RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2014, **4**, 1276

A highly efficient one-pot method for the synthesis of thioureas and 2-imino-4-thiazolidinones under microwave conditions†

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Received 30th September 2013
Accepted 18th November 2013

DOI: 10.1039/c3ra46270f

www.rsc.org/advances

A one-pot synthesis of symmetrical and unsymmetrical substituted thioureas and 2-imino-4-thiazolidinones from simple starting materials under microwave irradiation and solventless conditions without base additives is presented. Various di- and trisubstituted thioureas are obtained in good yields in a few minutes. The sequential, three-component, one-pot synthesis of 2-imino-4-thiazolidinone derivatives is also studied, with satisfactory results obtained.

Introduction

Thioureas are relevant compounds in the medical industry because their derivatives and metal complexes exhibit significant biological activities such as anti-inflammatory,[1] analgesic,[2] antimicrobial,[3] and anticancer activities,[4] and have potential functions as fungicides,[5] herbicides,[6] rodenticides,[7] and phenoloxidase enzymatic inhibitors.[8] They are also treated as essential intermediates for the synthesis of heterocyclic compounds,[9] as catalysts or auxiliaries in organocatalytic reactions,[10] and as anion recognition moieties in chemosensors.[11] Because of their usefulness in these fields, numerous procedures have been developed for the synthesis of substituted thioureas, including the condensation of primary and secondary amines with isothiocyanate,[12] thiophosgene,[13] or derivatives thereof,[14] the reaction of unsubstituted thioureas with primary alkyl amines or of *N*,*N*′-di-Boc-substituted thioureas with alkyl or arylamines,[15,16] and the reaction of primary amines with carbon disulfide in the presence of mercury acetate.[17]

Environmental protection has become a global concern. In both research and industrial fields, attempts are now being made to reduce the use of organic solvents, shorten reaction times, and eliminate the use of additive materials.[18] In addition, the concept of "pot economy" has been emphasized,[19] because chemists can combine a sequence of chemical transformations in a single reaction flask to complete a multistep synthesis without the need for product isolation and purification between each step, thus avoiding lengthy separation processes of intermediates and the generation of excess waste. Recently, microwave-assisted reaction technology has been recognized for its ability to enhance chemical reactions and generate clean and high-yielding chemical transformations. The traditional procedures used to prepare thioureas usually require bases and/or organic solvents. Recently, a method for the synthesis of thioureas in aqueous solution has been developed.[20] On the basis of green considerations, we hereby report an environmentally benign procedure for the synthesis of thioureas under microwave irradiation and solventless conditions without the use of base additives. The reaction works well in a one-pot fashion and is completed in a few minutes, with the desired products obtained in good yields. Furthermore, this reaction is also successfully extended to the synthesis of 2-imino-4-thiazolidinones, valuable compounds that have been applied in various fields including materials, dyes, and pharmaceuticals.

Results and discussion

For the optimisation of the reaction conditions for the synthesis of trisubstituted thioureas, diethylamine and aniline were used as model secondary and primary amines. The reaction parameters including the reaction solvents, heating mode, and reaction times as well as the base additives were screened (Table 1). For the preparation of trisubstituted thioureas, a sequential, one-pot reaction procedure was adopted. Diethylamine was reacted with carbon disulfide in THF under reflux conditions for 1 h. Subsequently, aniline was added, and the mixture was reacted for a further 20 h. The desired product **1d** was isolated in a yield of just 20%. We supposed that the reaction involved two sequential steps: intermediate dithiocarbamate formation followed by nucleophilic substitution of the primary amine. In order to understand why the yield of **1d** was so low, we monitored both steps by thin-layer chromatography (TLC) and nuclear magnetic resonance (NMR) spectroscopy. In the TLC experiments, a

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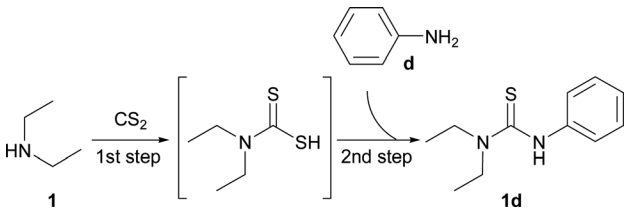
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra46270f

Table 1 Optimisation of the reaction conditions for the synthesis of trisubstituted thiourea **1d**



Entry	Heating mode/solvent	2 steps (one-pot)/reaction time	Additive	Yield[a] (%)
1	Reflux/THF	1 h + 20 h	No	20 (17)
2	Reflux/1,4-dioxane	1 h + 20 h	No	18 (15)
3	Reflux/acetonitrile	1 h + 20 h	No	20 (16)
4	Reflux/THF	1 h + 20 h	$CaCO_3$	19 (15)
5	Reflux/THF	1 h + 20 h	Cs_2CO_3	21 (16)
6	Reflux + uW/THF	1 h + 5 min	No	82
7	uW/THF	5 min + 5 min	No	86
8	uW/THF	5 min + 5 min	Cs_2CO_3	86
9	uW/neat	5 min + 5 min	No	87

[a] The yields in parenthesis are the yields after 10 h reactions.

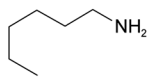
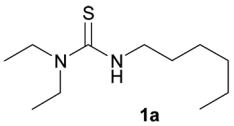
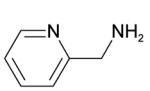
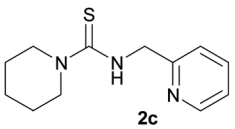
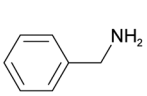
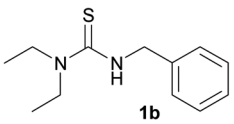
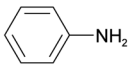
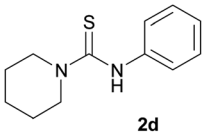
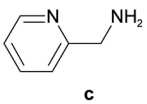
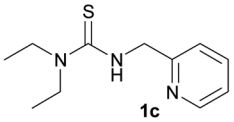
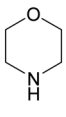
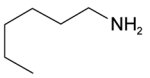
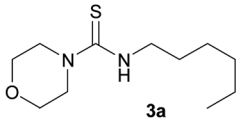
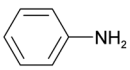
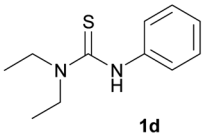
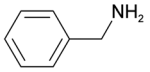
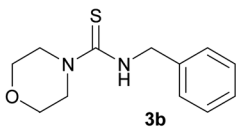
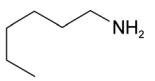
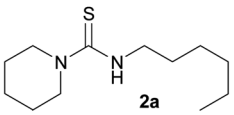
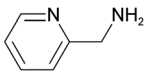
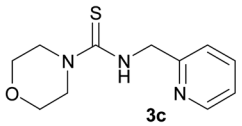
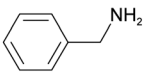
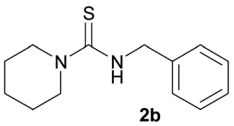
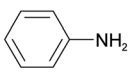
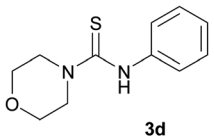
yellow spot appeared 10 min after the injection of diethylamine into an equimolar amount of CS_2, and the reaction mixture was characterized by NMR after a reaction time of 1 h. It was seen from the NMR spectrum that the diethylamine was consumed completely. We then checked the subsequent step with the addition of the same molar amount of aniline. The reaction mixture was characterized every hour. It was found that the formation rate of the thiourea product was not as fast as we expected. The aniline was only consumed completely after a reaction time of 20 h, but impurities started to appear when the reaction time exceeded 10 h. Therefore, on the basis of this evidence, we suggest that the ineffective nucleophilic substitution of the primary amine to the dithiocarbamate may contribute to the low yield of the reaction. In order to improve the efficacy of this step, we tried changing the solvent to 1,4-dioxane or acetonitrile, but the reaction times were still long and the yield was not improved. Bases such as $CaCO_3$ and Cs_2CO_3 were added to increase the nucleophilicity of the aniline, but the yield remained low. Finally, we carried out this step under microwave irradiation, since it was suggested that this may be able to provide efficient heating. Surprisingly, the aniline was consumed completely within 5 min, the formation of side products was avoided, and the yield of **1d** was increased dramatically to 82%. It is worth noting that this type of aryl substituted thiourea compounds could not been obtained by using the reported aqueous phase protocol.[20]

We then wanted to simplify the procedure and eliminate the use of the solvent if possible. Therefore, we carried out the first step under microwave irradiation instead of heating at reflux in THF, and the results were found to be very satisfactory. The yield was not increased further when Cs_2CO_3 was added. Finally, it was found that the reaction was also very successful when performed in solvent-free conditions. As shown in Table 2, under the optimized conditions, a number of trisubstituted thioureas were synthesized. Three secondary amines (including diethyl amine (**1**), piperidine (**2**), and morpholine (**3**)) and four different primary amines (such as *n*-hexylamine (**a**), benzyl amine (**b**), 2-(aminomethyl) pyridine (**c**), and aniline (**d**)) were used, and the trisubstituted thioureas were all prepared in satisfactory yields.

Besides the trisubstituted thioureas, symmetrical disubstituted thioureas could also be obtained easily. Two equivalents of amine and one equivalent of CS_2 were mixed together and subjected to microwave irradiation for 5 min, and the desired products were formed in excellent yields. The reactions can be performed in solventless conditions or in THF (Table 3, entry 4 and 6), depending on the amine properties and the scale of the synthesis. If the amine is a liquid or the scale is large enough so that the CS_2 can immerse the solid amine, solventless condition is a good choice. Because the method reported here is highly efficient and both user- and environment-friendly, it provides a good alternative for the production of these types of compounds. To the best of our knowledge, moreover, the one-step one-pot syntheses of diaryl-substituted thioureas directly from arylamines have not been reported until now.

We next considered whether it was possible to synthesize trisubstituted thioureas in a one-step, three-component, one-pot fashion. Thus, diethylamine (2 equiv.), *n*-hexylamine (2 equiv.), and CS_2 (1 equiv.) were mixed together and subjected to microwave irradiation for 10 min. It was found that the symmetrical dihexyl-substituted thiourea was the major product together with trace unsymmetrical one. It was revealed that the primary amine reacted with CS_2 more quickly than the secondary amine in the first step, resulting in the predominance of the symmetrical thiourea in the final.

Table 2 Synthesis of tri-substituted thioureas from simple amines in a sequential, one-pot, microwave-assisted procedure[a]

entry	2°amine	1°amine	product	Yield(%)	entry	2°amine	1°amine	product	Yield(%)
1	 1	 a	 1a	92	7	2	 c	 2c	80
2	1	 b	 1b	90	8	2	 d	 2d	81
3	1	 c	 1c	78	9	 3	 a	 3a	90
4	1	 d	 1d	87	10	3	 b	 3b	91
5	 2	 a	 2a	90	11	3	 c	 3c	80
6	2	 b	 2b	91	12	3	 d	 3d	82

[a] These reactions were carried out following the entry 9 condition in Table 1.

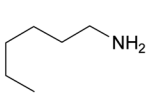
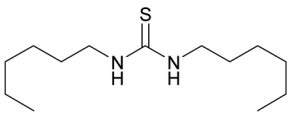
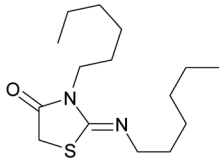
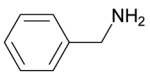
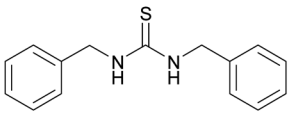
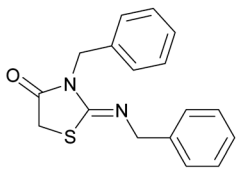
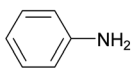
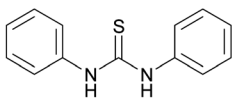
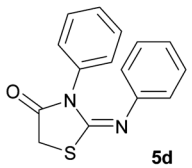
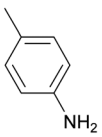
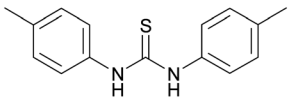
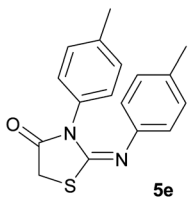
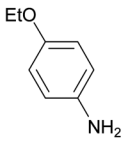
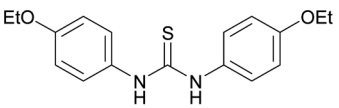
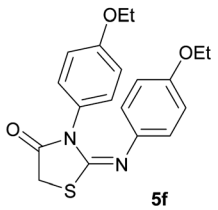
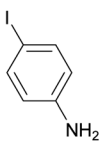
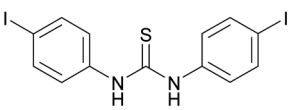
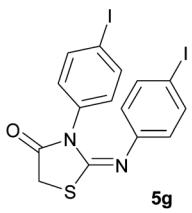
After several trials on adjusting the molar ratio of starting materials, the yield of the trisubstituted thiourea was not improved more. From this result, it is concluded that this one-step three-component reaction method is not suitable for the synthesis of unsymmetrical thioureas although it is very successful in the preparation of symmetrical ones. And the sequential one-pot procedure is the best choice for the synthesis of unsymmetrical thioureas.

Having established a greener method for the synthesis of thioureas, we wanted to apply it to the preparation of 2-imino-4-thiazolidinones. There have been many reports on the synthesis of 2-imino-4-thiazolidinones, with the best-known methods being the treatment of thioureas with α-haloalkanoic acids or their derivatives.[21] Following on from our microwave synthesis of thioureas, we wanted to develop a sequential one-pot strategy for the synthesis of 2-imino-4-thiazolidinones from simple amines. Through the reaction of a primary amine with CS_2 followed by the addition of chloroacetic chloride in the same microwave tube with irradiation for another 5 min, the 2-imino-4-thiazolidinone was successfully obtained. No base was needed in these reactions, because the chloroacetic chloride was reactive enough to react with the thiourea. Several 2-imino-4-thiazolidinones were synthesized in high yields, and the results are summarized in Table 3.

Conclusions

The proposed methodology provides an easier, safer, practically convenient, and environmentally benign approach for the one-pot synthesis of di- and trisubstituted thioureas and 2-imino-4-thiazolidinones. The base- and solvent-free microwave-assisted procedure provides an alternative greener method for the synthesis of these types of compounds. This is the first report on the one-pot synthesis of symmetrical diaryl-substituted thioureas from arylamines and the sequential three-component, one-pot synthesis of 2-imino-4-thiazolidinones from simple amines. Applications in the synthesis of natural products and derivatives as well as chemosensors possessing these skeletons are currently under development.

Table 3 Formation of symmetrical 1,3-disubstituted thioureas and 2-imino-4-thiazolidinones under microwave condition[a]

entry	1°amine	symmetrical thioureas	Yield[b](%)	2-imino-4-thiazolidinones	Yield[b](%)
1	 **a**	 **4a**	95	 **5a**	90 (87)
2	 **b**	 **4b**	93	 **5b**	91 (86)
3	 **d**	 **4d**	82	 **5d**	77 (69)
4	 **e**	 **4e**	93	 **5e**	85 (82)
5	 **f**	 **4f**	92	 **5f**	90 (85)
6	 **g**	 **4g**	83	 **5g**	81 (72)

[a] These reactions were carried out under solventless condition except entry 4 and 6 which were performed in THF. [b] Isolated yields. The yields in parenthesis are the yields in sequential one-pot procedure.

Experimental

General

All reagents were purchased from commercial sources and were used without prior purification and solvents were dried before use. Microwave irradiation experiments were carried out in a dedicated CEM Discover monomode microwave apparatus. The reactions were carried out in 10 mL glass tubes, sealed with Teflon septum, and placed in the microwave cavity. The reaction mixture was irradiated under power of 150 W for the stipulated time, and the reaction mixture temperatures were measured by the external IR sensor. The reaction tube was cooled to room temperature with air jet cooling. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60 F254) or aluminum-backed plates SILG/UV254 with UV indicator. Silica gel (230–400 mesh) was used for flash column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. IR spectra were

recorded on a Perkin-Elmer FTIR spectrophotometer. HRMS data was obtained from FOEL JMS-HX110 spectrometer.

General procedure for the synthesis of trisubstituted thioureas from secondary and primary amine

A mixture of the appropriate secondary amine and carbon disulfide was subjected to microwave irradiation. The power was set at 150 W and the temperature was set at 160 °C. After 5 min, the mixture was cooled to room temperature and the primary amine was added. The mixture was then irradiated for a further 5 min. The crude mixture was then cooled and subsequently purified by flash column chromatography.

General procedure for the synthesis of symmetrical disubstituted thioureas

A mixture of the appropriate primary amine and carbon disulfide was subjected to microwave irradiation. The power was set at 150 W and the temperature was set at 160 °C. After 5 min, the mixture was cooled to room temperature and the crude mixture was purified by flash column chromatography.

General procedure for the synthesis of 2-imino-4-thiazolidinones

A mixture of the appropriate primary amine and carbon disulfide was subjected to microwave irradiation for 5 min. The power was set at 150 W and the temperature was set at 160 °C. After cooling to room temperature, chloroacetyl chloride was added. The mixture was then irradiated for a further 5 min under the same setting. The crude mixture was then cooled and subsequently purified by flash column chromatography.

Selected data for typical compounds are given below

1,1-diethyl-3-hexylthiourea (1a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.78 (br, 1H), 3.63–3.56 (m, 4H), 3.36 (brs, 2H), 1.48–1.60 (m, 3H), 1.35–1.08 (m, 11H), 0.83 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 179.3, 45.8, 44.6, 31.1, 29.0, 26.3, 22.1, 13.6, 12.3; IR (neat, cm^{-1}) 3311, 2932, 1533, 1186, 1102, 998, 852, 725; HRMS (EI, m/z) calcd for $C_{11}H_{24}N_2S$ (M^+) 216.1660, found 216.1663.

3-Benzyl-1,1-diethylthiourea (1b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.40–7.20 (m, 5H), 5.52 (brs, 1H), 4.86 (d, J = 5.2 Hz, 2H), 3.67 (q, J = 7.2 Hz, 4H), 1.23 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 179.9, 138.1, 128.5, 128.4, 127.5, 127.4, 127.3, 49.8, 45.0, 12.5; IR (neat, cm^{-1}) 3310, 3038, 2975, 2931, 2871, 1538, 1454, 1408, 1375, 1278, 1136, 963, 861; HRMS (EI, m/z) calcd for $C_{12}H_{18}N_2S$ (M^+) 222.1191, found 222.1185.

1,1-Diethyl-3-((pyridin-2-yl)methyl)thiourea (1c). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.49 (d, J = 4.8 Hz, 2H), 7.66 (td, J = 7.6, 2.0 Hz, 2H), 7.38 (brs, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.20–7.15 (m, 4H), 4.93 (d, J = 4.0 Hz, 2H), 3.72 (q, J = 7.2 Hz, 4H), 1.25 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 179.1, 156.1, 148.0, 136.6, 122.3, 122.0, 49.6, 44.9, 12.3; IR (neat, cm^{-1}) 3321, 2961, 2924, 2855, 1594, 1571, 1535, 1495, 1446, 1329, 1303, 1184, 963, 861; HRMS (EI, m/z) calcd for $C_{11}H_{17}N_3S$ (M^+) 223.1143, found 223.1140.

1,1-Diethyl-3-phenylthiourea (1d). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.40–7.18 (m, 5H), 6.98 (brs, 1H), 3.75 (q, J = 7.2 Hz, 4H), 1.29 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 179.1, 139.2, 127.6, 125.8, 124.9, 44.9, 12.0; IR (neat, cm^{-1}) 3229, 3038, 2975, 2931, 2871, 1595, 1518, 1452, 1404, 1350, 1137, 1075, 1004, 910, 896, 761, 698; HRMS (EI, m/z) calcd for $C_{11}H_{16}N_2S$ (M^+) 208.1034, found 208.1031.

***N*-Hexylpiperidine-1-carbothioamide (2a).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.38 (brs, 1H), 3.78–3.70 (m, 4H), 3.62–3.58 (m, 2H), 1.68–1.55 (m, 8H), 1.35–1.22 (m, 6H), 0.86 (t, J = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 180.0, 48.4, 45.7, 31.1, 28.9, 26.2, 26.1, 23.8, 22.1, 13.5; IR (neat, cm^{-1}) 3286, 3064, 2931, 2856, 1537, 1443, 1385, 1334, 1244, 1119, 1022, 999, 878, 852, 727; HRMS (EI, m/z) calcd for $C_{12}H_{24}N_2S$ (M^+) 228.1660, found 228.1665.

***N*-Benzylpiperidine-1-carbothioamide (2b).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.32–7.15 (m, 5H), 6.27 (brs, 1H), 4.78 (d, J = 5.2 Hz, 2H), 3.70–3.65 (m, 4H), 1.62–1.43 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 180.1, 138.0, 127.9, 126.8, 126.6, 48.9, 48.4, 24.9, 23.6; IR (neat, cm^{-1}) 3311, 3036, 2930, 2871, 1538, 1454, 1408, 1383, 1243, 1117, 998, 878, 849, 723; HRMS (EI, m/z) calcd for $C_{13}H_{18}N_2S$ (M^+) 234.1191, found 234.1189.

***N*-((Pyridin-2-yl)methyl)piperidine-1-carbothioamide (2c).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.52 (d, J = 4.8 Hz, 1H), 7.68 (td, J = 8.0, 1.6 Hz, 1H), 4.47 (brs, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.21 (m, 1H), 7.95 (d, J = 4.0 Hz, 2H), 3.87 (brs, 4H), 1.68 (brs, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 180.1, 155.7, 148.4, 136.7, 122.3, 122.1, 50.1, 48.7, 25.4, 24.2; IR (neat, cm^{-1}) 3321, 2961, 2920, 2855, 1594, 1566, 1535, 1475, 1436, 1240, 1116, 877, 848, 724; HRMS (EI, m/z) calcd for $C_{12}H_{17}N_3S$ (M^+) 235.1143, found 235.1141.

***N*-Phenylpiperidine-1-carbothioamide (2d).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.35–7.26 (m, 2H), 7.12–7.04 (m, 3H), 3.75 (brs, 4H), 1.64 (brs, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 182.7, 140.3, 129.1, 124.8, 122.5, 51.0, 25.5, 24.1; IR (neat, cm^{-1}) 3230, 3033, 2971, 2930, 2873, 1595, 1518, 1454, 1409, 1385, 1243, 1115, 998, 879, 849; HRMS (EI, m/z) calcd for $C_{12}H_{16}N_2S$ (M^+) 220.1034, found 220.1037.

***N*-Hexylmorpholine-4-carbothioamide (3a).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.47 (brs, 1H), 3.77–3.67 (m, 8H), 3.65–3.58 (m, 2H), 1.54–1.44 (m, 2H), 1.28–1.10 (m, 6H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 181.3, 65.5, 47.0, 45.5, 30.8, 28.4, 25.9, 21.8, 13.3; IR (neat, cm^{-1}) 3280, 2932, 1537, 1334, 1277, 1234, 1109, 1066, 1025, 877, 759, 735; HRMS (EI, m/z) calcd for $C_{11}H_{22}N_2OS$ (M^+) 230.1453, found 230.1450.

***N*-Benzylmorpholine-4-carbothioamide (3b).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.35–7.18 (m, 5H), 5.70 (brs, 1H), 4.84 (d, J = 4.8 Hz, 2H), 3.78–3.66 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 181.9, 137.6, 128.2, 127.3, 127.1, 65.6, 49.3, 47.3; IR (neat, cm^{-1}) 3315, 2968, 2927, 2858, 1535, 1493, 1448, 1360, 1277, 1234, 1109, 1066, 1023, 953, 877, 759, 736; HRMS (EI, m/z) calcd for $C_{12}H_{16}N_2OS$ (M^+) 236.0983, found 236.0985.

***N*-((Pyridin-2-yl)methyl)morpholine-4-carbothioamide (3c).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.47 (d, J = 4.8 Hz, 1H),

7.69–7.58 (m, 2H), 7.30–7.15 (m, 2H), 4.92 (d, J = 4.0 Hz, 2H), 3.88–3.70 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 181.8, 156.1, 148.5, 137.1, 122.6, 122.4, 66.3, 50.2, 47.7; IR (neat, cm^{-1}) 3320, 2961, 2923, 2857, 1594, 1570, 1535, 1476, 1436, 1330, 1274, 1208, 1116, 1027, 890, 759; HRMS (EI, m/z) calcd for $C_{11}H_{15}N_3OS$ (M^+) 237.0936, found 237.0933.

***N*-Phenylmorpholine-4-carbothioamide (3d).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.40–7.28 (m, 3H), 7.16–7.09 (m, 3H), 3.90–3.60 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 183.5, 139.9, 129.1, 125.3, 123.2, 66.1, 49.5; IR (neat, cm^{-1}) 3204, 3034, 2962, 2921, 2855, 1595, 1528, 1497, 1448, 1335, 1308, 1228, 1209, 1113, 1030, 703; HRMS (EI, m/z) calcd for $C_{11}H_{14}N_2OS$ (M^+) 222.0827, found 222.0831.

1,3-Dihexylthiourea (4a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.72 (brs, 2H), 3.35 (brs, 4H), 1.65–1.53 (m, 4H), 1.34–1.23 (m, 12H), 0.86 (t, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 180.8, 44.1, 31.1, 28.7, 26.2, 22.1, 13.5; IR (neat, cm^{-1}) 3320, 3069, 2930, 2861, 1557, 1334, 1240, 1118, 997, 878, 845, 726; HRMS (EI, m/z) calcd for $C_{13}H_{28}N_2S$ (M^+) 244.1973, found 244.1976.

1,3-Dibenzylthiourea (4b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.33–7.20 (m, 10H), 6.06 (brs, 2H), 4.60 (brs, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 182.0, 136.7, 128.9, 127.9, 127.5, 48.5; IR (neat, cm^{-1}) 3324, 2972, 2912, 2876, 1645, 1634, 1557, 1451, 1315, 943, 807, 770; HRMS (EI, m/z) calcd for $C_{15}H_{16}N_2S$ (M^+) 256.1034, found 256.1036.

1,3-Diphenylthiourea (4d). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.02–7.82 (brs, 2H), 7.42–7.34 (m, 8H), 7.28–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 179.9, 137.0, 129.6, 127.1, 125.3; IR (neat, cm^{-1}) 3607, 3211, 3035, 3025, 2876, 1633, 1600, 1556, 1451, 1344, 1315, 1242, 1071, 933, 696; HRMS (EI, m/z) calcd for $C_{13}H_{12}N_2S$ (M^+) 228.0721, found 228.0719.

1,3-Di-*p*-tolylthiourea (4e). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.95 (brs, 2H), 7.16 (d, J = 8.4 Hz, 4H), 7.10 (d, J = 8.4 Hz, 4H), 2.26 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 180.0, 136.9, 134.5, 130.0, 125.4, 21.0; IR (neat, cm^{-1}) 3605, 3212, 3035, 3024, 1633, 1601, 1555, 1451, 1315, 1242, 1071, 938, 876, 845, 720; HRMS (EI, m/z) calcd for $C_{15}H_{16}N_2S$ (M^+) 256.1034, found 256.1031.

1,3-Bis(4-ethoxyphenyl)thiourea (4f). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.58 (brs, 2H), 7.18 (dd, J = 8.8, 3.2 Hz, 4H), 6.83 (d, J = 8.8 Hz, 4H), 3.95 (q, J = 7.2 Hz, 4H), 1.34 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 181.0, 158.0, 127.5, 115.2, 63.7, 14.7; IR (neat, cm^{-1}) 3214, 3025, 2975, 2911, 2876, 1578, 1554, 1535, 1512, 1360, 1339, 1299, 1245, 1222, 1171, 1116, 1051, 835, 817, 724; HRMS (EI, m/z) calcd for $C_{17}H_{20}N_2O_2S$ (M^+) 316.1245, found 316.1241.

1,3-Bis(4-iodophenyl)thiourea (4g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.25 (brs, 2H), 7.68 (d, J = 8.8 Hz, 4H), 7.23 (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 180.7, 139.5, 137.3, 125.6, 88.5; IR (neat, cm^{-1}) 3211, 3032, 3024, 2910, 2869, 1633, 1603, 1555, 1450, 1313, 1241, 1071, 934, 870; HRMS (EI, m/z) calcd for $C_{13}H_{10}I_2N_2S$ (M^+) 479.8654, found 479.8658.

(*E*)-3-Hexyl-2-(hexylimino)thiazolidin-4-one (5a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.75 (s, 2H), 3.67 (t, J = 7.4 Hz, 2H), 3.24 (d, J = 6.8 Hz, 2H), 1.64–1.52 (m, 6H), 1.38–1.22 (m, 10H), 0.90–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.2, 150.7, 51.9, 42.6, 32.2, 31.3, 31.1, 30.3, 26.7, 26.1, 22.4, 22.2, 13.8, 13.7; IR (neat, cm^{-1}) 2912, 1720, 1635, 1272, 1201, 692; HRMS (EI, m/z) calcd for $C_{15}H_{28}N_2OS$ (M^+) 284.1922, found 284.1925.

(*Z*)-3-Benzyl-2-(benzylimino)thiazolidin-4-one (5b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.39–7.35 (m, 2H), 7.28–7.15 (m, 8H), 4.88 (s, 2H), 4.44 (s, 2H), 3.78 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.4, 152.6, 139.2, 136.1, 129.0, 128.9, 128.7, 128.5, 128.3, 128.3, 128.1, 127.7, 127.3, 126.8, 55.3, 46.0, 32.7; IR (neat, cm^{-1}) 3052, 1720, 1635, 1590, 1495, 1374, 1272, 1201, 690; HRMS (EI, m/z) calcd for $C_{17}H_{16}N_2OS$ (M^+) 296.0983, found 296.0987.

(*Z*)-3-Phenyl-2-(phenylimino)thiazolidin-4-one (5d). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.48–6.82 (m, 10H), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.4, 154.9, 148.0, 134.7, 129.4, 129.1, 129.0, 128.0, 124.6, 120.9, 32.9; IR (neat, cm^{-1}) 3048, 2936, 1727, 1635, 1580, 1455, 1374, 1269, 1195, 693; HRMS (EI, m/z) calcd for $C_{15}H_{12}N_2OS$ (M^+) 268.0670, found 268.0673.

(*E*)-2-(*p*-Tolylimino)-3-*p*-tolylthiazolidin-4-one (5e). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.25 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 3.89 (s, 2H), 2.32 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.6, 154.8, 145.6, 139.0, 134.1, 132.1, 130.1, 129.7, 127.7, 120.7, 32.8, 21.3, 20.9; IR (neat, cm^{-1}) 3051, 2919, 1722, 1638, 1591, 1581, 1487, 1370, 1284, 1203, 1132, 693; HRMS (EI, m/z) calcd for $C_{17}H_{16}N_2OS$ (M^+) 296.0983, found 296.0979.

(*E*)-2-(4-Ethoxyphenylimino)-3-(4-ethoxyphenyl)thiazolidin-4-one (5f). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.20 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.77 (s, 4H), 3.98 (q, J = 7.2 Hz, 2H), 3.93 (q, J = 7.2 Hz, 2H), 3.88 (s, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.7, 159.1, 156.1, 155.0, 141.2, 129.0, 127.1, 121.9, 115.2, 114.9, 63.6, 63.5, 32.7, 14.9, 14.8; IR (neat, cm^{-1}) 3421, 2983, 1728, 1633, 1508, 1477, 1393, 1246, 1194, 1045, 837, 789; HRMS (EI, m/z) calcd for $C_{19}H_{20}N_2O_3S$ (M^+) 356.1195, found 356.1198.

(*E*)-2-(4-Iodophenylimino)-3-(4-iodophenyl)thiazolidin-4-one (5g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.83 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 3.98 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 155.1, 147.4, 138.6, 138.2, 134.2, 129.7, 123.0, 94.9, 88.7, 32.9; IR (neat, cm^{-1}) 3046, 2943, 2926, 2854, 1728, 1628, 1483, 1366, 1273, 1191, 1150, 1057, 874, 828, 808, 736; HRMS (EI, m/z) calcd for $C_{15}H_{10}I_2N_2OS$ (M^+) 519.8603, found 519.8600.

Acknowledgements

We acknowledge the National Science Council of the Republic of China and CEM Corporation for financial and instrument support. (NSC 100-2113-M-040-006, NSC 99-2113-M-040-003-MY2).

Notes and references

1 A. Ranise, A. Spallarossa, O. Bruno, S. Schenone, P. Fossa, G. Menozzi, F. Bondavalli, L. Mosti, A. Capuano, F. Mazzeo, G. Falcone and W. Filippelli, *Il Farmaco.*, 2003, **58**, 765.

2 J. Lee, J. Lee, M. Kang, M. Shin, J. M. Kim, S. U. Kang, J. O. Lim, H. K. Choi, Y. G. Suh, H. G. Park, U. Oh, H. D. Kim, Y. H. Park, H. J. Ha, Y. H. Kim, A. Toth, Y. Wang, R. Tran, L. V. Pearce, D. J. Lundberg and P. M. Blumberg, *J. Med. Chem.*, 2003, **46**, 3116.
3 S. Cunha, F. C. Macedo, G. A. N. Costa, M. T. Rodrigues, R. B. V. Verde, L. C. de Souza Neta, I. Vencato, C. Lariucci and F. P. Sá, *Monatsh. Chem.*, 2007, **138**, 511.
4 A. M. M. E. Omar, A. M. Farghaly, A. A. B. Hazzai, N. H. F. M. Sharabi and T. T. Daabees, *J. Pharm. Sci.*, 1981, **70**, 1075.
5 G. Crank, M. Neville and R. Ryden, *J. Med. Chem.*, 1973, **16**, 1402.
6 C. Walpole, S. Y. Ko, M. Brown, D. Beattie, E. Campbell, F. Dickenson, S. Ewan, G. A. Hughes, M. Lemaira, J. Lerpiniere, S. Patel and L. Urban, *J. Med. Chem.*, 1998, **41**, 3159.
7 (*a*) D. C. Schroeder, *Chem. Rev.*, 1955, **55**, 181; (*b*) G. Y. Sarkis and E. D. J. Faisal, *Heterocycl. Chem.*, 1985, **22**, 137.
8 A. G. Makhsumov, A. S. Safaev and S. V. Abidova, *Katal. Pererab. Uglevodorodnogo Syr'ya*, 1968, **2**, 101.
9 (*a*) S. Kasmi, J. Hamelin and H. Benhaoua, *Tetrahedron Lett.*, 1998, **39**, 8093; (*b*) P. C. Kearney, M. Fernandez and J. A. Flygare, *J. Org. Chem.*, 1998, **63**, 196; (*c*) C. Boga, L. Forlani, C. Silvestroni, A. B. Corradi and P. Sgarabotto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1363; (*d*) M. Kidwai, R. Venkataramanan and B. Dave, *Green Chem.*, 2001, **3**, 278; (*e*) W. Du and D. P. Curran, *Org. Lett.*, 2003, **5**, 1765.
10 (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*b*) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2004, **43**, 2062; (*c*) J. Wang, H. Li, X. Yu, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4293; (*d*) Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 4032; (*e*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*f*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*g*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418.
11 (*a*) E. B. Veale, G. M. Tocci, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2009, **7**, 3447; (*b*) Y. Shiraishi, S. Sumiya and T. Hirai, *Org. Biomol. Chem.*, 2010, **8**, 1310; (*c*) D. Maity and T. Govindaraju, *Chem.–Eur. J.*, 2011, **17**, 1410.
12 A. R. Katritzky, S. Ledoux, R. M. Witek and S. K. Nair, *J. Org. Chem.*, 2004, **69**, 2976.
13 S. Sharma, *Synthesis*, 1978, 803.
14 H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 351.
15 J. Erickson, *J. Org. Chem.*, 1956, **21**, 483.
16 B. Yin, Z. Liu, M. Yi and J. Zhang, *Tetrahedron Lett.*, 2008, **49**, 3687.
17 J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, *J. Am. Chem. Soc.*, 1951, **73**, 906.
18 (*a*) R. S. Varma, *Green Chem.*, 1999, **1**, 43; (*b*) C. R. Strauss, *Aust. J. Chem.*, 1999, **52**, 83; (*c*) R. S. Varma, *Pure Appl. Chem.*, 2001, **73**, 193; (*d*) P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225; (*e*) M. Larhed, C. Moberg and A. Hallberg, *Acc. Chem. Res.*, 2002, **35**, 717.
19 (*a*) S. Caddick and R. Fitzmaurice, *Tetrahedron*, 2009, **65**, 3325; (*b*) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (*c*) C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 3605; (*d*) A. Saha, R. B. Nasir Baig, J. Leazer and R. S. Varma, *Chem. Commun.*, 2012, **48**, 8889.
20 (*a*) M. R. Maddani and K. R. Prabhu, *J. Org. Chem.*, 2010, **75**, 2327; (*b*) S. F. Gan, J. P. Wan, Y. J. Pan and C. R. Sun, *Mol. Diversity*, 2011, **15**, 809.
21 (*a*) R. Maly, *Justus Liebigs Ann. Chem.*, 1873, **168**, 133; (*b*) J. Volhard, *Justus Liebigs Ann. Chem.*, 1873, **166**, 383; (*c*) S. P. Singh, S. S. Parmar, K. Raman and V. I. Stenberg, *Chem. Rev.*, 1981, **81**, 175; (*d*) F. C. Brown, *Chem. Rev.*, 1961, **61**, 463.

