Ionic liquid promoted simple and efficient synthesis of β-enamino esters and β-enaminones from 1,3-dicarbonyl compounds — One-pot, three-component reaction for the synthesis of substituted pyridines

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Abstract: A facile enamination of 1,3-dicarbonyl compounds with amines has been developed that affords good to excellent yields of β-enamino esters and β-enaminones using Brønsted acidic ionic liquid 1-methylimidazolium trifluoroacetate ([Hmim]$^+$Tfa$^-$) at room temperature. This methodology has been extended for the synthesis of substituted pyridines in excellent yield by a one-pot, three-component reaction of 1,3-dicarbonyl compounds, ammonium acetate, and alkynone in the presence of [Hmim]$^+$Tfa$^-$.

Key words: ionic liquid, β-enaminones, β-enamino esters, 1,3-dicarbonyl compounds, amines, pyridines.

Résumé : Opérant à la température ambiante et utilizant le trifluoroacétate de 1-méthylimidazolinum, [Hmim]$^+$Tfa$^-$, un liquide ionique agissant comme acide de Brønsted, on a mis au point une méthode facile d'énamination des composés 1,3-dicarbonyles par les amines qui fournit des rendements allant de bons à excellents en β-énaminoesters et β-énaminones. Cette méthode a été étendue à la synthèse de pyridines substituées réalisée avec d'excellents rendements par une réaction monotope à trois composants formés de composés 1,3-dicarbonyles, d'acétate d'ammonium et d'alkynone, en présence de [Hmim]$^+$Tfa$^-$.

Mots clés : liquide ionique, β-énaminones, β-énaminoesters, composés 1,3-dicarbonyles, amines, pyridines.

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β-Enamino esters and β-enaminones are important precursors for the synthesis of biologically active compounds such as amino acids (1), γ-aminols (1*d*), peptides (2), and heterocyclic compounds (3).

The most common route for the synthesis of these compounds involves the direct condensation of β-dicarbonyl compounds with amines at reflux in benzene–toluene with azeotropic removal of water (4). Recently, K_{10}clay/ultrasound (5*a*), silica-supported microwave irradiaton (5*b*), $NaAuCl_4$ (5*c*), $Bi(TFA)_3$ (5*d*), and $Zn(ClO_4)_2{\cdot}6H_2O$ (5*e*) have been used for the condensation of 1,3-dicarbonyl compounds with amines. However, these methods have not been entirely satisfactory owing to such drawbacks as low yields, long reaction time, nonreusable catalyst, and use of hazardous solvents such as benzene and chlorinated solvents.

Several improved methods have been reported for the Bohlmann–Rahtz pyridine synthesis (6) from β-enaminones. Recently Bagley and co-workers (7) have reported one-pot, three-component reactions for the synthesis of pyridines in toluene at reflux temperature by generating the enaminone from the corresponding β-ketoesters for in situ heteroannulation in the Bohlmann–Rahtz reaction. In these studies we set out to test similar methodology using an ionic liquid for the mild preparation of enaminones and their in situ heteroannulation reaction for the Bohlmann–Rahtz pyridine synthesis.

Room-temperature ionic liquids (RTILs) consisting of imidazolium cations have gained popularity as an alternative to conventional organic solvents (8). They are highly polar yet noncoordinating and dissolve a wide range of organic and organometallic compounds. Ionic liquids were shown to enhance reaction rates in a range of reactions (9), including acid-catalysed processes (10). Chloroaluminate ionic liquids have been reported as both solvents and Lewis acid catalysts for Diels–Alder reactions and the Friedel–Crafts reaction. However, chloroaluminate ionic liquids are sensitive to water, and lead to undesired side reactions due to the release of HCl. Several Brønsted acidic ILs are synthesized and used as catalysts and solvents for esterification and pinacol–benzopinacol rearrangement (11).

In continuation of our research interest in the application (12) of RTILs in organic synthesis, we report a facile, high-yielding protocol for the condensation of 1,3-dicarbonyl compounds with amines using 1-methylimidazolium tri-

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fluoroacetate ([Hmim]$^+$Tfa$^-$) at room temperature. The ionic liquids were prepared according to the procedures reported in the literature (13).

In our initial search for optimal reaction conditions, we explored the condensation of benzoyl acetone with aniline in [Hmim]$^+$Tfa$^-$, [Hmim]$^+$Tsa$^-$, and a neat solution. The results are summarized in Table 1.

Encouraged by these results, several β-diketones were condensed with amines giving the β-enaminones in excellent yields at room temperature. The results are summarized in Table 2.

Anilines and aliphatic amines reacted efficiently to produce the corresponding β-enaminones in excellent yields. Although an earlier report (10*d*) shows that anilines with strong electron-withdrawing groups, such as 4-nitro aniline, are unreactive, we have shown that they produce the corresponding β-enaminone in good yield (Table 2, entry 6). The stereochemistry of the compounds is Z because of the intramolecular H-bonding. The (Z)-s-cis configuration shown for β-enaminones and β-enamino esters was confirmed from their ^{1}H NMR. The characteristic signals of the vinylic proton (δ 4.5–5.1 ppm) and NH signals (δ 8.3–11.3 ppm) corroborate the proposed structure.

In the case of 1,2-diaminoethane, 2 equiv. of the 1,3-dicarbonyl compound were used giving bisenaminones in 80% yield (Table 2, entry 7). In the case of aryl alkyl dicarbonyl compounds, we observed the regioselective amination of the aliphatic carbonyl group. In addition, when the 1,1,1-trifluoro-pentan-2,4-dione (**1b**) reacted with benzylamine (Table 2, entry 8) only enaminones derived from the regioselective amination of the less reactive carbonyl-bound methyl group were observed.

The scope and generality of this method was also expanded for the condensation of β-ketoesters with amines to produce β-enamino esters. The results are summarized in Table 3.

Several β-ketoesters were subjected to condensation with amines to get the β-enamino esters in excellent yields at room temperature. Due to steric hindrance, the condensation of ethyl benzoyl acetate with benzylamine requires 60 °C heating to produce the corresponding β-enamino esters in 75% yield.

Finally, the reusability of ionic liquid was studied and we found that the ionic liquid could be reused at least four times without significant loss of activity (Table 4).

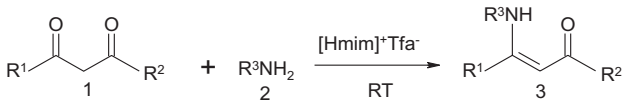
Next, we extended this methodology for a one-pot, three-component reaction of 1,3-dicarbonyl compounds, ammonium acetate, and alkynone in [Hmim]$^+$Tfa$^-$ to synthesize various substituted pyridines. The results are summarized in Table 5.

Ethyl acetoacetate reacts with ammonium acetate and 4-phenyl-3-butyn-2-one in the presence of [Hmim]$^+$Tfa$^-$ at room temperature to give ethyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate in 80% yield. When methyl acetoacetate or acetyl acetone was reacted with 4-(trimethylsilyl)but-3-yn-2-one, the corresponding protodesilylated pyridines **6b** and **6d** were obtained in 90% and 92% yield.

Conclusion

In summary, this paper describes a novel and efficient protocol for the synthesis of β-enamino esters and β-enaminones from 1,3-dicarbonyl compounds and amines. The advantage of this methodology lies in its operational simplicity and relatively shorter reaction time. This method also avoids the use of hazardous solvents such as benzene and azeotropic distillation conditions. The ionic liquid used can be recycled up to four times without an appreciable fall in yield, indicating that this protocol will be useful for the synthesis of natural products involving the intermediacy of β-enamino esters and β-enaminones. The one-pot, three-component reaction for the synthesis of substituted pyridines was achieved without using hazardous solvents, such as toluene or dichloromethane, at room temperature in excellent yields.

Table 1. Condensation of benzoyl acetone with aniline under various mediums.



Entry	Medium	Time (h)	Yield (%)
1	[Hmim]$^+$Tfa$^-$	0.25	95
2	[Hmim]$^+$Tsa$^-$	4	75
3	Neat	24	40

Experimental

IR spectra were recorded as solids in KBr pellets on a PerkinElmer FT IR spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz Joel spectrometer using TMS as the internal standard. ^{13}C NMR spectra were recorded on a 125 MHz spectrometer in $CDCl_3$, and chemical shifts are given in δ relative to the solvent peak. Mass spectra were recorded on a Joel DX-303 mass spectrometer. Analytical TLC was performed on precoated sheets of silica gel G of 0.25 mm thickness containing PF 254 indicator (Merck, Darmstadt). Column chromatography was performed with silica gel (60–120 mesh, S.d Fine, Boisar).

Typical experimental procedure for the preparation of β-enaminones 3a–3k and β-enamino esters 5a–5e

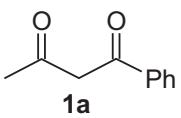
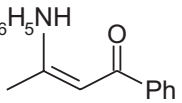
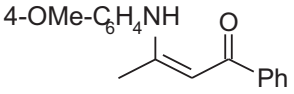
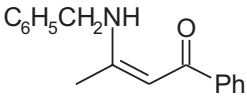
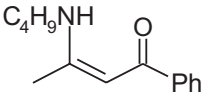
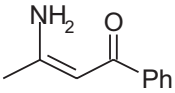
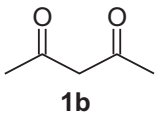
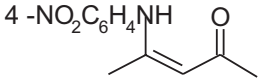
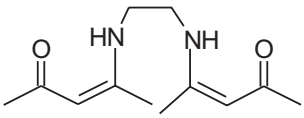
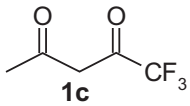
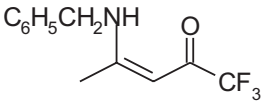
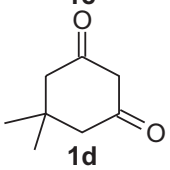
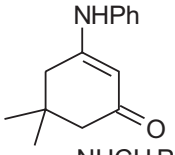
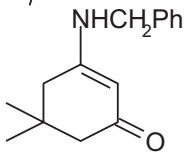
To a solution of 1,3-dicarbonyl compounds (1 mmol) in [Hmim]$^+$Tfa$^-$ (1 mL) was added amines (1.5 mmol). The reaction mixture was stirred at room temperature for the appropriate time (Tables 1 and 2). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with distilled water (20 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layer was dried over anhydr. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by filtration on a short silica gel column pretreated with Et_3N.

The aqueous layer was extracted with ether to remove residual reactants. Then the aqueous layer was collected and concentrated under reduced pressure at 70 °C to recover the IL, and was recycled.

Typical experimental procedure for the preparation of pyridines (6a–6e)

A solution of 1,3-dicarbonyl compounds (1 mmol), alkynone (1.2 mmol), and ammonium acetate (5 mmol) in

Table 2. Ionic liquid promoted condensation of 1,3-dicarbonyl compounds with amines.

Entry	1,3-Dicarbonyl	Amine	Time (h)	Product (**3a-3j**)[a]	Yield (%)[b]
1	 **1a**	$C_6H_5NH_2$	0.25		95
2	**1a**	4-OMe-$C_6H_4NH_2$	0.25		92
3	**1a**	$C_6H_5CH_2NH_2$	0.25		98
4	**1a**	$C_4H_9NH_2$	0.5		84
5	**1a**	$CH_3COO^-NH_4^+$	4		85
6	 **1b**	4 -$NO_2C_6H_4NH_2$	24		65[c]
7	**1b**	$H_2NCH_2CH_2NH_2$	0.25		80
8	 **1c**	$C_6H_5CH_2NH_2$	2		80
9	 **1d**	$C_6H_5NH_2$	1		82
10	**1d**	$C_6H_5CH_2NH_2$	0.5		85

[a]All the products were identified by IR, NMR, and MS.
[b]Isolated yield.
[c]Reaction was carried out at 80 °C.

[Hmim]$^+$Tfa$^-$ was stirred at room temperature for 24 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with distilled water (20 mL) and extracted with diethyl ether (3 × 15 mL). The combined ether extracts were dried over anhydr. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give pyridines **6a**–**6e**.

Spectral data

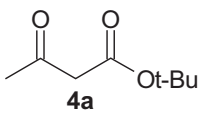
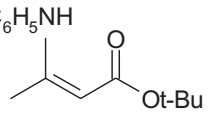
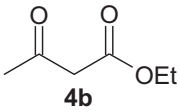
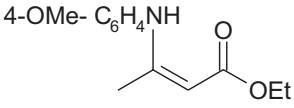
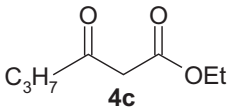
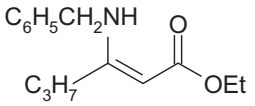
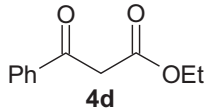
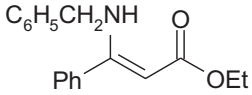
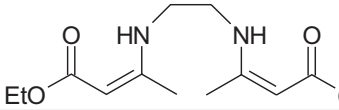
(2Z)-3-Anilino-1-phenylbut-2-en-1-one (3a)

IR (KBr, cm^{-1}): 1622, 1550. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 5.89 (s, 1H), 7.15–7.26 (m, 3H), 7.35–7.47 (m, 5H), 7.91–7.96 (m, 2H), 11.7 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.5, 94.3, 124.8, 125.8, 127.1, 128.4, 129.2, 131.0, 138.7, 140.0, 162.3, 188.7. MS (EI) *m*/*z* (%): 268 (20) [M$^+$], 105 (100). Anal. calcd. for $C_{16}H_{15}NO$: C 80.98, H 6.37, N 5.90; found: C 80.71, H 6.20, N 5.78.

(2Z)-3-[(4-Methoxyphenyl)amino]-1-phenylbut-2-en-1-one (3b)

IR (KBr, cm^{-1}): 1614, 1550. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.05 (s, 3H), 3.80 (s, 3H), 5.85 (s, 1H), 6.87–6.90 (m, 2H), 7.08–7.11 (m, 2H), 7.40–7.46 (m, 3H), 7.98–7.92 (m, 2H), 10.7 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.3, 55.5, 93.6, 114.4, 126.7, 127.1, 128.3, 130.8, 131.4,

Table 3. Ionic liquid promoted condensation of β-ketoesters with amines.

Entry	1,3-Dicarbonyl	Amine	Time (h)	Product (**5a**-**5e**)[a]	Yield (%)[b]
1	 **4a**	$C_6H_5NH_2$	0.25		90
2	 **4b**	4-OMe-$C_6H_4NH_2$	0.25		95
3	 **4c**	$C_6H_5CH_2NH_2$	1		82
4	 **4d**	$C_6H_5CH_2NH_2$	8		75[c]
5	**4b**	$H_2NCH_2CH_2NH_2$	5		80

[a]All the products were identified by IR, NMR, and MS.
[b]Isolated yield.
[c]Reaction was carried out at 60 °C.

Table 4. Results obtained with recycled ionic liquid – $[Hmim]^+Tfa^-$.

Entry	Product	Run	Yields (%)
1	**3a**	1	90
2	**3a**	2	89
3	**3a**	3	89
4	**3a**	4	87

140.2, 157.9, 163.2, 188.4. MS (EI) *m/z* (%): 268 (20) [M^+], 105 (100). Anal. calcd. for $C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found: C 76.62, H 6.30, N 4.98.

(2Z)-3-(Benzylamino)-1-phenylbut-2-en-1-one (3c)

IR (KBr, cm^{-1}): 1618, 1554. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.06 (s, 3H), 4.54 (d, 2H), 5.75 (s, 1H), 7.23–7.44 (m, 8H), 7.87–7.89 (m, 2H), 11.7 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.6, 47.1, 92.7, 126.9, 127.0, 127.6, 128.2, 128.9, 130.6, 137.8, 140.3, 165.0, 188.1. MS (EI) *m/z* (%): 251 (30) [M^+], 105 (100). Anal. calcd. for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57; found: C 80.12, H 6.97, N 5.45.

(2Z)-3-(Butylamino)-1-phenylbut-2-en-1-one (3d)

IR (neat, cm^{-1}): 1612, 1579. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J = 7.4 Hz), 1.34–1.41 (sex, 2H), 1.50–1.56 (pent, 2H), 1.88 (s, 3H), 1.96 (s, 3H), 3.17–3.21 (q, 2H, J = 6.85 Hz), 4.91 (s, 3H), 10.83 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.7, 18.8, 20.0, 28.7, 32.1, 42.7, 95.0, 123.9, 125.5, 129.3, 161.0, 186.4. MS (EI) *m/z* (%): 251 (30) [M^+], 77 (100). Anal. calcd. for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45; found: C 77.29, H 8.91, N 6.34.

(2Z)-3-Amino-1-phenylbut-2-en-1-one (3e)

IR (KBr, cm^{-1}): 1612, 1579. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.0 (s, 3H), 5.75 (s, 1H), 7.4 (m, 3H), 7.8 (m, 2H), 10.1 (brs, NH, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.97, 95.2, 123.9, 125.5, 129.3, 161.0, 185.63. MS (EI) *m/z* (%): 161 (60) [M^+], 160 (100). Anal. calcd. for $C_{10}H_{11}NO$: C 74.51, H 6.88, N 8.69; found: C 74.49, H 6.80, N 8.74.

(3Z)-4-(4-Nitrophenyl)pent-3-en-2-one (3f)

IR (KBr, cm^{-1}): 1618, 1554. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.85 (s, 3H), 1.92 (s, 3H), 5.80 (s, 1H), 6.82 (m, 2H), 7.02–6.99 (m, 2H), 10.4 (brs, NH, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.5, 28, 96.3, 14.7, 116.2, 126.9, 132.2, 147.6, 156.2, 185.0. MS (EI) *m/z* (%): 220 (45) [M^+], 85 (100). Anal. calcd. for $C_{11}H_{12}N_2O_3$: C 59.99, H 5.49, N 12.72; found: C 60.20, H 5.61, N 12.85.

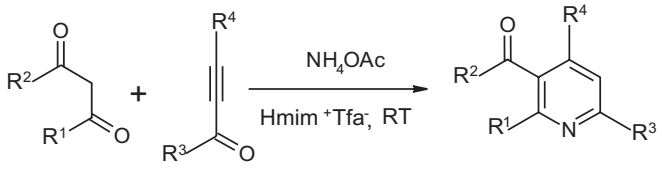
(3Z)-4-[(2-{[(1Z)-1-Methyl-3-oxobut-1-enyl]amino}ethyl)-amino]pent-3-en-2-one (3g)

IR (KBr, cm^{-1}): 1609, 1576. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.88 (s, 6H), 1.94 (s, 6H), 3.3 (t, 4H), 4.97 (s, 2H), 10.8 (bs, 2H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.8, 28.9, 43.6, 96.2, 162.9, 195.6. MS (EI) *m/z* (%): 225 (67.4) [M^+], 182.4 (71.7), 83.1 (100). Anal. calcd. for $C_{12}H_{20}N_2O_2$: C 64.26, H 8.99, N 12.49; found: C 64.17, H 9.14, N 12.54.

(3Z)-4-(Benzylamino)-1,1,1-trifluoropent-3-en-2-one (3h)

IR (KBr, cm^{-1}): 1612, 1579. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 4.54 (d, 2H), 5.39 (s, 1H), 7.25–7.39 (m, 5H), 11.421 (s, br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.5, 47.6, 89.9, 127.0, 128.1, 129.2, 136.0, 169.7, 175 (q, J = 32 Hz). MS (EI) *m/z* (%): 249 (41) [M + 2], 82.7 (100). Anal. calcd. for $C_{12}H_{12}F_3NO$: C 59.26, H 4.97, F 23.43, N 5.76; found: C 59.38, H 5.15, F 23.59, N 5.63.

Table 5. Synthesis of pyridines in a one-pot, three-component reaction.



R^1 = OEt, OMe, R^3 = CH_3, Ph 80%–94%

R^2 = Me, Ph R^4 = Ph, $SiMe_3$, H

	1,3-Dicarbonyl		Alkynones			
Entry	R^1	R^2	R^3	R^4	Product[a]	Yield (%)[b]
1	CH_3	OEt	CH_3	Ph	**6a**	80
2	CH_3	OMe	CH_3	$SiMe_3$	**6b** (R^4 = H)	90
3	CH_3	OMe	Ph	H	**6c**	94
4	CH_3	CH_3	CH_3	$SiMe_3$	**6d** (R^4 = H)	92
5	CH_3	CH_3	CH_3	Ph	**6e**	82

[a]All the products were identified by IR, NMR, and MS.
[b]Isolated yield.

3-Anilino-5,5-dimethylcyclohex-2-en-1-one (3i)

IR (KBr, cm^{-1}): 1618, 1554. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.05 (s, 6H), 2.17 (s, 2H), 2.34 (s, 2H), 5.54 (s, 1H), 7.00 (bs, 1H, NH), 7.10–7.13 (m, 3H), 7.28–7.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.3, 32.8, 43.5, 50.4, 98.3, 123.9, 125.5, 129.3, 138.3, 161.0, 198.1. MS (EI) *m/z* (%): 215 (45) [M^+], 159 (79), 85 (100). Anal. calcd. for $C_{14}H_{17}NO$: C 78.1, H 7.96, N 6.51; found: C 78.24, H 7.85, N 6.59.

3-Benzylamino-5,5-dimethylcyclohex-2-en-1-one (3j)

IR (KBr, cm^{-1}): 1620, 1554. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.05 (s, 6H), 2.17 (s, 2H), 2.36 (s, 2H), 4.50 (d, 2H), 5.52 (s, 1H), 7.00 (bs, 1H, NH), 7.10–7.13 (m, 3H), 7.28–7.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.3, 32.8, 43.4, 47.14, 50.4, 98.3, 123.9, 125.5, 129.3, 161.0, 198.1. MS (EI) *m/z* (%): 229 (40) [M^+], 85 (100). Anal. calcd. for $C_{15}H_{19}NO$: C 78.56, H 8.35, N 6.11; found: C 78.64, H 8.27, N 6.22.

tert-*Butyl (2Z)-3-anilinobut-2-enoate (5a)*

IR (KBr, cm^{-1}): 3416, 1640, 1610. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 1.95 (s, 3H), 4.60 (s, 1H), 7.05–7.23 (m, 3H), 7.22–7.35 (m, 2H), 10.4 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 02.3, 28.8, 78.5, 87.8, 124.3, 124.5, 128.9, 139.5, 158.1, 170.3. MS (EI) *m/z* (%): 233 (6) [M^+], 77 (30), 59 (100). Anal. calcd. for $C_{14}H_{19}NO_2$: C 72.97, H 8.21, N 6.08; found: C 72.82, H 8.34, N 6.20.

Ethyl (2Z)-3-[(4-methoxyphenyl)amino]but-2-enoate (5b)

IR (KBr, cm^{-1}): 3251, 1646, 1612. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, *J* = 6.9 Hz), 1.86 (s, 3H), 3.78 (s, 3H), 4.13 (q, 2H, *J* = 6.9 Hz), 4.63 (s, 1H), 6.87–6.82 (m, 2H), 7.02–6.99 (m, 2H), 10.7 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7, 20.1, 55.5, 58.7, 84.7, 114.2, 126.9, 132.2, 157.5, 160.1, 170.5. MS (EI) *m/z* (%): 235 (20) [M^+], 59 (100). Anal. calcd. for $C_{13}H_1NO_3$: C 66.36, H 7.28, N 5.95; found: C 66.22, H 7.40, N 5.83.

Ethyl (2Z)-3-(benzylamino)hex-2-enoate (5c)

IR (KBr, cm^{-1}): 3250, 1643, 1612. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.98 (s, 3H), 1.26 (t, 3H, *J* = 6.9 Hz), 1.61 (m, 2H), 2.55 (t, 2H), 4.13 (q, 2H, *J* = 6.9 Hz), 4.43 (q, 2H, *J* = 6.9 Hz), 5.35 (s, 1H), 7.05–7.23 (m, 3H), 7.22–7.35 (m, 2H), 10.4 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.17, 14.85, 23.3, 36.1, 45.38, 60.15, 94.79, 127.29, 128.56, 127.17, 138.47, 166.27. MS (EI) *m/z* (%): 247 (20) [M^+]. Anal. calcd. for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66; found: C 70.5, H 8.68, N 5.83.

Ethyl (2Z)-3-(benzylamino)-3-phenylacrylate (5d)

IR (neat, cm^{-1}): 1646, 1612. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, *J* = 6.9 Hz), 4.43 (q, 2H, *J* = 6.9 Hz), 5.35 (s, 1H), 7.2–7.4 (m, 8H), 7.87–7.89 (m, 2H), 10.6 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 45.30, 58.0, 86.2, 127.0, 127.12, 127.17, 127.39, 128.07, 136.54, 138.32, 166.65, 167.86. MS (EI) *m/z* (%): 281 (40) [M^+], 59 (100). Anal. calcd. for $C_{18}H_{19}NO_2$: C 76.84, H 6.81, N 4.98; found: C 76.97, H 6.69, N 5.19.

Ethyl (2Z)-3-[(2-{[(1Z)-3-ethoxy-1-methyl-3-oxoprop-1-enyl]amino}ethyl)amino]but-2-enoate (5e)

IR (KBr, cm^{-1}): 1648, 1605. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.20–1.23 (t, 2 × 3H, *J* = 6.85 Hz), 1.88 (s, 6H), 3.32–3.33 (t, 4H, *J* = 3.4 Hz), 4.03–4.07 (q, 4H, *J* = 6.9 Hz), 4.45 (s, 2H), 8.61 (s, 2H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 19.3, 43.8, 58.5, 83.61, 161.3, 170.6. MS (EI) *m/z* (%): 284 (20) [M^+], 81 (100). Anal. calcd. for $C_{14}H_{24}N_2O_4$: C 59.13, H 8.51, N 9.85; found: C 59.22, H 8.43, N 9.70.

Ethyl 2,6-dimethyl-4-phenylnicotinate (6a)

R_f 0.43 (20% EtOAc in petroleum ether). IR (neat, cm^{-1}): 1725, 1580. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.94–0.97 (t,

3H, J = 7.45 Hz), 2.59 (s, 3H), 2.65 (s, 3H), 4.04–4.09 (q, 2H, J = 7.45 Hz), 7.00 (s, 1H), 7.31–7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 24.3, 27.7, 61.3, 121.3, 125.9, 127.9, 128.51, 128.57, 138.7, 148.7, 155.1, 158.6, 169.04. MS (EI) *m/z* (%): 255 (95) [M^+], 210 (90), 115 (100). Anal. calcd. for $C_{16}H_{17}NO_2$: C 75.27, H 6.71, N 5.49; found: C 75.41, H 6.83, N 5.40.

Methyl 2,6-dimethylnicotinate (6b)

R_f 0.3 (20% EtOAc in petroleum ether). IR (neat, cm^{-1}): 1720. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 2.73 (s, 3H), 3.89 (s, 3H), 7.05–7.07 (s, 1H, J = 8 Hz), 8.08–8.10 (s, 1H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 24.3, 40.0, 120.8, 124.9, 139.1, 159.1, 161.0, 166.6. MS (EI) *m/z* (%): 179 (60) [M^+], 151 (100). Anal. calcd. for $C_{10}H_{13}NO_2$: C 67.02, H 7.31, N 7.82; found: C 66.91, H 7.44, N 7.89.

Methyl 2-methyl-4-phenylnicotinate (6c)

R_f 0.4 (20% EtOAc in petroleum ether). IR (neat, cm^{-1}): 1720. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.58 (s, 3H), 3.89 (s, 3H), 7.05–7.07 (s, 1H, J = 8 Hz), 8.08–8.10 (s, 1H, J = 8 Hz), 7.31–7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.1, 45.1, 121.3, 125.9, 127.9, 128.51, 128.57, 138.7, 148.7, 155.1, 158.6, 162.5, 169.04. MS (EI) *m/z* (%): 227 (80) [M^+], 115 (100). Anal. calcd. for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16; found: C 74.17, H 5.71, N 6.22.

1-(2,6-Dimethylpyridin-3-yl)ethanone (6d)

R_f 0.4 (20% EtOAc in petroleum ether). IR (neat, cm^{-1}): 1686. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 2.73 (s, 3H), 7.05–7.07 (s, 1H, J = 8 Hz), 8.08–8.10 (s, 1H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 24.3, 40.0, 120.8, 124.9, 139.1, 159.1, 161.0, 166.6. MS (EI) *m/z* (%): 149 (60) [M^+]. Anal. calcd. for $C_9H_{11}NO$: C 72.46, H 7.43, N 9.39; found: C 72.58, H 7.50, N 9.42.

1-(2,6-Dimethyl-4-phenylpyridin-3-yl)ethanone (6e)

R_f 0.34 (20% EtOAc in petroleum ether). IR (neat, cm^{-1}): 1686. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 2.75 (s, 3H), 7.00 (s, 1H), 7.31–7.39 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.3, 24.3, 27.7, 121.3, 125.9, 127.9, 128.51, 128.57, 138.7, 148.7, 155.1, 158.6, 169.04. MS (EI) *m/z* (%): 225 (60) [M^+], 115 (100). Anal. calcd. for $C_{15}H_{15}NO$: C 79.97, H 6.71, N 6.22; found: C 80.16, H 6.79, N 6.33.

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