Mild and High-Yielding Synthesis of β-Keto Esters and β-Ketoamides

Vellaisamy Sridharan, Miriam Ruiz, J. Carlos Menéndez*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain
Fax +34(91)3941822; E-mail: josecm@farm.ucm.es

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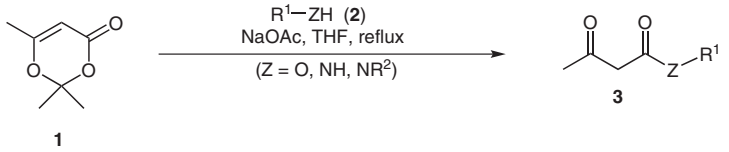
Abstract: In the presence of sodium acetate, the reaction between 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and secondary or tertiary alcohols (including chiral ones) or primary or secondary amines could be carried out in refluxing tetrahydrofuran, under much milder conditions than those described in the literature. In these new conditions, side products normally observed using the traditional protocol were avoided, and β-keto esters and β-ketoamides were normally obtained in quantitative yields.

Key words: acetoacetylation, chiral auxiliaries, dicarbonyl compounds, esters, amides



Scheme 1

β-Dicarbonyl compounds are recognized as very important building blocks in organic synthesis and are used for the construction of a variety of biologically relevant molecules.[1] They are also excellent starting materials for the synthesis of heterocyclic compounds such as dihydropyridines (Hantzsch), pyrroles (Knorr), dihydropyrimidines (Biginelli), indoles (Nenitzescu), quinolines (Combes, Conrad–Limpach, Friedländer, Knorr), often through multicomponent strategies.[1b,2] Furthermore, β-dicarbonyl compounds can also be used for the construction of carbocycles by means of C–C bond formation reactions.[3]

Among these compounds, β-keto esters are particularly interesting because they may contain suitable chiral auxiliary groups and, hence, be used to carry out asymmetric transformations.[4] The most straightforward synthetic entry into chiral β-keto esters involves either transesterification of ethyl or methyl acetoacetate or treatment of chiral alcohols with acetoacetylating reagents. Transesterification is an equilibrium process and an acidic or basic catalyst is required to promote the reaction, which, nevertheless, often gives poor yields. A number of modified procedures have been developed that employ Lewis acids to avoid the limitations of classical conditions.[5] Nevertheless, as shown by our own experience, many of these new methods have the drawback of poor reproducibility. The alternative method for the synthesis of chiral β-keto esters involves the reaction between chiral alcohols and acetoacetylating reagents, the first of which was diketene.[6] Although this reagent gives good yields, a number of problems are associated with its use, such as high reactivity and moisture sensitivity, coupled to its lachrymatory and toxic character. These drawbacks prompted Clemens and Hyatt to develop a convenient alternative to diketene, namely 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1**), a 1:1 acetone–diketene adduct.[7] Pyrolysis of compound **1** at 150 °C in high-boiling solvents gives acetylketene through a retro-hetero-Diels–Alder reaction and this intermediate can be trapped by nucleophiles to give their acetoacetylation products. In addition to the obvious disadvantages of the requirement for high temperatures, such as the impossibility of applying the reaction to thermally unstable substrates, at these temperatures acetylketene undergoes dimerization in a [4+2] fashion or reacts with acetone liberated during the reaction leading to side products that prevent complete conversion.[7–9] While derivatives of **1** with substituents other than methyl are known,[10] they are not commercially available and their use is normally limited to specialized applications.

In the course of our research on the application of β-dicarbonyl compounds for the synthesis of heterocycles and carbocycles using multicomponent reactions,[3,11] we needed to prepare chiral β-keto esters and found that currently existing methods were not wholly satisfactory. We report now the development of a modified synthetic procedure for the practical synthesis of acetoacetates **3** from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1**) and alcohols, including chiral alcohols, or primary or secondary amines under mild conditions that avoid side reactions and give essentially quantitative yields (Scheme 1, Table 1).

Initially, we carried out the reaction between **1** and borneol, a readily available, sterically hindered secondary chiral alcohol, in tetrahydrofuran under reflux. After 24

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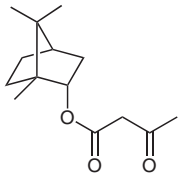
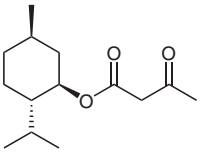
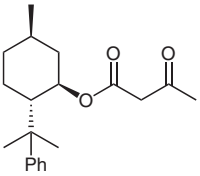
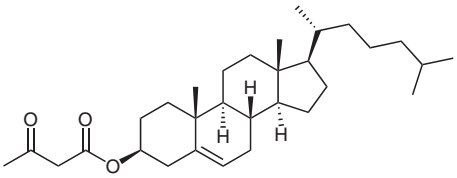
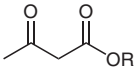
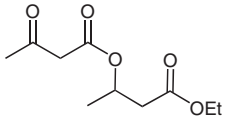
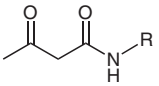
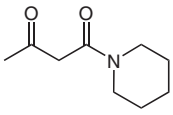
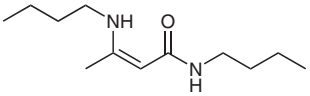
hours, we observed only 58% conversion (Table 1, entry 1), which made it obvious that the reaction needed high temperatures or a catalyst to promote acetylketene formation. However, when we carried out the reaction in the presence of one equivalent of sodium acetate, the reaction was completed in 30 hours with a quantitative yield of **3a** (entry 2). The use of a higher excess of **1** did not reduce the reaction time significantly (entries 3 and 4), and the use of potassium carbonate instead of sodium acetate had no effect upon the reaction, (cf. entries 1 and 5). It should also be mentioned that the reaction must be carried out in concentrated solutions (ca. 1.5 M) and was slow in more dilute reaction mixtures. Subsequently, we applied our optimal conditions to the synthesis of three additional chiral β-keto esters **3b–d** from other chiral alcohols often used as chiral auxiliaries, namely menthol (entry 6), 8-

Table 1 Conditions and Yields in the Synthesis of β-Keto Esters

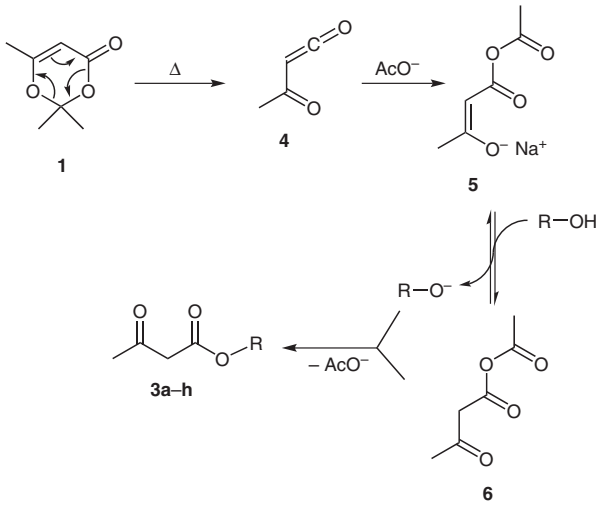
Entry	Product		Ratio **2/1**/NaOAc	Time (h)	Yield[a] (%)
1			1:1.3:0	24	58[b]
2			1:1.3:1	30	98[c]
3		**3a**	1:2:1	15	85[b]
4			1:2:1	24	99[c]
5			1:1.3:0[d]	24	57[b,d]
6		**3b**	1:1.3:1	24	98[c]
7		**3c**	1:1.3:1	24	99
8		**3d**	1:1.3:1	12	97[c]
9		**3e** R = *i*-Pr	–[e]	24	98
10		**3f** R = *c*-Hex	1:1.3:1	24	99
11		**3g** R = *t*-Bu	1:1.3:1	24	99
12		**3h**	1:1.3:1	24	98
13		**3i** R = Bn	1:1.3:0	24	45
14		**3i** R = Bn	1:1.3:1	24	79
15		**3j** R = *c*-Hex	1:1.3:1	24	98
16		**3k** R = Ph	1:1.3:1	24	98
17		**3l**	1:1.3:1	24	99
18		**3m**	2:1:1	24	93

[a] Yield after chromatography unless otherwise indicated.
[b] Yield calculated from the crude ^{1}H NMR spectra.
[c] This reaction was carried out on a 15 mmol scale.
[d] K_2CO_3 (1 equiv) was used instead of NaOAc.
[e] *i*-PrOH was used as solvent.

phenylmenthol (entry 7), and cholesterol (entry 8). In all cases, the yields were quantitative and it is worth mentioning that the less hindered cholesterol needed a reaction time of only 12 hours. Importantly, the reaction could be carried out on a scale of up to 15 mmol of the starting materials without any decrease in the yield (entries 6 and 8). In further experiments, involving simpler starting alcohols, we proved the feasibility of using the alcohol itself as the reaction medium (entry 9), and also of employing tertiary alcohols (entry 11), always giving the products **3e–g** in quantitative yields; the reaction leading to **3h** proved the compatibility of our conditions with additional functional groups in the reaction substrate (entry 12). An attempted reaction with pentane-2,4-dione, an enolizable ketone, gave a complex mixture.

While our initial attempts at carrying out the acetoacetylation of amines under our initial conditions were unsuccessful, we found subsequently that these reactions could be performed by using more concentrated (ca. 5 M) solutions. As in the case of alcohols, the reaction gave modest yields in the absence of sodium acetate (entry 13). Our studies showed that the acetoacetylation reaction worked very efficiently with primary aliphatic amines, including an α-branched amine (entries 14 and 15), primary aromatic amines (entry 16), and secondary amines (entry 17). When the reaction was performed in the presence of two equivalents of a primary amine the final product was a β-enaminone **3m**, arising from a three-component domino process involving an acetoacetylation reaction followed by condensation of the initial β-ketoamide with a second molecule of amine (entry 18).

Regarding the reaction mechanism, we suggest that, besides the expected reaction with acetylketene, the acetate anion traps the initially generated acetylketene **4** with formation of the enolate of a mixed anhydride **5**. In the reaction with alcohols, which seem to be more reactive than amines under our conditions since they require a less concentrated solution, this species can be assumed to be involved in a deprotonation equilibrium with the alcohol that leads to the corresponding alkoxide and compound **6**, which then react together through the more electrophilic carbonyl group of **6** to give the observed products **3a–h** (Scheme 2).



Scheme 2

In the case of amines, the above equilibrium is not possible and the reaction must take place on **5**, which explains the lower observed reactivity.

In summary, we have developed an experimentally simple and practical protocol for the synthesis of chiral β-keto esters, which will hopefully contribute to the use of these useful materials in asymmetric synthesis. Our procedure gives quantitative yields in a highly reliable way and requires mild reaction conditions and a very simple, environmentally harmless, and inexpensive additive.

All reagents were of commercial quality (Aldrich, Fluka) and were used as received. Compound **1** was purchased from Aldrich and used as received. After storing for more than ca. 6 months, it is advised to distill **1** under high vacuum before use. Solvents (from SDS) were dried and purified using standard techniques. Reactions were monitored by TLC on aluminum plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–240 mesh). Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as films on a NaCl disk. NMR spectra were obtained on a Bruker Avance instrument (250 MHz for ^{1}H, 62.9 MHz for ^{13}C), maintained by the Servicio de RMN, Universidad Complutense, with $CDCl_3$ as solvent. Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

Acetylation Reactions; General Procedure

A mixture of compound **2** (4 to 15 mmol), dioxinone **1** (5.2 to 19.5 mmol, 1.3 equiv), and anhyd NaOAc (4 to 15 mmol) in THF (10 mL for 15 mmol of **2** in the case of alcohols, 1 mL for 5 mmol of **2** in the case of amines; excess solvent reduced the reaction rate) was heated under reflux for the time given in Table 1. After completion of the reaction (TLC), the mixture was cooled, diluted with Et_2O and the soln was washed with H_2O and brine and dried (anhyd Na_2SO_4). The solvent was evaporated and products were purified by a flash column chromatography (silica gel, petroleum ether–EtOAc, 90:10).

Bornyl Acetoacetate (3a)[8]

Following the general procedures on a 15 mmol scale gave **3a** as a viscous liquid; yield: 3.49 g (98%).

$[\alpha]_D^{25}$ –39.3 (*c* 1.36, $CHCl_3$) [Lit.[8] –37.6 (*c* 1.3, $CHCl_3$)].

IR (neat, NaCl): 2956.1, 2881.3, 1738.6, 1716.2, 1649.9, 1244.6, 1151.9 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 0.89 (s, 3 H), 0.92 (s, 3 H), 1.03 (dd, *J* = 13.8, 3.5 Hz, 1 H), 1.19–1.38 (m, 2 H), 1.68–1.97 (m, 3 H), 2.30 (s, 3 H), 2.32–2.44 (m, 1 H), 3.48 (s, 2 H), 4.96 (ddd, *J* = 9.9, 3.5, 2.1 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8, 19.2, 20.0, 27.4, 28.3, 30.5, 36.9, 45.1, 48.2, 49.2, 50.7, 81.4, 167.8, 201.0.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.30; H, 9.18.

Menthyl Acetoacetate (3b)[5b]

Following the general procedure on a 15 mmol scale gave **3b** as a viscous oil; yield: 3.53 g (98%).

$[\alpha]_D^{25}$ –72.4 (*c* 3.08, EtOH) [Lit.[5b] –72.0 (*c* 10.4, benzene)].

IR (neat, NaCl): 2956.5, 2871.0, 1740.9, 1716.1, 1646.3, 1243.0, 1148.9 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H), 0.99–1.14 (m, 2 H), 1.34–2.08 (m, 7 H), 2.28 (s, 3 H), 3.46 (s, 2 H), 4.76 (td, *J* = 10.9, 4.4 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.5, 21.1, 22.4, 23.6, 26.5, 30.4, 31.8, 34.5, 41.1, 47.2, 50.9, 75.8, 167.1, 201.1.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.74; H, 9.91.

8-Phenylmenthyl Acetoacetate (3c)[4a]

Following the general procedure on a 4 mmol scale gave **3c** as a viscous oil; yield: 1.25 g (99%).

$[\alpha]_D^{25}$ +9.7 (*c* 0.64, CH_2Cl_2) [Lit.[4a] +10.6 (*c* 1.3, $CHCl_3$)].

IR (neat, NaCl): 2955.8, 2823.6, 1739.2, 1715.4, 1644.3, 1243.3, 1152.9 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.5 Hz, 3 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 0.92–2.10 (m, 8 H), 2.13 (s, 3 H), 2.67 (d, *J* = 15.7 Hz, 1 H), 2.80 (d, *J* = 15.7 Hz, 1 H), 4.86 (td, *J* = 10.8, 4.4 Hz, 1 H), 7.22–7.34 (m, 5 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.2, 23.8, 26.7, 29.6, 30.5, 31.7, 34.9, 39.9, 41.8, 50.2, 50.6, 75.5, 125.5, 125.8, 128.4, 152.3, 166.9, 201.3.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.58; H, 8.71.

Cholesteryl Acetoacetate (3d)[7,12]

Following the general procedure on a 15 mmol scale gave **3d** as a white solid; yield: 6.85 g (97%); mp 92–93 °C.

$[\alpha]_D^{25}$ –35.7 (*c* 0.7, $CHCl_3$) [Lit.[12] –35 (no concentration given, $CHCl_3$)].

IR (neat, NaCl): 2949.8, 2867.9, 1742.5, 1724.1, 1643.7, 1235.4, 1162.3 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.70 (s, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 1.04 (s, 3 H), 1.08–2.06 (m, 26 H), 2.29 (s, 3 H), 2.37 (d, *J* = 7.8 Hz, 2 H), 3.45 (s, 2 H), 4.63–4.76 (m, 1 H), 5.41 (d, *J* = 4.9 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 12.3, 19.1, 19.7, 21.4, 23.0, 23.3, 24.3, 24.7, 28.0, 28.4, 28.6, 30.5, 32.2, 32.3, 36.2, 36.6, 36.9, 37.3, 38.3, 39.9, 40.1, 42.7, 50.4, 50.8, 56.5, 57.0, 75.5, 123.3, 139.7, 166.9, 201.1.

Anal. Calcd for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71. Found: C, 78.88; H, 10.59.

Isopropyl Acetoacetate (3e)

Following the general procedure on a 5 mmol scale gave **3e** as a viscous oil; yield: 0.71 g (98%).

IR (neat, NaCl): 2984.9, 2939.9, 1742.0, 1715.2, 1641.9, 1273.1, 1107.3 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.3 Hz, 6 H), 2.27 (s, 3 H), 3.42 (s, 2 H), 5.05 (sept, *J* = 6.3 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.9, 30.3, 50.6, 69.1, 166.9, 201.1.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.02; H, 8.29.

Cyclohexyl Acetoacetate (3f)

Following the general procedure on a 5 mmol scale gave **3f** as a viscous liquid; yield: 0.91 g (99%).

IR (neat, NaCl): 2939.2, 2860.8, 1740.1, 1715.2, 1649.7, 1238.5, 1151.4 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.25–1.60 (m, 6 H), 1.82–1.90 (m, 2 H), 1.92–1.97 (m, 2 H), 2.28 (s, 3 H), 3.44 (s, 2 H), 4.79–4.86 (m, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.9, 25.6, 30.3, 31.7, 50.8, 74.0, 166.9, 201.1.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.00; H, 8.66.

***tert*-Butyl Acetoacetate (3g)**

Following the general procedure on a 5 mmol scale gave **3g** as a viscous liquid; yield: 0.78 g (99%).

IR (neat, NaCl): 2981.5, 2932.1, 1741.0, 1716.1, 1369.3, 1256.5, 1146.0 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 2.27 (s, 3 H), 3.37 (s, 2 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.2, 30.3, 51.7, 82.1, 166.7, 201.4.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.42; H, 8.79.

(±)-1-(Ethoxycarbonyl)prop-2-yl Acetoacetate (3h)

Following the general procedure on a 5 mmol scale gave **3h** as a viscous liquid; yield: 1.06 g (98%).

IR (neat, NaCl): 2938.5, 1739.0, 1638.4, 1360.1, 1192 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 2.28 (s, 3 H), 2.39 (dd, *J* = 15.7, 7.6 Hz, 1 H), 2.53 (dd, *J* = 15.7, 7.6 Hz, 1 H), 3.43 (s, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 5.27–5.45 (m, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.4, 19.9, 30.3, 40.8, 50.4, 60.9, 68.7, 166.6, 170.3, 200.8.

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.28; H, 7.32.

***N*-Benzylacetoacetamide (3i)**

Following the general procedure on a 5 mmol scale gave **3i** as a pale-yellow solid; yield: 0.75 g (79%); mp 92–93 °C.

IR (neat, NaCl): 3249.9, 3085.2, 2935.6, 1714.3, 1640.7, 1443.3, 1239.8, 1189.6 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 3.47 (s, 2 H), 4.48 (d, *J* = 5.8 Hz, 2 H), 7.29–7.36 (m, 5 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.2, 43.8, 50.2, 127.8, 128.1, 129.1, 138.4, 166.3, 204.8.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.84; H, 6.71; N, 7.18.

***N*-Cyclohexylacetoacetamide (3j)**

Following the general procedure on a 5 mmol scale gave **3j** as a pale-yellow solid; yield: 0.90 g (98%); mp 76–77 °C.

IR (neat, NaCl): 3295.9, 3076.1, 2932.9, 2855.6, 1721.6, 1644.0, 1555.6, 1359.3, 1159.8 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.12–1.46 (m, 5 H), 1.57–1.76 (m, 3 H), 1.87–1.92 (m, 2 H), 2.28 (s, 3 H), 3.40 (s, 2 H), 3.74–3.85 (m, 1 H), 6.87 (br s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.1, 25.8, 31.1, 33.1, 48.6, 50.6, 165.1, 204.9.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.34; H, 9.20; N, 7.55.

***N*-Phenylacetoacetamide (3k)**

Following the general procedure on a 5 mmol scale gave **3k** as a pale-yellow solid; yield: 0.90 g (98%); mp 85–86 °C.

IR (neat, NaCl): 3302.2, 2984.3, 1663.2, 1548.9, 1444.8, 1344.2 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 3.58 (s, 2 H), 7.13 (tt, *J* = 7.5, 1.1 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.56 (dd, *J* = 8.3, 1.1 Hz, 2 H), 9.21 (br s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 31.6, 50.4, 120.6, 125.0, 129.4, 137.9, 164.2, 205.5.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.44; H, 6.15; N, 7.76.

1-(3-Oxobutanoyl)piperidine (3l)[13]

Following the general procedure on a 5 mmol scale gave **3l** as a viscous liquid; yield: 0.84 g (99%).

IR (neat, NaCl): 2938.1, 2857.5, 1721.0, 1639.3, 1445.1, 1355.2 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.75–2.4 (m, 6 H), 2.19 (s, 3 H), 3.48–3.26 (m, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 24.6, 25.7, 26.6, 30.4, 43.1, 47.8, 50.4, 165.1, 202.9.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.52; H, 8.71; N, 8.15.

***N*-Butyl-3-(butylamino)but-2-enamide (3m)[14]**

Following the general procedure on a 5 mmol scale gave **3m** as a viscous liquid; yield: 0.99 g (93%).

IR (neat, NaCl): 3303.8, 2958.2, 2872.0, 1721.4, 1626.3, 1441.1, 1282.5, 1226.9 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.89–0.99 (m, 6 H), 1.24–1.60 (m, 8 H), 1.83 (s, 3 H), 3.13–3.25 (m, 4 H), 4.24 (s, 1 H), 4.82 (br s, 1 H), 9.03 (br s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.1 (two methyl signals merged together), 19.7, 20.4, 20.5, 32.6, 32.9, 38.8, 42.8, 85.2, 158.5, 171.4.

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.61; H, 11.18; N, 13.08.

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