A Facile and Practical One-Pot Synthesis of β-Oxo Thioamides from β-Oxo Amides and Isothiocyanates

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Abstract: A facile and practical one-pot synthesis of β-oxo thioamides from β-oxo amides has been developed. By treatment with isothiocyanates in ethanol in the presence of potassium carbonate, a series of β-oxo amides was converted, under reflux, in high yields into the corresponding β-oxo thioamides.

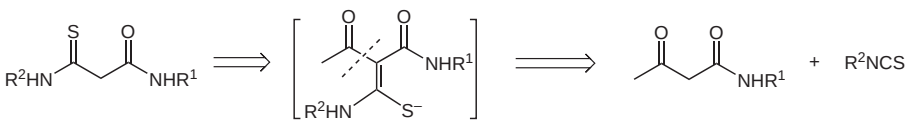
Key words: thioamides, 3-oxo amides, isothiocyanates, ethanol, potassium carbonate

Thioamides represent an important class of carboxylic acid derivatives with diverse bio- and pharmacological activities.[1,2] Over the past decades, they have found a variety of applications, for example as plant protection agents, drugs, flotation and vulcanization agents, additives to lubricating oils and greases, and ligands in coordination chemistry. They are also widely used as versatile synthons in organic synthesis, including in regio- and stereoselective heterocyclization reactions.[1–3] So far, extensive work has generated many approaches for the synthesis of thioamides. The most common approaches involve the thionation of their amide analogues.[2a,4] The direct thionation of amides has been extensively studied with various thionating reagents, such as phosphorus pentasulfide, diethylthiocarbamoyl chloride, boron sulfide, ethyl aluminum sulfide, and Lawesson's reagent.[5–7] To provide mild thionation conditions, the prior activation of amides with electrophilic reagents has been investigated.[8] Recently, polymer-supported thionating reagents have been developed for the thionation of amides.[3b,9] Thioamides can be synthesized directly by reaction of isothiocyanates with aromatic and heteroaromatic compounds in the presence of Lewis acids, in a Friedel–Crafts-type reaction.[10] Other methods reported for thioamide synthesis include the use of nitriles, aldehydes or ketones, amidines, or isothiocyanates as starting materials.[2a] Nevertheless, there is still a need for novel and practical methods for the synthesis of more elaborate and functionalized thioamides to be developed.

β-Oxo thioamides make up an important subset of thioamides, since another reactive site, that is, the β-carbonyl group, in the molecule turn them into more useful building blocks in organic synthesis. However, most of the available approaches for accessing thioamides are not general for the preparation of β-oxo thioamides. Recently, Liang and co-workers described an efficient synthetic route to β-oxo thioamides by fragmentation of the dithiolane ring of α-oxo ketene *S*,*S*-acetals.[11]

During the course of our studies on the chemistry and applications of α-oxo ketene *S*,*S*-acetals,[12] we successfully achieved thioacetalization using α-oxo ketene *S*,*S*-acetals as odorless and efficient thiol equivalents.[13] We also noticed that α-acyl ketene *S*,*S*-acetals are easily deacylated under the investigated conditions. In light of these studies, we envisaged a synthetic route to thioamides by the reaction of β-oxo amides and isothiocyanates, in which an acyl group of the substrate serves as an activated group (Scheme 1). Investigating this, we developed a facile and practical one-pot synthesis of β-oxo thioamides. We wish to describe our preliminary results here.

First, the reaction of 3-oxo-*N*-phenylbutanamide (**1a**) with phenyl isothiocyanate (**2a**) (1.2 equiv) in *N*,*N*-dimethylformamide in the presence of potassium carbonate (2.0 equiv) was investigated (Scheme 2). The reaction mixture was stirred at room temperature for five hours, and then neutralized with dilute hydrochloric acid. The precipitated yellow solid was washed with water and dried in vacuo, but was, unfortunately, found to be an inseparable mixture. Treatment of the solid with ethanol (95%) under reflux for 1.5 hours, followed by cooling to room temperature furnished a white crystalline product, which was characterized as 3-anilino-*N*-phenyl-3-thioxopropan-



Scheme 1 Proposed synthetic approach to β-oxo thioamides

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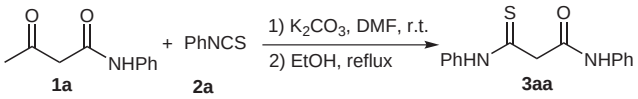


Scheme 2 Reaction of 3-oxo-*N*-phenylbutanamide (**1a**) with phenyl isothiocyanate (**2a**)

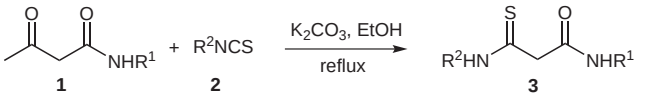
amide (**3aa**) on the basis of its spectral and analytical data (Scheme 2).

The results suggested that an intermediate α-oxo ketene monothiolate anion (see Scheme 1)[14] possibly forms during the reaction at room temperature, and that its deacylation might require a high temperature for complete conversion. This encouraged us to attempt to synthesize β-oxo thioamides from β-oxo amides in one pot. Thus, the reaction of **1a** and **2a** (1.2 equiv) was performed in *N*,*N*-dimethylformamide in the presence of potassium carbonate (2.0 equiv) at room temperature for one hour, followed by reaction at 80 °C for another hour. After workup and purification of the resulting reaction mixture, β-oxo thioamide **3aa** was obtained in 92% yield (Scheme 2).

Subsequently, the reaction conditions, including solvent, reaction temperature, base, and **1a**/**2a**/base ratio were investigated with the aim to optimize the yield of β-oxo thioamide **3aa** (Scheme 2). It was found that the reaction of **1a** and **2a** also proceeded in other organic solvents, such as dimethyl sulfoxide, ethanol, butanone, and tetrahydrofuran. The reaction was significantly accelerated by an increase of the reaction temperature. The use of a strong base, such as sodium hydroxide, shortens the reaction time, but at the same time results in lower product yield and the formation of byproducts. Longer reaction time accompanied by lower conversion resulted when the reaction was performed in the presence of weak organic bases, such as triethylamine. A series of experiments revealed that potassium carbonate and ethanol were the best base and solvent, respectively, among those tested, and that the optimal results were obtained when the reaction of **1a** and **2a** (1.0 equiv) was carried in the presence of 1.2 equivalents of potassium carbonate in ethanol under reflux for 1.5 hours; this gave **3aa** in 94% yield (Table 1, entry 1). In this case, the resulting reaction mixture was cooled to room temperature, neutralized with dilute hydrochloric acid, and the precipitated solid was filtered, washed with water, and dried in vacuo to furnish pure product **3aa**; thus, the thioamide synthesis was followed by a very simple, nonchromatographic separation process. It should be mentioned that a similar approach to β-oxo thioamide **3aa** was previously reported by Barnikow: the reaction was carried with a diarylmalonamide and an isothiocyanate with the aid of sodium alkoxide.[14a]

Having established the optimal conditions for the synthesis of β-oxo thioamide **3aa**, we investigated the scope of the reaction with regard to other R^1 and R^2 groups in starting materials **1** and **2** (Table 1). The results of the reactions of other β-oxo amides **1b**–**j** with isothiocyanates **2a** and **2b** (1.0 equiv) in ethanol in the presence of potassium carbonate (1.2 equiv) under reflux are summarized in

Table 1 One-Pot Synthesis of β-Oxo Thioamides from β-Oxo Amides **1** and Isothiocyanates **2**



Entry	**1**	R^1	**2**	R^2	**3**	Time[a] (h)	Yield[b] (%)
1	**1a**	Ph	**2a**	Ph	**3aa**	1.5	94
2	**1b**	4-ClC_6H_4	**2a**	Ph	**3ba**	1.7	96
3	**1c**	4-$MeOC_6H_4$	**2a**	Ph	**3ca**	1.8	93
4	**1d**	4-MeC_6H_4	**2a**	Ph	**3da**	1.5	92
5	**1e**	2-ClC_6H_4	**2a**	Ph	**3ea**	1.6	95
6	**1f**	2-$MeOC_6H_4$	**2a**	Ph	**3fa**	1.6	93
7	**1g**	2-MeC_6H_4	**2a**	Ph	**3ga**	1.5	94
8	**1h**	2,4-$Me_2C_6H_3$	**2a**	Ph	**3ha**	1.7	90
9	**2i**	2-MeO-5-ClC_6H_3	**2a**	Ph	**3ia**	1.8	89
10	**1j**	Me	**2a**	Ph	**3ja**	2.0	90
11	**1a**	Ph	**2b**	Bn	**3ab**	2.5	81
12	**1b**	4-ClC_6H_4	**2b**	Bn	**3bb**	2.2	83
13	**1c**	4-$MeOC_6H_4$	**2b**	Bn	**3cb**	2.1	77
14	**1d**	4-MeC_6H_4	**2b**	Bn	**3db**	2.0	78

[a] Reaction time under reflux.
[b] Isolated yields.

Table 1.[15] The reactions of β-oxo amides **1b**–**j** bearing various aryl- and alkylamide groups with phenyl isothiocyanate (**2a**) proceeded smoothly, affording the corresponding β-oxo thioamides **3ba**–**3ja** in excellent yields (Table 1, entries 2–10). The versatility of this facile β-oxo thioamide synthesis was demonstrated by the reactions of β-oxo amides **1a**–**d** with benzyl isothiocyanate (**2b**) under identical reaction conditions (Table 1, entries 11–14). It is worth noting that, in all cases, pure products **3** could be obtained by nonchromatographic separation. If necessary, the products can be further purified by recrystallization from ethanol–water (1:1) or flash chromatography (silica gel, Et_2O–PE, 3:2). However, we were unable to obtain the corresponding β-oxo thioamides when acetylacetone or ethyl 3-oxobutanoate were subjected to the identical conditions that were used for β-oxo amides **1**; this might be due to the instability of the intermediate α-oxo ketene monothiolate anions.[15]

In summary, we have described a facile and practical one-pot synthesis of β-oxo thioamides by the reactions of β-oxo amides with isothiocyanates in ethanol in the presence of potassium carbonate under reflux. The simple execution and separation, the use of commercially available substrates, the mild conditions, high yields, and wide range of synthetic potential of the products make this pro-

tocol very attractive for use in academic research and practical applications.

All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. IR spectra were recorded on a Magna-560 infrared spectrometer of samples prepared on KBr plates as neat films. NMR spectra of samples in $CDCl_3$ (unless stated otherwise) were recorded on a Varian Inova-500 spectrometer. Elemental analyses were carried out on a Perkin-Elmer PE-2400 analyzer. Starting materials and solvents were obtained from commercial sources and used without treatment.

3-Anilino-*N*-phenyl-3-thioxopropanamide (3aa);[14] Typical Procedure

A 50-mL round-bottomed flask was charged with K_2CO_3 (0.83 g, 6.0 mmol), 3-oxo-*N*-phenylbutanamide (**1a**; 0.89 g, 5.0 mmol) and EtOH (15 mL) at r.t. After the reaction mixture had stirred at r.t. for 0.5 h, PhNCS (**2a**; 0.68 g, 5.0 mmol) was added dropwise within 10 min. The mixture was heated and stirred under reflux for 1.5 h until complete conversion had taken place, as indicated by TLC. Then the resulting mixture was cooled to r.t. and neutralized with dilute aq HCl. The precipitated solid was collected by filtration, washed with H_2O, and dried in vacuo; this furnished pure product **3aa**.

Yield: 1.27 g (94%); white solid; mp 147–149 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.10 (s, 2 H), 7.17 (t, *J* = 7 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.34 (t, *J* = 8 Hz, 2 H), 7.41 (t, *J* = 8 Hz, 2 H), 7.54 (d, *J* = 7.5 Hz, 2 H), 7.79 (d, *J* = 7.5 Hz, 2 H), 8.86 (s, 1 H), 11.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.6, 120.5, 123.6, 125.2, 127.2, 128.9, 129.1, 137.0, 138.4, 166.5, 193.9.

Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.48; H, 5.17; N, 10.48.

3-Anilino-*N*-(4-chlorophenyl)-3-thioxopropanamide (3ba)

White solid; mp 158–160 °C.

IR (neat): 3246, 3183, 3106, 2951, 1680, 1603, 1541, 1492, 1430, 1398, 826, 735, 686 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.07 (s, 2 H), 7.29–7.31 (m, 3 H), 7.41 (t, *J* = 8 Hz, 2 H), 7.48 (d, *J* = 7 Hz, 2 H), 7.75 (d, *J* = 8 Hz, 2 H), 8.72 (s, 1 H), 11.02 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.4, 121.2, 123.4, 126.7, 127.6, 129.1, 129.2, 138.4, 139.9, 166.3, 194.9.

Anal. Calcd for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; N, 9.19. Found: C, 59.34; H, 4.13; N, 9.12.

3-Anilino-*N*-(4-methoxyphenyl)-3-thioxopropanamide (3ca)

White solid; mp 131–132 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 4.03 (s, 2 H), 6.89 (d, *J* = 8 Hz, 2 H), 7.42 (d, 5 H), 7.79 (s, 2 H), 8.43 (s, 1 H), 11.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.3, 55.5, 114.1, 122.4, 123.5, 127.1, 128.8, 129.9, 138.5, 157.0, 166.4, 193.9.

Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.79; H, 5.42; N, 9.46.

3-Anilino-3-thioxo-*N*-4-tolylpropanamide (3da)[14a]

White solid; mp 157–159 °C.

IR (neat): 3243, 3189, 3111, 3025, 2918, 1677, 1598, 1540, 1511, 1492, 1434, 815, 760, 711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 4.02 (s, 2 H), 7.11 (d, *J* = 8.5 Hz, 2 H), 7.24 (t, *J* = 7 Hz, 1 H), 7.37 (t, *J* = 8.5 Hz, 4 H), 7.75 (d, *J* = 8 Hz, 2 H), 8.35 (s, 1 H), 11.13 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 54.4, 120.6, 123.6, 127.1, 128.8, 129.5, 134.3, 135.0, 138.5, 166.3, 193.9.

Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.45; H, 5.81; N, 9.73.

3-Anilino-*N*-(2-chlorophenyl)-3-thioxopropanamide (3ea)

White solid; mp 151–152 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.13 (s, 2 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7 Hz, 3 H), 7.79 (d, *J* = 8 Hz, 2 H), 8.22 (d, *J* = 6.5 Hz, 1 H), 8.80 (s, 1 H), 11.08 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.6, 122.6, 123.4, 124.7, 125.9, 127.1, 127.5, 128.9, 129.5, 133.7, 138.6, 166.6, 193.2.

Anal. Calcd for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; N, 9.19. Found: C, 59.36; H, 4.23; N, 9.08

3-Anilino-*N*-(2-methoxyphenyl)-3-thioxopropanamide (3fa)

White solid; mp 138–140 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 4.06 (s, 2 H), 6.92 (d, *J* = 8 Hz, 1 H), 6.98 (t, *J* = 8 Hz, 1 H), 7.12 (t, *J* = 8 Hz, 1 H), 7.28 (s, 1 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.81 (d, *J* = 8 Hz, 2 H), 8.28 (d, *J* = 8.5 Hz, 1 H), 8.39 (s, 1 H), 11.37 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.0, 55.8, 110.3, 120.3, 120.8, 123.4, 125.0, 126.6, 126.9, 128.8, 138.7, 148.6, 166.4, 193.3.

Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.13; H, 5.44; N, 9.37.

3-Anilino-3-thioxo-*N*-2-tolylpropanamide (3ga)

White solid; mp 124–125 °C.

IR (neat): 3285, 3217, 3147, 3108, 1674, 1600, 1537, 1498, 1415, 811, 753, 684 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 4.14 (s, 2 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.17 (d, *J* = 7 Hz, 1 H), 7.21 (d, *J* = 8 Hz, 1 H), 7.28 (d, *J* = 7 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.73 (d, *J* = 8 Hz, 1 H), 7.78 (d, *J* = 8 Hz, 2 H), 8.70 (s, 1 H), 11.31 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.2, 55.4, 123.3, 123.4, 126.1, 126.5, 127.1, 128.8, 130.5, 130.8, 134.9, 138.6, 166.5, 194.1.

Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.74; H, 5.62; N, 9.94.

3-Anilino-*N*-(2,4-dimethylphenyl)-3-thioxopropanamide (3ha)

White solid; mp 116–117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 2.30 (s, 3 H), 4.09 (s, 2 H), 7.00 (t, *J* = 9 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.53 (d, *J* = 7.5 Hz, 1 H), 7.76–7.78 (m, 3 H), 8.36 (s, 1 H), 11.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 20.9, 55.1, 123.3, 123.7, 127.0, 127.1, 128.8, 130.8, 131.4, 132.2, 135.9, 138.7, 166.6, 194.1.

Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.58; H, 6.11; N, 9.45.

3-Anilino-*N*-(5-chloro-2-methoxyphenyl)-3-thioxopropanamide (3ia)

White solid; mp 152–153 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 4.06 (s, 2 H), 6.82 (d, *J* = 9 Hz, 1 H), 7.07 (q, *J* = 8.5, 2.5 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.80 (d, *J* = 7.5 Hz, 2 H), 8.37 (s, 1 H), 8.53 (s, 1 H), 11.18 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.2, 56.1, 111.1, 120.1, 123.4, 124.3, 125.8, 127.0, 127.5, 128.9, 138.6, 147.2, 166.4, 193.1.

Anal. Calcd for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; H, 4.52; N, 8.37. Found: C, 57.23; H, 4.43; N, 8.51.

3-Anilino-*N*-methyl-3-thioxopropanamide (3ja)
White solid; mp 118–120 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.85 (d, 3 H), 3.88 (s, 2 H), 6.73 (s, 1 H), 7.26 (t, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 8 Hz, 2 H), 7.79 (d, *J* = 8 Hz, 2 H), 11.60 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.7, 53.5, 123.4, 127.0, 128.9, 138.8, 169.1, 194.1.

Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.49; H, 5.90; N, 13.21.

3-(Benzylamino)-*N*-phenyl-3-thioxopropanamide (3ab)
White solid; mp 176–177 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 2 H), 4.84 (d, *J* = 5.5 Hz, 2 H), 7.27–7.44 (m, 10 H), 8.70 (s, 1 H), 9.23 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.2, 53.4, 121.2, 127.5, 127.8, 128.2, 128.9, 129.2, 137.4, 138.4, 166.3, 196.0.

Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.34; H, 5.72; N, 9.68

3-(Benzylamino)-*N*-(4-chlorophenyl)-3-thioxopropanamide (3bb)
White solid; mp 170–171 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 2 H), 4.84 (d, *J* = 5.5 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.37 (d, *J* = 7 Hz, 4 H), 7.43 (d, *J* = 9 Hz, 2 H), 8.71 (s, 1 H), 9.23 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.2, 53.5, 121.2, 127.5, 127.8, 128.2, 128.9, 129.2, 137.4, 138.4, 166.3, 196.0.

Anal. Calcd for $C_{16}H_{15}ClN_2OS$: C, 60.28; H, 4.74; N, 8.79. Found: C, 60.63; H, 4.61; N, 8.91.

3-(Benzylamino)-*N*-(4-methoxyphenyl)-3-thioxopropanamide (3cb)
White solid; mp 148–149 °C.

IR (neat): 3233, 3189, 3126, 3063, 2965, 1662, 1608, 1538, 1510, 1406, 1249, 1172, 1112, 1030, 828, 750, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.87 (s, 2 H), 4.85 (d, *J* = 5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.34–7.37 (m, 7 H), 8.21 (s, 1 H), 9.48 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.4, 52.8, 55.4, 114.1, 122.2, 128.0, 128.2, 128.8, 130.1, 135.6, 156.9, 165.8, 195.1.

Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.23; H, 5.65; N, 8.84.

3-(Benzylamino)-3-thioxo-*N*-4-tolylpropanamide (3db)
White solid; mp 163–164 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.87 (s, 2 H), 4.85 (d, *J* = 5 Hz, 2 H), 7.13 (d, *J* = 8 Hz, 2 H), 7.34–7.37 (m, 7 H), 8.15 (s, 1 H), 9.36 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 50.4, 52.9, 120.4, 128.0, 128.3, 128.8, 129.5, 134.4, 134.7, 135.6, 165.8, 195.0.

Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.28; H, 6.12; N, 9.47.

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