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Silica Gel-mediated Synthesis of β-Enamino Esters and its Application for the Synthesis of Indeno 4-Hydroxypyridin-2(1H)-Ones

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The full scope of SiO_2-based condensation of aliphatic or aromatic amines and β-keto esters to give β-enamino esters was examined. Functionalized linear β-enamino esters were easily obtained from SiO_2-based condensation of β-keto esters and amines only after simple filtration. It was also demonstrated that cyclic β-enamino esters with 99% purity can be prepared in a practically large scale (60 g) without using silica gel column chromatography. The utility of the present method was fortified by the preparation of pharmaceutically useful indeno-4-hydroxypyridin-2(1H)-one analogue **11**.

Keywords: SiO_2-based condensation, β-keto ester, β-enamino ester, 4-hydroxypyridine-2(1H)-one

Introduction

4-Hydroxypyridin-2(1H)-one comprises the core structure of several biologically active natural products and pharmaceutical compounds such as illicicolin H,[1] TAK-441,[2] and GSK360A[3] (Figure 1). The synthesis of core 4-hydroxypyridin-2(1H)-ones typically involves alkylation of corresponding cyclic anhydride with a malonate or amidation by heating of N-alkylated aniline and triesters such as triethyl methanetricarboxylate.[3] Similarly, Rigby *et al*. have utilized α,β-unsaturated isocyanates to produce 4-hydroxypyridin-2(1H)-one by the addition of ester enolates to the electrophilic carbonyl carbon of the isocyanate followed by cylization.[4] Alternatively, the pyridone core can be prepared from β-ketoesters by traditional amination to give β-enamino esters, followed by cyclization with diethyl malonate.[2] Among these methods, the formation of pyridinone core using β-ketoesters and amines as starting materials has been widely used in the area of medicinal chemistry research due to their experimental convenience and versatility. As Sasaki *et al*. described, this process typically involves the condensation of amines in protic solvents or in aprotic solvents with azeotropic removal of water.[2] However, it also possesses some significant limitations in practical use such as the long reaction time, harsh reaction conditions, low chemical yields, and a narrow substrate tolerability. To overcome these limitations, Xu *et al*. nicely described the formation of β-enamino carbonyl compounds through silica gel-based solvent-free reactions of β-keto carbonyl compounds, with amines as a starting material.[5] Intrigued by this synthetic methodology, we have decided to investigate the full scope of this type of SiO_2-based reaction for the formation of linear and cyclic β-enamino carbonyl compounds. Additionally, its practical application for the synthesis of pharmaceutically useful compounds such as indeno-pyridine carboxylates (*e.g.*, **11**) is demonstrated herein.

Results and Discussion

We initially screened the addition of various amines to 2-(methoxycarbonyl)cyclopentanone **1** (Table 1). In the presence of SiO_2 (1000 wt % was used for experimental convenience), the condensation of most primary alkyl amines with cyclic β-keto ester **1** (ratio 1:1) gave the desired cyclic β-enamino esters with good yields (Table 1, entry 1–8), while sterically bulkier aliphatic amines such as dimethylamine and t-butyl amine gave no or only trace amounts of desired products (entry 9 and 10). Functionalized amines such as allylic amine, propargylic amine, and ethanol amine were well tolerated to give cyclic β-enamino esters with various functionalities in 66–73% yield (entry 11–13). When enantiomerically pure amine **2n** was reacted with β-keto ester **1**, the condensation reaction was completed within an hour based on LCMS analysis. More importantly, in this case, the enantiomeric ratio of (S)-1-phenylethane-1-amine (**2n**) (>99.5:0.5, >99% ee) was fully maintained throughout the reaction to give cyclic β-enamino ester **3n** with >99% ee in a ratio of 99.6:0.4 based on chiral HPLC analysis (entry 14). Amines possessing *pri*- and *sec*-amines within the molecule, such as 4-amino piperidine **2o**, gave the desired cyclic β-amino ester in 85% yield without any competition with *sec*-amine on the piperidine ring as expected (entry 15). Aromatic amines with various substitutions (except electron withdrawing groups) on the phenyl ring were generally well

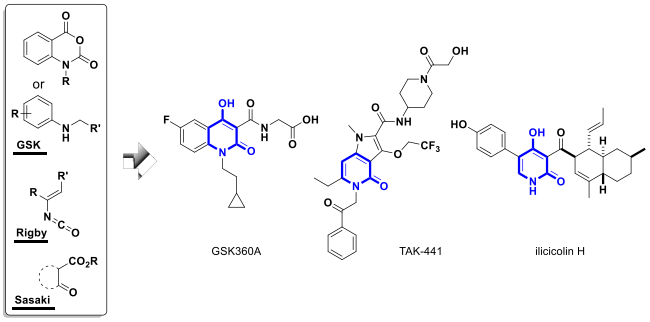


Figure 1. Representative synthetic methods for 4-hydroxypyridin-2(1H)-one core in natural products and pharmaceutically active compounds.

tolerated. Most electron donating groups and halogens were well suited to the condensation reactions and formed the desired products in over 70% yields (entry 16–22). However, strong electron withdrawing groups, such as CF_3, esters, and nitro groups, were poorly tolerated and gave the desired products in low yield or led to no reaction (entry 23–25). Finally, we were interested in finding out whether a bare amine, such as $AcONH_4$, can be tolerated in the SiO_2-based condensation reaction. It is clear from the literature that the desired product **3z** can be used as a key intermediate for the preparation of pharmaceutically important compounds. For example, LG Life Sciences and Novartis reported the synthesis of GPR120 agonists[6] and PDE4 inhibitors,[7] respectively, using 2-amino-1-cyclopentene carboxylate (**3z**) as a core intermediate. When 1.0 equiv of $AcONH_4$ was subjected to **1** in SiO_2 following a typical experimental procedure, the desired product cyclic priamine **3z** was obtained in 68% yield (entry 26).

Upon examining the scope of amine substrates, we paid our attention to the structurally more complex β-keto esters, such as **4a-d**, which possess previously unknown complexity (Table 2). Functionalized β-keto esters, such as 4-methoxy-3-oxobutanoate **4a** and 3-oxo-3-phenyl propanoate **4b**, gave the product in 74 and 52% yield, respectively (Table 2, entry 1 and 2). The E/Z ratio for 4-methoxy butenoate **5a** was moderate, by giving an inseparable mixture of E and Z isomers in a ratio of 1:1. However, phenylacrylate **5b** was obtained exclusively in the Z configuration. Cyclic β-keto esters larger than five-membered ring system presented some limitations in the reaction outcome. β-Keto ester on a six-membered ring gave an unidentifiable complex mixture probably due to inherent 1,3-diaxial steric interactions in the ring (entry 3). Seven-membered ring also gave the desired product in low yield (Table 2, entry 4). It is not surprising that the corresponding cyclic enamine was not obtained from cyclopetanone **4e**, which does not have β-esters on the ring; however, the imine obtained from the condensation reaction was stable enough to give **5e** after silica gel column in moderate yield (41%).

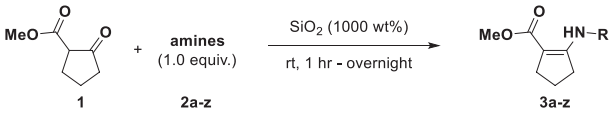
To understand the limitation of this SiO_2-based condensation reaction for β-enamino esters, we subjected 300 mg of methyl 2-oxocyclopentane 1-carboxylate (**1**, 2.11 mmol) to an amount of SiO_2 varying up to 1 wt % (Table 3). We found that 1 wt % SiO_2 still gave the desired product **7** in high yield (90%) (Table 3, entry 1–4). Encouraged by this result, we ran the reaction in multigram scale in order to demonstrate the practicality of our reaction. When 60 g of **1** was reacted with amine **6** in the presence of SiO_2 (500 wt %) under mechanical stirring, we obtained the desired product, after simple filtration using a glass filter, in quantitative yield with 99% purity based on HPLC analysis (Table 3, entry 5). No further purification such as silica gel column chromatography was necessary. We believe that this example strongly demonstrates the synthetic utility of SiO_2-based condensation of amines with β-keto esters for the preparation of cyclic β-enamino esters in a large scale setting.

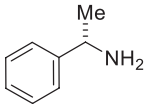
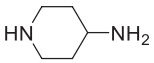
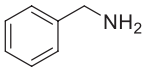
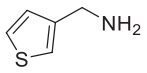
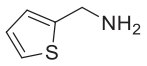
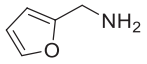
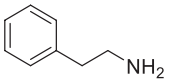
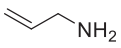
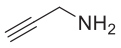
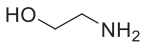
As mentioned earlier, the synthetic utility of 4-hydroxypyridin-2(1H)-one analogues for the preparation of pharmaceutically active compounds has been widely demonstrated in the literature. For example, Smithkline Beecham Co. (Philadelphia, PA, USA) has developed prolyl hydroxylase inhibitors for anemia,[3] and Martinez *et al.* have reported the synthesis of allosteric inhibitor of GSK-3β for chronic diseases such as congenital myotonic dystrophy type 1 (CDM1) and spinal muscular atrophy (SMA)[8] using 4-hydroxypyridin-2(1H)-one derivatives as a core intermediate. Therefore, we decided to provide another important example of synthesizing 4-hydroxypyridin-2(1H)-one analogues with more complexity such as **11** using SiO_2-based condensation of amines and β-keto esters as a key step, as shown in Scheme 1. 2,3-Dihydro-1H-indeno-1-one (**8**) (**2g**) was converted to indene carboxylate **9** in 83% yield by carboxylation with dimethyl carbonate. Upon reaction with phenethyl amine in the presence of SiO_2 (1000 wt %) at 80 °C, the desired β-enamino ester **10** was obtained in 66% yield within 4 h. Addition of ethyl malonyl chloride followed by *in situ* cyclization using NaOEt at room temperature directly gave the desired product **11** in over 80% yield.

Experimental

General. All commercially available reagents were purchased from Sigma Aldrich (St. Louis, MO, USA), Tokyo Chemical Industry Co., Ltd. (TCI), Alfa Aesar (Ward Hill, MA, USA), Fisher Scientific (Pittsburgh, PA, USA) and used as received. All reaction mixtures were stirred magnetically and monitored by thin-layer chromatography using silica gel precoated glass plates, which were visualized with UV light. Mass spectra were measured in positive electrospray ionization (ESI) mode on LCMS-2020 system (Shimadzu, Tokyo, Japan). Flash column chromatography was carried out using a CombiFlash® Rf system with

Table 1. Solvent-free synthesis of β-enamino esters with various amines.[a]



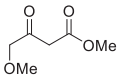
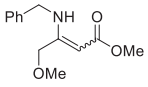
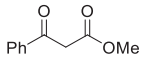
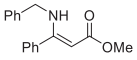
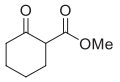
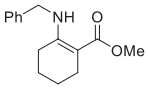
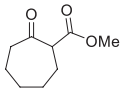
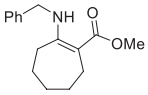
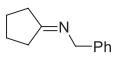
Entry	Amine	Yield (%)[b]	Entry	Amine	Yield (%)[b]
1	$MeNH_2$ **(2a)**	82	**14**	 **(2n)**	75
2	*i*-$PrNH_2$ **(2b)**	66	**15**	 **(2o)**	85
3	*c*-$HexylNH_2$ **(2c)**	70	**16**	$PhNH_2$ **(2p)**	70
4	 **(2d)**	85	**17**	*p*-Me-C_6H_4-NH_2 **(2q)**	76
5	 **(2e)**	76	**18**	*p*-MeO-C_6H_4-NH_2 **(2r)**	79
6	 **(2f)**	86	**19**	*p*-Me_2N-C_6H_4-NH_2 **(2 s)**	77
7	 **(2g)**	81	**20**	*p*-F-C_6H_4-NH_2 **(2 t)**	71
8	 **(2h)**	86	**21**	*p*-Cl-C_6H_4-NH_2 **(2u)**	58
9	Me_2NH **(2i)**	N/R	**22**	*p*-Br-C_6H_4-NH_2 **(2v)**	53
10	*t*-$BuNH_2$ **(2j)**	3	**23**	*p*-CF_3-C_6H_4-NH_2 **(2w)**	19
11	 **(2k)**	71	**24**	*p*-MeO_2C-C_6H_4-NH_2 **(2x)**	12
12	 **(2l)**	73	**25**	*p*-NO_2-C_6H_4-NH_2 **(2y)**	N/R
13	 **(2m)**	66	**26**	$AcONH_4$ **(2z)**	68

[a] Reaction conditions: **1** (0.711 g, 5 mmol), SiO_2 (7.11 g, 10 g per 1 g of **1**), **2a-z** (1.0 equiv), rt.
[b] Isolated yield by flash column chromatography.

RediSep® Rf (Teledyne Isco, Lincoln, NE, USA). All NMR spectra were recorded on Bruker 400 (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) spectrometer and calibrated to the residual solvent peak or tetramethylsilane (δ = 0 ppm). $CDCl_3$ or CD_3OD was used as the solvent. High-resolution mass spectra (HRMS) were acquired on a high-resolution Q-TOF mass spectrometer (ionization mode: ESI). Melting points were determined in open capillary tube using fully automatic melting point meter M5000 (A.KRÜSS Optronic). All known compounds, cyclic β-enamino esters **3a**,[9] **3m**,[10] **3n**,[11] **3p**,[12] **3r**,[13] **3z**,[14] **5a**,[15] **5b**,[16] **5e**,[17] and **9**,[18] were identical with known value.

Typical Experimental Procedure. To a mixture of **1** (621 μL, 0.711 g, 5 mmol) and SiO_2 (7.11 g, 10 g per 1 g of **1**), was added corresponding amines **2a-z** (1.0 equiv) dropwise while stirring at rt. The resulting solid mixture was typically stirred for 1 h to overnight at rt. Upon complete consumption of starting material based on LCMS

Table 2. Synthesis of β-enamino esters and imines with various β-keto esters and cyclic ketones.[a]

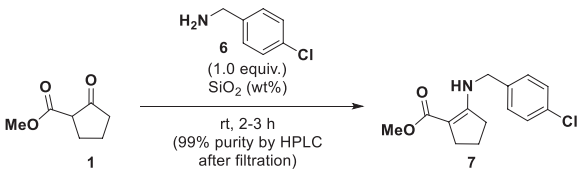
Entry	Ketone	Product	Yield (%)[b]
	β-ketones (**4a-e**) + Ph–NH$_2$ (1.0 equiv) (**2d**) → SiO_2 (1000 wt%), rt, overnight → product (**5a-e**)		
1	 **(4a)**	 **(5a)**	74 (E:Z = 1.0:1.1)
2	 **(4b)**	 **(5b)**	52 (Z only)
3	 **(4c)**	 **(5c)**	N/A (complex mixture)
4	 **(4d)**	 **(5d)**	17
5	 **(4e)**	 **(5e)**	41

[a] Reaction conditions: All reactions were performed following typical experimental procedure. **4** (1.0 equiv), SiO_2 (10 g per 1 g of **4**), **2d** (1.0 equiv), rt.
[b] Isolated yield by flash column chromatography.

analysis, the solid mixture was purified by silica gel column chromatography to give the desired products **3a-z** upon drying under vacuum (Table 1).

Methyl 2-(methylamino)cyclopent-1-ene-1-carboxylate (3a).[9] 1.06 mL (2.11 mmol, 2 M solution in THF) of **2a** was used to give 267 mg of **3a** (1.72 mmol, 82%) as a beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (brs, NH), 3.66 (s, 3H), 2.91 (d, *J* = 5.2 Hz, 3H), 2.57–2.50 (m, 4H), 1.83 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 165.9, 91.9, 50.0, 31.8, 31.0, 29.1, 20.8.

Table 3. Multigram scale synthesis of cyclic β-enamino ester **7**.[a]



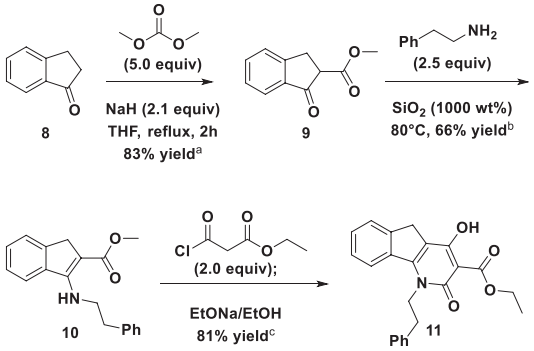
Entry	Amount of **1**	SiO_2 (wt %/**1**)	Yield[a] (%)
1	2.11 mmol (0.300 g)	1000	87
2	2.11 mmol (0.300 g)	100	88
3	2.11 mmol (0.300 g)	10	87
4	2.11 mmol (0.300 g)	1	90
5	422 mmol (60.0 g)	500	93

[a] No further purification was performed after filtration using a glass filter.

Methyl 2-(isopropylamino)cyclopent-1-ene-1-carboxylate (3b). 0.181 mL (2.11 mmol, 1.0 equiv) of **2b** was used to give 254 mg of **3b** (1.39 mmol, 66%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (brs, NH), 3.60 (s, 3H), 3.58–3.51 (m, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 7.4 Hz, 2H), 1.19 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 164.1, 91.6, 49.9, 46.2, 31.8, 28.7, 24.3, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{17}NO_2$ 184.1338, found 184.1329.

Methyl 2-(cyclohexylamino)cyclopent-1-ene-1-carboxylate (3c). 0.241 mL (2.11 mmol, 1.0 equiv) of **2c** was used to give 331 mg of **3c** (1.48 mmol, 70%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (brs, NH), 3.67 (s, 3H), 3.21–3.13 (m, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.49 (t, *J* = 7.18 Hz, 2H), 1.88–1.77 (m, 6H), 1.36–1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 164.3, 91.5, 53.3, 50.0, 34.6, 31.8, 28.7, 25.3, 24.7, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{21}NO_2$ 224.1651, found 224.1639.

Methyl 2-(benzylamino)cyclopent-1-ene-1-carboxylate (3d). 0.262 mL (2.11 mmol, 1.0 equiv) of **2d** was used to give 414 mg of **3d** (1.79 mmol, 85%) as brown solid. mp 64.2 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (brs, NH), 7.33 (m, 2H), 7.24 (m, 3H), 4.40 (d, *J* = 6.5 Hz, 2H), 3.69 (s, 3H), 2.54 (m, 4H), 1.82 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 164.8, 139.2, 128.7, 127.3,



Scheme 1. Application of SiO_2-based condensation of β-keto ester for pharmaceutically useful 4-hydroxypyridin-2(1H)-one derivatives. [a]**8** (15.1 mmol), dimethyl carbonate (76.0 mmol), NaH (31.8 mmol), THF (0.3 M), reflux, 2 h. [b]SiO_2 (2.70 g, 10 g per 1 g of **9**), **9** (1.43 mmol), phenethylamine (3.72 mmol), 80 °C, 4 h.[c] **10** (5.90 mmol) in DCE (0.5 M), ethyl malonyl chloride (11.8 mmol), reflux, 3 h; NaOEt (11.8 mmol), EtOH (0.5 M), rt., 2 h. All reaction yields are isolated yields.

126.7, 93.1, 50.1, 48.4, 32.0, 29.1, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}NO_2$ 232.1338, found 232.1325.

Methyl 2-((thiophen-3-ylmethyl)amino)cyclopent-1-enecarboxylate (3e). 239 mg (2.11 mmol, 1.0 equiv) of **2e** was used to give 298 mg of **3e** (1.256 mmol, 76%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (brs, NH), 7.31–7.29 (m, 1H), 7.11–7.10 (m, 1H), 6.98 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.39 (d, *J* = 6.36 Hz, 2H), 3.68 (s, 3H), 2.59–2.51 (m, 4H), 1.83 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 164.6, 140.3, 126.5, 126.4, 121.2, 93.2, 50.1, 44.1, 31.9, 29.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}NO_2S$ 238.0902, found 238.0890.

Methyl 2-((thiophen-2-ylmethyl)amino)cyclopent-1-enecarboxylate (3f). 239 mg (2.11 mmol, 1.0 equiv) of **2f** was used to give 408 mg of **3f** (1.719 mmol, 86%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (brs, NH), 7.21 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.95–6.91 (m, 2H), 4.54 (d, *J* = 6.4 Hz, 2H), 3.67 (s, 3H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.53 (t, *J* = 7.12 Hz, 2H), 1.84 (p, *J* = 7.64 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 163.9, 142.6, 126.9, 124.8, 124.7, 93.9, 50.2, 43.7, 31.9, 29.1, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}NO_2S$ 238.0902, found 238.0890.

Methyl 2-((furan-2-ylmethyl)amino)cyclopent-1-enecarboxy-late (3g). 205 mg (2.11 mmol, 1.0 equiv) of **2g** was used to give 379 mg of **3g** (1.713 mmol, 81%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (brs, NH), 7.35–7.34 (m, 1H), 6.31–6.29 (m, 1H), 6.17–6.16 (m, 1H), 4.33 (d, *J* = 6.4 Hz, 2H), 3.67 (s, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 1.84 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 164.2, 152.3, 142.2, 110.3, 106.7, 93.7, 50.2, 41.7, 31.8, 29.1, 20.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}NO_3$ 222.1130, found 222.1120.

Methyl 2-(phenethylamino)cyclopent-1-ene-1-carboxylate (3h). 0.262 mL (2.11 mmol, 1.0 equiv) of **2h** was used to give 447 mg of **3h** (1.822 mmol, 86%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (brs, NH), 7.31 (m, 2H), 7.24 (m, 1H), 7.19 (m, 2H), 3.67 (s, 3H), 3.41 (q, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.77 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 164.7, 138.7, 128.8, 128.6, 126.5, 92.4, 50.1, 46.4, 37.8, 31.9, 29.0, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{19}NO_2$ 246.1494, found 246.1482.

Methyl 2-(tert-butylamino)cyclopent-1-ene-1-carboxylate (3j). 0.739 mL (7.03 mmol, 1.0 equiv) of **2j** was used to give 37 mg of **3j** (0.188 mmol, 3%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (brs, NH), 3.67 (s, 3H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.81 (p, *J* = 7.4 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 164.9, 93.3, 51.7, 50.0, 33.4, 30.9, 27.8, 21.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{19}NO_2$ 198.1494, found 198.1489.

Methyl 2-(allylamino)cyclopent-1-enecarboxylate (3k). 120 mg (2.11 mmol, 1.0 equiv) of **2k** was used to give 271 mg of **3k** (1.495 mmol, 71%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (brs, NH), 5.90–5.81 (m, 1H), 5.20 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.82–3.78 (m, 2H), 3.68 (s, 3H), 2.55–2.50 (m, 4H), 1.82 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 164.9, 135.3, 115.6, 92.8, 50.1, 46.8, 31.7, 29.0, 20.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{15}NO_2$ 182.1181, found 182.1172.

Methyl 2-(prop-2-yn-1-ylamino)cyclopent-1-enecarboxy-late (3l). 116 mg (2.11 mmol, 1.0 equiv) of **2l** was used to give 276 mg of **3l** (1.540 mmol, 73%) as yellow solid. mp 59.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (brs, NH), 3.94 (dd, *J* = 6.4, 2.5 Hz, 2H), 3.68 (s, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.26 (t, *J* = 2.4 Hz, 1H), 1.86 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.5, 95.0, 80.3, 71.7, 50.2, 33.9, 31.7, 29.1, 20.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}NO_2$ 180.1025, found 180.1015.

Methyl 2-((2-hydroxyethyl)amino)cyclopent-1-ene-1-carboxylate (3m).[10] 129 mg (2.11 mmol, 1.0 equiv) of **2m** was used to give 257 mg of **3m** (1.388 mmol, 66%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (brs, NH), 3.69 (s, 1H), 3.66 (m, 4H), 3.36 (m, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 2.50 (t, *J* = 5.2 Hz, 2H), 1.83 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 168.9, 165.3, 92.5, 77.1, 62.1, 50.2, 47.0, 32.1, 28.9, 20.8.

Methyl (S)-2-((1-phenylethyl)amino)cyclopent-1-ene-1-carboxylate (3n).[11] 256 mg (2.11 mmol, 1.0 equiv) of **2n** was used to give 387 mg of **3n** (1.578 mmol, 75%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (brs, NH), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (m, 3H), 4.54 (q, *J* = 6.9 Hz, 1H), 3.69 (s, 1H), 2.45 (m, 3H), 2.19 (m, 1H), 1.67 (m, 1H), 1.49 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 164.5, 145.2, 128.4, 127.0, 125.5, 93.1, 77.1, 54.3, 50.1, 32.3, 28.8, 24.9, 20.9.

Methyl 2-(piperidin-4-ylamino)cyclopent-1-ene-1-carboxylate (3o). 0.232 mL (2.11 mmol, 1.0 equiv) of **2o** was used to give 404 mg of **3o** (1.80 mmol, 85%) as white solid. mp 100.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (brs, NH), 3.67 (s, 3H), 3.31–3.26 (m, 1H), 3.09 (dt, J = 12.9, 3.8 Hz, 2H), 2.68–2.62 (m, 2H), 2.57 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 7.0 Hz, 2H), 1.91–1.80 (m, 5H), 1.46–1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.8, 92.2, 51.8, 50.1, 45.1, 35.1, 31.9, 28.7, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{20}N_2O_2$ 225.1603, found 225.1591.

Methyl 2-(phenylamino)cyclopent-1-ene-1-carboxylate (3p).[12] 0.193 mL (2.11 mmol, 1.0 equiv) of **2p** was used to give 320 mg of **3p** (1.47 mmol, 70%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (brs, NH), 7.26 (m, 2H), 7.02 (m, 3H), 3.74 (s, 3H), 2.79 (t, J = 7.3 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 1.87 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.8, 140.6, 129.2, 123.2, 120.9, 97.3, 50.5, 33.6, 28.7, 21.9.

Methyl 2-(p-tolylamino)cyclopent-1-ene-1-carboxylate (3q). 226 mg (2.11 mmol, 1.0 equiv) of **2q** was used to give 371 mg of **3q** (1.604 mmol, 76%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (brs, NH), 7.06 (d, J = 7.9 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 3.72 (s, 3H), 2.72 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 2.28 (s, 3H), 1.84 (p, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 161.3, 138.0, 133.1, 129.3, 121.3, 96.5, 77.1, 50.4, 33.5, 28.8, 21.8, 20.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}NO_2$ 232.1338, found 232.1329.

Methyl 2-((4-methoxyphenyl)amino)cyclopent-1-ene-1-carboxylate (3r).[13] 260 mg (2.11 mmol, 1.0 equiv) of **2r** was used to give 412 mg of **3r** (1.667 mmol, 79%) as ivory oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (brs, NH), 6.98 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 9.1 Hz, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.1 Hz, 2H), 1.82 (p, J = 7.3 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 168.8, 161.9, 156.4, 133.6, 123.6, 114.3, 95.7, 77.1, 55.4, 50.3, 33.2, 28.8, 21.6.

Methyl 2-((4-(dimethylamino)phenyl)amino)cyclopent-1-ene-1-carboxylate (3s). 287 mg (2.11 mmol, 1.0 equiv) of **2s** was used to give 423 mg of **3s** (1.625 mmol, 77%) as orange solid. mp 89.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (brs, NH), 6.95 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 9.1 Hz, 2H), 3.72 (s, 3H), 2.90 (s, 6H), 2.61 (t, J = 7.7 Hz, 2H), 2.55 (t, J = 6.9 Hz, 2H) 1.82 (p, J = 7.5 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 168.8, 162.8, 147.9, 130.2, 124.0, 113.0, 94.6, 77.1, 50.3, 40.9, 38.0, 33.2, 28.9, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}N_2O_2$ 261.1603, found 261.1590.

Methyl 2-((4-fluorophenyl)amino)cyclopent-1-ene-1-carboxylate (3t). 235 mg (2.11 mmol, 1.0 equiv) of **2t** was used to give 353 mg of **3t** (1.498 mmol, 71%) as white solid. mp 51.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (brs, NH), 6.99 (m, 4H), 3.73 (s, 3H), 2.68 (t, J = 7.7 Hz, 2H), 2.56 (t, J = 7.7 Hz, 2H), 1.85 (p, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.4, 158.0, 136.6, 123.1, 115.9, 115.6, 97.1, 77.1, 50.4, 32.2, 28.7, 21.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}FNO_2$ 236.1087, found 236.1075.

Methyl 2-((4-chlorophenyl)amino)cyclopent-1-ene-1-carboxylate (3u). 269 mg (2.11 mmol, 1.0 equiv) of **2u** was used to give 310 mg of **3u** (1.23 mmol, 58%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (brs, NH), 7.23 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.73 (s, 3H), 2.76 (t, J = 7.3 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 1.88 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.1, 139.3, 129.2, 128.3, 121.9, 98.1, 50.6, 33.5, 28.7, 21.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}ClNO_2$ 252.0791, found 252.0783.

Methyl 2-((4-bromophenyl)amino)cyclopent-1-ene-1-carboxylate (3v). 363 mg (2.11 mmol, 1.0 equiv) of **2v** was used to give 330 mg of **3v** (1.11 mmol, 53%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (brs, NH), 7.37 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.73 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 1.88 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.0, 139.8, 132.2, 122.1, 98.3, 50.6, 33.6, 28.6, 21.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}BrNO_2$ 296.0286, found 296.0278.

Methyl 2-((4-(trifluoromethyl)phenyl)amino)cyclopent-1-enecarboxylate (3w). 0.262 mL (2.11 mmol, 1.0 equiv) of **2w** was used to give 110 mg of **3w** (0.386 mmol, 19%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (brs, NH), 7.50 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 3.75 (s, 3H), 2.89 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 7.3 Hz, 2H), 1.93 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 159.1, 148.3, 126.5 (q, $J_{C\text{-}F}$ = 3.7 Hz, CH), 124.2 (q, $J_{C\text{-}F}$ = 272 Hz, CF3), 124.1 (q, $J_{C\text{-}F}$ = 33 Hz, C), 119.0, 100.1, 50.7, 33.9, 28.5, 21.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}F_3NO_2$ 286.1055, found 286.1044.

Methyl 4-((2-(methoxycarbonyl)cyclopent-1-en-1-yl) amino)benzoate (3x). 319 mg (2.11 mmol, 1.0 equiv) of **2x** was used to give 69 mg of **3x** (0.251 mmol, 12%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (brs, NH), 7.93 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 2.94 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 7.3 Hz, 2H), 1.94 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 166.7, 158.7, 144.9, 131.1, 123.5, 118.2, 100.4, 51.9, 50.7, 34.1, 28.5, 21.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_4$ 276.1236, found 276.1226.

Methyl 2-aminocyclopent-1-ene-1-carboxylate (3z).[14] 27.1 mg (0.352 mmol, 1.0 equiv) of **2z** was used to give 33.8 mg of **3z** (0.239 mmol, 68%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.55–2.45 (m, 4H), 1.87–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 162.0, 95.1, 50.2, 35.1, 29.5, 20.8.

Methyl 3-(benzylamino)-4-methoxybut-2-enoate (5a).[15] 106 mg (0.725 mmol, 1.0 equiv) of **4a** was used to give 127 mg of **5a** (0.540 mmol, 74%; E:Z = 1.0:1.1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) *E* isomer: δ 7.40–7.27 (m,

5H), 5.90 (s, NH), 4.71 (s, 1H), 4.49 (d, J = 6.4 Hz, 2H), 3.98 (s, 2H), 3.60 (s, 3H), 3.42 (s, 3H); Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, NH), 7.40–7.27 (m, 5H), 4.74 (d, J = 0.9 Hz, 2H), 4.62 (s, 1H), 4.20 (d, J = 5.2 Hz, 2H), 3.65 (s, 3H), 3.35 (s, 3H).

(*Z*)-Methyl 3-(benzylamino)-3-phenylacrylate (5b).[16] 113 mg (0.634 mmol, 1.0 equiv) of **4b** was used to give 88 mg of **5b** (0.319 mmol, 52%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.42–7.31 (m, 4H), 7.31–7.23 (m, 4H), 7.17 (d, J = 6.9 Hz, 2H), 4.68 (s, 1H), 4.27 (d, J = 6.5 Hz, 2H), 3.69 (s, 3H).

Methyl 2-(benzylamino)cyclohept-1-ene-1-carboxylate (5d). 275 mL (1.763 mmol, 1.0 equiv) of **4d** was used to give 78 mg of **5d** (0.301 mmol, 17%) as white solid. mp 100.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (brs, NH), 7.33 (m, 2H), 7.25 (m, 3H), 4.45 (d, J = 6.2 Hz, 2H), 3.67 (s, 3H), 2.47 (m, 4H), 1.66 (m, 2H), 1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 167.6, 139.7, 128.6, 127.1, 126.7, 95.0, 50.4, 46.9, 31.8, 28.7, 28.4, 25.9, 25.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{21}NO_2$ 260.1651, found 260.1637.

N-Cyclopentylidene-1-phenylmethanamine (5e).[17] 300 mg (3.57 mmol, 1.0 equiv) of **4e** was used to give 254 mg of **5e** (1.47 mmol, 41%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 9.6, 3.4 Hz, 4H), 7.26–7.19 (m, 1H), 4.43 (s, 2H), 2.41 (t, J = 7.3 Hz, 2H), 2.30 (t, J = 7.0 Hz, 2H), 1.86 (dd, J = 14.0, 7.0 Hz, 2H), 1.78 (dd, J = 14.0, 7.2 Hz, 2H).

Methyl 2-((4-chlorobenzyl)amino)cyclopent-1-enecar boxylate (7). 300 mg (2.11 mmol, 1.0 equiv) of **1** was used to give 488 mg of **7** (1.836 mmol, 87%) as white solid. mp 96.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 4.36 (d, J = 6.5 Hz, 2H), 3.69 (s, 3H), 2.52 (dd, J = 15.3, 7.9 Hz, 4H), 1.87–1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.54, 137.80, 133.06, 128.86, 128.05, 93.69, 50.23, 47.73, 31.99, 29.07, 20.89; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{16}ClNO_2$ 266.0948, found 266.0938.

Multigram scale synthesis of methyl 2-((4-chloro-benzyl)amino)cyclopent-1-enecarboxylate (7). To a 2 L three neck round bottom flask was placed 300 g (500 wt %) of SiO_2 and equipped with a mechanical stirrer in the center and two dropping funnels on each side necks of the flask. 52.4 mL (60 g, 422 mmol) of **1** and 54.1 mL (62.8 g, 443 mmol) of **2** were added dropwise using each dropping funnels while stirring at rt. (Caution. Mild heat is being generated while stirring). The reaction mixture was stirred for 2 h until complete consumption of starting materials based on LCMS analysis. After completion of the condensation reaction, the solid reaction mixture was filtered through glass filter while rinsing it with CH_2Cl_2 (~1 L). Removal of the solvent and drying under vacuum gave 104.3 g of **7** as a pale yellow solid in 93% yield with >99% purity based on HPLC analysis. All the other spectral data were matched with those as described above.

Synthesis of Ethyl 4-Hydroxy-2-Oxo-1-Phenethyl-2,-5-Dihydro-1H-Indeno[1,2-*b*]Pyridine-3-Carboxylate (11). Methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (9).[18] A solution of 1-indanone **8** (2.00 g, 15.1 mmol) in THF (16.0 mL) was added dropwise to a stirred suspension of dimethyl carbonate (6.37 mL, 76.0 mmol) in THF (32.0 mL) containing sodium hydride 60% in oil (1.27 g, 31.8 mmol) under nitrogen atmosphere. The reaction mixture was heated to reflux for 2 h. Once completion, the reaction mixture was acidified with 1 M HCl (15 mL), and then extracted with Et_2O (20 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and filtered. The filtrate was concentrated, and purified by MPLC (0% to 30% EtOAc/hexanes) to give **9** as a yellow oil (2.38 g, 83% yield). The product was isolated as a mixture of keto and enol tautomer (ratio 6:1 by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$), keto tautomer: δ 7.78 (d, J = 7.7 Hz, 1H), 7.63 (td, J = 7.5 Hz, 1.0 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.1 Hz, 1H), 3.79 (s, 3H), 3.74 (dd, J = 8.3, 4.1 Hz, 1H), 3.57 (dd, J = 17.3, 4.0 Hz, 1H), 3.38 (dd, J = 17.3, 8.3 Hz, 1H); enol tautomer: δ 10.37 (brs, 1H), 7.63–7.67 (m, 1H), 7.45–7.49 (m, 1H), 7.42 (td, J = 7.3, 1.5 Hz, 1H), 7.35–7.37 (m, 1H), 3.86 (s, 3H), 3.52 (s, 2H).

Methyl 3-(phenethylamino)-1H-indene-2-carboxylate (10). Flask was filled with SiO_2 (2.70 g, 10 g per 1 g of **9**). While stirring, **9** (0.27 g, 1.43 mmol) was added dropwise to the silica gel, followed by the addition of phenethylamine (0.47 mL, 3.72 mmol) dropwise at 0 °C giving off some heat and solid chunk. The resulting solid mixture was stirred for 4 h at 80 °C. Upon the complete consumption of starting material based on LCMS analysis, the solid mixture was loaded on silica gel and purified by MPLC (0% to 30% EtOAc/Hexanes) to give **10** as a white gummy foam (0.28 g, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (brs, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.41–7.36 (m, 1H), 7.35–7.33 (d, J = 7.0 Hz, 2H), 7.31–7.26 (m, 4H), 4.00 (dd, J = 13.9, 6.8 Hz, 2H), 3.76 (s, 3H), 3.54 (s, 2H), 3.04 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 159.3, 145.8, 138.7, 138.1, 128.9, 128.8, 128.6, 126.8, 126.5, 125.3, 123.4, 96.6, 50.5, 46.6, 37.7, 34.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{19}NO_2$ 294.1494, found 294.1484.

Ethyl 4-hydroxy-2-oxo-1-phenethyl-2,5-dihydro-1H-indeno[1,2-*b*]pyridine-3-carboxylate (11). To a solution of **10** (1.73 g, 5.90 mmol) in DCE (11.8 mL) was added ethyl malonyl chloride (1.51 mL, 11.8 mmol) at room temperature. The reaction mixture was heated to reflux for 3 h. Upon completion of starting material based on LCMS analysis, the mixture was quenched with water (10 mL) and extracted with DCM (50 mL × 3). The organic layer was separated and washed with water (20 mL × 3). The combined organic layers were washed again with aq. sat. $NaHCO_3$ (20 mL) and brine (10 mL), dried over sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to give brown oil, which was subjected to the next step without further purification. To a solution of the crude

intermediate in EtOH (11.8 mL) was added slowly sodium ethoxide (4.62 mL, 11.8 mmol) and the resulting mixture was allowed to stir at room temperature for 2 h. Upon complete consumption of starting material based on LCMS analysis, the mixture was filtered through a glass filter with EtOAc rinsing. The filtered solid was dried under vacuum to give the desired product **11** as pale green solid (1.79 g) in 81% yield over 2 steps. mp >200 °C (burnt); ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.47–7.38 (m, 4H), 7.36 (dd, J = 10.3, 4.9 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 4.72–4.62 (m, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.68 (s, 2H), 3.16–3.07 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.9, 170.1, 164.5, 145.1, 144.7, 138.4, 136.7, 128.4, 128.3, 127.0, 126.5, 126.2, 125.2, 121.9, 121.6, 104.7, 59.8, 44.1, 35.1, 32.7, 13.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}NO_4$ 376.1549, found 376.1538.

Conclusion

In conclusion, we have examined the full scope of SiO_2-based condensation of amines and β-keto esters to give β-enamino esters. Aliphatic and aromatic amines were mostly well tolerated, and limitations were found in sterically bulkier amines and aromatic amines with electron withdrawing substitutions. Among cyclic β-keto esters, five-membered ring system showed optimum results. It was demonstrated that linear β-keto esters can be used in SiO_2-based condensation to form synthetically useful functionalized linear β-enamino esters, although stereoselective formation of olefin geometry still requires further investigation. It was also demonstrated that cyclic β-enamino esters were prepared in a large scale. The utility of the present method was fortified by the preparation of pharmaceutically useful 4-hydroxypyridin-2(1H)-one analogues with higher complexity than the related compounds known in the literature.

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Supporting Information. Additional supporting information is available in the online version of this article.

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