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A Direct Retro-Reformatsky Fragmentation: Formal Ring Enlargement of Cyclic Ketones for Novel and Practical Synthesis of Heterocyclic Enamines

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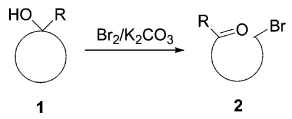
Abstract: A novel and practical synthesis of heterocyclic enamines has been developed from the formal ring enlargement of cyclic ketones, which comprised the retro-Reformatsky fragmentation reaction as a key step. Under alkaline bromination conditions, the Reformatsky adducts derived from five- to seven-membered cyclic ketones underwent efficiently a direct retro-Reformatsky fragmentation, followed by spontaneous α,α-dibromination, to produce α,α,*ω*-tribromo-*β*-ketoester compounds in a one-pot reaction. Highly regioselective reduction of α,α,*ω*-tribromo-*β*-ketoesters with Cu−Zn alloy under mild conditions afforded *ω*-bromo-*β*-ketoesters in good to excellent yields. Treatment of *ω*-bromo-*β*-ketoesters with sodium azide followed by intramolecular aza-Wittig reaction or catalytic hydrogenation furnished heterocyclic secondary enamines, while a straightforward cyclocondensation of *ω*-bromo-*β*-ketoesters with amines led to the formation of heterocyclic tertiary enamines.

Heterocyclic enamines, also known as exocyclic enamino esters, are powerful and versatile intermediates in the preparation of natural products[1,2] and fused heterocyclic compounds.[1,3] The syntheses of heterocyclic enamines have been extensively studied mainly utilizing *N*-heterocyclic compounds as starting materials.[1] The Eshenmoser synthesis,[4] the widely used method, for example, employed the reaction of a thiolactam with a bromomethyl ketone or ester, followed by sulfur extrusion in the presence of triphenylphosphine. The condensation reaction between active methylene or methyl compounds and lactim ethers,[5] pioneered by Eshenmoser and co-workers[6] during the synthetic study of corrin, and lactam-derived iminium salts[7,8] or acetals[7] has been developed into another popular approach to heterocyclic enamines. Other methods reported comprise coupling reactions of organometallic reagents with lactams[9] and thiolactams[10] and their derivates.[11] In contrast, the synthesis of heterocyclic enamines by constructing an *N*-heterocyclic ring moiety has only been reported in a few cases. The reaction of *ω*-mesylated alkylnitriles with methyl bromoacetate, developed by Kishi,[12] provided an efficient route to pyrroline-containing heterocyclic enamines. Carrie and co-workers[13] reported a more general approach utilizing intramolecular aza-Wittig reaction of *ω*-azido *β*-dicarbonyl intermediates that were prepared through the *γ*-alkylation of *β*-dicarbonyl dianions with α,*ω*-dihaloalkanes compounds followed by a nucleophilic substitution by sodium azide. The reaction was extended by Michael and co-workers[14] to synthesize alkyl (*E*)-(1-aryl-2-pyrrolidinylidene)acetates by reacting anilines bearing electron-donating substituent(s) with 6-chloro-3-oxohexanoate. Very recently, we have shown a general and practical method for the preparation of heterocyclic enamines from lactones via a formal ring transformation.[15]

CHART 1



Li and his co-worker[16] have recently reported a direct retro-Barbier fragmentation reaction of cyclic tertiary alcohols that proceeds efficiently under mild conditions to produce *ω*-bromoketones in high yields (Chart 1, R = alkyl). We envisaged that the cyclic *β*-tertiary alcohols (Chart 1, R = CH_2CO_2Et), derived easily from the

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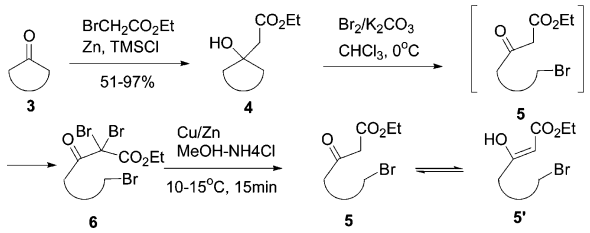
SCHEME 1. Synthesis of ω-Bromo-β-ketoesters 5 from Cyclic Ketones 3 via Retro-Reformatsky Fragmentation Reaction of 4

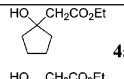
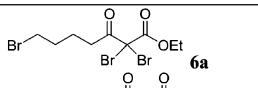
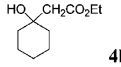
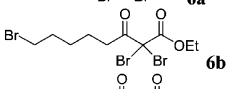
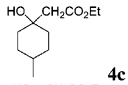
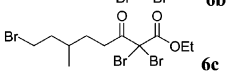
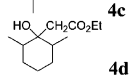
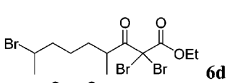
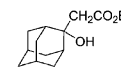
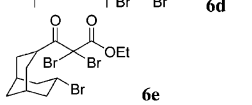
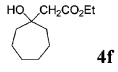
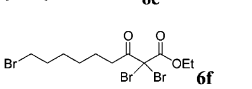
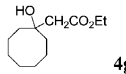


Reformatsky reaction of cyclic ketones, might undergo analogous retro-Reformatsky fragmentation to form ω-bromo-β-ketoesters that are the key intermediates for the preparation of heterocyclic enamines.[13−15] The use of different cyclic ketones might yield heterocyclic enamines with different ring sizes and substituents that are not readily obtainable from the known methods. Our interest in the synthesis and intriguing reactivity of heterocyclic enamines and their application in organic synthesis[3a−c,15] led us to undertake the current study.

We first examined the retro-Reformatsky reaction of tertiary alcohol **4a** derived from cyclopentanone. In the presence of an excess amount of bromine (5 equiv) and potassium carbonate (6 equiv), compound **4a** underwent a smooth and high-yielding ring fragmentation reaction at 0 °C in chloroform. In contrast to the expected ω-bromo-β-ketoester **5a**, spectroscopic data revealed the product to be α,α,ω-tribromo-β-ketoester **6a** (Scheme 1). To obtain monobrominated β-ketoester product **5a**, we attempted reaction under various conditions including the use of a decreased amount of bromine and potassium carbonate. However, it turned out to be unsuccessful. For example, when an equimolar bromine and potassium carbonate were employed in the reaction, the consumption of starting alcohol **3a**, monitored by thin-layer chromatography (TLC), became very slow and α,α,ω-tribromo-β-ketoester **6a** was produced again as the sole product. The straightforward formation of tribrominated compound **6a** was not surprising since the β-ketoester intermediate **5a** exhibited much higher reactivity than tertiary alcohol **4a** toward bromine, and β-ketoester **5a** formed from initial retro-Reformatsky fragmentation underwent a rapid and spontaneous dibromination at α-carbon under alkaline bromination conditions. It should be pointed out that neither the starting cyclic ketone **3a** (via the retro-Reformatsky reaction) nor the α,β-unsaturated ester (via intramolecular dehydration reaction) was obtained, indicating the retro-Reformatsky fragmentation reaction proceeded preferentially over other reaction pathways under the reaction conditions employed.

To test the generality of the retro-Reformatsky fragmentation reaction, a number of tertiary alcohols **4** with different ring sizes and substituents were synthesized from the corresponding cyclic ketones **3** following the Reformatsky reaction procedure.[17] Under alkaline bromination conditions (Scheme 1), almost all Reformatsky adducts examined were converted efficiently into α,α,ω-tribromo-β-ketoesters **6**. As summarized in Table 1, all tertiary alcohols **4b**−**d** bearing a cyclohexyl moiety gave the corresponding products **6b**−**d** in good yields (entries 2−4). The reaction of 2-adamantanone-derived Reformatsky adduct **4e** proceeded equally well to afford

TABLE 1. Retro-Reformatsky Fragmentation Reaction

Entry	Reformasky adduct **4**	α,α,ω-Tribromo-β-ketoester **6**	Yield[a] (%)
1	 **4a**	 **6a**	87
2	 **4b**	 **6b**	71
3	 **4c**	 **6c**	81
4	 **4d**	 **6d**	82
5	 **4e**	 **6e**	87
6	 **4f**	 **6f**	41
7	 **4g**	—	—

[a] Isolated yields.

bicyclo[3.3.1]nonane derivative **6e** in high yield (entry 5). An increase of the carbocyclic ring size from 6 to 7 led to a decrease of the chemical yield, which was exemplified by the isolation of **4f** in only 41% yield (entry 6). A further increase of the ring size to 8 resulted in an uncharacterizable mixture under the same reaction conditions (entry 7). The reason for the ring size dependence of the retro-Reformatsky fragmentation, which differs from the retro-Barbier fragmentation as reported by Li and co-worker,[16] remains unclear at the current stage, although a strong tendency of the medium-sized ring compounds for ring-opening oligomerization might be accounted for.

Multifunctionalized α,α,ω-tribromo-β-ketoesters **6** are versatile and important synthetic intermediates. On the basis of the chemistry of vicinal tricarbonyl compounds developed by Wasserman,[18] for example, α,α,ω-tribromo-β-ketoesters **6** can be readily transformed into ω-bromo-substituted vicinal tricarbonyl compounds (see the Supporting Information) that are the key precursors to a wide variety of heterocycles and natural products. To prepare heterocyclic secondary enamines, α,α,ω-tribromo-β-ketoester compounds **6** were reduced utilizing Cu−Zn alloy in saturated ammonium chloride methanol solution at 10−15 °C.[19] This mild and efficient reduction reaction took place in a highly regioselective fashion, and ω-bromo-β-ketoesters **5** were produced as the sole product in very high yields (Scheme 1, Table 2). It should be noted that, however, the prolonged reduction time and higher reaction temperature caused complete reduction of **6** to give β-ketoesters. Treatment of ω-bromo-β-ketoesters **5** with sodium azide in dimethyl sulfoxide solution at 60 °C gave ω-azido-β-ketoester derivatives **7** in 71−89% yield. As evidenced by the observation of a vinyl proton signal in their ^{1}H NMR spectra, both ω-bromo- and azido-β-ketoesters **5** and **7** coexisted in equilibrium with their enol ester tautomers **5′** and **7′**, respectively (Schemes 1

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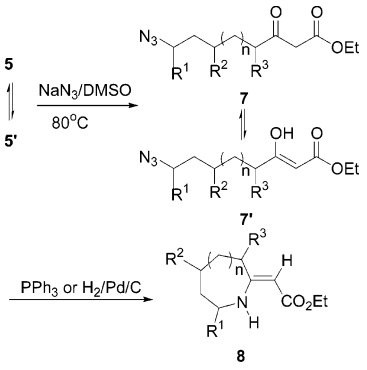
TABLE 2. Preparation of Heterocyclic Secondary Enamines 8

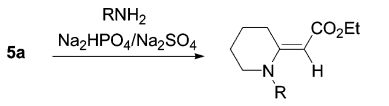
entry	compd **6**	compd **5** (%)	compd **7** (%)	heterocyclic enamines **8** (%)[a]
1	**6a**	**5a** ⇌ **5a** (84)	**7a** ⇌ **7a** (71)	**8a** ($R^1 = R^2 = R^3 = H$, $n = 0$) (80)[b]
2	**6b**	**5b** ⇌ **5b** (90)	**7b** ⇌ **7b** (89)	**8b** ($R^1 = R^2 = R^3 = H$, $n = 1$) (89)[c]
3	**6c**	**5c** ⇌ **5c** (82)	**7c** ⇌ **7c** (72)	**8c** ($R^1 = R^3 = H$, $R^2 = Me$, $n = 1$) (86)[b]
4	**6d**	**5d** ⇌ **5d** (85)	**7d** ⇌ **7d** (81)	**8d** ($R^1 = R^3 = Me$, $R^2 = H$, $n = 1$) (28)[d] (72)[e]
5	**6f**	**5f** ⇌ **5f** (93)	**7f** ⇌ **7f** (89)	**8f** ($R^1 = R^2 = R^3 = H$, $n = 2$) (35)[f] (25)[e]

[a] Isolated yield. [b] In refluxing benzene. [c] In ether at room temperature. [d] No solvent was used. [e] Catalytic hydrogenation (H_2/Pd/C) at room temperature. [f] In a mixture of THF and H_2O at room temperature for 5 days.

SCHEME 2. Synthesis of Heterocyclic Secondary Enamines



SCHEME 3. Synthesis of Heterocyclic Tertiary Enamines



9a (R = CH_2Ph, 48%)
9b (R = Ph, 42%)

and 2). Heterocyclic secondary enamines **8** were readily obtained from intramolecular aza-Wittig reaction. A lower chemical yield of product **8d** (28%) was probably due to the steric hindrance caused by two methyl groups during the intramolecular aza-Wittig reaction. To circumvent this problem, the azide **7d** was subjected to catalytic hydrogenation, and the chemical yield was then improved dramatically to 72% (Scheme 2, Table 2). The usefulness of the retro-Reformatsky fragmentation reaction has been further demonstrated by the straightforward synthesis of heterocyclic tertiary enamines **9** from cyclocondensation reaction between ω-bromo-β-ketoester **5a** and amines such as benzylamine and aniline (Scheme 3). The configuration of heterocyclic secondary enamines **8** was assigned as the *Z*-form because of the formation of an intramolecular hydrogen bond between the secondary amino and ester carbonyl moieties, which was observed by the downfield shift of the amino proton signal in the ^{1}H NMR spectra. Heterocyclic tertiary enamines **9**, on the contrary, have been shown to adopt the *E*-configuration as the proton signals of the 3-methylene of the piperidine ring appeared at 3.23 ppm in the ^{1}H NMR spectra, a downfield shift caused by the deshielding effect of the neighboring cis-orientated ester group.[15]

In conclusion, we have shown that, under alkaline bromination conditions, the Reformatsky adducts derived readily from five- to seven-membered cyclic ketones including 2-adamantanone underwent efficiently a direct retro-Reformatsky fragmentation reaction, followed by spontaneous α,α-dibromination, to produce multifunctionalized α,α,ω-tribromo-β-ketoester compounds in high yields in a one-pot reaction. α,α,ω-Tribromo-β-ketoesters, the important precursor to the Wassermann ω-bromo vicinal tricarbonyls, were reduced highly regioselectively with Cu−Zn alloy to afford ω-bromo-β-ketoesters in good to excellent yields. Treatment of ω-bromo-β-ketoesters with sodium azide followed by intramolecular aza-Wittig reaction or catalytic hydrogenation furnished heterocyclic secondary enamines. A straightforward cyclocondensation of ω-bromo-β-ketoesters with amines led to the formation of heterocyclic tertiary enamines. Since only the readily available starting materials and reagents and very mild reaction conditions were required, and the experimental operations were very simple and convenient, the method appeared practical and applicable in the synthesis of various heterocyclic enamines. This formal ring enlargement transformation approach would also open a new venue to synthetically versatile heterocyclic enamines from various (chiral) cyclic ketones, which is being actively investigated in this laboratory.

Experimental Section

General Procedure for the Retro-Reformatsky Fragmentation Reaction of 4. After a mixture of the Reformatsky adduct **4** (3 mmol) and potassium carbonate (2.48 g, 18 mmol) in chloroform (10 mL) was stirred at 0 °C for 10 min, bromine (2.4 g, 15 mmol) was added. The resulting mixture was continuously stirred at 0 °C overnight. After completion of the reaction, which was monitored by TLC analysis, the mixture was washed consecutively with saturated aqueous sodium thiosulfate solution and water, and the organic layer was then dried over anhydrous $MgSO_4$. Chromatography on a silica gel column with a mixture of petroleum ether and ethyl acetate (30:1) as an eluent gave pure α,α,ω-tribromo-β-ketoester **6**.

Ethyl 3-Oxo-2,2,7-tribromoheptanoate (6a). Pale yellow oil; yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (q, J = 7.2 Hz, 2H), 3.44 (t, J = 6.6 Hz, 2H), 2.98 (t, J = 6.9 Hz, 2H), 1.98−1.83 (m, 4H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 163.5, 64.8, 59.9, 34.9, 33.1, 31.5, 23.4, 13.8; IR (KBr): 1740, 1738, 1736 cm^{-1}; MS (FAB) m/z 413, 411, 409, 407 (M + 1); HRMS m/z calcd for $C_9H_{14}Br_3O_3$ (M + 1) 410.8447, 408.8467, found 410.8439, 408.8465.

Ethyl 3-Oxo-2,2,8-tribromooctanoate (6b). Pale yellow oil; yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (q, J = 7.2 Hz, 2H), 3.44 (t, J = 6.9 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H), 1.92 (quin, J = 7.2 Hz, 2H), 1.76 (quin, J = 7.7 Hz, 2H), 1.58−1.50 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 193.1, 163.4, 64.5, 59.8, 35.5, 33.4, 32.1, 27.1, 23.8, 13.6; IR (KBr): 1740, 1738 cm^{-1}; MS (FAB) m/z 427, 425, 423, 421 (M + 1); HRMS m/z calcd for $C_{10}H_{16}Br_3O_3$ (M + 1) 424.8603, 422.8623, found 424.8605, 422.8635.

Ethyl 6-Methyl-3-oxo-2,2,8-tribromooctanoate (6c). Pale yellow oil; yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (q, J = 7.2 Hz, 2H), 3.49−3.41 (m, 2H), 2.97−2.91 (2H, m,), 1.92−1.87 (m, 1H), 1.78−1.69 (m, 3H), 1.57−1.54 (m, 1H), 1.37 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 163.5, 64.7, 60.1, 39.4, 33.5, 31.7, 31.3, 30.9, 18.6, 13.8; IR (KBr): 1741, 1738, 1736 cm^{-1}; MS (FAB) m/z 441, 439, 437, 435 (M + 1); HRMS m/z calcd for $C_{11}H_{18}Br_3O_3$ (M + 1) 438.8760, 436.8780, found 438.8752, 436.8777.

Ethyl 4-Methyl-3-oxo-2,2,8-tribromononanoate (6d). Pale yellow oil; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (q, J =

7.2 Hz, 2H), 4.11−4.04 (m, 1H), 3.22−3.16 (m, 1H), 1.81−1.64 (m, 4H), 1.65 (d, J = 6.6 Hz, 3H), 1.50−1.46 (m, 2H), 1.32−1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 163.4, 64.7, 59.8, 51.2, 40.8, 40.6, 34.2, 26.5, 25.2, 19.5, 13.8; IR (KBr) 1759, 1732 cm^{-1}; MS (FAB) m/z 455, 453, 451, 449 (M + 1); HRMS m/z cacld for $C_{12}H_{20}Br_3O_3$ (M + 1) 452.8916, 450.8936, found 452.8920, 450.8948,

Ethyl 2,2-Dibromo-3-{*endo*-7-bromobicyclo[3.3.1]nonyl}-3-oxopropionate (6e). White crystals; yield 87%; mp 48−49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60−4.50 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.23−3.12 (m, 1H), 2.34−2.14 (m, 6H), 1.86(t, J = 12.3 Hz, 2H), 1.70 (d, J = 13.2 Hz, 1H) 1.52 (t, J = 12.3 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 163.3, 64.6, 59.9, 45.8, 44.8, 38.2, 31.6, 27.5, 27.2, 13.6; IR (KBr) 1756, 1726 cm^{-1}; MS (FAB) m/z 477, 475, 473 (M + 1). Anal. Calcd for $C_{14}H_{19}Br_3O_3$: C, 35.40; H, 4.03. Found: C, 34.95; H, 3.92.

Ethyl 3-Oxo-2,2,9-tribromononanoate (6f). Pale yellow oil; yield 41%; ^{1}H NMR ($CDCl_3$) δ 4.41 (q, J = 7.2 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 1.92 (quin, J = 7.0 Hz, 2H), 1.77 (quin, J = 7.4 Hz, 2H), 1.55−1.44 (m, 4H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 163.5, 64.5, 59.8, 35.5, 33.6, 32.3, 27.7, 27.6, 24.5, 13.6; IR (KBr) 1750, 1738 cm^{-1}; MS (FAB) m/z 441, 439, 437, 435 (M + 1); HRMS m/z calcd for $C_{11}H_{18}Br_3O_3$ (M + 1) 438.8760, 436.8780, found 438.8755, 436.8784.

General Procedure for Selective Reduction of α,α,ω-Tribromo-β-ketoester 6. To a solution of α,α,ω-tribromo-β-ketoester **6** (2 mmol) in saturated ammonium chloride/methanol solution (10 mL) was added the cupper−zinc alloy powder (32 mmol), and the resulting mixture was stirred at 10−15 °C for 15 min. After complete consumption of **6**, which was monitored by TLC analysis, the mixture was filtered and the filtrate was subjected to column chromatography using silica gel with a mixture of petroleum ether and ethyl acetate (30:1) as an eluent to give ω-bromo-β-ketoester **5**.

General Procedure for the Substitution Reaction of ω-Bromo-β-keto Esters by Sodium Azide. To a solution of ω-bromo-β-ketoester **5** (2 mmol) in dimethyl sulfoxide (10 mL) were added with stirring powdered sodium azide (3 mmol) and a catalytic amount of sodium iodide (ca. 10 mg). The mixture was heated at 60 °C for 18 h. After the mixture was cooled to room temperature, water (10 mL) was added, and the mixture was then extracted with diethyl ether (3 × 15 mL). The organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the residue was chromatographyed on a silica gel column using a mixture of petroleum ether and ethyl acetate (30:1) as an eluent to afford ω-azido-β-ketoester **7**.

General Procedure for the Preparation of Heterocyclic Secondary Enamines 8. Method A. To a solution of azide **7** (3 mmol) in anhydrous benzene or diethyl ether (10 mL) was added triphenylphosphine (873 mg, 3 mmol), and the mixture was refluxed for 3 h in benzene or kept at room temperature for 24 h in diethyl ether. After removal of solvent, the residue was subjected to chromatography using a silica gel column with a mixture of petroleum ether and ethyl acetate (5:1) as an eluent to yield heterocyclic secondary enamine **8**.

Method B. A mixture of azide **7** (0.86 mmol) and Pd on charcoal (10%, 10 mg) in methanol was stirred under hydrogen atmosphere at room temperature for 1 h. Pure heterocyclic secondary enamine **8** was obtained after a similar workup procedure.

Ethyl 2-(2-Piperdinylidene)acetate (8a).[13] Colorless oil; yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br. 1H), 4.31 (s, 1H), 4.04 (q, J = 7.2 Hz, 2H), 3.27−3.23 (m, 2H), 2.31 (t, J = 6.3 Hz, 2H), 1.78−1.60 (m, 4H), 1.20 (d, J = 7.2 Hz, 3H).

Ethyl 2-(2-Azepinylidene)acetate (8b).[13] Colorless oil; yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (br., 1H), 4.42 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.31−3.26 (m, 2H), 2.29−2.26 (m, 2H), 1.67−1.54 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H).

Ethyl 2-(5-Methyl-2-azepinylidene)acetate (8c). White solid; mp 41−42 °C; yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 4.46 (s, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.34−3.31 (m, 2H), 2.41−2.37 (m, 1H), 2.28−2.25 (m, 1H), 1.87−1.77 (m, 2H), 1.68−1.64 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.24−1.17 (m, 2H), 0.98 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.4, 80.5, 58.3, 42.7, 38.2, 36.6, 34.4, 33.6, 22.9, 14.7; IR (KBr) 3309, 1649, 1606 cm^{-1}; MS (EI) m/z 197 (M$^+$, 62) 152 (100), 125 (95), 108 (20), 96(42); HRMS m/z calcd for $C_{11}H_{20}NO_2$ (M + 1) 197.1410, found 197.1408.

Ethyl 2-(3,7-Dimethyl-2-azepinylidene)acetate (8d). Colorless oil; yield 28% (method A), 72% (method B); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 4.50 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.62 (m, 1H), 2.62−2.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 170.3, 80.9, 76.3, 58.2, 50.4, 49.8, 40.6, 38.1, 37.4, 36.1, 34.8, 31.4, 29.1, 23.2, 23.1, 22.7, 19.2, 16.6, 14.6; IR (KBr) 3272, 1651, 1604 cm^{-1}; MS (EI) m/z 211 (M$^+$, 100), 196 (32), 182 (35), 166 (66), 150 (43), 138 (73); HRMS m/z calcd for $C_{12}H_{22}NO_2$ (M + 1) 212.1645, found 212.1646.

Ethyl 2-(2-Azocinylidene)acetate (8f).[13] Colorless oil; yield 35%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (br, 1H), 4.41 (s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.39−3.32 (m, 2H), 2.28 (t, J = 6.6 Hz, 2H), 1.71−1.51 (m, 6H), 1.28 (t, J = 7.2 Hz, 3 H).

General Procedure for the Preparation of Heterocyclic Tertiary Enamines 9.[14] To a mixture of ω-bromo-β-ketoester **5a** (2 mmol) and amine (2 mmol) were added a small amount of iodine, disodium hydrogen phosphate (2 mmol), and anhydrous sodium sulfate (2 mmol). The resulting heterogeneous mixture was heated in an oil bath at 65 °C for 24 h with stirring. After the mixture was cooled to room temperature, dichloromethane (100 mL) was added immediately, and the mixture was washed with water (100−150 mL). The aqueous phase was then extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and subjected to chromatography using a silica gel column with a mixture of petroleum ether and ethyl acetate (8:1) as an eluent to give *N*-substituted heterocyclic enamines **9**.

Ethyl 2-[2-(*N*-Benzyl)piperdinylidene]acetate (9a). White solid; mp 70−71 °C (lit.[20] mp 66 °C); yield 48%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.24 (m, 3H), 7.18 (d, J = 7.5 Hz, 2H), 4.69 (s, 1H), 4.42 (s, 2H), 4.04 (q, J = 7.2 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H), 3.23 (t, J = 6.0 Hz, 2H), 1.86−1.72 (m, 4H), 1.21 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 162.4, 135.9, 128.5, 126.9, 126.4, 82.5, 57.9, 55.0, 49.6, 26.7, 23.2, 19.5, 14.5; IR (KBr) 1681, 1565, 1135 cm^{-1}; MS (EI) m/z 259 (M$^+$, 26), 214-(46), 186(75), 91(100), 82(72). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.85; H, 8.19; N, 5.12.

Ethyl 2-[2-(*N*-Phenyl)piperdinylidene]acetate (9b). White solid; mp 94−95 °C; yield 42%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, J = 7.5 Hz, 2H), 7.27−7.25 (m, 1H), 7.15 (d, J = 7.8 Hz, 2H), 4.33 (s, 1H), 3.97 (q, J = 6.9 Hz, 2H), 3.45 (t, J = 6.0 Hz, 2H), 3.23 (t, J = 6.3 Hz, 2H), 1.91−1.76 (m, 4H), 1.14 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 163.2, 146.1, 129.9, 126.9, 126.8, 86.7, 58.2, 52.0, 26.4, 23.7, 20.1, 14.6; IR (KBr) 1673, 1556, 1132 cm^{-1}; MS (EI) m/z 245 (M$^+$, 13), 200 (22), 172 (71), 130 (32), 77 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.27; H, 7.84; N, 5.43.

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Supporting Information Available: Synthesis of **4** and the vicinal tricarbonyl derivatives **10**, spectral data of **5** and **7**, and ^{1}H and ^{13}C NMR of **6**, **8c,** and **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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