

Synthesis of fused heterocycles utilizing the heterocyclic enamine protocol

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Dedicated to Professor Zhi-Tang Huang on His 75th Birthday

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Abstract

Heterocyclic enamines **1** underwent regioselective *C*-benzylation and *C*-benzoylation with *o*-bromobenzyl bromide and *o*-halobenzoyl chloride to yield the corresponding *C*-benzylated and *C*-benzoylated heterocyclic enamines **2** and **8**, respectively. Subsequent intramolecular substitution reactions of **2** and of **8** led to, respectively, the fused 1,4-dihydroquinolines **3** and quinolin-4-ones **9**. The ring size effect of the heterocyclic enamines on the reactivity of both the enaminic carbon and the secondary amine was observed.

Keywords: Heterocyclic enamines, benzylation, benzoylation, fused 1,4-dihydroquinolines, fused quinolin-4-ones

Introduction

Heterocyclic secondary enamines **1** (Figure 1), also known as *exo*-cyclic enaminoesters, enaminones, and enamino nitriles and the like, are versatile intermediates for the synthesis of natural products and heterocyclic compounds. The chemistry of heterocyclic enamines was pioneered by Eschenmoser and his coworkers¹ in the 1960s during their synthetic studies of corrin. They used the reaction of an enamino nitrile with iminoether as one of the key steps in the construction of the corrin ring system. Since the late 1970s, heterocyclic enamines have been investigated by Kishi,² Danishefsky,³⁻⁵ Rapoport⁶ and others in the synthesis of saxitoxin, camptothecin, mitomycins and alkaloids.⁷⁻¹² And recently, *exo*-cyclic enaminoesters have been employed in the the synthesis of carbacephem¹³, a new class of β -lactam antibiotics.

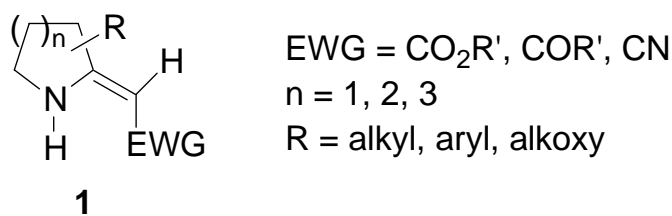


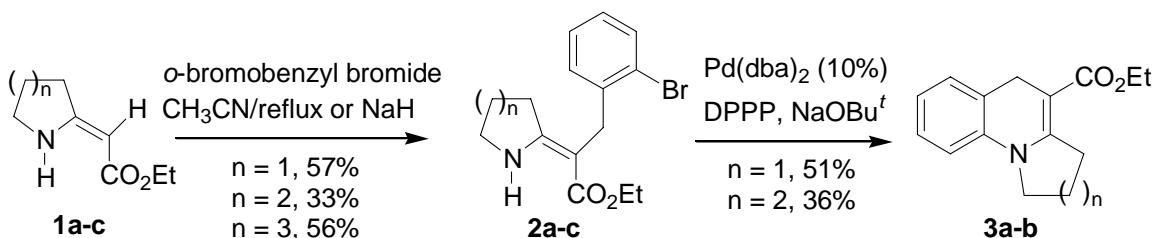
Figure 1. Structure of heterocyclic enamines

One of the most noticeable features of heterocyclic secondary enamines **1** is their ambident bisnucleophilicity; nucleophilic reaction can occur at the enaminic carbon and/or the secondary amino nitrogen. This has been exemplified^{14,15} by the acylation reaction using simple carboxylic acid chlorides, which gave rise to C- and/or N-acylated products depending upon both the heterocyclic structure of enamines and the structure of carboxylic acids. Much attention has been given to the annulation reactions between heterocyclic enamines and α,β -unsaturated compounds in the past decades^{16,17} and a systematic investigation of the reaction of *exo*-cyclic enamino esters with electrophilic alkynes has been reported.¹⁸ Very recently, the unexpected diversity of reaction patterns of heterocyclic enamines when treated with aliphatic and aromatic dicarboxylic acid chlorides has been discovered.¹⁹ Our interest^{18,19} in exploiting the intriguing reactivity of heterocyclic enamines and their application in the synthesis of natural products such as polyhydroxylated pyrrolizidine²⁰ and indolizidine²¹ alkaloids and their analogs led us to the current study. We wish to report herein the convenient synthesis of fused N-heterocycles from selective C-benylation and benzylation of heterocyclic enamines followed by intramolecular cyclization.

Results and Discussion

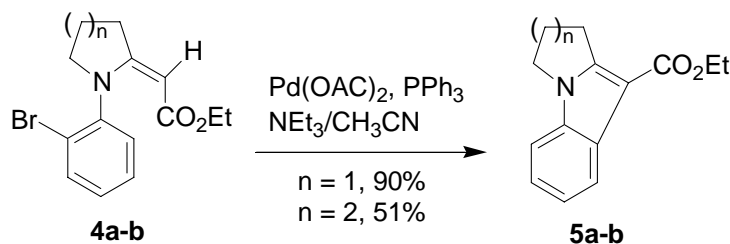
We first tested the reaction of heterocyclic enamines **1a-c**²² with *o*-bromobenzyl bromide, and found an interesting ring size effect on the reaction. For example, seven-membered heterocyclic enamine **1c** reacted with *o*-bromobenzyl bromide in refluxing acetonitrile to provide **2c** in 56% yield, while no reaction was observed for five- and six-membered enamine analogs **1a** and **1b** under the same neutral conditions. Only in the presence of a strong base such as NaH, did the reaction proceed smoothly to give C-benzylated product **2a** or **2b** in moderate yields (Scheme 1). Although a mixture of uncharacterizable by-products was formed, no N-benzylated compound was observed and isolated. It is interesting to note that the reaction of heterocyclic enamines **1** proceeded in a totally different pathway from its analogous heterocyclic enediamines or heterocyclic ketene aminals, powerful and versatile synthetic intermediates developed by Professor Zhi-Tang Huang, which afforded exclusively N-benzylated products under identical basic conditions²³ (see also the Tribute). The C-benzylated heterocyclic enamine structure **2** and Z-configuration of the double bond was evidenced by the observation of disappearance of the vinyl proton signal and of the downfield shift of NH proton signal, due to the strong

intramolecular hydrogen bonding to the ester carbonyl, in ^1H NMR spectrum. Intramolecular cyclization of **2a** or **2b** via Pd-catalyzed coupling reaction of secondary enamine nitrogen with bromobenzene moiety furnished the fused heterocyclic compounds **3a** or **3b**. The same reaction of **2c**, however, gave a mixture of decomposed compounds and no **3c** was obtained. The isomerization of enaminoester double bond occurred during the cyclization reaction. The lower chemical conversion was most probably due to the weaker nucleophilicity of secondary amine resulted from the formation of conjugative enaminoester system.

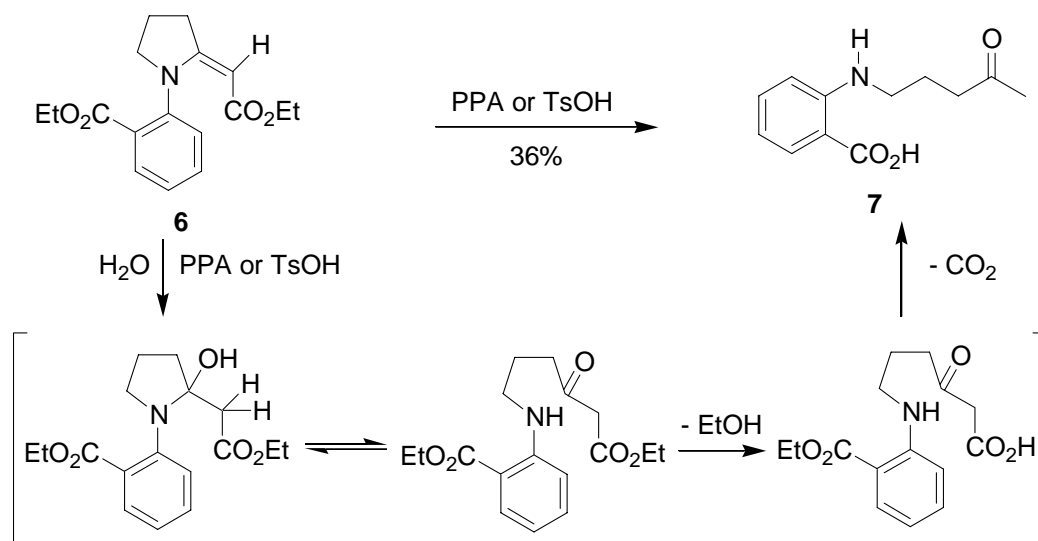


Scheme 1. Synthesis of fused 1,4-dihydroquinoline derivatives.

Michael *et al.*²⁴ once reported that intramolecular Heck reaction of N-arylated heterocyclic enamine **4a** yielded indole derivative **5a**.²⁵ We concurred with their finding and extended this method to the preparation of piperidino[1,2-b]indole product **5b** (Scheme 2). Encouraged by these results, the synthesis of pyrrolo[1,2-b]quinolin-4-one **9**²⁶ through enaminc cyclization of N-(2-ethoxycarbonyl)phenyl heterocyclic enamine **6** was then attempted. However, no reaction was effected under both neutral and basic conditions, probably because of the lower enaminc reactivity of **6** towards ester group. In the presence of polyphosphoric acid (PPA) or *p*-toluenesulfonic acid (TsOH), enamine **6** did undergo a smooth reaction to yield, instead of the desired fused heterocycle, the ring-opening product **7**. The proposed reaction pathway, which depicted in Scheme 3, comprised the hydration of enamine double bond followed by ring-chain tautomerization and hydrolytic decarboxylation steps.

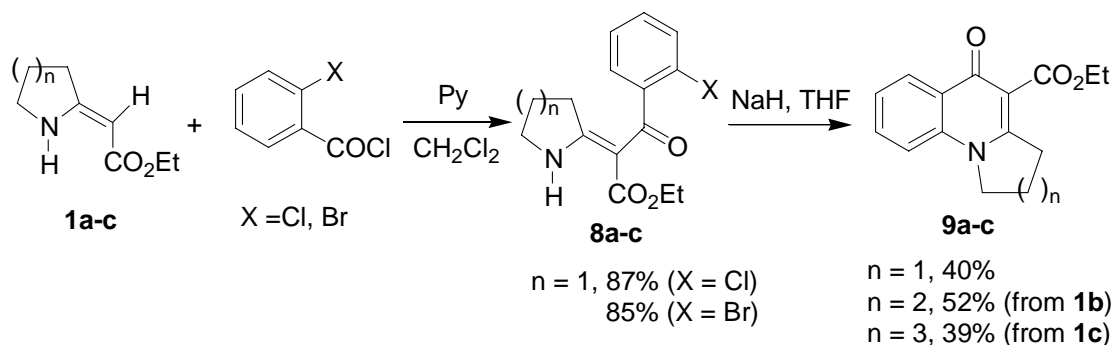


Scheme 2. Synthesis of fused indole derivatives **5**.



Scheme 3. Hydrolysis of heterocyclic enamine **6**.

To prepare fused quinolin-4-one derivatives **9** we then took an alternative strategy based on annulation reaction of heterocyclic enamines **1** with *o*-halobenzoic acid chloride. In the presence of pyridine, enamine **1a** underwent a regiospecific *C*-benzoylation with *o*-chlorobenzoyl chloride to give **8a**. No *N*-benzoylated product was observed. Subsequent cyclization reaction was examined by the treatment with NaH in THF at 60°C. However, no reaction was observed, even at higher temperature such as in refluxing DMF or 1,4-dioxane. When Cl was replaced by Br using *o*-bromobenzoyl chloride as the starting benzoylation reagent, the resulting **8a'** cyclized readily under basic conditions to afford pyrrolo[1,2-*a*]quinolone **9a** in 40% yield. Around 12% yield of enamine **1a** was also obtained, which probably resulted from debenzoylation reaction of **8a'**. In the case of the six- and the seven-membered enamines, however, the *C*-benzoylated products **8b** and **8c** (X = Cl), which were not purified, underwent effective cyclization reaction to yield fused quinolin-4-ones **9b** and **9c**, respectively. The ready conversion of **8b,c** to tricyclic compounds **9b,c** was most likely due to the combined effect of higher nucleophilic reactivity of the secondary amino group of the six- and seven-membered heterocyclic enamine species and the less ring strain of the fused heterocyclic ring systems of **9b** and **9c**.



Scheme 4. Synthesis of fused quinolin-4-one derivatives **9**.

In conclusion, we have shown that heterocyclic enamines **1** are versatile bis-nucleophiles able to react with bis-electrophiles such as *o*-bromobenzyl bromide and *o*-halobenzoic acid chloride, and their synthetic application has been demonstrated by the preparation of fused 1,4-dihydroquinoline and quinolin-4-one derivatives. It would be highly interesting and challenging to prepare chiral (poly)hydroxylated fused *N*-heterocycles, that are analogs or precursors of (poly)hydroxylated alkaloids, starting from chiral (poly)hydroxylated heterocyclic enamines.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker 300 spectrometer. IR spectra were obtained on a HITACHI-260-50 spectrometer as liquid films or KBr discs. Mass spectra were measured on AEI MS-50 (EI) and KYKY-ZHT-5 (FAB) mass spectrometers. Exact mass spectra were obtained on a Bruker APEX-2 mass spectrometer. Elemental analyses were performed at the Analytical Laboratory of the Institute. All chemicals were dried or purified according to standard procedures prior to use.

Synthesis of *C*-benzylated heterocyclic enamines **2a-c**

(Z)-Ethyl 3-(2-bromophenyl)-2-pyrrolidin-2-ylidene propionate (2a). To a solution of **1a** in DMF at 0 °C was added NaH (1.2 eq.) in one portion. After stirring for 30 min at 0 °C, *o*-bromobenzyl bromide (1.2 eq.) was added. The mixture was heated at 80 °C for 24h and then cooled to room temperature. The reaction was quenched by adding saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The extracts combined were washed with H_2O , brine and dried over with Na_2SO_4 . Column chromatography afforded **2a** as white solid in 57% yield: mp 75-76 °C; IR (KBr) 3371, 1657, 1588 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.37 (s, br., 1H, NH), 7.52 (d, J 7.8 Hz, 1H, ArH), 7.20-7.00 (m, 3H, ArH), 4.13 (q, J 7.1 Hz, 2H, OCH_2), 3.63 (s, 2H, CH_2), 3.57 (t, J 7.0 Hz, 2H, CH_2), 2.52 (t, J 7.7 Hz, 2H, CH_2), 1.99 (quin, J 7.3 Hz, 2H, CH_2), 1.16 (t, J 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 166.4, 141.9, 132.5, 129.1, 127.5, 127.3, 125.0, 86.1, 59.1, 47.7, 34.1, 31.4, 22.3, 15.0; MS (EI) m/z 325 (30), 323 (M^+-1 , 30%), 296 (17), 294 (18), 278 (18), 252 (40), 250 (48), 244 (100). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_2\text{Br}$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.77; H, 5.66; N, 4.14.

(Z)-Ethyl-3-(2-bromophenyl)-2-piperidin-2-ylidene propionate (2b). Following the same procedure as for **2a**, product **2b** was obtained in 33% yield as white solid: mp 52-53 °C; IR (KBr) 3150, 1636, 1601 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.78 (s, br., 1H, NH), 7.44 (d, J 7.8 Hz, 1H, ArH), 7.13-6.92 (m, 3H, ArH), 3.99 (q, J 7.0 Hz, 2H, OCH_2), 3.55 (s, 2H, CH_2), 3.27 (t, J 5.8 Hz, 2H, CH_2), 2.18 (t, J 6.4 Hz, 2H, CH_2), 1.64-1.54 (m, 4H, CH_2CH_2), 1.07 (t, J 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 170.8, 161.7, 141.4, 131.9, 128.3, 127.0, 126.7, 124.5, 86.7, 58.4, 41.3, 32.0, 25.8, 22.0, 19.8, 14.4; MS (EI) m/z 339 (26), 337 (M^+-1 , 28%), 310 (18), 308 (18), 292 (14), 266 (54), 264 (61) 258 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_2\text{Br}$: 337.0671. Found: 337.0674.

(Z)-Ethyl 2-azepan-2-ylidene-3-(2-bromophenyl)propionate (2c). A mixture of **1c** and *o*-bromobenzyl bromide (1.2 eq.) in acetonitrile was refluxed 24h. After removal of solvent, the residue was subjected to column chromatography to afford **2c** in 56% yield as oil: IR (KBr) 3272, 1638, 1589 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.84 (s, br., 1H, NH), 7.49 (d, *J* 7.8 Hz, 1H, ArH), (7.20-6.97 (m, 3H, ArH), 4.06 (q, *J* 6.9 Hz, 2H, OCH_2), 3.70 (s, 2H, CH_2), 3.36-3.31 (m, 2H, CH_2), 2.32-2.28 (m, 2H, CH_2), 1.64-1.15 (m, 4H, CH_2CH_2), 1.48-1.142 (m, 2H, CH_2), 1.14 (t, *J* 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 171.5, 168.4, 142.5, 132.4, 129.5, 127.4, 127.3, 124.7, 87.8, 59.1, 44.3, 33.4, 30.7, 30.4, 29.4, 25.6, 14.9; MS (EI) *m/z* 353 (57), 351 (M^+-1 , 58%), 324 (32), 322 (32), 308 (18), 306 (19), 280 (68), 278 (77), 272 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_2\text{Br}$: 351.0828. Found: 351.0829.

General procedure for the synthesis of fused 1,4-dihydroquinolines (3)

To a solution of **2** in toluene was added $\text{Pd}(\text{dba})_2$ (10% mol), DPPP (10% mol) and NaOBU^t (1.2 eq.). The mixture was heated at 110°C for 24h under argon. After filtration of the catalyst, the filtrate was diluted with ether, washed with H_2O , brine and dried over Na_2SO_4 . After removal of the solvents, the residue was subjected to column chromatography to yield **3**.

Ethyl 1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (3a). 51%; oil; IR (KBr) 1665, 1634 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.11 (t, *J* 8.4 Hz, 1H, ArH), 7.10 (d, *J* 8.3 Hz, 1H, ArH), 6.94 (t, *J* 7.2 Hz, 1H, ArH), 6.65 (d, *J* 7.9 Hz, 1H, ArH), 4.18 (q, *J* 7.1 Hz, 2H, OCH_2), 3.79 (s, 2H, CH_2), 3.59 (t, *J* 7.0 Hz, 2H, CH_2), 3.14 (t, *J* 7.7 Hz, 2H, CH_2), 2.12 (quin, *J* 7.3 Hz, 2H, CH_2), 1.30 (t, *J* 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 168.5, 155.9, 138.9, 129.2, 127.3, 124.3, 123.2, 112.9, 90.9, 59.6, 48.7, 32.4, 30.1, 28.1, 22.0, 15.1; MS (EI) *m/z* 243 (M^+ , 21%), 242 (27), 214 (100). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_2$: 242.1175. Found: 242.1174.

Ethyl 2,3,4,6-tetrahydro-1H-pyrido[1,2-*a*]quinoline-5-carboxylate (3b). 36%; oil; IR (KBr) 1683, 1604 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.16 (t, *J* 8.0 Hz, 1H, ArH), 7.10 (d, *J* 7.2 Hz, 1H, ArH), 6.99 (t, *J* 7.3 Hz, 1H, ArH), 6.88 (d, *J* 8.2 Hz, 1H, ArH), 4.18 (q, *J* 7.1 Hz, 2H, OCH_2), 3.66 (s, 2H, CH_2), 3.63 (t, *J* 5.9 Hz, 2H, CH_2), 3.22 (t, *J* 7.0 Hz, 2H, CH_2), 1.93 (quin, *J* 6.3 Hz, 2H, CH_2), 1.75 (quin, *J* 6.8 Hz, 2H, CH_2), 1.31 (t, *J* 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 167.9, 153.6, 141.4, 128.1, 126.5, 125.0, 122.8, 112.4, 94.6, 59.3, 45.0, 28.0, 26.5, 22.6, 19.2, 14.6. Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$: 256.1332. Found: 256.1329.

General procedure for the synthesis of fused indole derivatives (5)

To a solution of **4** in CH_3CN was added Et_3N (2 eq.), $\text{Pd}(\text{OAc})_2$ (1 eq.) and PPh_3 (2 eq.). The mixture was heated at 80°C for 24h under argon. After filtration of the catalyst, the filtrate was subjected to column chromatography to give **5**.

Ethyl 2,3-dihydro-1H-pyrrolo[1,2-*a*]indole-9-carboxylate 5a. 90% as white solid; mp $94-95^\circ\text{C}$ (lit. $96-98.5^\circ\text{C}^{25a}$, $95.6-96^\circ\text{C}^{25b}$); ^1H NMR (300 MHz, CDCl_3) δ 8.04 (d, *J* 7.9 Hz, 1H, ArH), 7.19-7.13 (m, 3H, ArH), 4.30 (q, *J* 7.1 Hz, 2H, CH_2), 4.05 (t, *J* 7.2 Hz, 2H, CH_2), 3.23 (t, *J* 7.6 Hz, 2H, CH_2), 2.59 (quin, *J* 7.3 Hz, 2H, CH_2), 1.35 (t, *J* 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 165.6, 152.8, 132.6, 130.9, 121.6, 121.5, 121.4, 109.8, 99.3, 59.3, 44.4, 26.6, 26.1, 14.7; MS (EI) *m/z* 230 (12), 229 (M^+ , 42%), 200 (27), 184 (54), 58 (100).

Ethyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carboxylate 5b. 51%; IR (KBr) 1684 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.14 (d, *J* 7.4 Hz, 1H, ArH), 7.26-7.20 (m, 3H, ArH), 4.39 (q, *J* 7.0

Hz, 2H, OCH₂), 4.07 (t, *J* 6.0 Hz, 2H, CH₂), 3.34 (t, *J* 6.2 Hz, 2H, CH₂), 2.11-2.08 (m, 2H, CH₂), 1.98-1.92 (m, 2H, CH₂), 1.45 (t, *J* 7.0 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 146.2, 136.3, 127.0, 122.3, 122.0, 121.5, 109.2, 102.9, 59.6, 42.8, 25.0, 22.9, 20.4, 15.0; MS (EI) *m/z* 244 (25), 243 (M⁺, 46%), 214 (82), 197 (61), 168 (100). Anal. Calcd for C₁₅H₁₇NO₂: 243.1254. Found: 243.1254.

Attempted synthesis of fused quinolin-4-one derivative **8a** from the reaction of heterocyclic enamine (**6**)

A mixture of **6** and TsOH (2 eq.) in ethanol or acetonitrile was refluxed for 2h. After removal of solvent, the residue was neutralized with saturated aqueous Na₂CO₃ solution and extracted with EtOAc. The organic layer was washed with brine and H₂O and then dried over with Na₂SO₄. After column chromatography, ethyl 2-(4-oxopentylamino)benzoate **7** was obtained in 36% yield as a colorless oil; IR (KBr) 3362, 1716, 1680 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, *J* 7.9 Hz, 1H, ArH), 7.77 (s, br., 1H, NH), 7.39 (t, *J* 7.8 Hz, 1H, ArH), 6.74 (d, *J* 8.5 Hz, 1H, ArH), 6.62 (t, *J* 7.5 Hz, 1H, ArH), 4.35 (q, *J* 7.1 Hz, 2H, OCH₂), 3.27 (q, *J* 5.9 Hz, 2H, CH₂), 2.63 (t, *J* 7.1 Hz, 2H, CH₂), 2.20 (s, 3H, CH₃), 1.99 (quin, *J* 7.0 Hz, 2H, CH₂), 1.42 (t, *J* 7.0 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 207.8, 168.6, 151.1, 134.5, 131.6, 114.4, 111.1, 110.0, 60.1, 41.9, 40.7, 29.9, 23.0, 14.3; MS (EI) *m/z* 249 (M⁺, 15%), 191 (29), 178 (20), 145 (17), 132 (100). Anal. Calcd for C₁₄H₁₉NO₃: 249.1359. Found: 249.1353.

Synthesis of fused quinolin-4-one derivatives (**9**)

A. Benzoylation reaction of heterocyclic enamines **1**

(Z)-Ethyl 3-(2-chlorophenyl)-3-oxo-2-(pyrrolidin-2-ylidene)propionate (8a). To a mixture of **1a** and pyridine (2 eq.) in CH₂Cl₂ at 0°C was added *o*-chlorobenzoyl chloride. After stirring for 30min at room temperature, the mixture was refluxed for 6h, and then cooled and diluted with CH₂Cl₂. The organic solution was washed with saturated sodium bicarbonate solution, H₂O, citric acid (10%) and brine, and then dried over with anhydrous Na₂SO₄. Column chromatography of the residue gave **8a** (87%) as white solid: mp 124-125 °C; IR (KBr) 3137, 1699, 1669, 1615 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, *J* 8.3 Hz, 1H, ArH), 7.43-7.29 (m, 3H, ArH), 6.84 (s, br., 1H, NH), 4.14 (q, *J* 7.1 Hz, 2H, OCH₂), 3.53 (s, br., 2H, CH₂), 3.25 (t, *J* 7.6 Hz, 2H, CH₂), 1.91 (quin, *J* 7.3 Hz, 2H, CH₂), 1.26 (t, *J* 7.1 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 168.4, 167.4, 156.0, 130.7, 129.8, 129.4, 127.4, 127.1, 100.6, 59.4, 51.0, 31.7, 21.9, 14.3; MS (EI) *m/z* 258 (M⁺-35, 33%), 141 (32), 139 (100). Anal. Calcd for C₁₅H₁₆NO₃Cl: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.35; H, 5.52; N, 4.66.

(Z)-Ethyl 3-(2-bromophenyl)-3-oxo-2-(pyrrolidin-2-ylidene)propionate (8a'). Following the same procedure as for **8a**, the reaction of **1a** with *o*-bromobenzoyl chloride produced **8a'** (85%) as white solid: mp 119-120 °C; IR (KBr) 3136, 1698, 1669, 1615 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, *J* 8.3 Hz, 1H, ArH), 7.43-7.29 (m, 3H, ArH), 6.95 (s, br., 1H, NH), 4.15 (q, *J* 7.0 Hz, 2H, OCH₂), 3.58-3.47 (m, 2H, CH₂), 3.29 (t, *J* 7.8 Hz, 2H, CH₂), 1.96 (quin, *J* 7.3 Hz, 2H, CH₂), 1.28 (t, *J* 7.0 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 168.3, 167.9, 155.8, 138.8, 132.7, 130.6, 127.8, 126.9, 118.0, 100.6, 59.3, 51.1, 31.6, 21.8, 14.2; MS (EI) *m/z* 294 (8), 292

(M^+ -45, 8%), 258 (45), 214 (16), 212 (13), 168 (65), 165 (98), 183 (100). Anal. Calcd for $C_{15}H_{16}NO_3Br$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.26; H, 4.75; N, 3.97.

B. Synthesis of fused quinolin-4-one derivatives 9 from 8. Ethyl 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (9a). To a solution of **8a'** in THF was added sodium hydride 9 (1 eq.), and the mixture was heated at 50 °C for 6h. After removal of the solvent, the residue was subjected to flash chromatography to afford **9a** and **1a** in 40% and 12% yield, respectively. **9a**: colorless crystals; mp 164-5 °C (lit.²⁶ 140-2 °C); IR (KBr) 1692, 1653 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* 8.4 Hz, 1H, ArH), 8.43 (d, *J* 7.9 Hz, 1H, ArH), 7.47 (t, *J* 7.5 Hz, 1H, ArH), 6.69 (t, *J* 7.9 Hz, 1H, ArH), 4.42 (q, *J* 6.9 Hz, 2H, OCH_2), 4.24 (t, *J* 7.4 Hz, 2H, CH_2), 3.50 (t, *J* 7.8 Hz, 2H, CH_2), 2.22 (quin, *J* 7.5 Hz, 2H, CH_2), 1.44 (t, *J* 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 161.2, 150.9, 135.3, 132.7, 127.3, 126.2, 124.9, 124.5, 104.2, 60.8, 48.6, 34.0, 21.2, 14.4; MS (EI) *m/z* 258 (18), 257 (M^+ , 100%), 229 (24), 228 (22), 212 (87), 210 (40). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.05; H, 5.86; N, 5.30.

Ethyl 6-oxo-2,3,4,6-tetrahydro-1H-pyrido[1,2-*a*]quinoline-5-carboxylate (9b). The intermediate **8b**, obtained following the same procedure as for **8a**, was not purified by column chromatography. Following the cyclization reaction as for **9a**, **9b** was obtained in 52% yield based on starting heterocyclic enamine **1b**. **9b**: colorless crystals; mp 133-4 °C (lit.²⁶ 132-5 °C); IR (KBr) 1716, 1619 1600 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, *J* 7.9 Hz, 1H, ArH), 7.65 (t, *J* 7.3 Hz, 1H, ArH), 7.54 (d, *J* 8.7 Hz, 1H, ArH), 7.39 (d, *J* 7.5 Hz, 1H, ArH), 4.41 (q, *J* 7.1 Hz, 2H, OCH_2), 4.12 (t, *J* 6.3 Hz, 2H, CH_2), 3.04 (t, *J* 6.5 Hz, 2H, CH_2), 2.12 (quin, 6.1 Hz, 2H, CH_2), 1.93-1.85 (m, 2H, CH_2), 1.40 (t, *J* 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 167.5, 149.9, 140.8, 132.2, 126.7, 126.6, 124.0, 116.7, 114.7, 61.2, 46.4, 27.6, 22.5, 18.3, 14.2; MS (EI) *m/z* 272 (5), 271 (M^+ , 24%), 226 (47), 199 (100). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.64; H, 6.33; N, 5.04.

Ethyl 5-oxo-5,7,8,9,10,11-hexahydroazapino[1,2-*a*]quinoline-6-carboxylate (9c). Similar to **9b**, the reaction of **1c** with *o*-chlorobenzoyl chloride, followed by the NaH-promoted cyclization gave **9c** in 39% yield (based on **1c**). **9c**: colorless crystals; mp 153-4 °C (lit.²⁶ 146-8 °C); IR (KBr) 1735, 1616, 1595 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* 8.1 Hz, 1H, ArH), 7.60 (t, *J* 7.5 Hz, 7.46 (d, *J* 8.7 Hz, 1H, ArH), 7.31 (t, *J* 7.5 Hz, 1H, ArH), 4.38 (q, *J* 7.0 Hz, 2H, OCH_2), 4.30-4.27 (m, 2H, CH_2), 2.96-2.93 (m, 2H, CH_2), 1.84-1.81 (m, 6H, $CH_2CH_2CH_2$), 1.37 (t, *J* 6.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 167.5, 154.2, 140.3, 132.2, 126.4, 126.0, 123.2, 116.9, 115.0, 61.0, 46.9, 31.5, 27.5, 26.4, 25.4, 14.1; MS (EI) *m/z* 286 (4), 285 (M^+ , 22%), 240 (40), 213 (100). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.23; H, 6.70; N, 4.70.

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