methyl crotonate relative to Brønsted acidity (pK_a) in various alcohols at 10 kbar.

Michael acceptor but incapable of deactivating the aniline by protonation (Scheme 1).[2c,d] It has been reported that the K_a of protic compounds increases according to pressure,[5i] thus reinforcing the effect of HFIP. Moreover, high pressure positively affects reactions with a negative activation volume ($\Delta V^{\ddagger} < 0$); because of electrostriction, the aza-Michael reaction goes through a highly favorable zwitterionic compact transition state (Scheme 1).

The scope of this addition was examined next and anilines or their *N*-methyl homologues were reacted with challenging Michael acceptors (esters and nitriles) bearing substituent(s) in the α or β position (Table 2). The optimized conditions determined above were retained (HFIP, $P \geq 10$ kbar, 12 h). If aniline itself was added quantitatively to crotonate (entry 3), 4-

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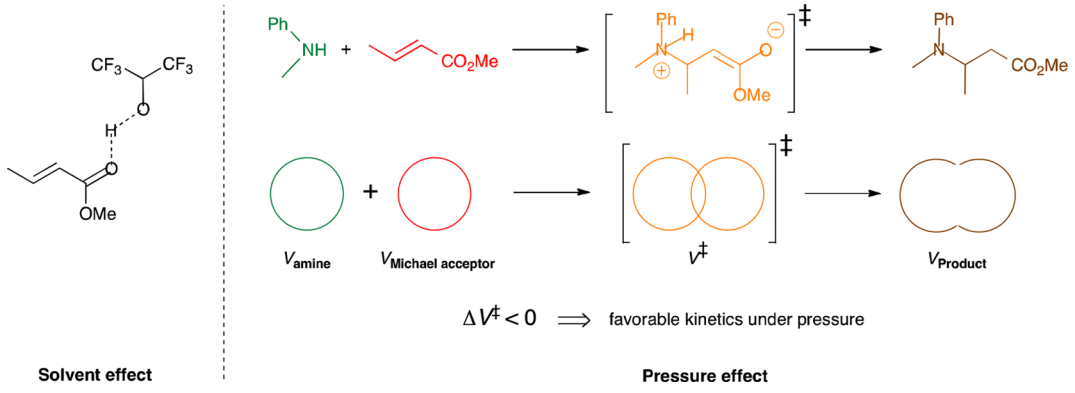
Scheme 1. Solvent and Pressure Effect on the Reaction Between *N*-Methyl Aniline and Methyl Crotonate



chloro-*N*-methylaniline also behaved as a powerful nucleophile (90% yield, entry 2). In contrast, the reaction with 4-chloroaniline was more sluggish (53% yield, entry 4).

To our delight, the sterically hindered 2,6-xylidine behaved very well (73% yield, entry 5). With the cumbersome trifluorocrotonate as Michael acceptor, however, aniline only afforded a moderate 45% yield (entry 6). The case of the very challenging senecioate (*β*,*β*-dimethyl acrylate or *β*-methylcrotonate) is to be noted, as the addition led to the creation of a quaternary center in 54% yield (entry 7).[14] It is well-established that *α*-substituted acrylates are sluggish electrophiles in hetero-Michael reactions,[15,16] and examination of the reaction of methyl methacrylate with *N*-methylaniline and aniline afforded *β*-aminoesters in poor to moderate yields (9 and 40%, respectively; entries 8 and 9). The scope of Michael acceptors was then extended to acrylonitriles (entries 10−17). With simple acrylonitrile, *N*-substituted anilines (methyl, cyclohexyl) afforded the corresponding products in >99% yield (entries 10 and 11). Crotonitrile also appeared to be an excellent partner because the 1,4-addition with *N*-methylaniline proceeded very well (81% yield, entry 12). The last reactions were performed with 2-chloroacrylonitrile (entries 13−17); the reaction occurred smoothly with primary and secondary aromatic amines and the corresponding *α*-chloro-*β*-aminonitriles were obtained as sole products in moderate to good yields (60−86%). One of the salient points of this procedure is that the product can be recovered by simple distillation of the reaction solvent, which is in contrast to most protocols that require hydrolysis and multiple extractions with an organic solvent, even if the reaction is conducted neat.[17]

In conclusion, the unprecedented combination of hyperbaric conditions and HFIP solvent promoted the challenging 1,4-addition of poorly nucleophilic aromatic amines (primary and secondary anilines) onto Michael acceptors when one of the reagents exhibits a sterically hindered reaction center. Notably, the first addition of an aniline onto a *β*,*β*-disubstituted Michael acceptor, leading to the creation of a quaternary center, is reported. This dual physical/chemical activation leads to a procedure sober in energy for the facile synthesis of *β*-amino acid derivatives (esters and nitriles) without any external promoter or workup/extraction; beyond the well-appreciated interest of *β*-aminoesters in biosciences,[18] it has been recently reported that 2-(alkoxycarbonyl)ethyl moieties are attractive removable *N*-protecting groups.[19] The effectiveness of the HFIP/pressure combination in the aza-Michael addition possibly rests on an increase of the acidity of HFIP under high pressure, affording an enhanced activation of the Michael acceptor as well as a favorable compact transition state in the transformation. For perspective, it is planned to combine the organizing properties of high pressure with chiral fluorinated alcohols (e.g., (*S*)- or (*R*)-trifluoroisopropanol or phenyl-trifluoroethanol) to perform enantioselective transformations in chiral media. This strategy, initiated by Seebach 40 years ago,[20] leading to significant ee in a few cases,[21] could benefit from being re-examined in a well-organized medium, such as that resulting from the application of hyperbaric conditions.

EXPERIMENTAL SECTION

General Methods. High-pressure reactions were performed in a piston−cylinder type apparatus U101 and U22 (Unipress, Warsaw, Poland), designed for pressures up to 12 and 15 kbar, respectively, and a piston−cylinder type apparatus (Ollivaud/Lebas, France) for pressures from 12 to 14 kbar. The silica gel used for flash chromatography was 230−400 mesh. ^{1}H, ^{19}F, and ^{13}C spectra were recorded at 300, 282, and 75 MHz, respectively, for solution in $CDCl_3$. Chemical shift (*δ*) in ppm are reported using residual chloroform (7.26 for ^{1}H and 77.16 for ^{13}C) as the internal reference. The coupling constants (*J*) are given in hertz (Hz). High-resolution mass data were recorded on a Micromass Q-TOF (Quadrupole time-of-flight) instrument with an electrospray source in EI or ESI mode.

General Procedure for the Reaction of Michael Acceptors with Anilines. The mixture of amine (1 mmol) and Michael acceptor (2 mmol) in HFIP (0.5−1.5 mL) was placed in a Teflon reaction vessel and kept under 0.5−15 kbar at room temperature overnight (17 h). Then, the pressure was released, and the mixture was concentrated in vacuo. The crude product was purified by column chromatography over silica gel (cyclohexane/AcOEt, from 90:10 to 60:40). Compounds **3a−q** were prepared according to this procedure.

3-(Methyl(phenyl)amino)butanoate ***3a.*** Brown oil, 230 mg, 81% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 1.22 (d, *J* = 6.6 Hz, 3H), 2.46 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.66 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.75 (s, 3H), 3.63 (s, 3H), 4.48 (m, 1H), 6.73−6.93 (m, 3H), 7.21−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 17.2, 30.2, 39.0, 51.6, 51.9, 114.2, 117.5, 129.1, 150.0, 172.2; IR (neat) *ν* (cm^{-1}) 1730 (C═O); HRMS (ES+) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}NO_2$ 208.1338, found 208.1332.

Methyl 3-((4-Chlorophenyl)(methyl)amino)butanoate ***3b.*** Brown oil, 217 mg, 90% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 1.18 (d, *J* = 6.9 Hz, 3H), 2.43 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.62 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.69 (s, 3H), 3.61 (s, 3H), 4.39 (m, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 17.2, 30.4, 39.0, 51.8, 52.2, 115.3, 122.2, 128.9, 148.7, 172.2; IR (neat) *ν* (cm^{-1}) 810 (C−Cl), 1732 (C═O); HRMS (ES+) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{17}ClNO_2$ 242.0949, found 242.0948.

Methyl 3-(Phenylamino)butanoate ***3c.***[22a] Brown oil, 192 mg, quantitative yield; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 1.29 (d, *J* = 9.6 Hz, 3H), 2.44 (dd, *J* = 22.5, 10.5 Hz, 1H), 2.68 (dd, *J* = 22.5, 7.8 Hz, 1H), 3.70 (s, 4H, CH_3), 3.89−4.07 (m, 1H), 6.60−6.80 (m, 3H), 7.15−7.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 20.7, 40.8, 46.0, 51.6, 113.6,

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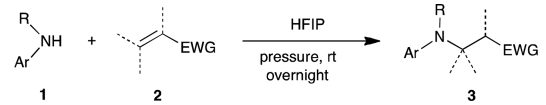
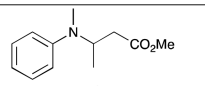
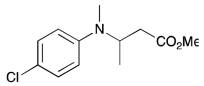
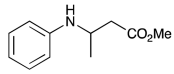
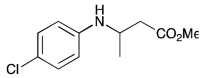
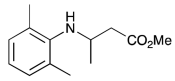
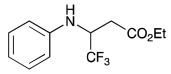
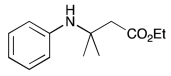
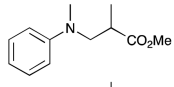
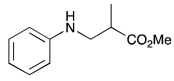
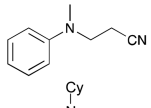
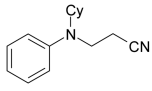
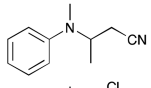
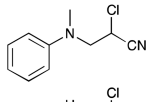
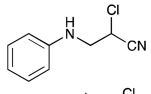
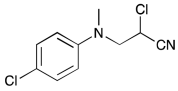
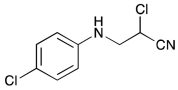
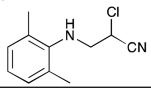
Table 2. HFIP-Promoted aza-Michael Addition of Anilines under Hyperbaric Conditions[a]



1 2 3

Entry	P (kbar)	Product		Yield (%)[b]
1	14		**3a**	81
2	14		**3b**	90
3	10		**3c**	100
4	14		**3d**	53
5	10		**3e**	73
6[c]	15		**3f**	45
7	10		**3g**	54
8	14		**3h**	40
9[d]	15		**3i**	9
10	14		**3j**	100
11	14		**3k**	99
12	14		**3l**	81
13	14		**3m**	65
14	14		**3n**	86
15	14		**3o**	83
16	14		**3p**	73
17	14		**3q**	60

[a]Conditions: **1** (1 mmol) and **2** (2 mmol) in HFIP (0.5−1.5 mL) at rt under pressure. [b]Isolated yield. [c]Reaction performed for 24 h. [d]Conversion of 20% to product observed by ^{1}H NMR.

117.7, 129.4, 146.8, 172.3; IR (neat) ν (cm^{-1}) 1726 (C═O), 3387(NH).

Methyl 3-((4-Chlorophenyl)amino)butanoate ***3d***.[22b] Brown oil, 121 mg, 53% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, J = 6.3 Hz, 3H), 2.43 (dd, J = 15.0, 6.6, Hz, 1H), 2.60 (dd, J = 15.0, 5.1 Hz, 1H), 3.67 (s, 3H), 3.50−3.75 (mask, 1H), 3.88 (m, 1H), 6.53 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 40.6, 46.2, 51.7, 114.7, 122.2, 129.2, 145.5, 172.2; IR (neat) ν (cm^{-1}) 815 (C−Cl), 1725 (C═O), 3390 (NH).

Methyl 3-((2.6-Dimethylphenyl)amino)butanoate ***3e***. Brown oil, 161 mg, 73% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, J = 6.6 Hz, 3H), 2.27 (s, 6H), 2.44 (dd, J = 15.0, 6.6 Hz, 1H), 2.51 (dd, J = 15.0, 6.0 Hz, 1H), 3.22 (br.s, 1H), 3.65 (s, 3H), 4.48 (m, 1H), 6.75−6.84 (m, 1H), 6.95−7.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 21.2, 42.1, 49.8, 51.7, 121.9, 129.1, 129.7, 144.3, 172.6; IR (neat) ν (cm^{-1}) 1731 (C═O), 3378 (NH); HRMS (ES+) m/z [M + H]$^+$ calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1489.

Ethyl 4,4,4-Trifluoro-3-(phenylamino)butanoate ***3f***.[22c] Brown oil, 118 mg, 45% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J = 7.2 Hz, 3H), 2.62 (dd, J = 15.6, 8.7 Hz, 1H), 2.84 (dd, J = 15.6, 4.5 Hz, 1H), 3.90 (br.s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.40−4.60 (m, 1H), 6.70−6.85 (m, 3H), 7.17−7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 35.2, 53.5 (q, $^2J_{CF}$ = 30.2 Hz), 61.5, 125.7 (q, J = 282 Hz), 114.1, 119.6, 129.5, 145.9, 169.6; ^{19}F NMR ($CDCl_3$, 300 MHz) −76.10 (d, J = 7.2 Hz); IR (neat) ν (cm^{-1}) 1117 (CF), 1728 (C═O), 3391 (NH).

Ethyl 3-Methyl-3-(phenylamino)butanoate ***3g***. Brown oil, 119 mg, 54% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (m, 4H, NH), 1.40 (s, 6H), 2.56 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 6.80−6.85 (m, 3H), 7.10−7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 28.7, 45.4, 53.5, 60.5, 119.6, 119.9, 129.0, 146.3, 171.9; IR (neat) ν (cm^{-1}) 1722(C═O), 3395 (NH); HRMS (ES+) m/z [M + H]$^+$ calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1492.

Methyl 2-Methyl-3-(methyl(phenyl)amino)propanoate ***3h***. Brown oil, 83 mg, 40% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, J = 6.0 Hz, 3H), 2.89−3.01 (m, 4H, CH), 3.35 (dd, J = 14.7, 6.6 Hz, 1H), 3.72 (dd, J = 14.7, 7.8 Hz, 1H), 3.66 (s, 3H), 6.70−6.77 (m, 3H), 7.23−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2, 38.4, 39.2, 51.8, 56.4, 112.3, 116.6, 129.3, 149.0, 172.1; IR (neat) ν (cm^{-1}) 1732 (C═O); HRMS (ES+) m/z [M + H]$^+$ calcd for $C_{12}H_{18}NO_2$ 208.1338, found 208.1341.

Methyl 2-Methyl-3-(phenylamino)propanoate ***3i***.[22d] Brown oil, 17 mg, 9% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, J = 6.0 Hz, 3H), 2.74−2.85 (m, 1H), 3.23 (dd, J = 13.2, 5.7 Hz, 1H), 3.42 (dd, J = 13.2, 8.1 Hz, 1H), 3.70 (s, 3H), 3.98 (br.s, 1H), 6.60−6.75 (m, 3H), 7.14−7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2, 39.3, 47.0, 52.0, 113.0, 117.7, 129.4, 147.9, 176.0; IR (neat) ν (cm^{-1}) 1724 (C═O), 3408 (NH).

3-(Methyl(phenyl)amino)propanenitrile ***3j***.[22e] Brown oil, 160 mg, quantitative yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (t, J = 6.9 Hz, 2H), 3.03 (s, 3H), 3.72 (t, J = 6.9 Hz, 2H), 6.70−6.85 (m, 3H), 7.25−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3, 38.7, 49.0, 112.7, 117.8, 118.6, 129.6, 147.7; IR (neat) ν (cm^{-1}) ν 2247 (C≡N).

3-(Cyclohexyl(phenyl)amino)propanenitrile ***3k***. Brown oil, 225 mg, 99% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10−2.00 (m, 10H), 2.54 (t, J = 6.9 Hz, 2H), 3.48−3.68 (m, 3H), 6.75−6.85 (m, 3H), 7.23−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 25.8, 26.1, 31.0, 58.8, 41.1, 114.7, 118.4, 118.5, 129.5, 147.3; IR (neat) ν (cm^{-1}) 2247 (C≡N); HRMS (ES+) m/z [M + H]$^+$ calcd for $C_{15}H_{21}N_2$ 229.1705, found 229.1709.

3-(Methyl(phenyl)amino)butanenitrile ***3l***.[22f] Brown oil, 141 mg, 81% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (d, J = 6.6 Hz, 3H), 2.49 (dd, J = 16.8, 7.2 Hz, 1H), 2.57 (dd, J = 16.8, 6.0 Hz, 1H), 2.80 (s, 3H), 4.30 (m, 1H), 6.75−6.87 (m, 3H), 7.25−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.3, 21.9, 30.5, 51.7, 114.4, 118.3, 118.5, 129.4, 149.3; IR (neat) ν (cm^{-1}) 2248 (C≡N).

2-Chloro-3-(methyl(phenyl)amino)propanenitrile ***3m***. Brown oil, 126 mg, 65% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.18 (s, 3H), 3.92−4.00 (m, 2H), 4.62 (t, J = 6.9 Hz, 1H), 6.70−6.95 (m, 3H), 7.30−7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.2, 39.8, 57.8, 112.2, 116.8, 118.3, 129.7, 147.0; IR (neat) ν (cm^{-1}) 2247 (C≡N); HRMS (EI+) m/z [M]$^{\cdot+}$ calcd for $C_{10}H_{11}ClN_2$ 194.06108, found 194.05992.

2-Chloro-3-(phenylamino)propanenitrile ***3n***.[22g] Brown oil, 155 mg, 86% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64−3.86 (m, 2H), 4.30 (br.s, 1H), 4.57 (t, J = 6.6 Hz, 1H), 6.60−6.90 (m, 3H), 7.21−

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7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.1, 48.6, 113.3, 116.4, 119.4, 129.7, 145.2; IR (neat) ν (cm^{-1}) 2249 (C≡N), 3407 (NH).

2-Chloro-3-((4-chlorophenyl)(methyl)amino)propanenitrile **3o**. Brown oil, 190 mg, 83% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11 (s, 3H), 3.85−3.95 (m, 2H), 4.57 (dd, J = 7.5, 6.9 Hz, 1H), 6.64 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.1, 39.9, 57.9, 113.5, 116.6, 123.4, 129.5, 145.8; IR (neat) ν (cm^{-1}) 809 (C−Cl), 2247 (C≡N); HRMS (EI+) m/z [M]$^{\cdot+}$ calcd for $C_{10}H_{10}Cl_2N_2$ 228.02210, found 228.02156.

2-Chloro-3-((4-chlorophenyl)amino)propanenitrile **3p**.[22g] Brown oil, 157 mg, 73% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60−3.83 (m, 2H), 4.33 (br.s, 1H), 4.55 (dd, J = 6.9, 6.6 Hz, 1H), 6.58 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.1, 48.5, 114.4, 116.3, 123.9, 129.5, 143.9; IR (neat) ν (cm^{-1}) 802 (C−Cl), 2247(C≡N), 3424 (NH).

2-Chloro-3-((2.6-dimethylphenyl)amino)propanenitrile **3q**. Brown oil, 125 mg, 60% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 6H), 3.46−3.72 (m, 3H), 4.44 (dd, J = 6.0, 5.7 Hz, 1H), 6.90−7.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.6, 42.5, 52.2, 116.4, 123.4, 129.3, 130.1, 142.5; IR (neat) ν (cm^{-1}) 2254 (C≡N), 3402 (NH); HRMS (EI+) m/z [M]$^{\cdot+}$ calcd for $C_{11}H_{13}ClN_2$ 208.07673, found 208.07716.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01756.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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