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SOLVENT-FREE CONVERSION OF THIOAMIDES TO THIOESTERS

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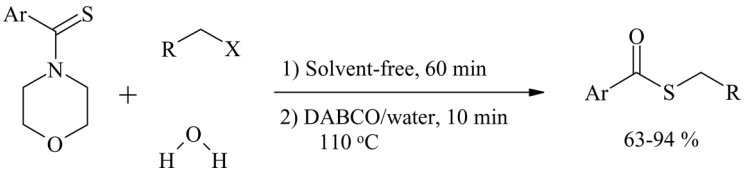
GRAPHICAL ABSTRACT



Abstract *Diverse thioesters were efficiently prepared via the solvent-free reaction of thioamide derivatives with alkyl halides in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO) in small quantities of water and in good to excellent yields.*

Keywords Alkyl halides; S-alkylation; thioamides; thioesters; thiols

INTRODUCTION

Recently, thioesters have attracted considerable interest in organic synthesis because of their distinctive chemical properties compared to oxoesters,[1] and their enhanced reactivity has been employed successfully in a wide range of synthetic organic transformations.[2] Thioesters of coenzyme A (*CoA*) are ubiquitous in all living organisms and play central roles in their metabolism.[3] Also, they exhibit a wide range of biological activities and have considerable applications in drug development[4–8] and industry.[9–11]

Hence, developing a simple and versatile method for the preparation of thioesters is still an urgent need. The most known approach to the synthesis of thioesters is the direct reaction of the corresponding thiols with a suitable acid chloride[12] or acid anhydride.[13–15] Moreover, thioesters have been synthesized by direct reaction of carboxylic acids with thiols and in various reaction conditions and catalysts.[16–18] Thioesters have also been prepared by the reaction of esters[19] or *N*-acylbenzotriazoles[20] with thiols. Recently, *tert*-butyl protected thiols have been utilized for the

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preparation of thioesters.[21] More recently, the *N*-*S* acyl shift mediated by attaching a thiol auxiliary residue to the peptide backbone has been applied for peptide thioester syntheses.[22] This method employs thiols in long reaction times, and the overall yields are not satisfactory (16–31%). Dess–Martin periodinane (DMP)–mediated reaction of thiols and aldehydes is another method for the synthesis of thioesters.[23]

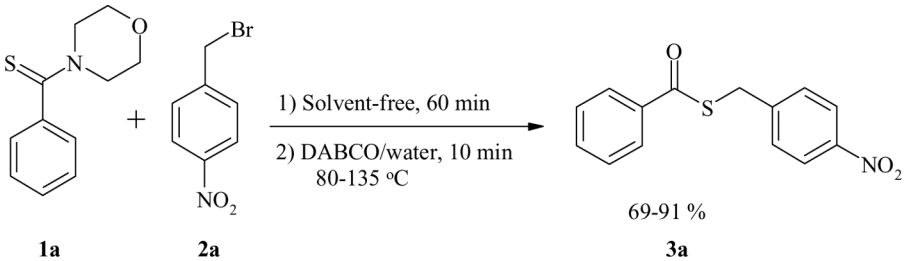
Although most of these approaches provide efficient access to thioesters, they suffer from the use of corrosive reagents, harsh reaction conditions, expensive catalysts or reagents, and unfriendly organic solvents. Nevertheless, the greatest disadvantage of the previously mentioned methods is application of thiols as starting materials, which are very unpleasant and noxious compounds. However, despite the efficiency of the latter protocols, the development of less expensive and environmentally benign reactions is a major goal for organic synthesis. Therefore, designing a single-step and quite ecofriendly method for the synthesis of diverse thioesters without using thiols was the main goal of the present study.

It is well known that thioamides are very prominent building blocks in organic synthesis and particularly in construction of heterocyclic compounds.[24] Recently, we studied the use of tertiary thioamides for thioester synthesis in various solvents.[25] Herein, an efficient and fast method for the preparation of miscellaneous thioesters using tertiary thioamides in solvent-free condition is reported.

The study was started by examining the reaction of thioamide **1a** as a test thioamide starting material, prepared by one of the known methods[26] with 4-nitrobenzyl bromide **2a** and in various reaction conditions to produce the corresponding *S*-4-nitrobenzyl benzothioate **3a** (Scheme 1).

At the outset of our study, a test temperature of 80 °C was chosen for the reaction course. Therefore, the starting thioamide and equimolar amounts of 4-nitrobenzyl bromide were heated to 80 °C for 75 min. Afterward, catalytic amounts of 1, 4-diazabicyclo[2.2.2]octane (DABCO) (5 mol %) in small amounts of water were added to the reaction mixture, and heating was continued for a further 15 min and at the same temperature to produce thioester **3a** in good isolated yield (69%).

Various temperatures were also examined to obtain the best reaction condition, and the screening results indicate that a remarkable yield was achieved in the temperature 110 °C (Table 1). It is also worthwhile to note that increasing the reaction times and temperatures does not lead to an increase in the yield of thioester, and the investigations revealed that in these conditions the reaction mixture was



Scheme 1.

Table 1. Temperature screening in synthesis of thioesters

Entry	Temperature (°C)	Product	Yield[a] (%)
1	80	**3a**	69
2	95	**3a**	83
3	110	**3a**	93
4	130	**3a**	85[b]

[a]Yields refer to isolated products.
[b]Formation of some colored impurities was observed.

contaminated with some colored or tarry materials. A variety of substituted phenyl groups were tolerated on thioamides and reacted with various alkyl halides, leading to different thioesters.

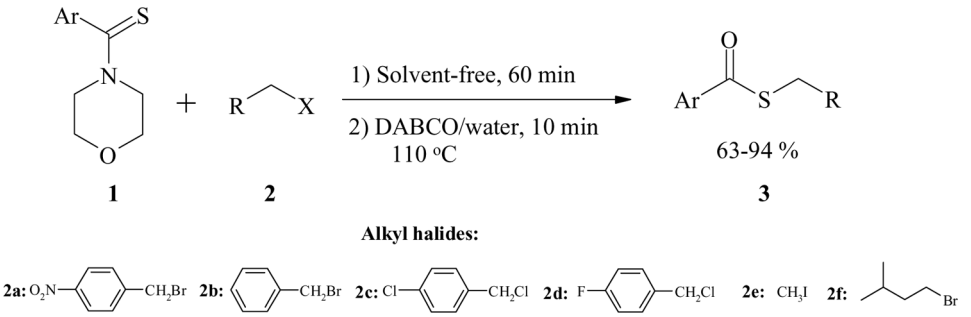
The generality of the method has been demonstrated by the successful synthesis of several thioesters in rather good to excellent yields (63–94%) (Scheme 2), and Table 2 summarizes our results.

These experiments obviously revealed that all kind of alkyl halides (chloride, bromide, and iodide) could be successfully applied in the course of reaction, but better results were obtained with bromomethyl aromatics.

A mechanism is also proposed and shown in Scheme 3. Thioamide **1** first undergoes an *S*-alkylation with the alkyl halide **2** to form thioformamidinium salt **4**, and subsequent hydrolysis catalyzed by DABCO affords the corresponding thioesters **3**.

To assess the feasibility of applying this method on a preparative scale, we carried out the reaction of thiobenzamide **1a** with 4-nitrobenzyl bromide **2a** on a 20-mmol scale. As expected, the reaction proceeded gently, similar to the case on a smaller scale (Table 2, entry 1), and the desired *S*-4-nitrobenzyl benzothioate **3a** was obtained in 90% isolated yield.

In addition to the simplicity of the method, good yields, and easy workup, the salient futures of this methodology lie in the fact that the reactions are carried out in solvent-free conditions and in short times. Furthermore, purification of thioester products is achieved with simple recrystallization in MeOH. Moreover, the method is compatible with many substituents such as halogen, alkoxy, dialkylamino, and



Scheme 2.

Table 2. Efficient synthesis of thioesters in solvent-free conditions[a]

Entry	1	Ar	2	Product 3[b]	Yield[c]
1	**a**	Ph	**2a**	**3a**	93
2	**b**	4-Tolyl	**2a**	**3b**	93
3	**c**	4-Cl-Ph	**2a**	**3c**	90
4	**d**	4-Me2N-Ph	**2e**	**3d**	66[d,e]
5	**d**	4-Me2N-Ph	**2f**	**3e**	63[d]
6	**d**	4-Me2N-Ph	**2b**	**3f**	94
7	**e**	4-biphenyl	**2b**	**3g**	89
8	**e**	4-biphenyl	**2a**	**3h**	91
9	**f**	2-naphthyl	**2b**	**3i**	90
10	**f**	2-naphthyl	**2a**	**3j**	91
11	**f**	2-naphthyl	**2c**	**3k**	72
12	**g**	4-is-Pr-Ph	**2a**	**3l**	92
13	**h**	3,4-di-MeO-Ph	**2a**	**3m**	88
14	**i**	2-quinolyl	**2e**	**3n**	64[d,e]
15	**i**	2-quinolyl	**2d**	**3o**	67
16	**i**	2-quinolyl	**2b**	**3p**	89

[a]Thioamide derivative (1 mmol), alkyl halide (1 mmol), DABCO (0.05 mmol), temperature = 110 °C, time = 70 min.

[b]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

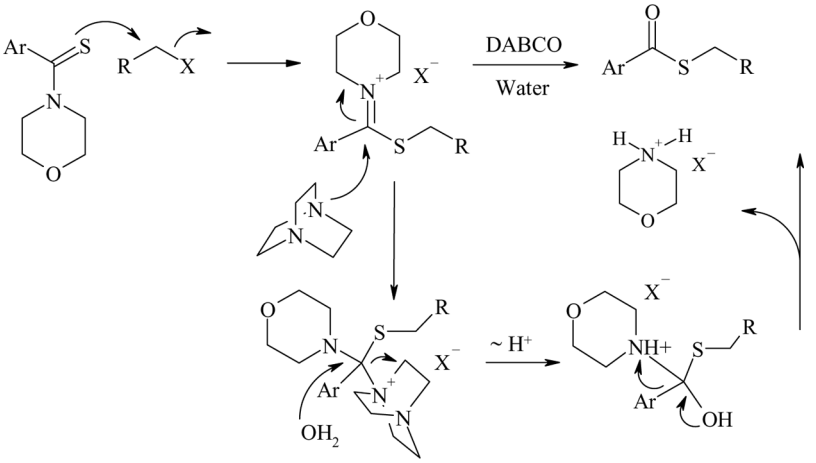
[c]All yields refer to pure isolated products.

[d]Colorless to pale yellow liquids, which were crystallized very slowly (12–24 h), isolated by flash chromatography (silica gel, EtOAc–Hexane, 1:8).

[e]An excess amount of CH_3I was added (2 mmol).

nitro in the thioamide substrates and works efficiently with both types of alkyl and aralkyl halides.

In conclusion, the methodology reported herein is expected to be a genuinely general route for the efficient synthesis of a wide range of thioesters in solvent-free



Scheme 3.

conditions. Apart from being an environmentally benign reaction, the method profits from the use of cheap and safe starting materials and avoids from the use of very unpleasant and noxious thiols as well as corrosive acid chlorides in the course of reaction.

EXPERIMENTAL

General Experimental Information

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Starting thioamides were readily obtained by the Willgerodt–Kindler reaction of the corresponding benzaldehydes.[26] Thin-layer chromatography (TLC) was performed on ultraviolet (UV)–active aluminum-backed plates of silica gel (TLC silica gel $60\,F_{254}$). Flash chromatography was performed using silica gel (60 Å, 230–400 mesh) with reagent-grade solvents. NMR spectra were recorded at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) referenced to an internal standard [tetramethylsilane (TMS)] or residual solvent protons and signals are reported in ppm (δ). Low-resolution mass spectra (LRMS) were recorded on Bell and Howell 21–490 spectrometers. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Fourier transform (FT)–IR spectra were obtained on a Perkin-Elmer Spectrum 1000 with samples loaded as KBr discs.

Typical Experimental Procedure

In a 5-ml round-bottom flask, thioamide **1** (2 mmol) and alkyl halide **2** (2 mmol) were added. The reaction mixture was heated at 110 °C for 75 min. Thereafter, DABCO (0.1 mmol, 11.2 mg) in water (0.5 ml) was added, and heating was continued for a further 15 min at the same temperature. After cooling to room temperature, an oily residue was left, which slowly solidified. Then, the solid was filtered and washed with water (2×10 ml). Finally, the solid compound was recrystallized from MeOH (in some cases with MeOH-$CHCl_3$) to afford pure thioesters as white or pale yellow needles.

Spectroscopic Data for Compounds 3a–3p

Compound 3a. Mp (MeOH): 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, $J = 8.8$ Hz, 2H), 7.97 (d, d, $J = 8.5$ Hz, $J = 1.3$ Hz, 2H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.58 (d, $J = 8.8$, 2H), 7.48 (t, $J = 7.5$, 2H), 4.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 147.1, 145.6, 136.3, 133.9, 129.9, 128.8, 127.4, 124.0, 32.6. Anal. calcd. for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.48; H, 3.95; N, 5.23; 11.81.

Compound 3b. Mp (MeOH): 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, $J = 8.9$ Hz, 2H), 7.86 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 8.9$ Hz, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 4.36 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 147.1, 145.8, 144.9, 133.7, 130.1, 129.2, 127.5, 123.8, 32.4; Anal. calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.53; H, 4.43; N, 5.01; S, 11.28.

Compound 3c. Mp (MeOH): 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, $J = 8.7$ Hz, 2H), 7.91 (d, $J = 8.6$ Hz, 2H), 7.57 (d, $J = 8.7$ Hz, 2H), 7.45 (d, $J = 8.6$ Hz, 2H), 4.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.3, 147.2, 145.2, 140.3, 134.6, 129.9, 129.1, 128.7, 123.9, 32.6. Anal. calcd. for $C_{14}H_{10}ClNO_3S$: C, 54.64; H, 3.28; N, 4.55; S, 10.42. Found: C, 54.45; H, 3.19; N, 4.71; S, 10.61.

Compound 3d[1]. Mp (MeOH): 54–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, $J = 9.0$ Hz, 2H), 6.67 (d, $J = 9.0$ Hz, 2H), 3.06 (s, 6H), 2.45 (s, 3H).

Compound 3e. Mp (MeOH-$CHCl_3$): 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, $J = 9.0$ Hz, 2H), 7.41 (d, $J = 7.1$ Hz, 2H), 7.33 (t, $J = 7.3$ Hz, 2H), 7.26 (t, $J = 7.3$ Hz, 1H), 6.71 (d, $J = 9.0$ Hz, 2H), 4.32 (s, 2H), 3.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 153.6, 138.3, 129.4, 129.0, 128.6, 127.1, 126.4, 110.9, 40.2, 32.9. Anal. calcd. for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16; S, 11.82. Found: C, 70.64; H, 6.12; N, 5.21; S, 11.94.

Compound 3f. Mp (MeOH): 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, $J = 8.3$ Hz, 2H), 7.71 (d, $J = 8.3$ Hz, 2H), 7.66 (d, $J = 7.3$ Hz, 2H), 7.51 (d, $J = 7.4$ Hz, 2H), 7.43–7.46 (m, 3H), 7.38 (t, $J = 7.4$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 1H), 4.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 146.2, 139.8, 137.6, 135.5, 129.1, 129.0, 128.9, 128.7, 128.4, 127.9, 127.4, 127.3, 33.4. Anal. calcd. for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 78.77; H, 5.11; S, 10.76.

Compound 3g. Mp (MeOH): 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, $J = 8.7$ Hz, 2.H), 8.05 (d, $J = 8.5$ Hz, 2H), 7.71 (d, 8.5 Hz, 2H), 7.64 (d, $J = 5.2$ Hz, 2H), 7.59 (d, $J = 8.7$ Hz, 2H), 7.50 (t, $J = 6.8$, 2H), 7.44 (t, $J = 7.3$, 1H), 4.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 147.1, 146.6, 145.6, 139.6, 134.9, 129.9, 129.0, 128.5, 128.0, 127.6, 127.3, 123.9, 32.6. Anal. calcd. for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.33; N, 4.01; S, 9.18. Found: C, 68.61; H, 4.14; N, 4.11; S, 9.30.

Compound 3h. Mp (MeOH): 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.04 (d, d, $J = 8.6$ Hz, $J = 1.5$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.90 (t, $J = 8.3$ Hz, 2H), 7.56–7.64 (m, 2H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.31 (t, $J = 7.1$ Hz, 1H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 137.6, 135.8, 134.1, 132.5, 129.6, 129.1, 128.8, 128.7, 128.6, 127.8, 127.4, 127.0, 125.9, 123.2, 33.5. Anal. calcd. for $C_{18}H_{14}OS$: C, 77.66; H, 5.07; S, 11.52. Found: C, 77.55; H, 5.01; S, 11.65.

Compound 3i. Mp (MeOH): 127–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.20 (d, $J = 8.6$ Hz, 2H), 7.99 (t, $J = 9.6$ Hz, 2H), 7.90 (t, $J = 8.3$ Hz, 2H), 7.57–7.65 (m, 4H), 4.43 (s 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 147.2, 145.6, 136.0, 133.6, 132.4, 129.9, 129.6, 129.1, 128.8, 128.7, 127.9, 127.1, 123.9, 123.0, 32.7. Anal. calcd. for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.33; S, 9.92 Found: C, 66.61; H, 3.98; N, 4.45; S, 10.02.

Compound 3j. Mp (MeOH): 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H) 8.02 (d, d, $J = 8.6$ Hz, $J = 1.7$ Hz, 1H), 8.97 (d, $J = 8.0$ Hz, 1H), 7.90 (t, $J = 8.3$ Hz, 2H), 7.56–7.64 (m, 2H), 7.40 (t, $J = 4.6$ Hz, 2H), 7.04 (t, $J = 8.7$ Hz,

2H), 4.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 163.3, 160.9, 135.8, 134.0, 130.7, 130.6, 129.6, 128.8, 128.6, 127.8, 127.0, 123.1, 115.7, 115.4, 32.7.

Compound 3k. Mp (MeOH): 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, $J = 9.3$ Hz, 2H), 7.91 (d, $J = 8.3$ Hz, 2H), 7.57 (d, $J = 8.7$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 4.37 (s, 2H), 2.97 (sep, $J = 6.9$ Hz, 1H), 1.28 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 155.6, 147.1, 145.8, 134.1, 129.8, 127.6, 126.9, 123.8, 34.3, 32.4, 32.6. Anal. calcd. for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.62; H, 5.32; N, 4.60; S, 10.29.

Compound 3l. Mp (MeOH): 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, $J = 8.6$ Hz, 2H), 7.63 (d, d, $J = 8.5$ Hz, $J = 1.9$ Hz, 1H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.44 (d, $J = 1.9$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 4.34 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 153.8, 149.0, 147.1, 145.8, 130.0, 129.2, 123.8, 122.0, 110.3, 109.4, 56.2, 56.0, 32.5. Anal. calcd. for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20; S, 9.62. Found: C, 57.57; H, 4.41; N, 4.42; S, 9.75.

Compound 3m[2]. Mp (MeOH): 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, $J = 8.6$ Hz, 1H), 8.24 (d, $J = 8.6$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.78 (t, $J = 7.1$ Hz, 1H), 7.63 (t, $J = 7.1$ Hz, 1H), 2.49 (s, 3H).

Compound 3n. Mp (MeOH): 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, $J = 8.5$ Hz, 1H), 8.23 (d, $J = 8.5$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.87 (d, $J = 10.3$ Hz, 1H), 7.81 (t, d, $J = 8.4$ Hz, $J = 1.3$ Hz, 1H), 7.67 (t, $J = 7.9$ Hz, 1H), 7.42 (t, d, $J = 5.4$ Hz, $J = 3.2$ Hz, 2H), 7.02 (t, $J = 8.7$ Hz, 2H), 4.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 163.2, 160.8, 151.3, 147.0, 137.6, 130.8, 130.7, 130.4, 128.8, 127.7, 117.1, 115.6, 115.3, 32.6. Anal. calcd. for $C_{17}H_{12}FNOS$: C, 68.67; H, 4.07; N, 4.71; S, 10.78. Found: C, 68.55; H, 4.14; N, 4.84; S, 10.89.

Compound 3o. Mp (MeOH): 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, $J = 8.5$ Hz, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.89 (d, $J = 8.0$, 1H), 7.80 (t, d, $J = 8.4$ Hz, 1.4 Hz, 1H), 7.66 (t, d, $J = 7.0$ Hz, $J = 1.1$ Hz, 1H), 7.45 (d, $J = 7.0$ Hz, 2H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.27 (t, $J = 7.0$ Hz, 1H), 4.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 151.5, 147.1, 137.6, 137.5, 130.4, 130.2, 129.6, 129.1, 128.8, 128.6, 127.7, 127.2, 117.1, 33.4. Anal. calcd. for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01; S, 11.48. Found: C, 72.91; H, 4.56; N, 5.09; S, 11.57.

Compound 3p. Mp (MeOH): 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, $J = 8.8$ Hz, 2H), 6.64 (d, $J = 8.8$ Hz, 2H), 3.06 (s, 6H), 3.05 (t, $J = 8.0$ Hz, 2H), 1.73 (sep, $J = 6.4$ Hz, 1H), 1.54–1.59 (m, 2H), 0.95 (d, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 153.6, 129.2, 124.9, 110.6, 40.0, 38.8, 27.7, 26.7, 22.3. Anal. calcd. for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57; S, 12.76. Found: C, 68.65; H, 8.56; N, 5.79; S, 12.83.

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