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One-pot synthesis of functionalized thioureas by reaction of benzoyl isothiocyanates, secondary amines, and alkyl propiolates

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Abstract An efficient one-pot synthesis of functionalized thioureas is described *via* three-component reaction of benzoyl isothiocyanates, secondary amines, and alkyl propiolates in the presence of triphenylphosphine (20 mol%).

Keywords Benzoyl isothiocyanate; Activated acetylenes; Secondary amines; Triphenylphosphine; Three-component reaction.

Introduction

Thiourea and its derivatives are biologically important compounds and are useful fungicides, herbicides, and antibacterial agents [1, 2]. There are several reports on the synthesis of thioureas, which include hazardous and toxic procedures [3, 4]. For example, thioureas have been synthesized by the reaction of primary and secondary amines with thiophosgene or isothiocyanates [5–7], which are hazardous protocols. Therefore, safer, non-toxic, and user-friendly procedures to synthesize thioureas are still required [8].

Zwitterionic species often result from addition of nucleophiles to activated alkynes. Triphenylphosphine (Ph_3P) has been the most studied nucleophilic species. As early as 1961, *Tebby* observed that the addition of Ph_3P to various activated alkynes like dibenzoylacetylene, dicyanoacetylene, or dimethyl acetylenedicarboxylate (*DMAD*) generates zwitterionic intermediates [9]. The chemistry of these intermediates has been studied in detail [10, 11]. As part of our current studies on thioureas [12], we report an efficient synthesis of functionalized thioureas through the reaction of alkyl propiolates **1**, secondary amines **2**, and benzoyl isothiocyanates **3** in the presence of Ph_3P (Scheme 1).

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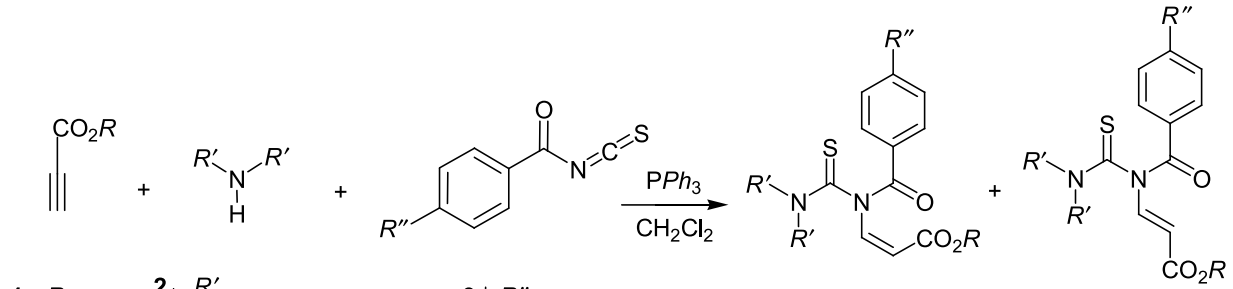
Results and discussion

The above three-component reaction leads to tetrasubstituted thioureas **4** in 70–90% yields. Structures of compounds **4a**–**4g** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H and ^{13}C NMR spectra of **4a**–**4g** are consistent with the presence of two geometrical isomers, the (*Z*) isomer being the major one. The (*Z*) and (*E*) isomers were readily identified by the value of the coupling constant for their olefinic protons. The $^3J_{HH}$ value for (*Z*)-**4** was 10.1–10.5 Hz, while the $^3J_{HH}$ for (*E*)-**4** was 15.0–15.6 Hz. The ^{13}C NMR spectrum of (*E*)-**4a** shows thiocarbonyl ($\delta = 172.1$ ppm), carbonyl ($\delta = 164.4$ and 168.2 ppm), and olefinic ($\delta = 120.6$ and 140.0 ppm) carbons.

A tentative mechanism for this transformation is proposed in Scheme 2. It is concievable that the initial event is the formation of a 1,3-dipolar intermediate **6** from Ph_3P and the acetylenic ester, which



1	R
a	*Me*
b	*Et*

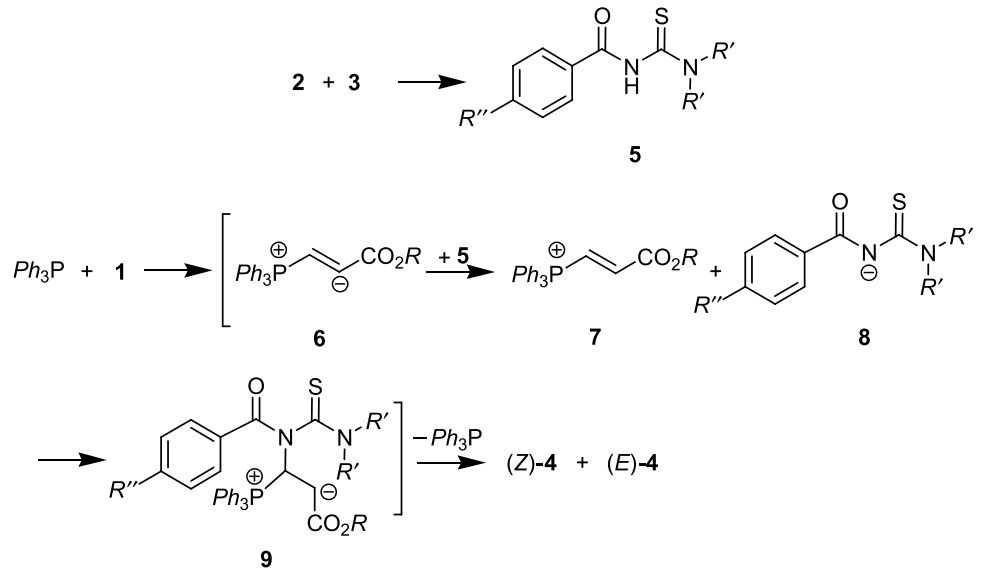
2	R′
a	*Et*
b	$(CH_2)_4$
c	$(CH_2)_4$
d	$(CH_2)_2O(CH_2)_2$

3	R″
a	H
b	Br

(*Z*)-**4** (*E*)-**4**

4	R″	R′	R	Yield/%	*Z*/*E*
a	H	C_2H_5	*Et*	85	3
b	H	C_2H_5	*Me*	80	2
c	H	$(CH_2)_5$	*Et*	90	3.8
d	H	$(CH_2)_5$	*Me*	87	5.8
e	Br	$(CH_2)_5$	*Et*	75	2
f	H	$(CH_2)_4$	*Et*	80	4
g	H	$(CH_2)_2O(CH_2)_2$	*Me*	90	3

Scheme 1



Scheme 2

is subsequently protonated by the benzoyl thiourea **5**, generated from addition of amine **2** to aroyl isothiocyanate **3**. Nucleophilic attack of the nitrogen atom of the conjugate base **8** to the vinylphosphonium cation **7** leads to ylide **9**, which is converted to **4** by elimination of Ph_3P (Scheme 2).

In conclusion, we described a convenient route to tetrasubstituted thioureas from the one-pot three-component reaction of benzoyl isothiocyanates, secondary amines, and alkyl propiolates, in the presence of Ph_3P. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present procedure makes it an interesting alternative to other approaches.

Experimental

Compounds **1**–**3** were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 ap-

paratus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

General procedure for the prepration of compounds ***4***

To a stirred solution of 2 mmol **3** in 10 cm^3 CH_2Cl_2 were added 2 mmol **2**. After 45 min, a solution of 2 mmol alkyl propiolate in 5 cm^3 CH_2Cl_2 was added slowly. Then, a solution of 0.11 g Ph_3P (20 mol%) in 10 cm^3 CH_2Cl_2 was added drop-wise at r.t. to the reaction mixture and allowed to stand for 24 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) column chromatography using *n*-hexane: *Et*OA*c* (1:1) mixture as eluent.

(Z)- and (E)-Ethyl 3-{[benzoyl(diethylamino)carbothioyl]-amino}-2-propenoate (**4a**, $C_{17}H_{22}N_2O_3S$)

Pale yellow oil; yield: 0.57 g (85%); IR (KBr): $\bar{\nu} = 1717$, 1540, 1449, 874, 715 cm^{-1}; EI-MS: m/z (%) = 334 (M^+, 5), 305 (50), 289 (66), 262 (28), 261 (64), 229 (85), 105 (100), 45 (43), 29 (60); (*Z*)-**4a** (75%): ^{1}H NMR: $\delta = 0.98$ (t, $^3J = 7.1$ Hz, 2*Me*), 1.29 (t, $^3J = 7.4$ Hz, *Me*), 3.65 (q, $^3J = 7.1$ Hz, $2CH_2$), 4.19 (q, $^3J = 7.1$ Hz, OCH_2), 5.88 (d, $^3J = 10.5$ Hz, CH), 7.12 (d, $^3J = 10.5$ Hz, CH), 7.39–7.51 (m, 3CH), 8.11 (dd, $^3J = 9.2$, $^4J = 1.4$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.6$ (2*Me*), 14.6 (*Me*), 46.2 ($2CH_2$), 61.1 (OCH_2), 116.3 (CH), 128.5 (2CH), 129.7 (2CH), 131.9 (CH), 132.9 (C), 141.0 (N–CH), 165.2 (C=O), 166.6 (C=O), 170.9 (C=S) ppm; (*E*)-**4a** (25%): ^{1}H NMR: $\delta = 0.91$ (t, $^3J = 7.4$ Hz, 2*Me*), 1.27 (t, $^3J = 7.5$ Hz, *Me*), 3.62 (q, $^3J = 7.1$ Hz, $2CH_2$), 3.95 (q, $^3J = 7.1$ Hz, OCH_2), 6.00 (d, $^3J = 15.6$ Hz, CH), 7.47 (d, $^3J = 15.6$ Hz, CH), 7.39–7.51 (m, 3CH), 8.11 (dd, $^3J = 9.2$, $^4J = 1.4$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 11.4$ (2*Me*), 14.2 (*Me*), 46.1 ($2CH_2$), 60.8 (OCH_2), 120.6 (CH), 128.4 (2CH), 130.3 (2CH), 132.1 (CH), 133.7 (C), 140.0 (N–CH), 164.4 (C=O), 168.2 (C=O), 172.1 (C=S) ppm.

(Z)- and (E)-Methyl 3-{[benzoyl(diethylamino)carbothioyl]-amino}-2-propenoate (**4b**, $C_{16}H_{20}N_2O_3S$)

Pale yellow oil; yield: 0.51 g (80%); IR (KBr): $\bar{\nu} = 1701$, 1596, 1419, 931, 772 cm^{-1}; EI-MS: m/z (%) = 320 (M^+, 7), 305 (60), 289 (60), 261 (74), 248 (75), 215 (85), 105 (100), 29 (65), 15 (32); (*Z*)-**4b** (67%): IR (KBr): ^{1}H NMR: $\delta = 0.95$ (t, $^3J = 7.4$ Hz, 2*Me*), 3.72 (s, O*Me*), 3.76 (q, $^3J = 7.1$ Hz, $2CH_2$), 5.97 (d, $^3J = 10.4$ Hz, CH), 7.23 (d, $^3J = 10.4$ Hz, CH), 7.43–7.78 (m, 3CH), 8.01 (dd, $^3J = 8.1$, $^4J = 1.3$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.8$ (2*Me*), 45.9 ($2CH_2$), 51.4 (O*Me*), 115.3 (CH), 128.4 (2CH), 130.8 (2CH), 131.9 (CH), 142.1 (N–CH), 161.5 (C=O), 166.5 (C=O), 171.6 (C=S) ppm; (*E*)-**4b** (33%): ^{1}H NMR: $\delta = 0.91$ (t, $^3J = 7.4$ Hz, 2*Me*), 3.50 (s, O*Me*), 3.73 (q, $^3J = 7.1$ Hz, $2CH_2$), 6.07 (d, $^3J = 15.6$ Hz, CH), 7.45 (d, $^3J = 15.6$ Hz, CH), 7.43–7.78 (m, 3CH), 8.01 (dd, $^3J = 8.1$, $^4J = 1.3$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.0$ (2*Me*), 43.2 ($2CH_2$), 51.2 (O*Me*), 116.0 (CH), 128.1 (2CH), 130.2 (2CH), 132.4 (CH), 139.8 (C), 141.0 (N–CH), 160.5 (C=O), 165.3 (C=O), 170.8 (C=S) ppm.

(Z)- and (E)-Ethyl 3-[benzoyl(1-piperidylcarbothioyl)-amino]-2-propenoate (**4c**, $C_{18}H_{22}N_2O_3S$)

Pale yellow oil; yield: 0.62 g (90%); IR (KBr): $\bar{\nu} = 1736$, 1553, 1422, 880, 719 cm^{-1}; EI-MS: m/z (%) = 346 (M^+, 10), 317 (15), 301 (56), 273 (34), 262 (80), 241 (72), 105 (100), 45 (84), 29 (57); (*Z*)-**4c** (78%): ^{1}H NMR: $\delta = 1.30$ (t, $^3J = 7.1$ Hz, *Me*), 1.70–1.73 (m, $3CH_2$), 3.74–3.77 (m, $2CH_2$), 4.22 (q, $^3J = 7.1$ Hz, OCH_2), 5.94 (d, $^3J = 10.1$ Hz, CH), 7.43 (d, $^3J = 10.1$ Hz, CH), 7.40–7.57 (m, 3CH), 8.13 (dd, $^3J = 8.8$, $^4J = 1.8$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 14.7$ (*Me*), 24.5 ($2CH_2$), 26.2 (CH_2), 50.3 ($2CH_2$), 61.1 (OCH_2), 116.2 (CH), 128.5 (2CH), 129.8 (2CH), 132.1 (CH), 136.9 (C), 141.3 (N–CH), 165.3 (C=O), 166.8 (C=O), 171.4 (C=S) ppm; (*E*)-**4c** (22%): ^{1}H NMR: $\delta = 1.08$ (3H, t, $^3J = 7.1$ Hz, *Me*), 1.66–1.69 (6H, m, $3CH_2$), 3.50–3.53 (4H, m, $2CH_2$), 4.04 (2H, q, $^3J = 7.1$ Hz, OCH_2), 6.03 (1H, d, $^3J = 15.6$ Hz, CH), 7.53 (1H, d, $^3J = 15.6$ Hz, CH), 7.40–7.57 (3H, m, 3CH), 8.13 (2H, dd, $^3J = 8.8$, $^4J = 1.8$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 14.3$ (*Me*), 24.6 ($2CH_2$), 26.3 (CH_2), 50.2 ($2CH_2$), 60.9 (OCH_2), 119.4 (CH), 128.4 (2CH), 129.8 (2CH), 131.5 (CH), 136.7 (C), 140.5 (N–CH), 165.4 (C=O), 166.5 (C=O), 171.5 (C=S) ppm.

(Z)- and (E)-Methyl 3-[benzoyl(1-piperidylcarbothioyl)-amino]-2-propenoate (**4d**, $C_{17}H_{20}N_2O_3S$)

Pale yellow oil; yield: 0.58 g (87%); IR (KBr): $\bar{\nu} = 1733$, 1541, 1435, 805, 706 cm^{-1}; EI-MS: m/z (%) = 332 (M^+, 8), 317 (12), 301 (46), 273 (74), 248 (54), 227 (65), 105 (100), 31 (74), 15 (54); (*Z*)-**4d** (83%): ^{1}H NMR: $\delta = 1.71$–174 (m, $3CH_2$), 3.72 (s, O*Me*), 3.80–3.83 (m, $2CH_2$), 6.02 (d, $^3J = 10.2$ Hz, CH), 7.51 (d, $^3J = 10.2$ Hz, CH), 7.43–7.60 (m, 3CH), 8.09 (dd, $^3J = 8.7$ Hz, $^4J = 2.8$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 24.4$ ($2CH_2$), 24.5 (CH_2), 49.9 ($2CH_2$), 51.3 (O*Me*), 115.2 (CH), 128.4 (2CH), 128.7 (2CH), 129.5 (CH), 136.8 (C), 142.5 (N–CH), 162.8 (C=O), 166.8 (C=O), 171.4 (C=S) ppm; (*E*)-**4d** (17%): ^{1}H NMR: $\delta = 1.60$–1.64 (m, $3CH_2$), 3.48–3.51 (m, $2CH_2$), 3.71 (s, O*Me*), 6.08 (d, $^3J = 15.5$ Hz, CH), 7.71 (d, $^3J = 15.5$ Hz, CH), 7.43–7.60 (m, 3CH), 7.97 (dd, $^3J = 8.7$, $^4J = 2.8$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 24.2$ ($2CH_2$), 24.1 (CH_2), 48.1 ($2CH_2$), 51.6 (O*Me*), 116.5 (CH), 128.3 (2CH), 128.5 (2CH), 129.7 (CH), 136.7 (C), 141.4 (N–CH), 161.3 (C=O), 166.3 (C=O), 171.4 (C=S) ppm.

*(Z)- and (E)-Ethyl 3-[(4-bromobenzoyl)(1-piperidylcarbothioyl)amino]-2-propenoate (***4e**, $C_{18}H_{21}BrN_2O_3S$)

Yellow oil; yield: 0.64 g (75%); IR (KBr): $\bar{\nu} = 1699$, 1538, 1418, 836, 711 cm^{-1}; EI-MS: m/z (%) = 425 (M^+, 4), 396 (9), 390 (15), 380 (58), 352 (84), 341 (67), 285 (90), 140 (34), 84 (100), 45 (64), 29 (57); (*Z*)-**4e** (66%): ^{1}H NMR: $\delta = 1.26$ (t, $^3J = 7.1$ Hz, *Me*), 1.74–1.77 (m, $3CH_2$), 3.83–3.86 (m, $2CH_2$), 4.19 (q, $^3J = 7.1$ Hz, OCH_2), 6.02 (d, $^3J = 10.1$ Hz, CH), 7.40 (d, $^3J = 10.1$ Hz, CH), 7.63 (d, $^3J = 6.7$ Hz, CH), 7.71 (d, $^3J = 8.6$ Hz, CH), 7.87 (d, $^3J = 8.6$ Hz, CH), 8.02 (d, $^3J = 6.7$ Hz, CH) ppm; ^{13}C NMR: $\delta = 14.0$ (*Me*), 24.3 ($2CH_2$), 26.1 (CH_2), 50.1 ($2CH_2$), 60.6 (OCH_2), 115.8 (CH), 126.0 (C), 131.5 (2CH), 131.6 (2CH), 136.5 (C), 141.8 (N–CH), 164.4 (C=O), 166.1 (C=O), 169.9 (C=S) ppm; (*E*)-**4e** (34%): ^{1}H NMR: $\delta = 1.09$ (t, $^3J = 7.1$ Hz, *Me*), 1.74–1.77 (m,

$3CH_2$), 3.83–3.86 (m, $2CH_2$), 4.02 (q, $^3J = 7.1$ Hz, OCH_2), 6.08 (d, $^3J = 15.6$ Hz, CH), 7.53 (d, $^3J = 15.6$ Hz, CH), 7.65 (d, $^3J = 8.1$ Hz, CH), 7.73 (d, $^3J = 7.4$ Hz, CH), 7.86 (d, $^3J = 7.4$ Hz, CH), 8.00 (d, $^3J = 8.1$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.8$ (*Me*), 24.3 ($2CH_2$), 26.1 (CH_2), 50.0 ($2CH_2$), 60.4 (OCH_2), 120.0 (CH), 126.0 (C), 131.5 (2CH), 131.6 (2CH), 136.4 (C), 140.6 (N–CH), 160.6 (C=O), 164.0 (C=O), 170.4 (C=S) ppm.

(Z)- and (E)-Ethyl 3-[benzoyl(1-pyrrolidinylcarbothioyl)-amino]-2-propenoate (**4f**, $C_{17}H_{20}N_2O_3S$)
Pale yellow oil; yield: 0.56 g (85%); IR (KBr): $\bar{\nu} = 1713$, 1556, 1449, 904, 707 cm^{-1}; EI-MS: m/z (%) = 332 (M^+, 5), 303 (5), 287 (66), 262 (64), 259 (64), 227 (85), 105 (100), 45 (84), 29 (68); (*Z*)-**4f** (80%): ^{1}H NMR: $\delta = 1.32$ (t, $^3J = 7.1$ Hz, *Me*), 2.00–2.04 (m, $2CH_2$), 2.64–2.68 (m, $2CH_2$), 4.26 (q, $^3J = 7.1$ Hz, OCH_2), 6.03 (d, $^3J = 10.2$ Hz, CH), 7.94 (d, $^3J = 10.2$ Hz, CH), 7.42–7.45 (m, 3CH), 8.13 (dd, $^3J = 8.2$, $^4J = 1.5$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 14.1$ (*Me*), 25.3 ($2CH_2$), 60.0 ($2CH_2$), 60.6 (OCH_2), 115.5 (CH), 128.3 (2CH), 129.6 (2CH), 131.6 (CH), 137.5 (C), 141.5 (N–CH), 162.0 (C=O), 166.3 (C=O), 169.6 (C=S) ppm; (*E*)-**4f** (20%): ^{1}H NMR: $\delta = 1.16$ (t, $^3J = 7.1$ Hz, *Me*), 2.00–2.04 (m, $2CH_2$), 2.63–2.68 (m, $2CH_2$), 4.11 (q, $^3J = 7.1$ Hz, OCH_2), 6.07 (d, $^3J = 15.0$ Hz, CH), 7.95 (d, $^3J = 15.0$ Hz, CH), 7.38–7.56 (m, 3CH), 8.14 (dd, $^3J = 8.4$, $^4J = 1.6$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 13.9$ (*Me*), 25.5 ($2CH_2$), 60.2 ($2CH_2$), 60.8 (OCH_2), 118.8 (CH), 128.6 (2CH), 129.3 (2CH), 131.8 (CH), 137.7 (C), 140.9 (N–CH), 160.1 (C=O), 164.3 (C=O), 169.0 (C=S) ppm.

(Z)- and (E)-Methyl 3-[benzoyl(morpholin-4-ylcarbothioyl)-amino]-2-propenoate (**4g**, $C_{16}H_{18}N_2O_4S$)
Pale yellow oil; yield: 0.60 g (90%); IR (KBr): $\bar{\nu} = 1732$, 1577, 1447, 801, 696 cm^{-1}; EI-MS: m/z (%) = 334 (M^+, 9); 319 (6), 303 (46), 275 (76), 248 (57), 229 (46), 105 (100), 31 (67), 15 (50); (*Z*)-**4g** (75%): ^{1}H NMR: $\delta = 3.52$–3.58 (m, $2CH_2$), 3.66–3.68 (m, $2CH_2$), 3.81 (s, O*Me*), 6.02 (d, $^3J = 11.8$ Hz, CH), 7.48 (d, $^3J = 11.8$ Hz, CH), 7.42–7.55 (m, 3CH), 7.93 (dd, $^3J = 8.8$, $^4J = 2.0$ Hz, CH), 8.10 (dd, $^3J = 8.8$, $^4J = 2.2$ Hz, CH) ppm; ^{13}C NMR: $\delta = 49.13$ ($2CH_2$), 51.4 (O*Me*), 66.4 ($2CH_2$), 115.5 (CH), 127.8 (2CH), 128.6 (2CH), 129.6 (CH), 132.2 (C), 142.2 (N–CH), 162.0 (C=O), 166.5 (C=O), 169.4 (C=S) ppm; (*E*)-**4g** (25%): ^{1}H NMR: $\delta = 3.41$–3.43 (m, $2CH_2$), 3.51–3.54 (m, $2CH_2$), 3.71 (s, O*Me*), 6.10 (d, $^3J = 15.4$ Hz, CH), 7.75 (d, $^3J = 15.4$ Hz, CH), 7.42–7.55 (m, 3CH), 7.93 (dd, $^3J = 8.8$, $^4J = 2.2$ Hz, CH), 8.10 (dd, $^3J = 8.8$ Hz, $^4J = 2.0$ Hz, CH) ppm; ^{13}C NMR: $\delta = 49.1$ ($2CH_2$), 51.4 (O*Me*), 66.7 ($2CH_2$), 116.7 (CH), 128.4 (2CH), 128.7 (2CH), 129.7 (CH), 131.6 (C), 139.6 (N–CH), 160.2 (C=O), 165.9 (C=O), 167.9 (C=S) ppm.

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