J IRAN CHEM SOC (2013) 10:725–732
DOI 10.1007/s13738-012-0206-0

ORIGINAL PAPER

Efficient synthesis of functionalized dithiocarbamate derivatives through one-pot three-component reaction and evaluation of their antimicrobial activities

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Received: 15 August 2012 / Accepted: 5 December 2012 / Published online: 15 January 2013

Abstract The one-pot three-component reaction of primary and secondary amines, carbon disulfide and β-nitrostyrene derivatives in neat condition at room temperature afforded functionalized dithiocarbamate derivatives in good to high yields. High bond-forming efficiency and easy work-up are advantages of this reaction. In vitro antimicrobial activities of synthesized compounds were studied against four Gram-positive bacteria, four Gram-negative bacteria and four fungi. The screening for the antimicrobial activity was performed by twofold serial dilution technique. Notably, some synthesized compounds displayed comparable or even better antibacterial and antifungal activities against some tested strains than the reference drugs ampicillin, streptomycin and amphotericin B, respectively.

Keywords One-pot multicomponent reactions (MCRs) · β-Nitrostyrene · Michael addition · Neat reaction conditions · Functionalized dithiocarbamates · Antimicrobial activity

Introduction

Multicomponent reactions (MCRs) have gained a wide interest in organic and medicinal chemistry. The development of convenient approaches and selective synthetic transformations through new one-pot MCRs is a major challenge in modern organic synthesis [1–5]. Meanwhile, solvent-free synthetic methods are being discovered for eco-friendly synthesis of many organic compounds [6–8]. The reactions under solvent-free conditions are considerably safe, non-toxic and prevent energy consumption [9–11]. Carrying out one-pot multi-component reactions in solvent-free conditions is of great importance in the context of green synthesis.

Dithiocarbamates are important sulfur-containing compounds, which possess broad applications in organic and medicinal chemistry [12–14]. They have been widely used in organic synthesis [15–19], and they have a variety of applications in agriculture [20–22], as well as in the rubber industry as vulcanization accelerators and antioxidants [23–25]. Furthermore, some of the dithiocarbamates have direct antibacterial [26–28] and antitumor [29–32] functions and are also cell apoptosis inhibitors [33]. Consequently, the synthesis of dithiocarbamate derivatives with different substitution patterns at the thiol chain has become a field of increasing interest in synthetic organic chemistry during the past years. A survey of the literature revealed relatively few methods for the synthesis of dithiocarbamate derivatives in one-pot fashion, [34–48]

Electronic supplementary material The online version of this article (doi:10.1007/s13738-012-0206-0) contains supplementary material, which is available to authorized users.

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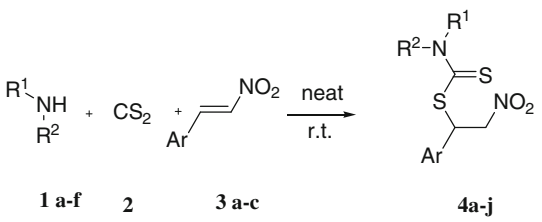
while some bases such as NaOH, $NaOC_2H_5$, Et_3N, and Cs_2CO_3 in different organic solvents were used for this goal. In addition, some of the reported methods require toxic reagents in the presence of a catalyst. Recently, Michael addition of electron-deficient alkenes with aryl amines and CS_2 in solid media alkaline Al_2O_3 was used for the preparation of dithiocarbamic acid esters [49]. In this regard, β-nitrostyrene and its derivatives which are important synthetic intermediates and starting materials for the synthesis of a variety of useful building blocks [50–54] are considered attractive candidates, as Michael acceptor, for the synthesis of dithiocarbamates.

In continuation of our research, interest for developing novel domino reactions [55–59], herein we have presented a new and one-pot three-component methodology for the synthesis of functionalized dithiocarbamates containing nitro group via the reaction of carbon disulfide, primary or secondary amines, and β-nitrostyrene derivatives (Scheme 1).

Results and discussion

We began our investigations with the synthesis of β-nitrostyrene **3a** (Ar = Ph), which could be synthesized according to the reported methods [60]. The reaction of **3a** with piperidine and carbon disulfide was chosen as the model reaction. Stirring of the mixture in the ionic liquid [bmim][BF_4] (*n*-butyl-1-methylimidazoium *tetra*-fluoro borate) did not provide any product. Therefore, other solvents such as MeOH and CH_2Cl_2 were used and the desired product **4c** was obtained at room temperature in 55, and 73 % yields, respectively. But, we were pleased to find that the reaction under neat condition provided the desired dithiocarbamate **4c** in 95 % yield. The results are summarized in Table 1.

To explore the generality and scope of this reaction, a series of amines **1a-f** and β-nitrostyrenes were studied for the synthesis of dithiocarbamates **4a-j** and the results are illustrated in Table 2. The results showed that the reaction time varied according to the nature of substituents on the β-nitrostyrenes. For example, β-nitrostyrene, bearing the electron-donating group such as methyl, required longer



Scheme 1 Synthesis of functionalized dithiocarbamates using one-pot three-component reaction

Table 1 Solvent effect on the formation of dithiocarbamate **4c**

Entry	Solvent	Yield %
1	Neat	95
2	CH_2Cl_2	73
3	MeOH	55
4	Ionic liquid	–

reaction time (8 h) to obtain its corresponding adduct. Furthermore, β-nitrostyrenes are more reactive toward secondary amines such as diallylamine compared to the primary ones. In general, this methodology provided good to high yields for the substrates.

In order to extend the scope of the our protocol, we scaled-up the reaction using 20 mmol of β-nitrostyrene **3a** in the presence of carbon disulfide and diallylamine at room temperature. The reaction proceeded without difficulty to obtain a high yield of product **4a** (95 %). The products are nitro dithiocarbamates which may be converted to various valuable products. Nitro compounds are versatile precursors of diverse functionalities, for example, they could be converted into carbonyl group through Nef reaction, [61] or into amine group via reduction, etc. [51].

A proposed reaction mechanism is depicted in Scheme 2. In the first step, in the synthetic sequence, the reaction of primary or secondary amines with carbon disulfide leads to thiocarbamates as *S*-nucleophiles. Addition of *S*-nucleophiles to the synthesized β-nitrostyrenes leads to the desired products.

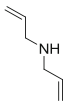
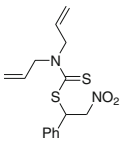
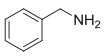
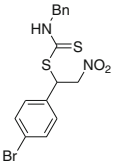
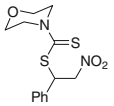
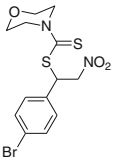
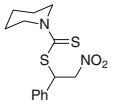
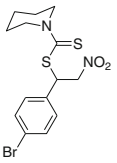
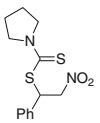
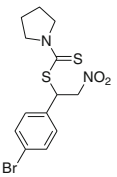
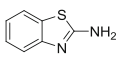
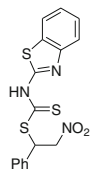
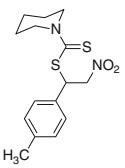
The formation of dithiocarbamates was confirmed by an X-ray diffraction study of single crystals of **4c**. The molecular structure of the compound is shown in Fig. 1.

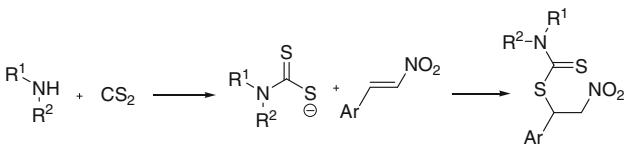
The structures of the products were determined from spectroscopic data and high-resolution mass spectrometry (HR-Mass-ESI). Characteristic resonances for the compounds **4a-j** in the ^{1}H-NMR spectra are three distinguished doublet of doublet peaks for the three different magnetic non-equivalent hydrogen atoms S–CH–CH_2–NO_2. The geminal coupling for hydrogens (H_1 and H_2) in compound **3c** is 13.3 Hz and coupling constant $J_{H1H3} = 10.5$ Hz, which is in accordance with the dihedral angle. The X-ray crystallographic data could confirm the dihedral angle in the crystal structure. ($J_{12} = 13.3$ Hz, $J_{13} = 10.5$ Hz, $J_{23} = 4.9$ Hz).

Finally, the antimicrobial activity of some synthesized compounds on standard fungi and bacterial strains was evaluated.

Minimum inhibitory concentration (MIC) values of four synthesized dithiocarbamate (**4a**, **4b**, **4c** and **4d**) were determined using agar dilution method as recommended by national committee on clinical laboratory standards (NCCLS) [62, 63]. Some Standard and clinically isolated

Table 2 Synthesis of dithiocarbamates using three-component reaction of β-nitrostyrene, primary or secondary amines, and carbon disulfide

Entry	Aryl	Amine	Product	Entry	Aryl	Amine	Product
1	Ph	 **1a**	 **4a**(95%, 2h)	**6**	4-Br-C_6H_4	 **1f**	 **4f**(70%, 7h)
2	Ph	 **1b**	 **4b**(75%, 2.5h)	**7**	4-Br-C_6H_4	 **1b**	 **4g**(65%, 5h)
3	Ph	 **1c**	 **4c**(81%, 3h)	**8**	4-Br-C_6H_4	 **1c**	 **4h**(77%, 5h)
4	Ph	 **1d**	 **4d**(70%, 2h)	**9**	4-Br-C_6H_4	 **1d**	 **4i**(83%, 4h)
5	Ph	 **1e**	 **4e**(68%, 4h)	**10**	4-H_3C-C_6H_4	 **1c**	 **4j**(80%, 8h)



Scheme 2 Plausible mechanism for the synthesis of compounds **4a-j**

strains of the bacteria including; *Escherichia coli* (ATCC8739), *Pseudomonas aeruginosa* (ATCC9027), *Salmonella typhi* (NCTC5761), and *Enterobacter aerogenes* (*PTCC1221*) as Gram-negative bacteria and *Bacillus subtilis* (ATCC6633), *Entrococcus faecalis* (PTCC1237), *Staphylococcus aureus* (ATCC25923) as gram-positive bacteria were used to determine antimicrobial activity. A clinically isolated strain of methicillin-resistant *Staphylococcus aureus* (MRSA) as well as four fungi including; *Candida albicans* (ATCC10231), *Candida tropicalis* (*ATCC750*), *Fusarium oxysporum* (*DSM62060*) and *Aspergillus niger* (CBS513.88) were also examined ampicillin, streptomycin and amphotericin B were used as the reference antibiotics. The bacteria and fungi were cultivated in Mueller–Hinton agar and potato dextrose agar (PDA),

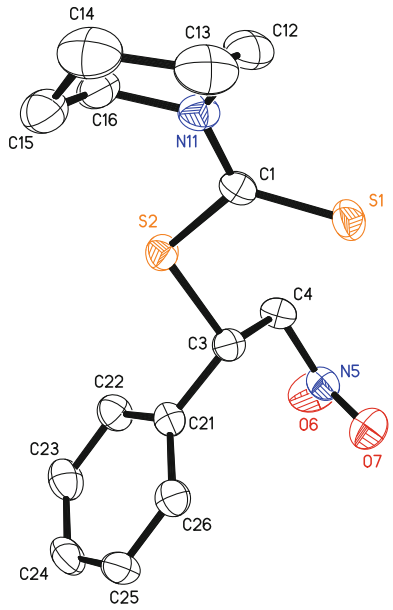


Fig. 1 ORTEP structure of compound **4c**

respectively. The synthesized dithiocarbamate and antibiotics were dissolved in DMSO before mixing with Mueller–Hinton Agar or PDA. Final concentrations of the test compounds in the medium were 512, 265, 128…0.0.01 μg/mL. The lowest concentration, in which no visible growth was detected, was taken as the MIC. The control of experiments was done using DMSO. Each measurement was repeated three times.

Tables 3 and 4 represent antimicrobial activity of some synthesized dithiocarbamates which show significant activity against bacterial and fungal strains. It was also found that Gram-positive microorganisms were more sensitive than Gram-negative bacteria and fungi. The compound **4d** demonstrated the highest potency against tested strains while **4b** exhibited the lowest activity.

The compound **4a** exhibited highly antibacterial activity. Moreover, the MIC of compound **4d** against most tested microorganisms was comparable or superior to standard antibiotics. The MIC value for the Gram-negative bacteria was 32 μg/mL except for *P. aeruginosa*. Furthermore the MIC values, ranging from 0.5 to 2 μg/mL, were found for the Gram-positive bacteria (Table 3).

However, the antibacterial activity of compound **4d** against Gram-positive bacteria was comparable to ampicillin as a reference drug (Table 3).

The compounds **4b** and **4c** were slightly less active than the compounds **4a** and **4d**. The screening data revealed that these compounds have moderate activity against bacteria (Table 3).

While all tested compounds showed a weak activity against drug resistance *P. aeruginosa* (MIC 128–256 μg/mL), they had high activity against methicillin-resistant *S. aureus*.

Methicillin-resistant *Staphylococcus aureus* was known to be the most virulent organism that caused a broad array of problems to hospitalized patients, and showed multi-drug resistance to numerous currently available agents. The compound **4b** showed the highest anti-MRSA activity (2 μg/mL) that was twofold more active than Streptomycin and fourfold active than ampicillin. The MIC value of compound **4a** against MRSA (4 μg/mL) was the same as Streptomycin and threefold more active than ampicillin. These results suggested that dithiocarbamate derivatives have anti-MRSA potential and can be considered as a lead compound for future study.

Moreover, synthesized dithiocarbamate compounds showed strong to moderate antifungal activity (Table 4). These compounds exhibited strong antifungal activity against pathogenic yeast and moderate activity against pathogenic mould. The compound 4d showed the highest antifungal activity with the MIC values ranging from 2 to 32 μg/mL (Table 4).

Experimental section

General

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal 9100* apparatus and were uncorrected. IR spectra

Table 3 Minimum inhibitory concentration (MIC) against some Gram-negative and Gram-positive bacteria

MIC (μg/mL)								
Compound	*B. subtilis* ATCC 6633	*E. faecalis* PTCC 1237	*S. aureus* ATCC 25923	MRSA	*E. coli* ATCC 8739	*P. aeruginosa* ATCC9027	*S. typhi* NCTC 5761	E. *aerogenes* PTCC1221
4a	2	16	2	4	64	128	64	64
4b	64	64	64	128	128	256	128	128
4c	16	16	32	64	64	128	64	64
4d	0.5	2	1	2	32	128	32	32
Ampicillin	2	4	0.5	16	4	R	8	256
Streptomycin	1	128	1	4	0.5	16	0.5	2

Table 4 Minimum inhibitory concentration (MIC) against some fungi

MIC (μg/mL)				
Compound	*C. albicans* ATCC10231	*C.tropicalis* ATCC750	*F.oxysporum* DSM62060	*A. niger* CBS513.88
4a	8	8	64	64
4b	32	32	128	128
4c	32	8	64	64
4d	2	4	32	16
Amphotericin B	2	1	4	4

were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker DRX-500 AVANCE spectrometer at 500 or 300 MHz for ^{1}HNMR, and 125 or 75 MHz for ^{13}CNMR. $CDCl_3$ was used as solvent. HRMS was recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer. CCDC 818603 for compound **4c** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the synthesis of 4a-j

Carbon disulfide (83.6 mg, 1.1 mmol) and the unsubstituted or substituted β-nitrostyrene (1 mmol; 1.0 eq.) were stirred at room temperature; after 10 min amine (1 mmol) was added slowly. The progress of the reaction was monitored by TLC (Eluent:petroleum ether:ethyl acetate, 1:1). After completion of the reaction (2–8 h), the excess CS_2 was removed in vacuum and the residue was further purified by recrystallization in a mixture of petroleum ether –CH_2Cl_2 (3:1).

2-Nitro-1-phenylethyl diallylcarbamodithioate(**4a**) (95 %)

Mp: 60–62 °C, IR (KBr, cm^{-1}): *v* 1,555, 1,406, 1,175, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.27 (d, 2H, $J = 4.3$ Hz, 2-CH),4.57–4.69 (m, 2H, 2-CH), 4.9 (dd, 1H, $J = 13.3$, 10.5 Hz, –CH), 5.20(dd, 2H, $J = 12.9$, 4.3 Hz, –CH), 5.28 (d, 2H, $J = 12.9$ Hz, =CH), 5.32 (dd, 1H, $J = 12.9$, 4.9 Hz), 5.74 (dd, 1H, $J = 10.5$, 4.9 Hz, –CH), 5.79–5.94 (m, 2H, 2-CH), 7.27–7.4 (m, 5H, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 51.9, 53.7, 56.5, 77.6, 119.0, 128.4, 128.9, 129.1, 129.9, 130.5, 134.7, 194.2, HR-Mass (ESI) Calc. for $C_{15}H_{18}N_2O_2S_2$ $[M+H]^+$ 323.08850, found 323.08844.

2-Nitro-1-phenylethyl morpholine-4-carbodithioate(**4b**) (75 %)

MP: 87–90 °C, IR(KBr, cm^{-1}): *v* 1,555, 1,370,1,113, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.77(s, 4H, 2 –CH_2), 3.88 (brs, 2H, 2-CH), 4.29 (brs, 2H, 2-CH), 4.90 (dd, 1H, $J = 13.3$, 10.5 Hz, –CH), 5.31 (dd, 1H, $J = 13.3$, 4.9 Hz, –CH), 5.79 (dd, 1H, $J = 10.5$, 4.9 Hz, –CH), 7.27–7.39 (m, 5H, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 51.5, 66.1, 77.6, 128.4, 129.0, 129.2, 134.7, 193.6, HR- Mass (ESI) Calc. for $C_{13}H_{16}NaN_2O_3S_2$ $[M+Na]^+$ 335.05006, found 335.04992.

2-Nitro-1-phenylethyl piperidine-1-carbodithioate(**4c**) (81 %)

Mp: 86–88 °C, IR (KBr, cm^{-1}): *v* 1,557, 1,375, 1,020, ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.60–1.70 (m, 6H, 3CH_2), 3.83 (brs, 1H, –CH), 3.77 (brs, 1H, –CH), 4.18 (brs, 1H, –CH), 4.32 (brs, 1H, –CH), 4.88 (dd, 1H, $J = 13.3$, 10.5 Hz, –CH), 5.33 (dd, 1H, $J = 13.3$, 4.9 Hz, –CH), 5.74 (dd, 1H, $J = 10.5$, 4.9 Hz, –CH), 7.25–7.40 (m, 5H, H–Ar), ^{13}C-NMR(125 MHz, $CDCl_3$):δ 24.6, 25.8, 52.0, 53.4, 78.3,128.8, 129.3, 129.5, 135.4, 192.1, HR-Mass (ESI) Calc. for $C_{14}H_{19}N_2O_2S_2$ $[M+H]^+$ 311.08866, found 311.08856.

Colorless crystal (polyhedron), dimensions 0.31 × 0.21 × 0.07 mm^3, crystal system monoclinic, space group $P2_1/n$, $Z = 4$, $a = 13.3431(16)$ Å, $b = 6.3809(8)$ Å, $c = 18.117(2)$ Å, alpha = 90°, beta = 90.037(3)°, gamma = 90°, $V = 1{,}542.5(3)$ $Å^3$, rho = 1.337 g/cm^3, $T = 200(2)$ K, $Theta_{max} = 28.32°$, radiation Mo Kalpha, lambda = 0.71073 Å, 0.3° omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 15,454 reflections measured, 3,836 unique (R(int) = 0.0462), 3,225 observed ($I > 2(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS [61] based on the Laue symmetry of the reciprocal space, mu = 0.35 mm^{-1}, $T_{min} = 0.90$, $T_{max} = 0.98$, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package [64, 65], 181 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.16 for observed reflections, final residual values $R1(F) = 0.072$, $wR(F^2) = 0.142$ for observed reflections, residual electron density −0.37–0.50 $eÅ^{-3}$. CCDC 818603 contains the supplementary crystallographic data for this paper. These data can be obtained

free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

2-Nitro-1-phenylethyl pyrrolidine-1-carbodithioate (**4d**) (70 %)

Mp: 110–112 °C, IR(KBr, cm^{-1}): *v* 1,555, 1,370, 1,165, ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.94–2.11 (m, 4H, 2-CH_2), 3.54–3.64 (m, 2H, 2-CH), 3.84–3.94 (m, 2H, 2-CH), 4.9 (dd, 1H, *J* = 10.5, 4.9 Hz, –CH), 5.32 (dd, 1H, *J* = 13.3, 4.9 Hz, –CH), 5.78 (dd, 1H, *J* = 13.3, 10.5 Hz, –CH), 7.27–7.41 (m, 5H, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.2, 26.1, 50.7, 50.9, 55.1, 77.7, 128.3, 128.8, 129.1, 135.0, 189.0.HR-Mass (ESI) Calc. for $C_{13}H_{17}N_2O_2S_2$ $[M+H]^+$ 297.41433, found 297.41425.

2-Nitro-1-phenylethyl benzo[d]thiazol-2-ylcarbamodithioate(**4e**) :(68 %)

Mp: 130–133 °C, IR(KBr, cm^{-1}): *v* 3,209, 1,550, 1,400, 1,110, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.85 (dd, 1H, *J* = 13.0, 5.6 Hz, –CH), 5.09 (dd, 1H, *J* = 13.0, 6.8 Hz, –CH), 5.68 (t, 2H, *J* = 6.6 Hz, –CH_2), 7.14 (td, 1H, *J* = 6.7, 1 Hz, H–Ar), 7.30 (td, 1H, *J* = 5.6, 1 Hz, –CH, H–Ar), 7.36–7.42 (m, 5H, H–Ar), 7.56 (dd, 1H, *J* = 4.3, 1.0 Hz, –CH, HAr), 7.58 (dd, 1H, *J* = 4.3, 1.0 Hz, –CH, H–Ar), ^{13} C-NMR (75 MHz, $CDCl_3$): δ 56.8, 78.3, 119.5, 120.9, 122.5, 126.2, 126.6, 129.1, 129.4, 130.5, 136.1, 151.3, 165.3.HR-Mass (ESI) Calc. for $C_{16}H_{14}N_3O_2S_3$ $[M+H]^+$ 376.49875, found 376.49859.

1-(4-Bromophenyl)-2-nitroethyl benzylcarbamodithioate(**4f**) (70 %)

Mp: 104–108 °C, IR (KBr, cm^{-1}): *v* 3,322, 1,550, 1,324, 1,100, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.85 (brs, 2H, –CH_2), 4.82–4.90 (m, 1H, –CH), 5.17 (dd, 1H, *J* = 13.5,4.9 Hz, –CH), 5.73 (dd, 1H, *J* = 10, 4.9 Hz, –CH), 7.07 (brs, 1H, NH), 7.25 (d, 2H, *J* = 8.0 Hz, 2-CH, H–Ar), 7.29–7.38 (m, 5H, 5-CH, H–Ar), 7.50 (d, 2H, *J* = 8.0 Hz, 2-CH, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 49.7, 51.5, 77.7, 123.0, 128.4, 128.5, 129.1, 129.8, 132.3, 134.0, 135.4, 193.6. HR-Mass (ESI) Calc. for $C_{16}H_{16}N_2O_2S_2^{79}Br$ $[M+H]^+$ 412.34385, found 412.34394; Calc. for $C_{16}H_{16}N_2O_2S_2^{81}Br$ $[M+H]^+$414.33405, found 412.33396.

1-(4-Bromophenyl)-2-nitroethyl morpholine-4-carbodithioate(**4g**) (65 %)

Mp: 95–100 °C, IR (KBr, cm^{-1}): *v* 1,550, 1,421, 1,117, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.80 (brs, 6H, 2-CH_2O, –CH_2N), 4.30 (brs, 2H, 2-CH), 4.85 (dd, 1H, *J* = 13.3, 10.5 Hz, –CH), 5.26 (dd, 1H, –CH, *J* = 13.3, 4.9 Hz), 5.76 (dd, 1H, *J* = 10.5, 4.9 Hz, –CH), 7.26 (d, 2H, *J* = 8 Hz, 2-CH, H–Ar,), 7.495(d, 2H, *J* = 8 Hz, 2-CH, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 50.8, 65.9, 77.0, 123.1, 130.0, 132.3, 133.8, 192.9. HR-Mass (ESI) Calc. for $C_{13}H_{16}N_2O_3S_2^{79}Br$ $[M+H]^+$392.31043, found 392.31035; Calc.for $C_{13}H_{16}N_2O_3S_2^{81}Br$ $[M+H]$ $^+$394.22365, found 394.22357.

1-(4-Bromophenyl)-2-nitroethylpiperidine-1-carbodithioate(**4h**) (77 %)

Mp: 90–92 °C, IR (KBr,cm^{-1}): *v* 1,550, 1,380, 1,113, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 6H, 3-CH_2), 3.8 (brs, 2H, 2-CH), 4.18 (d, 1H, *J* = 15.3 Hz, –CH), 4.34 (d, 1H, *J* = 15.3 Hz, –CH), 4.835 (dd, 1H, *J* = 13.5, 10.5 Hz, –CH), 5.30 (dd, 1H, *J* = 13.5, 4.9 Hz, –CH,), 5.75 (dd, 1H, *J* = 10.5, 4.9 Hz, –CH), 7.28 (d, 2H, *J* = 8.5 Hz, 2-CH, H–Ar), 7.47 (d, 2H, *J* = 8.5 Hz, 2-CH, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$–): δ 24.1, 51.6, 77.6, 122.9, 130.37, 132.25, 134.17, 191.07. HR-Mass (ESI) Calc. for $C_{14}H_{18}N_2O_2S_2^{79}Br$ $[M+H]^+$ 390.34086, found 390.34080; Calc. for $C_{14}H_{18}N_2O_2S_2^{81}Br$ $[M+H]^+$ 392. 23365, found 392.23350.

1-(4-Bromophenyl)-2-nitroethylpyrrolidine-1-carbodithioate(**4i**): (83 %)

Mp: 70–75 °C, IR(KBr, cm^{-1}): *v* 1,550, 1,370, 1,165, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.95–2.12 (m, 4H, 2-CH_2), 3.54–3.64 (m, 2H, 2-CH), 3.9–3.94 (t, 2H, *J* = 6.7 Hz), 4.83 (dd, 1H, *J* = 10.5, 13.3 Hz, –CH), 5.29 (dd, 1H, *J* = 4.9, 13.3 Hz, –CH), 5.77 (dd, 1H, *J* = 4.9, 10.5 Hz, –CH), 7.27(d, 2H, *J* = 8.3 Hz, H–Ar), 7.48 (d, 2H, *J* = 8.3 Hz, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.2, 26.1, 50.3, 50.7, 55.2, 77.5, 122.9, 129.9, 132.3, 134.3, 188.5.HR-Mass (ESI) Calc. for $C_{13}H_{16}N_2O_2S_2^{79}Br$ $[M+H]^+$ 376.31255, found 376.31242; Calc. for $C_{13}H_{16}N_2O_2S_2^{81}Br$ $[M+H]^+$ 378. 22415, found 392.22405.

2-Nitro-1-p-tolylethyl piperidine-1-carbodithioate(**4j**): (80 %)

MP: 90–92 °C, IR (KBr, cm^{-1}): *v* 1,552, 1,377, 1,120, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.71 (brs, 6H, 3–CH_2), 2.33 (s, 3H, –CH_3), 3.8 (d, 2H, *J* = 17.4 Hz), 4.18 (brs, 1H, –CH), 4.34 (brs, 1H, –CH), 4.87 (dd, 1H, –CH, *J* = 13.3, 10.5 Hz), 5.36 (dd, 1H, *J* = 13.3, 4.9 Hz), 5.71 (dd, 1H, –CH, *J* = 10.5, 4.9 Hz), 7.16 (d, 2H, *J* = 8.0 Hz, H–Ar), 7.28 (d, 2H, *J* = 8.0 Hz, H–Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.2, 24.2, 25.4, 26.0, 51.4, 77.81, 128.3, 129.8,

131.7, 138.9, 191.8.HR-Mass (ESI) Calc. for $C_{15}H_{21}N_2O_2S_2$ $[M+H]^+$ 325.47753, found 325.47742.

General procedure for the biological tests

Bacteria and fungi were cultivated in Mueller–Hinton Agar and PDA, respectively. The synthesized dithiocarbamate and reference antibiotics were dissolved in DMSO before mixing with Mueller–Hinton agar or PDA. Final concentration of test compounds in the medium was 512–265–128…0.0.01 μg/mL. The medium was then poured into sterilized Petri dishes. The lowest concentration at which there was no visible growth was taken as the MIC. Control experiments using DMSO were done as a negative control.

Conclusions

In conclusion, we report a novel one-pot and three-component methodology for the synthesis of functionalized dithiocarbamate derivatives in good to high yields. The simple reaction conditions, inexpensive initial materials, simple work-up and short reaction time are the advantages of the presented method, compared to the previously reported procedures. Moreover, the evaluation of antimicrobial activity of these synthesized dithiocarbamate demonstrated a considerable antimicrobial activity against bacteria and fungi. The results revealed that the synthesized dithiocarbamate has a good potency in inhibiting the growth of *B. subtilis*, *E. faecalis*, *S. aureus*, MRSA, *C.albicans* and *C. tropicalis* and are less active against *E. coli*, *P.aeruginosa*, *S. typhi*, *E. aerogenes*, *F. oxysporum* and *A. niger.*

Acknowledgments S.B gratefully acknowledges Iran National Science Foundation (INSF) for financial support. We thank Prof. R. Gleiter for his valuable discussions. We express our gratitude to Mr. M. Jalilevand, managing director of Kimia Exir Company for donation of the chemicals and financial support.

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