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Willgerodt–Kindler reaction of arylglyoxals with amines and sulfur in aqueous media: a simple and efficient synthesis of α -ketothioamides

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A simple and efficient method for the synthesis of α -ketothioamides *via* the Willgerodt–Kindler reaction is developed. Reactions were carried out between arylglyoxal hydrates, amines and elemental sulfur in water at 80°C to afford corresponding α -ketothioamides in good to high yields in a short reaction time.



Keywords: Willgerodt–Kindler reaction; α -ketothioamides; arylglyoxals; water; sulfur

1. Introduction

Carrying out organic reactions in water have attracted increasing interest in the last few decades (1-3), not only because water is one of the most abundant and cheap solvents and makes the reactions safer, easier to handle and environmentally amenable (4, 5), but also because reactions in water show different reactivity and selectivity in comparison with conventional organic solvents.

The Willgerodt–Kindler reaction is one of the most important methods for the construction of thioamide moiety ((6, 8) and references cited therein, (7)), which exhibit a wide range of biological activities such as pesticidal (9), fungicidal (10), insecticidal (11), antioxidant (12) and antitubercular (13) activities. Also, thioamides have widely been used in the field of peptide chemistry (14–16), polymers (17, 18) and as building blocks in organic synthesis (19–22), especially

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2 B. Eftekhari-Sis et al.

for the synthesis of five- and six-membered heterocycles (23-28). A number of methods are available in the literature for the preparation of thioamides, such as thionation of amides (29-35) and Friedel–Crafts reaction of aromatic compounds with KSCN (36). However, α -ketothioamides were isolated in very low yields as by-products in the Willgerodt–Kindler reaction of aryl methyl ketones (37, 38); modified Willgerodt–Kindler reaction using IR energy was reported to produce α -ketothioamides in 12–67% yields, in which also the corresponding aryl methyl thioamides were isolated in 0–42% yields (39). Also, α -ketothioamides were prepared by a number of other limited different approaches (40–42), which have some disadvantages, such as limited scope of the products, expensive reagent or catalyst, harsh reaction conditions, and toxic solvents.

In continuation of our studies on arylglyoxals chemistry (43–45), herein we wish to report the first Willgerodt–Kindler reaction of arylglyoxal hydrates 1 with amines 2 and elemental sulfur in water to afford α -ketothioamides 3.

2. Results and discussion

The Willgerodt–Kindler reaction in water was first studied using phenylglyoxal hydrate **1a** and piperidine **2a** and elemental sulfur under different conditions and 1-phenyl-2-(piperidin-1-yl)-2-thioxoethanone **3a** was obtained in good yield (61%) when a mixture of **1a** (0.5 mmol), **2a** (1 mmol) and elemental sulfur (1 mmol) in water was heated at 80°C for 1 h (Scheme 1).



Scheme 1. Synthesis of 1-phenyl-2-(piperidin-1-yl)-2-thioxoethanone 3a.

The scope of the reaction was investigated using different arylglyoxal hydrates 1 and amines 2, which are summarized in Table 1. Reactions were carried out by heating of a mixture of 1 (0.5 mmol) with 2 (1 mmol) and sulfur (1 mmol) in 2 ml water at 80°C for 0.6–1 h, and filtration of the obtained solid followed by recrystallization and filtration in hot EtOH to remove unreacted sulfur or *in situ* generated ammonium polysulfide. As shown in Table 1, phenylglyoxal and arylglyoxals with electron-withdrawing groups such as chloro and bromo worked as well as substrates with electron-donating substituents such as methoxy group in the Willgerodt–Kindler reaction with heterocyclic amines 2a-2c. Due to the low nucleophilicity and steric repulsion of diethylamine 2d and benzylamine 2e, the Willgerodt–Kindler reaction did not occur, and instead a non-identified mixture (Entries 4 and 5) was obtained. Also, the Willgerodt–Kindler reaction of phenylglyoxal 1a with aniline 2f under similar conditions was investigated, in which corresponding imine 4 was obtained without incorporation of sulfur in the reaction (Entry 6). In the case of 4-nitrophenylglyoxal 1h, a polymeric material was produced, which can be attributed to the reduction of nitro group to amine in the presence of elemental sulfur and then reaction with carbonyl groups of other arylglyoxal molecules (Entry 20).

In a plausible mechanism for the Willgerodt–Kindler reaction (Scheme 2) of **1a** with **2a** and elemental sulfur in water, the insoluble solid **1a** in water rapidly formed a white suspension by the addition of **2a**, leading to the conclusion that rapid equilibria between **1a** and iminium salts **5** were established. Nucleophilic addition of **2a** to sulfur generated piperidinium sulfide **6** which subsequently lost S_7 to give intermediate **6**. Intermediate **7** was then produced by nucleophilic addition of **a** molecule of piperidine (Scheme 2).



Table 1. Willgerodt-Kindler reaction of arylglyoxal hydrates with amines in water.

(Continued)

Table 1. Continued



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(Continued)





Notes: "Yields refer to isolated products.

^bNon-identified mixture were obtained.

^cA polymeric material was produced.



Scheme 2. Plausible mechanism for the Willgerodt–Kindler reaction of **1a** with **2a** and sulfur in water.

Also, as shown in Scheme 3, the chemoselectivity of the Willgerodt–Kindler reaction of **1a** with **2a** and sulfur in water at 80°C was investigated by carrying out the reaction in the presence of an equimolar amount of either benzaldehyde **8** or acetophenone **9**, and after 1 h, only **3a** was isolated and **8** or **9** were recovered without any change.

3. Conclusion

In conclusion, we have reported a simple and efficient approach for the synthesis of α -ketothioamides *via* the Willgerodt-Kindler reaction of arylglyoxal hydrates with secondary



Scheme 3. Chemoselectivity of the Willgerodt-Kindler reaction.

amines and elemental sulfur in water. Arylglyoxals with electron-donating and electronwithdrawing groups worked equally well in the Willgerodt–Kindler reaction. Heterocyclic secondary amines afforded the corresponding α -ketothioamides in good to high yields, while reactions with secondary acyclic and primary amines produced a non-identified mixture. Also, the reaction shows excellent chemoselectivity toward phenylglyoxal in preference to benzaldehyde and acetophenone.

4. Experimental

Melting points were determined with an electrothermal 9100 apparatus. Fourier transform infrared (FT-IR) spectra were recorded on a Unicam/Mattson 8700 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker 400 spectrometer in CDCl₃. The chemicals used in this work were purchased from Fluka and Mreck and were used without further purification. Arylglyoxal hydrates were prepared by the oxidation of acetophenones using SeO₂ in refluxing dioxane in the presence of water as done in the Riley *et al.* (47) method.

4.1. General procedure for the Willgerodt-Kindler reaction

Arylglyoxal hydrate 1 (1 mmol) was added to a mixture of amine 2 (2 mmol) and elemental sulfur (2 mmol) in 2 ml water and heated at 80°C for 0.6–1 h. After completion of the reaction, monitored by TLC (*n*-hexane/EtOAc: 7/3), the obtained solid was removed by filtration. The unreacted sulfur was removed by adding 2 ml EtOH, heating and then hot filtration. By cooling, corresponding α -ketothioamides were crystallized and separated by simple filtration. Further purification for elemental analysis was carried out by recrystallization in *n*-hexane or EtOH. In the case of oily products, column chromatography was used for purification. Compounds **3a**, **3b**, **3d**, **3e** and **3h** are known and were characterized using FT-IR, ¹H NMR and ¹³C NMR spectra in comparison with reported ones (*39*, *40*). Unknown compounds were characterized using FT-IR, ¹H NMR, ¹³C NMR and elemental analysis.

4.1.1. 1-Phenyl-2-(piperidin-1-yl)-2-thioxoethanone (3a) (39)

Yellow solid; m.p. 60–62°C, FT-IR (KBr) (ν_{max} cm⁻¹): 3237, 2942 (C–H), 1663 (C=O), 1638 (C=C), 1618, 1506 (C=S), 1441 (CH₂ bending), 1272 (C–O), 1249 (C–N), 1123 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.61–1.68 (2H, m, br, CH₂), 1.77–1.86 (4H, m, CH₂), 3.55–3.58 (2H, m, CH₂–N), 4.27–4.3 (2H, m, CH₂–N), 7.51 (2H, t, ³ J_{HH} = 7.6 Hz, CH_{Ar}), 7.63

 $(1H, t, {}^{3}J_{HH} = 7.6 \text{ Hz}, \text{ CH}_{Ar}), 8.01 (2H, d, {}^{3}J_{HH} = 8.4 \text{ Hz}, \text{ CH}_{Ar}) \text{ ppm. } {}^{13}\text{C} \text{ NMR} (100 \text{ MHz}, \text{CDCl}_{3}): 24.1, 25.4, 26.5, 48.1, 53.0, 128.9, 129.8, 133.4, 134.2, 188.0 (C=O), 194.4 (C=S) \text{ ppm.}$

4.1.2. 2-Morpholino-1-phenyl-2-thioxoethanone (3b) (39)

Yellow Solid; m.p. 114–116°C, FT-IR (KBr) (ν_{max} cm⁻¹): 3110, 2970 (C–H), 1664 (C=O), 1595 (C=C), 1500 (C=S), 1443 (CH₂ bending), 1267 (C–O), 1233 (C–N), 1111 (C=S). ¹H NMR (400 MHz, CDCl₃): 3.62–3.64 (2H, m, CH₂–N), 3.71–3.73 (2H, m, CH₂–N), 3.92–3.95 (2H, m, CH₂–O), 4.34–4.37 (2H, m, CH₂–O), 7.47 (2H, t, ³J_{HH} = 7.6 Hz, CH_{Ar}), 7.57 (1H, t, ³J_{HH} = 7.6 Hz, CH_{Ar}), 8.02 (2H, d, ³J_{HH} = 8.4 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 47.1, 51.9, 66.5, 66.8, 129.2, 130.1, 133.3, 134.5, 187.4 (C=O), 195.7 (C=S) ppm.

4.1.3. 1-Phenyl-2-(pyrrolidin-1-yl)-2-thioxoethanone (3c)

Yellow oil, FT-IR (KBr) (ν_{max} cm⁻¹): 3100, 2971 (C–H), 1665 (C=O), 1620 (C=C), 1501 (C=S), 1449 (CH₂ bending), 1260 (C–N), 1172 (C=S). ¹H NMR (400 MHz, CDCl₃): 2.14–2.04 (4H, m, CH₂), 3.58–3.55 (2H, m, CH₂–N), 3.99–3.96 (2H, m, CH₂–N), 7.50 (2H, t, ³*J*_{HH} = 7.6 Hz, CH_{Ar}), 7.63 (1H, t, ³*J*_{HH} = 7.2 Hz, CH_{Ar}), 8.01 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 23.9, 26.1, 51.1, 51.3, 128.9, 130.1, 132.8, 134.2, 188.8 (C=O), 192.8 (C=S) ppm. Anal. Calcd for C₁₂H₁₃NOS: C, 65.72; H, 5.97; N, 6.39%. Found: C, 65.64; H, 6.01; N, 6.87.

4.1.4. 1-(4-Chlorophenyl)-2-(piperidin-1-yl)-2-thioxoethanone (3d) (39)

Yellow solid; m.p. 108–110°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2940 (C–H), 1665 (C=O), 1586 (C=C), 1506 (C=S), 1445 (CH₂ bending), 1223 (C–N), 1011 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.58–1.72 (2H, m, br., CH₂), 1.80–1.86 (4H, m, CH₂), 3.54–3.57 (2H, m, CH₂–N), 4.25–4.28 (2H, m, CH₂–N), 7.65 (2H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}), 7.88 (2H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}) ppm.¹³C NMR (100 MHz, CDCl₃): 24.1, 25.4, 26.5, 48.1, 53.0, 128.9, 129.8, 133.4, 134.2, 188.0 (C=O), 194.4 (C=S) ppm.

4.1.5. 1-(4-Chlorophenyl)-2-morpholino-2-thioxoethanone (3e) (39)

Yellow solid; m.p. 130–132°C, FT-IR (KBr) (ν_{max} cm⁻¹): 3100, 2990 (C–H), 1655 (C=O), 1617 (C=C), 1568, 1498 (C=S), 1437 (CH₂ bending), 1274 (C–O), 1235 (C–N), 1113 (C=S). ¹H NMR (400 MHz, CDCl₃): 3.62–3.64 (2H, m, CH₂–N), 3.73–3.75 (2H, m, CH₂–N), 3.93–3.95 (2H, m, CH₂–O), 4.34–4.37 (2H, m, CH₂–O), 7.50 (2H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}), 7.97 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}) ppm. ¹³C NMR (400 MHz, CDCl₃): 47.2, 52.0, 66.4, 66.6, 129.4, 131.2, 131.7, 141.1, 186.5 (C=O), 194.9 (C=S) ppm.

4.1.6. 1-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)-2-thioxoethanone (3f)

Brown yellow solid; m.p. 112–114°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2970 (C–H), 1664 (C=O), 1638 (C=C), 1589, 1505 (C=S), 1448 (CH₂ bending), 1263 (C–N), 1087 (C=S), 620 (C–Cl). ¹H NMR (400 MHz, CDCl₃): 2.06–2.20 (4H, m, CH₂), 3.56–3.59 (2H, m, CH₂–N), 4.00–3.96 (2H, m, CH₂–N), 7.48 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}), 7.98 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 23.8, 26.1, 51.2, 51.3, 129.2, 131.4, 131.5, 140.8, 187.0 (C=O), 192.0 (C=S) ppm. Anal. Calcd for C₁₂H₁₂ClNOS: C, 56.80; H, 4.77; N, 5.52%. Found: C, 55.98; H, 4.74; N, 5.03.

4.1.7. 1-(4-Bromophenyl)-2-(piperidin-1-yl)-2-thioxoethanone (3g)

Brown yellow solid; m.p. 119–121°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2932 (C–H), 1663 (C=O), 1583 (C=C), 1505 (C=S), 1445 (CH₂ bending), 1223 (C–N), 1010 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.62–1.66 (2H, m, br, CH₂), 1.76–1.88 (4H, m, br, CH₂), 3.54–3.57 (2H, m, CH₂–N), 4.25–4.28 (2H, m, CH₂–N), 7.65 (2H, d, ³J_{HH} = 8.4 Hz, CH_{Ar}), 7.88 (2H, d, ³J_{HH} = 8.4 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 24.1, 25.4, 26.5, 48.2, 53.1, 129.2, 131.2, 131.9, 140.7, 186.5 (C=O), 193.7 (C=S) ppm. Anal. Calcd for C₁₃H₁₄BrNOS: C, 50.01; H, 4.52; N, 4.49%. Found: C, 50.30; H, 4.51; N, 4.59.

4.1.8. 1-(4-Bromophenyl)-2-morpholino-2-thioxoethanone (3h) (40)

Yellow solid; m.p. 115–117°C, FT-IR (KBr) (ν_{max} cm⁻¹): 3200, 2990 (C–H), 1636 (C=O), 1621 (C=C), 1584, 1503 (C=S), 1435 (CH₂ bending), 1271 (C–O), 1231 (C–N), 1112 (C=S). ¹H NMR (400 MHz, CDCl₃): 3.61–3.64 (2H, m, CH₂–N), 3.72–3.75 (2H, m, CH₂–N), 3.92–3.95 (2H, m, CH₂–O), 4.34–4.37 (2H, m, CH₂–O), 7.67 (2H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}), 7.89 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}) ppm. ¹³C NMR (400 MHz, CDCl₃): 47.2, 52.0, 66.4, 66.5, 129.4, 131.2, 132.3, 141.2, 188.1 (C=O), 193.8 (C=S) ppm.

4.1.9. 1-(4-Bromophenyl)-2-(pyrrolidin-1-yl)-2-thioxoethanone (3i)

Yellow solid; m.p. 102–104°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2990, 2923 (C–H), 1638 (C=O), 1613 (C=C), 1498 (C=S), 1453 (CH₂ bending), 1260 (C–N), 1080 (C=S). ¹H NMR (400 MHz, CDCl₃): 2.07–2.16 (4H, m, CH₂), 3.55–3.58 (2H, m, CH₂–N), 3.96–3.99 (2H, m, CH₂–N), 7.63–7.66 (2H, m, CH_{Ar}), 7.88–7.93 (2H, m, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 23.8, 26.1, 51.2, 51.3, 129.7, 131.6, 131.8, 132.2, 187.5 (C=O), 191.9 (C=S) ppm. Anal. Calcd for C₁₂H₁₂BrNOS: C, 48.33; H, 4.06; N, 4.70%. Found: C, 47.88; H, 4.09; N, 5.01.

4.1.10. 1-(4-Biphenyl)-2-(piperidin-1-yl)-2-thioxoethanone (3j)

Yellow solid; m.p. 104–106°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2936 (C–H), 1659 (C=O), 1601 (C=C), 1503 (C=S), 1443 (CH₂ bending), 1226 (C–N), 1131 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.65–1.74 (2H, m, br, CH₂), 1.82–1.88 (4H, m, CH₂), 3.60–3.62 (2H, m, CH₂–N), 4.29–4.32 (2H, m, CH₂–N), 7.44 (1H, t, ³*J*_{HH} = 7.2 Hz, CH_{*ph*}), 7.51 (2H, t, ³*J*_{HH} = 7.4 Hz, CH_{*ph*}), 7.50 (2H, d, ³*J*_{HH} = 7.4 Hz, CH_{*ph*}), 7.73 (2H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}), 8.05 (2H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 24.1, 25.4, 26.5, 48.2, 53.1, 127.4, 127.5, 128.5, 129.0, 130.4, 132.2, 139.7, 147.0, 187.7 (C=O), 194.5 (C=S) ppm. Anal. Calcd for C₁₉H₁₉NOS: C, 73.75; H, 6.19; N, 4.53%. Found: C, 73.25; H, 6.21; N, 4.88.

4.1.11. 1-(4-Biphenyl)-2-(pyrrolidin-1-yl)-2-thioxoethanone (3k)

Orange yellow solid; m.p. 120–122°C, FT-IR (KBr) (ν_{max} cm⁻¹): 3237, 2974 (C–H), 1663 (C=O), 1618 (C=C), 1559, 1503 (C=S), 1449 (CH₂ bending), 1266 (C–N), 1180 (C=S). ¹H NMR (400 MHz, CDCl₃): 2.09–2.16 (4H, m, CH₂), 3.61–3.64 (2H, m, CH₂–N), 3.99–4.03 (2H, m, CH₂–N), 7.45–7.47 (1H, m, CH_{*ph*}), 7.49–7.53 (2H, m, CH_{*ph*}), 7.64–7.66 (2H, m, CH_{*ph*}), 7.72 (2H, d, ³ J_{HH} = 8.4 Hz, CH_{Ar}), 8.10 (2H, d, ³ J_{HH} = 8.4 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 23.9, 26.1, 51.1, 51.3, 127.4, 127.5, 128.5, 129.0, 130.7, 131.6, 139.7, 147.0, 188.5 (C=O), 192.8 (C=S) ppm. Anal. Calcd for C₁₈H₁₇NOS: C, 73.19; H, 5.80; N, 4.74%. Found: C, 73.77; H, 5.83; N, 4.65.

4.1.12. 1-(4-Methoxyphenyl)-2-(piperidin-1-yl)-2-thioxoethanone (31)

Yellow solid; m.p. 83–85°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2939 (C–H), 1653 (C=O), 1593 (C=C), 1511, 1456 (C=S), 1321 (CH₂ bending), 1272 (C–O), 1237 (C–N), 1129 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.60–1.68 (2H, m, br, CH₂), 1.79–1.85 (4H, m, CH₂), 3.52–3.59 (2H, m, br, CH₂–N), 4.24–4.31 (2H, m, br, CH₂–N), 6.97 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}), 7.98 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 24.1, 25.4, 26.5, 48.1, 53.0, 55.6, 114.2, 126.3, 132.3, 164.4, 187.4 (C=O), 194.9 (C=S) ppm. Anal. Calcd for C₁₄H₁₇NO₂S: C, 63.85; H, 6.51; N, 5.32%. Found: C, 63.83; H, 6.51; N, 5.23.

4.1.13. 1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)-2-thioxoethanone (3m)

Brown yellow solid; m.p. 112–114°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2939 (C–H), 1653 (C=O), 1593 (C=C), 1511, 1456 (C=S), 1321 (CH₂ bending), 1272 (C–O), 1237 (C–N), 1129 (C=S). ¹H NMR (400 MHz, CDCl₃): 2.05–2.13 (4H, m, CH₂), 3.55–3.59 (2H, m, CH₂–N), 3.90 (3H, s, OCH₃), 3.96–4.00 (2H, m, CH₂–N), 6.97 (2H, d, ³*J*_{HH} = 9.2 Hz, CH_{Ar}), 8.00 (2H, d, ³*J*_{HH} = 8.8 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 23.9, 26.1, 51.1, 51.2, 55.6, 114.2, 125.7, 132.6, 164.5, 188.1 (C=O), 193.2 (C=S) ppm. Anal. Calcd for C₁₃H₁₅NO₂S: C, 62.62; H, 6.06; N, 5.62%. Found: C, 62.60; H, 6.06; N, 5.77.

4.1.14. 1-(3-Methoxyphenyl)-2-(piperidin-1-yl)-2-thioxoethanone (3n)

Yellow oil, FT-IR (KBr) (ν_{max} cm⁻¹): 2940 (C–H), 1665 (C=O), 1584 (C=C), 1505 (C=S), 1447 (CH₂ bending), 1282 (C–O), 1250 (C–N), 1101 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.61–1.68 (2H, m, br, CH₂), 1.78–1.84 (4H, m, CH₂), 3.54–3.56 (2H, m, CH₂–N), 3.87 (3H, s, OCH₃), 4.24–4.27 (2H, m, CH₂–N), 7.14–7.17 (1H, m, CH_{Ar}), 7.39 (1H, t, ³*J*_{HH} = 8.0 Hz, CH_{Ar}), 7.52–7.57 (2H, m, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 24.1, 25.4, 26.4, 48.1, 53.0, 55.6, 113.3, 120.9, 122.7, 129.9, 134.8, 160.0, 187.8 (C=O), 194.3 (C=S) ppm. Anal. Calcd for C₁₄H₁₇NO₂S: C, 63.85; H, 6.51; N, 5.32%. Found: C, 63.76; H, 6.50; N, 5.18.

4.1.15. 1-(3-Methoxyphenyl)-2-(pyrrolidin-1-yl)-2-thioxoethanone (30)

Yellow solid; m.p. 111–113°C, FT-IR (KBr) (ν_{max} cm⁻¹): 3100, 2990 (C–H), 1644 (C=O), 1615 (C=C), 1515 (C=S), 1274 (C–O), 1245 (C–N), 1035 (C=S). ¹H NMR (400 MHz, CDCl₃): 2.06–2.13 (4H, m, CH₂), 3.56–3.59 (2H, m, CH₂–N), 3.88 (3H, s, OCH₃), 3.96–3.97 (2H, m, CH₂–N), 7.16–7.18 (1H, m, CH_{Ar}), 7.4 (1H, t, ³*J*_{HH} = 8.4 Hz, CH_{Ar}), 7.52–7.58 (2H, m, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 23.9, 26.1, 51.1, 51.3, 55.6, 113.7, 121.0, 123.1, 129.9, 134.2, 160.0, 188.6 (C=O), 192.7 (C=S) ppm. Anal. Calcd for C₁₃H₁₅NO₂S: C, 62.62; H, 6.06; N, 5.62%. Found: C, 62.80; H, 6.18; N, 6.04.

4.1.16. *1-(3,4-Dimethoxyphenyl)-2-(piperidin-1-yl)-2-thioxoethanone (3p)*

Brown yellow solid; m.p. 148–150°C, FT-IR (KBr) (ν_{max} cm⁻¹): 2993, 2947 (C–H), 1652 (C=O), 1618 (C=C), 1586, 1507 (C=S), 1444, (CH₂ bending), 1273 (C–O), 1246 (C–N), 1129 (C=S). ¹H NMR (400 MHz, CDCl₃): 1.60–1.72 (2H, m, br, CH₂), 1.80–1.85 (4H, m, CH₂), 3.53–3.61 (2H, m, br, CH₂–N), 3.96 (3H, s, OCH₃), 3.98 (3H, s, OCH₃), 4.24–4.32 (2H, m, br, CH₂–N), 6.91 (1H, d, ³*J*_{HH} = 8.4 Hz, CH_{Ar}), 7.78 (1H, dd, ³*J*_{HH} = 2.0, 8.4 Hz, CH_{Ar}), 7.63 (1H, d, ³*J*_{HH} = 2.0 Hz, CH_{Ar}) ppm. ¹³C NMR (100 MHz, CDCl₃): 24.1, 25.4, 26.5, 48.2, 53.0, 56.1,

56.2, 110.3, 111.0, 125.5, 126.4, 149.4, 154.2, 187.5 (C=O), 194.8 (C=S) ppm. Anal. Calcd for C₁₅H₁₉NO₃S: C, 61.41; H, 6.53; N, 4.77%. Found: C, 61.39; H, 6.52; N, 4.53.

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