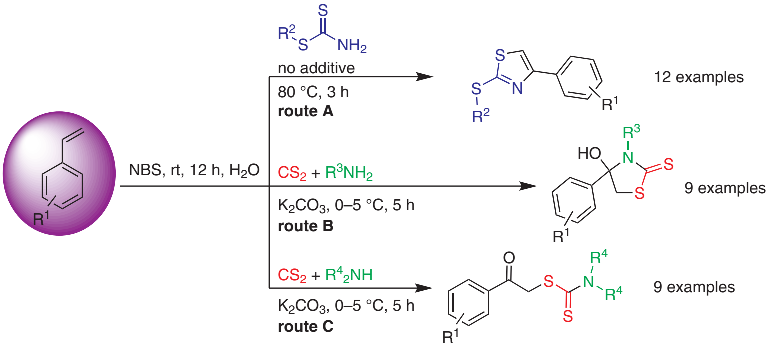
Synlett Letter

Utility of *N*-Bromosuccinimide–Water Combination as a Green Reagent for Synthesis of N,S-Heterocycles and Dithiocarbamates from Styrenes

Firouz Matloubi Moghaddam*
Mehri Goudarzi

Laboratory of Organic Synthesis and Natural Products,
Department of Chemistry, Sharif University of Technology,
Azadi Street, P.O. Box 111559516, Tehran, Iran
matloubi@sharif.edu



Received: 22.05.2020
Accepted after revision: 10.07.2020

DOI: 10.1055/s-0040-1707258; Art ID: st-2020-b0304-l

Abstract An efficient and unprecedented green protocol has been developed for the synthesis of N,S-heterocycles from styrenes and alkyl dithiocarbamates with high to excellent yields. The reaction of primary or secondary amines, CS_2, and styrenes was carried out in water in the presence of a catalytic amount of an inorganic base. All products were made by using an *N*-bromosuccinimide–H_2O combination as a green and inexpensive reagent.

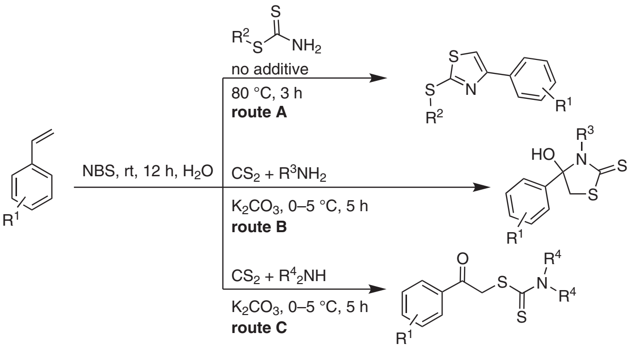
Key words dithiocarbamates, styrenes, green chemistry, thiazoles, bromosuccinimide

Due to their interesting properties and applications in unique syntheses of chemical compounds, styrenes have attracted considerable attention from synthetic chemists in recent years. Although these versatile small molecules are chemically quite reactive and can polymerize rapidly, styrenes can be used directly in syntheses of important classes of heterocycles and α-X-acetophenones (X = C, N, O, S, Br).[1] For example, Zhang and co-workers reported a copper-catalyzed aerobic difunctionalization of styrenes with cyclic ethers for the synthesis of the oxyalkylated products.[2] Sudalai and co-workers developed an I_2-catalyzed regioselective oxo- and hydroxyacyloxylation of alkenes with carboxylic acids under mild conditions.[3] Recently, the same group developed an efficient method for the synthesis of regioselective oxoamination of styrenes by an NBS–DMSO system and secondary amines.[4] More recently, the Yang group reported difunctionalization of alkenes by a one-pot four-component reaction of two alkenes, an aromatic or aliphatic aldehyde, and *tert*-butyl hydroperoxide.[5]

Dithiocarbamates are valuable compounds due to their wide utility in syntheses of small organic molecules and biologically active compounds.[6] They are also widely used in agriculture, rubber manufacturing, RAFT polymerizations, and medicinal chemistry.[7] Moreover, dithiocarbamic acids can be easily prepared in situ from carbon disulfide and primary or secondary amines, and they can act as efficient binucleophiles or nucleophiles, respectively. Recently, various N,S-heterocycles have been prepared from dithiocarbamic acids.[8]

N-Bromosuccinimide (NBS) is one of the most important nontoxic sources of cationic and radical bromine. It is widely used in various reactions for the bromination of such chemical compounds as 1,3-diketones,[9] chalones,[10] unsymmetrical indodicarbocyanine dyes,[11] and ethynylbenzene.[12]

In this letter, we report a difunctionalization of commercially available styrenes for the synthesis of dithiocarbamates or N,S-heterocycles in water as solvent and a source of oxygen. Furthermore, NBS plays a dual role, acting as an oxidant and a safe source of bromine (Scheme 1; routes A–C).



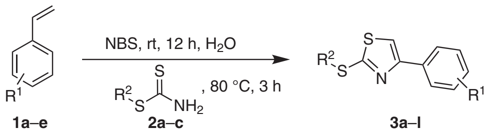
Scheme 1 Synthesis of N,S-heterocycles and dithiocarbamates by using an NBS–H_2O combination

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Initially, we investigated the one-pot reaction of an alkyl dithiocarbamate with a styrene for the synthesis of a 2-(alkylsulfanyl)-4-phenyl-1,3-thiazole. We observed that treatment of one equivalent of styrene (**1a**) with two equivalents of NBS in H_2O at room temperature for 12 hours, followed by the addition of one equivalent of benzyl dithiocarbamate (**2a**) and further heating at 80 °C for three hours, gave 2-(benzylsulfanyl)-4-phenyl-1,3-thiazole (**3a**) in 86% isolated yield. Changing the solvent system from water to a water–organic solvent mixture provided an unsatisfactory yield of **3a**. A further increase in the amount of the dithiocarbamate **2a** did not improve the yield. Whereas the replacement of NBS by NIS afforded **3a** in 28% yield, **3a** was not formed with NCS.

With the optimized reaction conditions in hand,[13] we examined the scope of the reaction of various styrenes **1a–e** with alkyl dithiocarbamates **2a–c** (Table 1).

Table 1 Diversity in the Synthesis of 2-(Alkylsulfanyl)-4-phenyl-1,3-thiazoles[a]

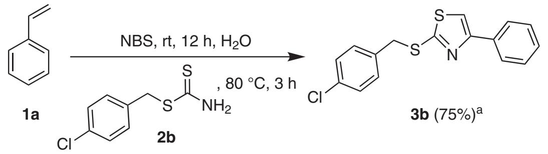


Entry		R^1		R^2	Product	Yield[b] (%)
1	**1a**	H	**2a**	Bn	**3a**	86
2	**1a**	H	**2b**	4-chlorobenzyl	**3b**	91
3	**1b**	4-Me	**2a**	Bn	**3c**	83
4	**1b**	4-Me	**2b**	4-chlorobenzyl	**3d**	87
5	**1c**	4-MeO	**2a**	Bn	**3e**	91
6	**1c**	4-MeO	**2b**	4-chlorobenzyl	**3f**	93
7	**1c**	4-MeO	**2c**	Pr	**3g**	73
8	**1d**	$3\text{-}O_2N$	**2a**	Bn	**3h**	84
9	**1d**	$3\text{-}O_2N$	**2b**	4-chlorobenzyl	**3i**	87
10	**1e**	4-Br	**2a**	Bn	**3j**	74
11	**1e**	4-Br	**2b**	4-chlorobenzyl	**3k**	79
12	**1e**	4-Br	**2c**	Pr	**3l**	68

[a] Reaction conditions: styrene **1** (1 mmol), NBS (2 mmol), H_2O (2 mL), rt, 12 h, then dithiocarbamate **2** (1 mmol), 80 °C, 3 h.
[b] Isolated yield.

The structures of products **3a–l** were confirmed by ^{13}C NMR spectroscopy. The C-2 peak of the thiazole ring appeared at $\delta = 163$ ppm, and the peaks for the C-4 and C-5 atoms of the thiazole ring appeared at $\delta = 154$ and 136 ppm, respectively.

To demonstrate the synthetic utility of this reaction, we performed it at a 5 mmol scale and obtained product **3b** in 75% yield (Scheme 2).

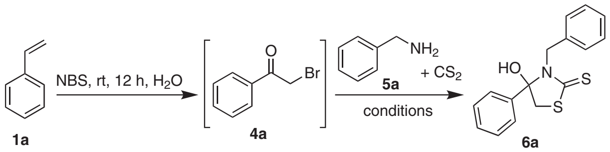


Scheme 2 Synthesis of thiazole **3b** on a 5 mmol scale

Inspired by this green and simple approach for the synthesis of 2-(alkylsulfanyl)-4-phenyl-1,3-thiazoles, we expanded the utility of this protocol by using primary amines. To study this reaction, styrene (**1a**; 1 mmol) was treated with NBS (2 mmol) at 25 °C in water for 12 hours to give α-bromoacetophenone (**4a**); subsequent addition of mixture of benzylamine and carbon disulfide gave the desired product **6a** in a trace amount (Table 2, entry 1). As expected, the addition of an inorganic or organic base was effective in giving **6a** in yields of 14–45% (entries 2–5). The yield was not improved by performing the reaction in refluxing H_2O (entry 6), but on changing the temperature from 25 °C to 0 °C, an increase in the yield of **6a** was observed (entry 7). In addition, neither lowering nor increasing the catalyst concentration significantly improved the yield (entries 8–10). Finally, a higher yield (76%) of **6a** was obtained by increasing the amount of **5a** to 1.5 equivalents (entry 11).

Various primary amines and styrenes were then examined under the optimized reaction conditions (Scheme 3).[14] Moderate to high yields (37–81%) of racemic products were

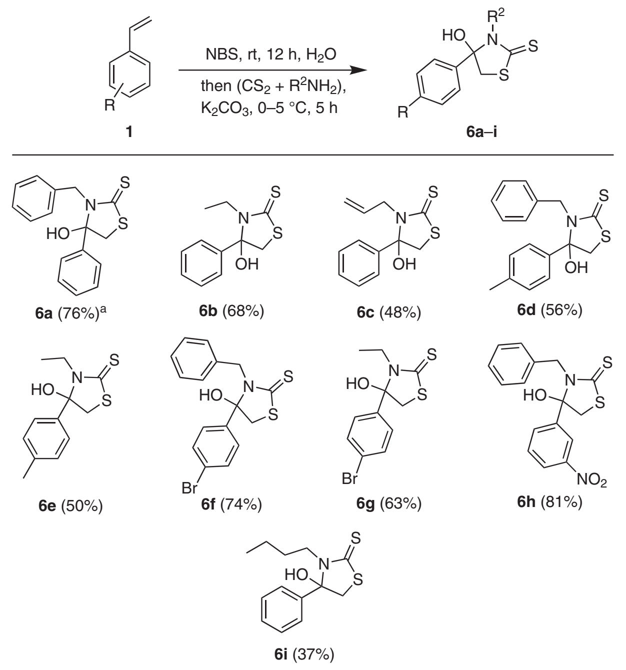
Table 2 Optimization of the Reaction of Benzylamine (**5a**) with Styrene (**1a**)[a]



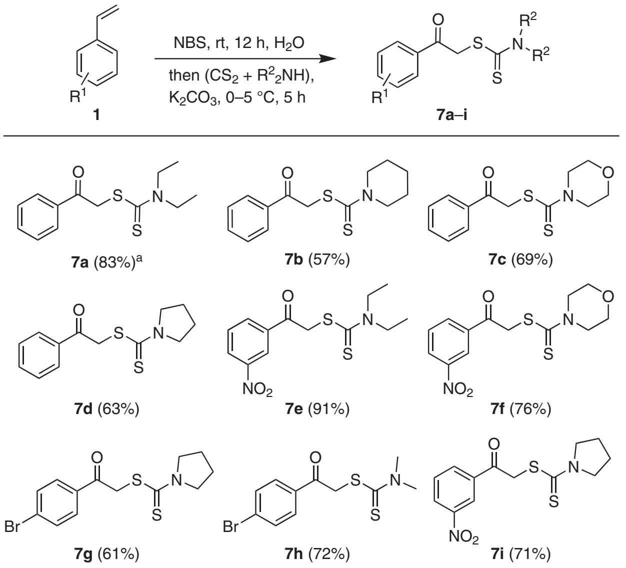
Entry	Base (equiv)	Temp	Yield[a] (%)
1	–	rt	trace
2	NaOH (1)	rt	38
3	KOH (1)	rt	32
4	K_2CO_3 (1)	rt	45
5	DABCO (1)	rt	14
6	K_2CO_3 (1)	reflux	22
7	K_2CO_3 (1)	0 °C	68
8	K_2CO_3 (0.5)	0 °C	68
9	K_2CO_3 (0.25)	0 °C	66
10	K_2CO_3 (1.5)	0 °C	63
11[b]	**K_2CO_3 (0.25)**	**0 °C**	**76**

[a] Isolated yield
[b] **5a** (1.5 equiv).

obtained. Higher yields were obtained by using benzylamine and styrenes containing an electron-withdrawing group on the phenyl ring.



Scheme 3 Synthesis of 1,3-thiazolidine-2-thiones. *Reagents and conditions*: styrene **1** (1 mmol), NBS (2 mmol), H_2O (2 mL), rt, 12 h, then amine **5** (1.5 equiv), CS_2 (3 equiv), K_2CO_3 (0.25 equiv), 0 to 5 °C, 5 h. [a] Isolated yield.

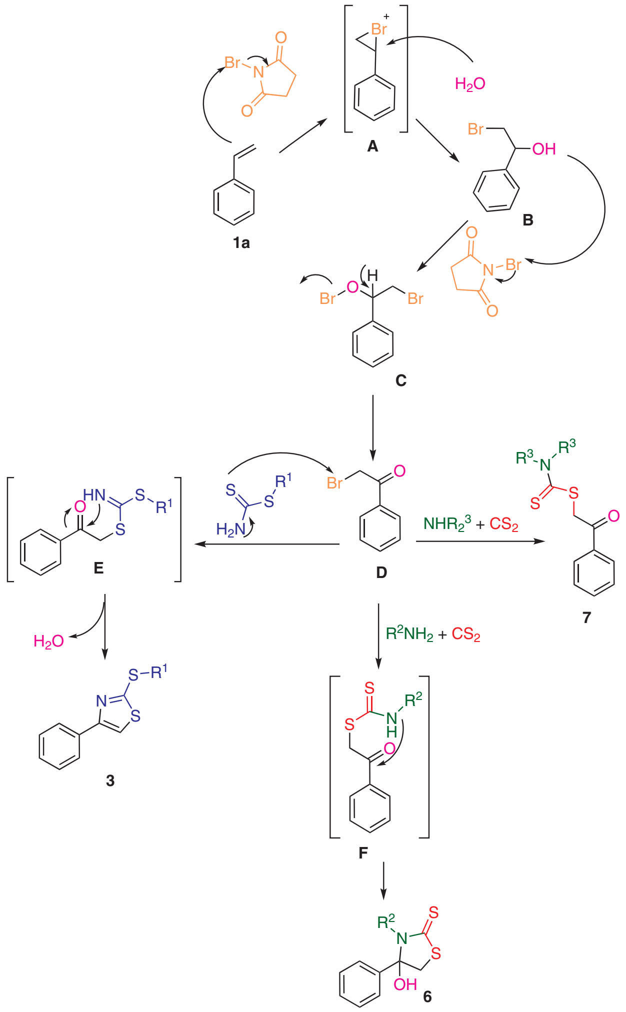


Scheme 4 Synthesis of 2-aryl-2-oxoethyl carbamates. *Reagents and conditions*: styrene **1** (1 mmol), NBS (2 mmol), H_2O (2 mL), rt, 12 h, then amine (1.5 equiv), CS_2 (3 equiv), K_2CO_3 (0.25 equiv), 0 to 5 °C, 5 h. [a] Isolated yield.

ithiocarbamic acids derived from secondary amines then were selected as nucleophilic partners for this protocol.[15] 2-Oxo-2-phenylethyl diethylcarbamate (**7a**) was synthesized in a satisfactory yield by a one-pot reaction of diethylamine, CS_2, and styrene with an NBS–H_2O combination for five hours (Scheme 4). The scope of this reaction was extended by using various secondary amines and styrenes. The corresponding products **7a–i** were obtained in moderate to high yields.

Finally, gram-scale reactions were performed to demonstrate the industrial application of the method in the syntheses of 3-benzyl-4-hydroxy-4-phenyl-1,3-thiazolidine-2-thione (**6a**) and 2-oxo-2-phenylethyl diethylcarbamate (**7a**) on 5 mmol scale, and the desired products were obtained in yields of 63 and 68%, respectively.

Based on previous studies,[16] a plausible mechanism for the formation of the various products is proposed (Scheme 5). Initially, NBS reacts with styrene (**1a**) to form the bromonium ion **A**. Bromohydrin **B** is then formed by regio-



Scheme 5 Proposed mechanism

selective addition of H_2O. The hypobromite intermediate **C**, produced by the reaction of the bromohydrin **B** with NBS, then undergoes cleavage to form phenacyl bromide (**D**). Finally, phenacyl bromide (**D**) reacts with an alkyl dithiocarbamate or a dithiocarbamic acid derived from a primary or a secondary amine to give the desired products **3**, **6**, and **7**, respectively.

In conclusion, we have demonstrated the synthesis of dithiocarbamates and two types of N,S-heterocycle through the reaction of styrenes with dithiocarbamic acids or alkyl dithiocarbamates. More importantly, the NBS–H_2O combination is a green and inexpensive reagent for converting styrenes into the corresponding phenacyl bromides in a single step. The reactions are characterized by the use of mild and effective reaction conditions, short reaction times, and moderate to excellent product yields.

Acknowledgment

We are grateful to the faculty of chemistry of the Sharif University of Technology for supporting this work.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707258.

References and Notes

(1) (a) Tomotsu, N.; Ishihara, N.; Newman, T. H.; Malanga, M. T. *J. Mol. Catal. A: Chem* **1998**, *128*, 167. (b) Chien, J. C. W.; Salajka, Z.; Dong, S. *Macromolecules* **1992**, *25*, 3199.

(2) Cheng, K.; Huang, L.; Zhang, Y. *Org. Lett.* **2009**, *11*, 2908.

(3) Reddi, R. N.; Prasad, P. K.; Sudalai, A. *Org. Lett.* **2014**, *16*, 5674.

(4) Prasad, P. K.; Reddi, R. N.; Sudalai, A. *Org. Lett.* **2016**, *18*, 500.

(5) Wu, C.-S.; Liu, R.-X.; Ma, D.-Y.; Luo, C.-P.; Yang, L. *Org. Lett.* **2019**, *21*, 6117.

(6) (a) Li, G.; Yan, Q.; Gan, Z.; Li, Q.; Dou, X.; Yang, D. *Org. Lett.* **2019**, *21*, 7938. (b) Halimehjani, A. Z.; Hasani, L.; Alaei, M. A.; Saidi, M. R. *Tetrahedron Lett.* **2016**, *57*, 883. (c) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634. (d) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 5275. (e) Khoudary, K.; Mona, S.; Matar, M.; Haffar, S. *Asian J. Chem.* **2013**, *25*, 962. (f) Gan, S.-F.; Wan, J.-P.; Pan, Y.-J.; Sun, C.-R. *Synlett* **2010**, 973.

(7) (a) Marinovich, M.; Viviani, B.; Capra, V.; Corsini, E.; Anselmi, L.; D'Agostino, G.; Di Nucci, A.; Binaglia, M.; Tonini, M.; Galli, C. L. *Chem. Res. Toxicol.* **2002**, *15*, 26. (b) Nieuwenhuizen, P. J.; Ehlers, A. W.; Haasnoot, J. G.; Janse, S. R.; Reedijk, J.; Baerends, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 163. (c) Lai, J. T.; Shea, R. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 4298. (d) Bala, V.; Jangir, S.; Mandalapu, D.; Gupta, S.; Chhonker, Y. S.; Lal, N.; Kushwaha, B.; Chandasana, H.; Krishna, S.; Rawat, K. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 881.

(8) (a) Shaabani, A.; Hooshmand, S. E. *Ultrason. Sonochem.* **2018**, *40*, 84. (b) Gabillet, S.; Lecerclé, D.; Loreau, O.; Carboni, M.; Dézard, S.; Gomis, J.-M.; Taran, F. *Org. Lett.* **2007**, *9*, 3925. (c) Hajibabaei, K.; Zali-Boeini, H. *Synlett* **2015**, *26*, 108.

(9) Zou, L.-H.; Li, Y.-C.; Li, P.-G.; Zhou, J.; Wu, Z. *Eur. J. Org. Chem.* **2018**, *2018*, 5639.

(10) (a) Wang, Z.; Lin, L.; Zhou, P.; Liu, X.; Feng, X. *Chem. Commun.* **2017**, *53*, 3462. (b) Li, W.; Zhou, P.; Li, G.; Lin, L.; Feng, X. *Adv. Synth. Catal.* **2020**, *362*, 1982. (c) Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 6160.

(11) Miltsov, S.; Goikhman, M.; Yakimansky, A.; Misharev, A.; Puyol, M.; Alonso, J. *Tetrahedron Lett.* **2019**, *60*, 151005.

(12) Gao, Y.; Wu, W.; Huang, Y.; Huang, K.; Jiang, H. *Org. Chem. Front.* **2014**, *1*, 361.

(13) **2-(Alkylsulfanyl)-4-aryl-1,3-thiazoles 3a–l; General Procedure**

NBS (2.0 mmol) was added to a solution of the appropriate styrene **1** (1.0 mmol) in H_2O (2 mL), and the mixture was stirred for 12 h. The appropriate alkyl dithiocarbamate **2** (1.0 mmol) was added, and the mixture was stirred at 80 °C for 3 h. The resulting mixture was cooled to rt and extracted with EtOAc (3 × 5 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography [silica gel, hexane–EtOAc (9:1)].

2-(Benzylsulfanyl)-4-phenyl-1,3-thiazole (3a)

White crystalline solid; yield: 243 mg (86%); mp 58–60 °C. IR (KBr): 3102, 3065, 2918, 1953, 1888, 1590, 1443, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.56 (s, 2 H), 7.30–7.41 (m, 5 H), 7.46–7.50 (m, 4 H), 7.97 (d, *J* = 8.0, Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.8, 112.8, 126.3, 127.7, 128.2, 128.6, 129.1, 134.5, 136.7, 138.1, 155.4, 163.9. Anal. Calcd for $C_{16}H_{13}NS_2$: C, 67.81; H, 4.62; N, 4.94. Found: C, 67.91; H, 4.72; N, 4.62.

(14) **3-Alkyl-4-aryl-4-hydroxy-1,3-thiazolidine-2-thiones 6a–i; General Procedure**

NBS (2.0 mmol) was added to a solution of the appropriate styrene **1** (1.0 mmol) in H_2O (2 mL), and the mixture was stirred for 12 h at rt, then cooled to 0 °C. A mixture of the appropriate primary amine (1.5 mmol) and CS_2 (3 mmol) in H_2O (1 mL) was added, followed by K_2CO_3 (0.25 mmol), and the resulting mixture was stirred for 5 h. The mixture was then extracted with EtOAc (3 × 5 mL) and the organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Finally, the residue was purified by chromatography [silica gel, hexane–EtOAc (1:2)].

3-Benzyl-4-hydroxy-4-phenyl-1,3-thiazolidine-2-thione (6a)

White solid; yield: 229 mg (76%); mp 138–140 °C. IR (KBr): 3745, 3230, 3050, 2923, 2743, 1964, 1490, 1442, 1143, 699 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 3.63 (d, *J* = 12.5 Hz, 1 H), 3.75 (d, *J* = 12.5 Hz, 1 H), 4.50 (d, *J* = 15.5 Hz, 1 H), 4.83 (d, *J* = 15.5 Hz, 1 H), 7.14–7.21 (m, 5 H), 7.31–7.42 (m, 5 H), 7.79 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.9, 49.2, 100.9, 126.1, 127.1, 128.1, 128.2, 128.9, 129.2, 137.1, 141.2, 196.0. Anal. Calcd for $C_{16}H_{15}NOS_2$: C, 63.75; H, 5.02; N, 4.65. Found: C, 63.72; H, 5.11; N, 4.01.

(15) **2-Aryl-2-Oxoethyl Dithiocarbamates 7a–i; General Procedure**

NBS (2.0 mmol) was added to a solution of the appropriate styrene **1** (1.0 mmol) in H_2O (2 mL), and the mixture was stirred for 12 h at rt, then cooled to 0 °C. A mixture of the appropriate

secondary amine (1.5 mmol) and CS_2 (3 mmol) in H_2O (1 mL) was added, followed by K_2CO_3 (0.25 mmol), and the resulting mixture was stirred for 5 h. The mixture was extracted with EtOAc (3 × 5 mL), and the organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Finally, the residue was purified by chromatography [silica gel, hexane–EtOAc (1:2)].

2-Oxo-2-phenylethyl Diethyldithiocarbamate (7a)

White solid; yield: 222 mg (83%); mp 108–110 °C. IR (KBr): 3736, 3354, 3058, 2978, 2930, 2874, 1683, 1586, 1492, 1205, 991, 687 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.0 Hz, 3 H), 1.37 (t, J = 7.0 Hz, 3 H), 3.82–3.87 (m, 2 H), 4.02–4.06 (m, 2 H), 4.92 (s, 2 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.0 Hz, 1 H), 8.09 (dd, J = 9.5 and 1.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 12.6, 45.1, 47.1, 50.1, 128.6, 128.7, 133.5, 136.2, 193.5, 194.0. Anal. Calcd for $C_{13}H_{17}NOS_2$: C, 58.39; H, 6.41; N, 5.24. Found: C, 58.44; H, 6.47; N, 4.96.

(16) Shinde, M. H.; Kshirsagar, U. A. *Org. Biomol. Chem.* **2016**, *14*, 858.