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Direct Amination of γ-Halo-β-ketoesters with Anilines

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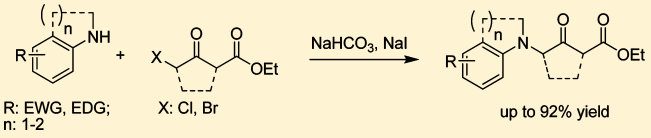
Supporting Information

ABSTRACT: The direct amination of α-haloacetoacetates with anilines is described. Compared to existing methods, this simple protocol provides an attractive strategy to prepare diverse γ-anilino-β-ketoesters in one step. Good to excellent yields of the amination products were obtained under robust conditions, providing versatile and useful scaffolds.



INTRODUCTION

β-Ketoesters are key intermediates in organic synthesis, with wide-ranging applications in asymmetric catalysis, heterocyclic ring construction, and medicinal chemistry.[1] Although a variety of β-ketoesters have been investigated extensively since the Claisen condensation was reported 125 years ago,[2] syntheses and applications of γ-heteroatom substituted β-ketoesters are still limited. In our efforts to make analogues of this scaffold, we found that thiophenols and phenols as typical S_N2 nucleophiles readily produced the γ-heteroatom substituted β-ketoesters in moderate to high yields under basic conditions,[3] but the desired products were not obtained when employing aniline as the nucleophile. An alternative way to prepare γ-anilino-β-ketoesters came from a Weinreb ketone synthesis (Scheme 1, route a).[4] The S_N2 reaction with aniline **1**, however, resulted in poor yields (20−25%) of Weinreb amide **2**; the activated carbonyl group was then condensed with the enol anion of ethyl acetate, giving the γ-anilino-substituted β-ketoesters in 40−60% yields. The low S_N2 reactivity is derived from the weak nucleophilicity of aniline as a result of the resonance of the nitrogen lone pair with the adjacent phenyl group.[5] A common procedure for improving nucleophilicity is to enhance the acidity of the NH group. When a toluenesulfonyl group was employed, the nitrogen anion was produced under basic conditions, which increased the yield to 44% (Scheme 1, route b).[6] However, this modification did not change the moderate yield in the next ketonization step, and the use of *n*-BuLi at low temperature led to loss of cost effectiveness and atom economy.

One attractive strategy would be direct amination of ethyl 4-chloroacetoacetate (**5**) with the aniline (Scheme 1, route c). This strategy should be superior and avoids the unnecessary reagents and steps of the other routes. However, because of the acidity of the methylene protons between the carbonyl groups of **5**, base conditions should be carefully modulated. It is possible that the chlorine of **5**, bearing a large p*-π* orbital overlap with the carbonyl group, may allow nucleophilic attack to occur more easily.[7] In addition, electron-donating R groups can further increase the nucleophilic strength of the anilines, which is convenient in light of our desired pharmacophore. Here we report a direct amination method to synthesize γ-anilino-β-ketoesters, providing important advantages of ease and economy compared to existing methods. This robust reaction is generally high-yielding and produces a new scaffold that should have extensive use in organic synthesis.

RESULTS AND DISCUSSION

For one of our current drug discovery programs, we were interested in preparing *N*-alkyl-γ-anilino-β-ketoesters using *N*-methyl 3,5-dichloroaniline (**7**) as the primary nucleophilic reagent (Scheme 2).[8] Although the same strategy was reported to give the product in 33% yield as well as self-condensation to the dihydroquinone in 22% yield,[9] we failed to get desired compound **3** with this method, as well as two other procedures, using NaH and Cs_2CO_3, respectively, as bases (Scheme 2). The main products under these conditions were recovered starting aniline **7**, byproduct **6**, and its precursor **8**, suggesting that the electron deficiency of the aniline diminished its reactivity, a strong base favored enolization of **5**, and concomitant self-condensation consumed **5**. It was thought that the yield of our desired product might be boosted if self-condensation were prevented; therefore, we investigated the use of a weak base to minimize acetoacetate enolization. This approach might restrain the side reaction and allow a direct nucleophilic attack of the γ-halo-β-ketoester by anilines.

To test the above hypothesis, 2 equiv of **5**, aniline **7**, and disodium phosphate were heated at 80 °C for 16 h (Table 1, entry 1). The desired product was observed by NMR spectroscopy using 1-bromo-3,5-dichlorobenzene as an internal standard. A catalytic phase transfer catalyst was initially added to determine if it might enhance the leaving group ability of chlorine (Table 1, entry 2). With the slight increase in yield, 2 equiv of NaI was added to displace the chlorine for activation (Table 1, entry 2), which increased the yield to 66%. Several other weak bases, as well as a silver salt, and other iodide sources were explored in an attempt to increase the yield; sodium bicarbonate exhibited the best crude yield and moderate isolated yield (Table 1, entries 4−11). Further optimization focused on

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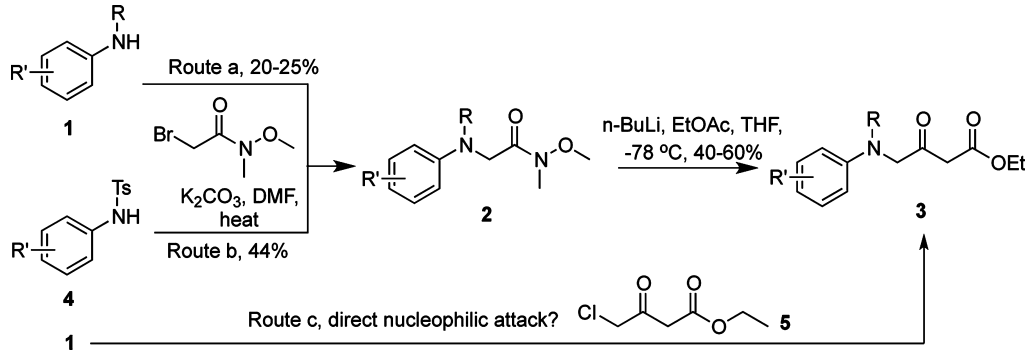
Scheme 1. Direct Nucleophilic Attack for the Synthesis of 3



Scheme 2. Initial Direct Amination Attempts Following Literature Procedures

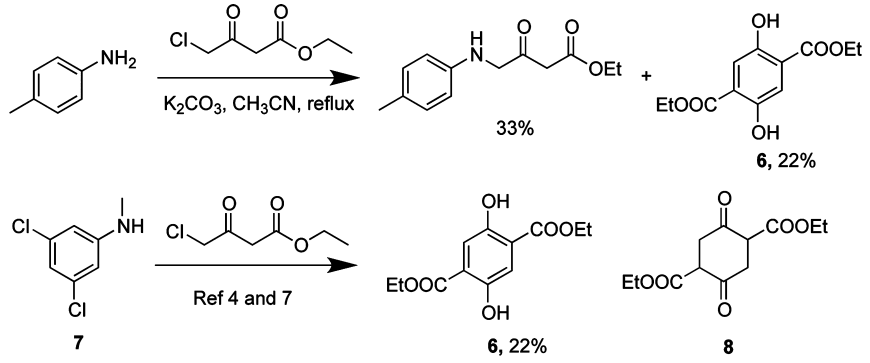
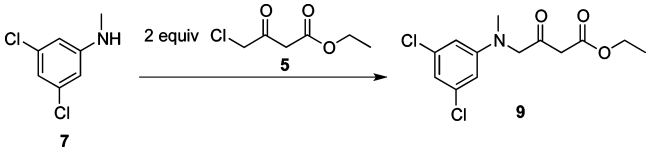


Table 1. Conditions Explored for the Direct Nucleophilic Attack of 5 with 7[a]



entry	conditions	yield[b] (%)
1	2 equiv $Na_2HPO_4·7H_2O$	~5
2	2 equiv $Na_2HPO_4·7H_2O$, 0.1 equiv BuN_4I	10
3	2 equiv $Na_2HPO_4·7H_2O$, 2 equiv NaI	66
4	2 equiv Na_2HPO_4, 2 equiv NaI	65
5	2 equiv $NaH_2PO_4·H_2O$, 2 equiv NaI	59
6	2 equiv Na_3PO_4, 2 equiv NaI	<5
7	2 equiv NaOAc, 2 equiv NaI	<5
8	2 equiv AgOOCPh	<5
9	2 equiv $NaHCO_3$, 2 equiv NaI	65 (52)
10	2 equiv $NaHCO_3$, 2 equiv KI	50
11	2 equiv $NaHCO_3$, 2 equiv NaBr	58
12[c]	2 equiv $NaHCO_3$, 2 equiv NaI	66 (51)
13[d]	2 equiv $NaHCO_3$, 2 equiv NaI,	17
14[e]	2 equiv $NaHCO_3$, 2 equiv NaI,	>95 (83)
15[f]	2 equiv $NaHCO_3$, 2 equiv NaI,	(88)

[a]Unless specified, the reaction was carried out with 7 (0.1 mmol) and 5 (0.2 mmol) in 0.5 mL of CH_3CN under air and refluxed at 80 °C for 16 h. The addition of bases and other additives are listed in the conditions column. [b]NMR spectral yield of 9 by comparison with 0.1 mmol of 1-bromo-3,5-dichlorobenzene, which was added after the reaction was cooled. The yield in parentheses is the isolated yield after standard workup and purification on silica gel. [c]Four equivalents of 5 were added. [d]At room temperature. [e]CH_3CN (0.1 mL) as solvent. [f]The reaction was carried out with 7 (1 mmol) and 5 (2 mmol) in 1 mL of CH_3CN under ambient air and reflux at 80 °C for 16 h.

solvents (data not shown), stoichiometry of reactants, temperature, and substrate concentration (Table 1, entries 12−14). Isolated yield enhancement was observed when concentrated conditions were used. Finally, to avoid the workup loss and confirm the results, the reaction was repeated on a larger scale to afford the desired product in an 88% yield.

The generality of $NaHCO_3$ and NaI-promoted aminations was probed, indicating the reliability of this method for the synthesis of γ-anilino-β-ketoesters having significant structural variations. The reaction scope with regard to the phenyl ring was first investigated (Table 2). It was found that the electronic properties had a minimal influence on the yield. The reactions can tolerate electron-neutral (Table 2, entry 2), electron-donating (Table 2, entry 4), and electron-withdrawing (Table 2, entries 3 and 5−11) substituents, and little yield difference was observed with substitution at the *meta*- or *para*-positions (Table 2, entries 7 and 8). Disubstituted phenyl groups, as well as other aromatic scaffolds, such as 1-naphthyl, also gave good yields (Table 2, entries 9, 10, and 12). The 2-naphthyl substituted aniline afforded a mixture of the desired γ-methyl(naphthalen-2-yl)amino-β-ketoester and an unexpected α-methyl(naphthalen-2-yl)amino acetate in a 4:1 ratio, which were difficult to isolate by chromatography (data not shown). This can be attributed to the possibility that 2-naphthyl methylamine might cause a retro-aldol process, converting ethyl α-chloroacetoacetate to ethyl acetate.

The reaction scope by variation of the alkyl substituents on the nitrogen also was studied (Table 3). Larger alkyl substituents greatly diminished the reaction yield (Table 3, entries 1−4), indicating that steric effects of these substituents play a more important role than their electronic effects. It is notable that indoline and tetrahydroquinoline gave excellent yields, even at room temperature.

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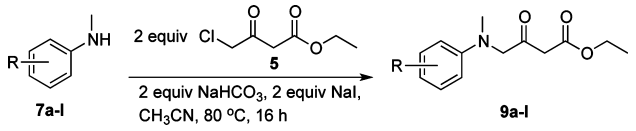
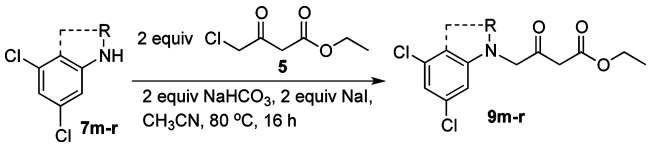
Table 2. Reaction Scope Related to Phenyl Ring Substitution[a]

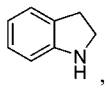
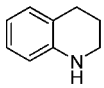


entry	R	yield[b] (%)
1	3,5-diCl, **9a**	88
2[c]	H, **9b**	92
3	4-acetyl, **9c**	79
4	3-OMe, **9d**	62
5	4-F, **9e**	87
6	4-Cl, **9f**	85
7	4-Br, **9g**	81
8	3-Br, **9h**	73
9	3,4-diCl, **9i**	73
10	2,4-diCl, **9j**	84
11	4-CN, **9k**	58
12[d]	1-naphthyl, **9l**	88

[a]Unless specified, the reaction was carried out with **7** (1 mmol) and **5** (2 mmol) in 1 mL CH_3CN under air and refluxed at 80 °C for 16 h. [b]Isolated yield [c]4 h reaction time [d]2 h reaction time

Table 3. Reaction Scope Related to *N*-Alkyl Substituents[a]



entry	R	yield[b](%)
1	Et, **9m**	71%
2	iPr, **9n**	29%
3	C≡CSiMe$_3$, **9o**	28%
4	Bn, **9p**	<10%
5[c]	 , **9q**	85%
6[c]	 , **9r**	92%

[a]Unless specified, the reaction was carried out with **7** (1 mmol) and **5** (2 mmol) in 1 mL of CH_3CN under air and refluxed at 80 °C for 16 h. [b]Isolated yield. [c]At room temperature.

The scope of the ketoester also was investigated (Scheme 3). A γ-ketoester, methyl 5-bromo-4-oxopentanoate, was used, and **10** was obtained in an 89% yield under the optimized conditions. A cyclic β-ketoester containing a secondary bromide, methyl 3-bromo-2-oxocyclopentanecarboxylate, gave desired product **11** in a 40% yield and **12** in a 29% yield, which may have resulted from iodine or air oxidation. Removal of the iodide source and air increased the product yield to 57%. Because **11** is a mixture of diastereoisomers and an enol regioisomer, further transformation to **13** was carried out to obtain a clean spectrum. Self-condensation of the cyclic α-bromo-β-ketoesters, as in Scheme 2, did not occur, presumably because of steric hindrance of the secondary bromide.

We also investigated the synthetic versatility of the multifunctional γ-anilino-β-ketoester derivatives, especially for scaffold diversification (Scheme 4). The ketoester served as a very valuable functionality in several different reaction types, such as in pyrazolone formation (**14**),[10] in a Biginelli dihydropyrimidine synthesis (**15**),[11] and diazo formation (**16**).[12] All transformations proceeded in good yields under non-optimized conditions. Considering the fact that there is a wide range of transformations of β-ketoesters,[13] γ-aniline intermediates should be useful to prepare a number of other important building blocks.

In summary, we have developed a simple, direct amination method for α-haloacetoacetates with inexpensive inorganic salts. It has broad substrate scope with respect to a variety of secondary anilines, and the yields are good to excellent. Performed under mild conditions, this protocol provides a highly economical and functional group compatible method to construct γ-anilino substituted β-ketoesters, as well as to generate a range of versatile and useful scaffolds.

EXPERIMENTAL SECTION

General Experimental Methods. Thin-layer chromatography was carried out on silica gel 60 F254 plates. Column chromatography was performed with silica gel 60 (230−400 mesh). Proton and carbon NMR spectra were recorded in deuterated solvents on a 500 MHz spectrometer. The chemical shifts are reported in δ (ppm) (^{1}H NMR: $CDCl_3$, δ 7.26 ppm; DMSO-d_6, δ 2.50 ppm; ^{13}C NMR: $CDCl_3$, δ 77.23 ppm; DMSO-d_6, δ 39.52 ppm). The following abbreviations were used to describe the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Electrospray mass spectra (ESMS) were obtained with methanol as the solvent in the positive ion mode. All reagents were used directly without further purification.

General Procedure for the Amination Reaction. To a solution of $NaHCO_3$ (168 mg, 2.0 mmol), NaI (300 mg, 2.0 mmol), and the aniline (1.0 mmol) in 1 mL of acetonitrile was added ethyl α-chloracetoacetate (270 μL, 2.0 mmol). The resulting reaction mixture was stirred at 80 °C for 16 h. After the mixture was cooled to room temperature, 1 mL of saturated $Na_2S_2O_3$ solution was added. The resulting solution was extracted with ethyl acetate, and the organic layer was collected and washed with water and brine. The collected organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography using a mixture of hexane and ethyl acetate as eluent to afford the product.

Ethyl 4-((3,5-Dichlorophenyl)(methyl)amino)-3-oxobutanoate (9a) (Table 2, entry 1). The title compound was prepared as a pale yellow solid in 88% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (t, J = 1.5 Hz, 1H), 6.48 (d, J = 2.0 Hz, 2H), 4.23−4.18 (m, 2H), 3.46 (s, 2H), 3.02 (s, 3H) 1.30 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.5, 166.9, 150.4, 135.9 (2C), 117.4, 110.6 (2C), 62.3, 62.1, 46.5, 39.9, 14.3 ppm; MS (ESI) m/z 304.1 [M + H]$^+$; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}Cl_2NO_3$ 326.0327, found 326.0330.

Ethyl 4-(Methyl(phenyl)amino)-3-oxobutanoate (9b) (Table 2, entry 2). The title compound was prepared as a pale yellow oil in 87% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (t, J = 7.5 Hz, 2H), 6.77 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 4.16 (q, J = 7.0 Hz, 2H), 3.45 (s, 2H), 3.05 (s, 3H) 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.9, 167.2, 157.1, 155.2, 145.5 129.6 (2C), 117.9, 112.4 (2C), 63.1, 61.7, 46.4, 40.0, 14.3 ppm; MS (ESI) m/z 236.1 [M + H]$^+$; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{18}NO_3$ 236.1281, found 236.1276.

Ethyl 4-((4-Acetylphenyl)(methyl)amino)-3-oxobutanoate (9c) (Table 2, entry 3). The title compound was prepared as a pale yellow oil in 79% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (dd, J = 2.0, 7.0 Hz, 2H), 6.62 (dd, J = 2.0, 7.0 Hz, 2H), 4.31 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 3.46 (s, 2H), 3.12 (s, 3H), 2.51 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H);

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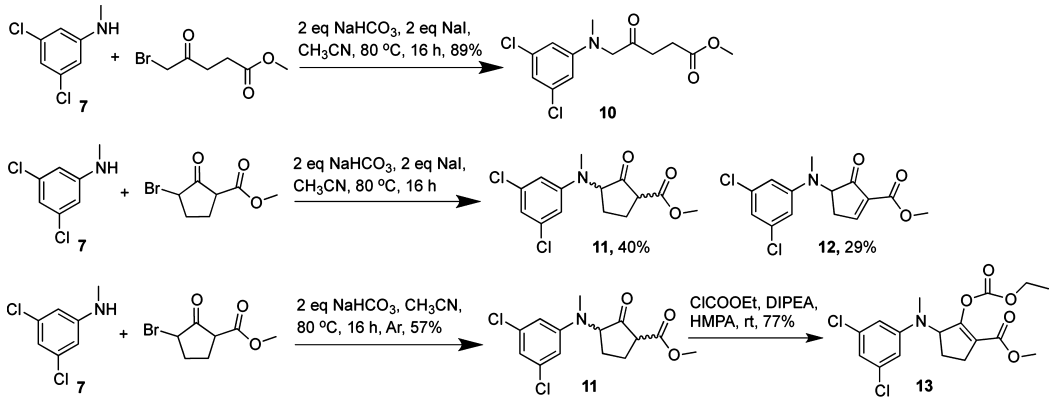
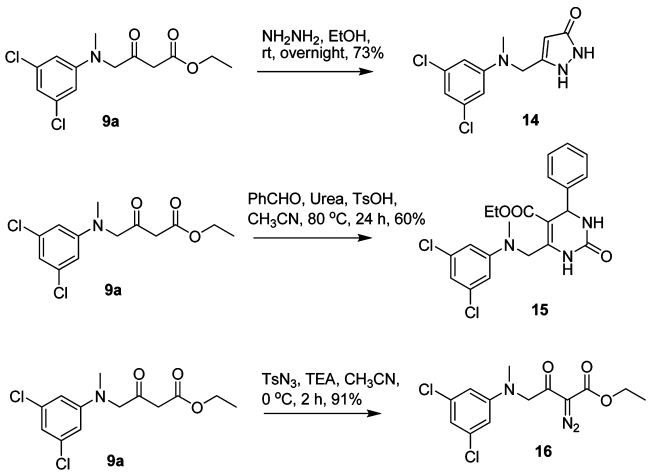
Scheme 3. Reaction Scope Related to the Ketoester



Scheme 4. Synthetic Transformations of 9a



^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.7, 196.7, 167.0, 152.2, 130.9 (2C), 127.0, 111.1 (2C), 62.3, 62.0, 46.4, 39.9, 26.3, 14.3 ppm; MS (ESI) m/z 278.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_4$ 278.1387, found 278.1383.

Ethyl 4-((3-Methoxyphenyl)(methyl)amino)-3-oxobutanoate (9d). (Table 2, entry 4). The title compound was prepared as a pale yellow oil in 62% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (t, J = 8.0 Hz, 1H), 6.33 (m, 1H), 6.24 (m, 1H), 6.19 (t, J = 2.0 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 4.13 (s, 2H), 3.78 (s, 3H), 3.44 (s, 2H), 3.03 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.2, 167.3, 160.1, 150.2, 130.3, 105.3, 102.6, 99.1, 63.0, 61.7, 55.3, 46.3, 40.0, 14.3 ppm; MS (ESI) m/z 266.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{20}NO_4$ 266.1387, found 266.1391.

Ethyl 4-((4-Fluorophenyl)(methyl)amino)-3-oxobutanoate (9e) (Table 2, entry 5). The title compound was prepared as a pale yellow oil in 87% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (t, J = 9.0 Hz, 2H), 6.58 (dd, J = 4.0, 9.0 Hz, 2H), 4.16 (q, J = 7.5 Hz, 2H), 4.12 (s, 2H), 3.44 (s, 2H), 3.00 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.7, 167.0, 157.1, 155.2, 145.5, 116.0 (d, J = 22.5 Hz, 2C), 113.6 (d, J = 7.5 Hz, 2C), 63.6, 61.8, 46.4, 40.5, 14.3 ppm; MS (ESI) m/z 254.1 $[M + H]^+$; HRMS (ESI) m/z $[M - H]^-$ calcd for $C_{13}H_{15}FNO_3$ 252.1041, found 252.1038.

Ethyl 4-((4-Chlorophenyl)(methyl)amino)-3-oxobutanoate (9f) (Table 2, entry 6). The title compound was prepared as a pale yellow oil in 85% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (d, J = 9.5 Hz, 2H), 6.55 (d, J = 9.0 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 4.16 (s, 2H), 3.43 (s, 2H), 3.02 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 167.1, 147.4, 129.3 (2C), 122.8, 113.5 (2C), 63.0, 61.9, 46.4, 40.1, 14.3 ppm; MS (ESI) m/z 270.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{17}ClNO_3$ 270.0891, found 270.0895.

Ethyl 4-((4-Bromophenyl)(methyl)amino)-3-oxobutanoate (9g) (Table 2, entry 7). The title compound was prepared as a pale yellow oil in 81% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 7.5 Hz, 2H), 6.51 (d, J = 8.0 Hz, 2H), 4.18 (q, J = 7.5 Hz, 2H), 4.15 (s, 2H), 3.43 (s, 2H), 3.02 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.2, 167.1, 147.8, 132.2 (2C), 114.0 (2C), 109.9, 62.8, 61.8, 46.4, 40.0, 14.3 ppm; MS (ESI) m/z 314.0 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{17}BrNO_3$ 314.0386, found 314.0378.

Ethyl 4-((3-Bromophenyl)(methyl)amino)-3-oxobutanoate (9h) (Table 2, entry 8). The title compound was prepared as a pale yellow oil in 73% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.77 (t, J = 2.0 Hz, 1H), 6.52 (dd, J = 2.0, 8.0 Hz, 1H), 4.18 (m, 4H), 3.44 (s, 2H), 3.02 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.8, 167.1, 150.0, 130.7, 123.8, 120.6, 115.2, 110.8, 66.6, 61.9, 46.4, 39.9, 14.3 ppm; MS (ESI) m/z 314.0 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{17}BrNO_3$ 314.0386, found 314.0367.

Ethyl 4-((3,4-Dichlorophenyl)(methyl)amino)-3-oxobutanoate (9i) (Table 2, entry 9). The title compound was prepared as a pale yellow oil in 73% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (d, J = 9.0 Hz, 1H), 6.70 (d, J = 3.5 Hz, 1H), 6.45 (dd, J = 3.0, 8.0 Hz, 1H), 4.20 (m, 4H), 3.44 (s, 2H), 3.02 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1, 167.0, 148.3, 133.2, 130.8, 120.6, 113.8, 111.8, 62.5, 62.0, 46.4, 40.0, 14.3 ppm; MS (ESI) m/z 326.0 $[M + Na]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}Cl_2NO_3$ 304.0502, found 304.0509.

Ethyl 4-((2,4-Dichlorophenyl)(methyl)amino)-3-oxobutanoate (9j) (Table 2, entry 10). The title compound was prepared as a pale yellow oil in 84% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, J = 2.5 Hz, 1H), 7.17 (dd, J = 2.5, 9.0 Hz, 1H), 7.07 (d, J = 3.0 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 4.01 (s, 2H), 3.53 (s, 2H), 2.87 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 167.3, 147.2, 130.5, 128.6, 128.5, 127.8, 122.6, 64.6, 61.7, 46.5, 41.6, 14.3 ppm; MS (ESI) m/z 326.0 $[M + Na]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}Cl_2NO_3$ 304.0502, found 304.0508.

Ethyl 4-((4-Cyanophenyl)(methyl)amino)-3-oxobutanoate (9k) (Table 2, entry 11). The title compound was prepared as a pale yellow solid in 58% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 9.0 Hz, 2H), 4.32 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 3.46 (s, 2H), 3.09 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.0, 167.0, 151.5, 133.8 (2C), 120.4, 111.9 (2C), 99.4, 62.1, 46.4, 39.8, 14.3 ppm; MS (ESI) m/z 261.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3$ 261.1234, found 261.1232.

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Ethyl 4-(Methyl(naphthalen-1-yl)amino)-3-oxobutanoate (9l) (Table 2, entry 12). The title compound was prepared as a pale yellow oil in 88% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (dd, J = 1.5, 7.5 Hz, 1H), 7.84 (dd, J = 2.0, 7.5 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.50 (m, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 4.05 (s, 2H), 3.50 (s, 2H), 2.92 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.1, 167.5, 148.8, 135.1, 129.0, 129.7, 126.2, 126.0, 125.9, 124.3, 123.7, 116.1, 66.3, 61.6 46.7, 44.0, 14.2 ppm; MS (ESI) m/z 286.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$ 286.1438, found 286.1437.

Ethyl 4-((3,5-Dichlorophenyl)(ethyl)amino)-3-oxobutanoate (9m) (Table 3, entry 1). The title compound was prepared as a pale yellow solid in 71% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.70 (t, J = 2.0 Hz, 1H), 6.44 (d, J = 2.0 Hz, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.16 (s, 2H), 3.47 (s, 2H), 3.39 (q, J = 7.0 Hz, 2H), 1.30 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.9, 167.1, 149.3, 136.0 (2C), 117.2, 110.6 (2C), 62.1, 60.2, 46.6, 46.3, 14.3, 12.2 ppm; MS (ESI) m/z 318.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{18}Cl_2NO_3$ 318.0658, found 318.0656.

Ethyl 4-((3,5-Dichlorophenyl)(isopropyl)amino)-3-oxobutanoate (9n) (Table 3, entry 2). The title compound was prepared as a pale yellow oil in 29% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.70 (t, J = 1.5 Hz, 1H), 6.46 (d, J = 1.5 Hz, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.08 (m, 3H), 3.50 (s, 2H), 1.30 (t, J = 7.0 Hz, 3H), 1.15 (d, J 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.9, 167.1, 150.1, 135.9 (2C), 117.4, 111.3 (2C), 62.0, 54.4, 49.1, 46.1, 20.0 (2C), 14.3 ppm; MS (ESI) m/z 332.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{20}Cl_2NO_3$ 332.0815, found 332.0817.

Ethyl 4-((3,5-Dichlorophenyl)(3-(trimethylsilyl)prop-2-ynyl)-amino)-3-oxobutanoate (9o) (Table 3, entry 3). The title compound was prepared as a pale yellow oil in 28% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.79 (d, J = 1.5 Hz, 1H), 6.60 (d, J = 1.5 Hz, 2H), 4.28 (s, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.07 (s, 2H), 3.51 (s, 2H), 1.30 (t, J = 7.0 Hz, 3H), −0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.6, 167.0, 149.4, 135.9 (2C), 118.7, 112.0 (2C), 99.8, 91.4, 62.1, 60.4, 46.5, 42.6, 14.3, 0.0 (3C) ppm; MS (ESI) m/z 400.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{24}Cl_2NO_3Si$ 400.0897, found 400.0904.

Ethyl 4-(Indolin-1-yl)-3-oxobutanoate (9q) (Table 3, entry 5). The title compound was prepared as a pale yellow oil in 85% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.72 (m, 1H), 6.36 (d, J = 8.0 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.91 (s, 2H), 3.55 (s, 2H), 3.46 (t, J = 8.0 Hz, 2H), 3.04 (t, J = 8.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.7, 167.4, 151.5, 129.8, 127.6, 124.8, 118.9, 106.8, 61.7, 59.8, 46.7, 28.9, 14.3 ppm; MS (ESI) m/z 248.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{18}NO_3$ 248.1281, found 248.1275.

Ethyl 4-(3,4-Dihydroquinolin-1(2H)-yl)-3-oxobutanoate (9r) (Table 3, entry 6). The title compound was prepared as a pale yellow oil in 92% yield according to the general procedure as described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (m, 2H), 6.65 (dt, J = 1.0 7.5 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 4.03 (s, 2H), 3.48 (s, 2H), 3.35 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.00 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.0, 167.4, 144.8, 129.6, 127.4, 123.0, 117.5, 110.6, 62.1, 61.7, 51.2, 46.4, 28.0, 22.5, 14.3 ppm; MS (ESI) m/z 262.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$ 262.1438, found 262.1432.

Methyl 5-((3,5-Dichlorophenyl)(methyl)amino)-4-oxopentanoate (10). The title compound was prepared as a pale yellow oil in 89% yield according to the general procedure described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (t, J = 1.5 Hz, 1H), 6.47 (d, J = 1.5 Hz, 2H), 4.14 (s, 2H), 3.68 (s, 3H), 3.02 (s, 3H), 2.66 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 173.2, 150.5, 135.8 (2C), 117.1, 110.5 (2C), 62.3, 52.2, 39.9, 34.1, 28.0 ppm; MS (ESI) m/z 304.0 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{16}Cl_2NO_3$ 304.0502, found 304.0507.

Methyl 3-((3,5-Dichlorophenyl)(methyl)amino)-2-oxocyclopentanecarboxylate (11). The title compound was prepared as a pale yellow oil in 40% yield according to the general procedure described above. The NMR spectra demonstrated that the compounds are a mixture of diastereoisomers and regioisomers of keto and enol forms (see Supporting Information). MS (ESI) m/z 316.1 $[M + H]^+$.

(±)-Methyl 4-((3,5-Dichlorophenyl)(methyl)amino)-5-oxocyclopent-1-enecarboxylate (12). The title compound was prepared as a pale yellow oil in 29% yield according to the general procedure described above. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (t, J = 3.5 Hz, 1H), 6.90 (t, J = 1.5 Hz, 1H), 6.72 (d, J = 1.5 Hz, 2H), 3.79 (s, 3H), 3.54 (dd, J = 2.5, 7.0 Hz, 1H), 3.16 (s, 3H), 2.99 (dt, J = 3.0, 19.0 Hz, 1H), 2.90 (ddd, J = 3.0, 7.0, 19.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.4, 169.3, 148.9, 146.6, 143.8, 135.3 (2C), 121.3, 117.1 (2C), 53.1, 51.0, 39.6, 28.5 ppm; MS (ESI) m/z 314.0 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{14}Cl_2NO_3$ 314.0345, found 314.0347.

(±)-Methyl 3-((3,5-Dichlorophenyl)(methyl)amino)-2-(ethoxycarbonyloxy)cyclo-pent-1-enecarboxylate (13). To a solution of $NaHCO_3$ (168 mg, 2.0 mmol) and the aniline (1.0 mmol) in 1 mL of acetonitrile was added methyl 3-bromo-2-oxocyclopentanecarboxylate (442 mg, 2.0 mmol) under Ar. The resulting reaction mixture was stirred at 80 °C for 16 h. After the mixture was cooled to room temp, 1 mL of saturated $Na_2S_2O_3$ solution was added. The resulting solution was extracted with ethyl acetate, and the organic layer was collected and washed with water and brine. The collected organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography using a mixture of hexane and ethyl acetate (10:1) as eluent to afford **11** as a pale yellow oil (180 mg, 57%).

To a solution of diisopropylethylamine (53 μL, 0.3 mmol) and **11** (64 mg, 0.2 mmol) in 0.4 mL of hexamethylphosphoramide was added ethyl chloroformate (28 μL, 0.3 mmol) under Ar. The resulting reaction mixture was stirred at room temp for 16 h. The resulting solution was extracted with ethyl acetate, and the organic layer was collected and washed with water and brine. The collected organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography using a mixture of hexane and ethyl acetate as eluent (25:1) to afford **13** as a colorless oil (60 mg, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (t, J = 1.5 Hz, 1H), 6.65 (d, J = 2.0 Hz, 2H), 5.20 (dt, J = 3.5, 8.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.76 (s, 3H), 2.75 (s, 3H), 2.73−2.63 (m, 1H), 2.36−2.33 (m, 1H), 1.83−1.80 (m, 1H), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.7, 155.8, 151.4, 151.3, 135.7 (2C), 120.7, 117.5, 112.0 (2C), 65.7, 63.5, 52.0, 32.6, 27.0, 23.5, 14.2 ppm; MS (ESI) m/z 388.1 $[M + H]^+$; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{19}Cl_2NNaO_5$ 410.0532, found 410.0538.

5-(((3,5-Dichlorophenyl)(methyl)amino)methyl)-1*H*-pyrazol-3(2*H*)-one (14). To a solution of **9a** (61 mg, 0.2 mmol) in 2 mL of EtOH was added NH_2NH_2 (13 μL, 0.4 mmol). The reaction mixture was stirred overnight at room temperature. After the volatiles were evaporated, the residue was subjected to chromatography using a mixture of dichloromethane and methanol (30:1) as eluent to afford the product (40 mg, 73%) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.72 (s, 3H), 5.24 (s, 1H), 4.40 (s, 2H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.8, 134.6 (2C), 114.8, 110.7 (2C), 38.6 ppm; MS (ESI) m/z 272.0 $[M + H]^+$; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{15}Cl_2NO_3$ 326.0327, found 326.0330.

Ethyl 6-(((3,5-Dichlorophenyl)(methyl)amino)methyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (15). Benzaldehyde (20 μL, 0.2 mmol), **9a** (30 mg, 0.1 mmol), urea (12 mg, 0.1 mmol), and TsOH (1.9 mg, 0.01 mmol) were mixed together in 0.4 mL of CH_3CN in a vial. The vial was stirred for 24 h at 80 °C until all of the **9a** was consumed. The residue was subjected to chromatography using a mixture of hexane and EtOAc (2:1) to afford the product (20 mg, 60%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 4H), 7.17 (s, 1H), 6.85 (t, J = 1.5 Hz, 1H), 6.58 (d, J = 1.5 Hz, 2H), 5.60 (s, 1H), 5.41 (d, J = 2.5 Hz, 1H), 4.72 (d,

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J = 19.0 Hz, 1H), 4.51 (d, J = 19.0 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.02 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 152.0, 151.1, 146.1, 143.7, 136.0 (2C), 129.2 (2C), 128.5, 126.8 (2C), 119.1, 111.9 (2C), 100.5, 60.6, 56.3, 55.2, 40.4, 14.3 ppm; MS (ESI) m/z 434.1 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{22}Cl_2N_3O_3$ 434.1033, found 434.1024.

Ethyl 2-Diazo-4-((3,5-dichlorophenyl)(methyl)amino)-3-oxobutanoate (16). To a solution of **9a** (61 mg, 0.2 mmol) and TEA (35 μL, 0.24 mmol) in 2 mL of CH_3CN at 0 °C was added TsN_3 (315 μL, 0.24 mmol, 15% in toluene). The reaction mixture was stirred for 2 h, and the temperature was allowed to rise to room temperature. After the volatiles were evaporated, the residue was subjected to chromatography using a mixture of hexane and ethyl acetate (20:1) as eluent to afford the product (60 mg, 91%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.68 (t, J = 1.5 Hz, 1H), 6.47 (d, J = 1.5 Hz, 2H), 4.59 (s, 2H), 4.34 (q, J = 7.0 Hz, 2H), 3.01 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.7, 161.6, 150.8, 135.7 (2C), 117.0, 110.6 (2C), 62.1, 60.0, 39.9, 14.6 ppm; MS (ESI) m/z 330.0 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{13}Cl_2N_3NaO_3$ 352.0226, found 352.0230.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **9a−r** and **10−16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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