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SYNTHESIS OF SOME NOVEL THIOPHENE AND THIAZOLE DERIVATIVES AND THEIR ANTIMICROBIAL EVALUATION

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Abstract – Reactions of phenyl isothiocyanate with several active methylene compounds **1** (3-oxo-3-phenylpropanenitrile, ethyl 2-cyanoacetate, pentane-2,4-dione and ethyl acetoacetate) and a molar equivalent of potassium hydroxide in dimethylformamide afforded potassium 1-(phenylamino)ethenethiolates as intermediates **2**. Reactions of **2** and 2-bromo-1-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone (**3**) afforded novel thiazole and thiophene derivatives **4**, **12**, **13** and **23a,b** in 68–78% yields. The structures of the synthesized products were confirmed using various spectroscopic techniques and single X-ray crystal structures. The novel thiophenes and thiazoles showed good antimicrobial activities against the tested bacteria and fungi.

INTRODUCTION

Ketene *N,S*-acetals, have unique structural features. They are more reactive toward electrophiles compared to ethylene.[1–3] They can activate the olefinic connection *via* an electron-releasing groups (*e.g.* amino and alkylthio) over p–π conjugation.[1–3] Functionalized ketene *N,S*-acetals such as enaminones (Figure 1; EWG = -COR) have been proven to be particularly useful intermediates in organic synthesis due to their reactivity and flexibility and can act as 1,3-dipoles or 1,3-*C,N*-dinucleophiles.[4–8]

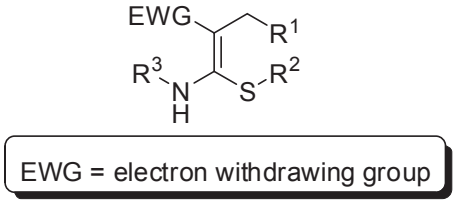


Figure 1. Ketene *N,S*-acetals

Ketene *N,S*-acetals can be used in the synthesis of multifunctionalized thiophenes and thiazoles.[9] For example, they are involved in the synthesis of CDK inhibitor anticancer agent[10] and PI3K inhibitors.[11,12]

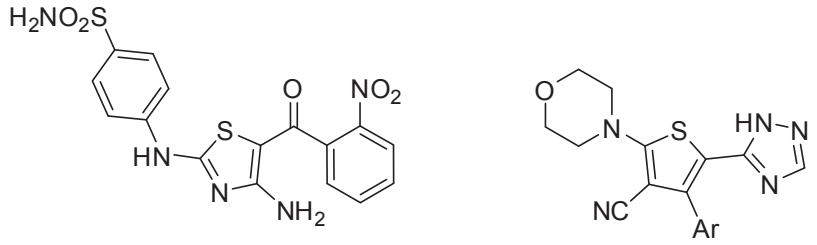


Figure 2. Examples of biologically active multifunctionalized thiazoles and thiophenes

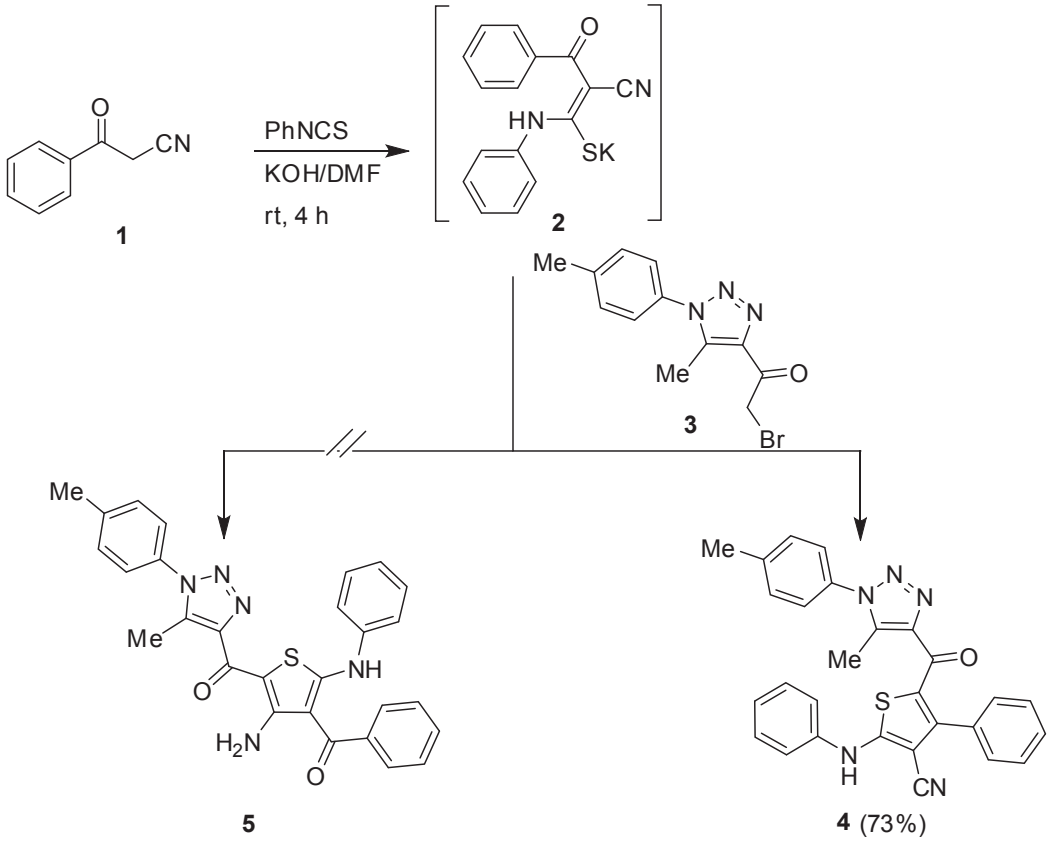
In the current study, we synthesized polyfunctionalized novel thiophenes and thiazoles *via* one-pot three-components reaction involving active methylene compounds, phenyl isothiocyanate and 2-bromo-1-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone in basic medium as part of our continuing interest in the area of heterocycles with potential applications.[13–20]

RESULTS AND DISCUSSION

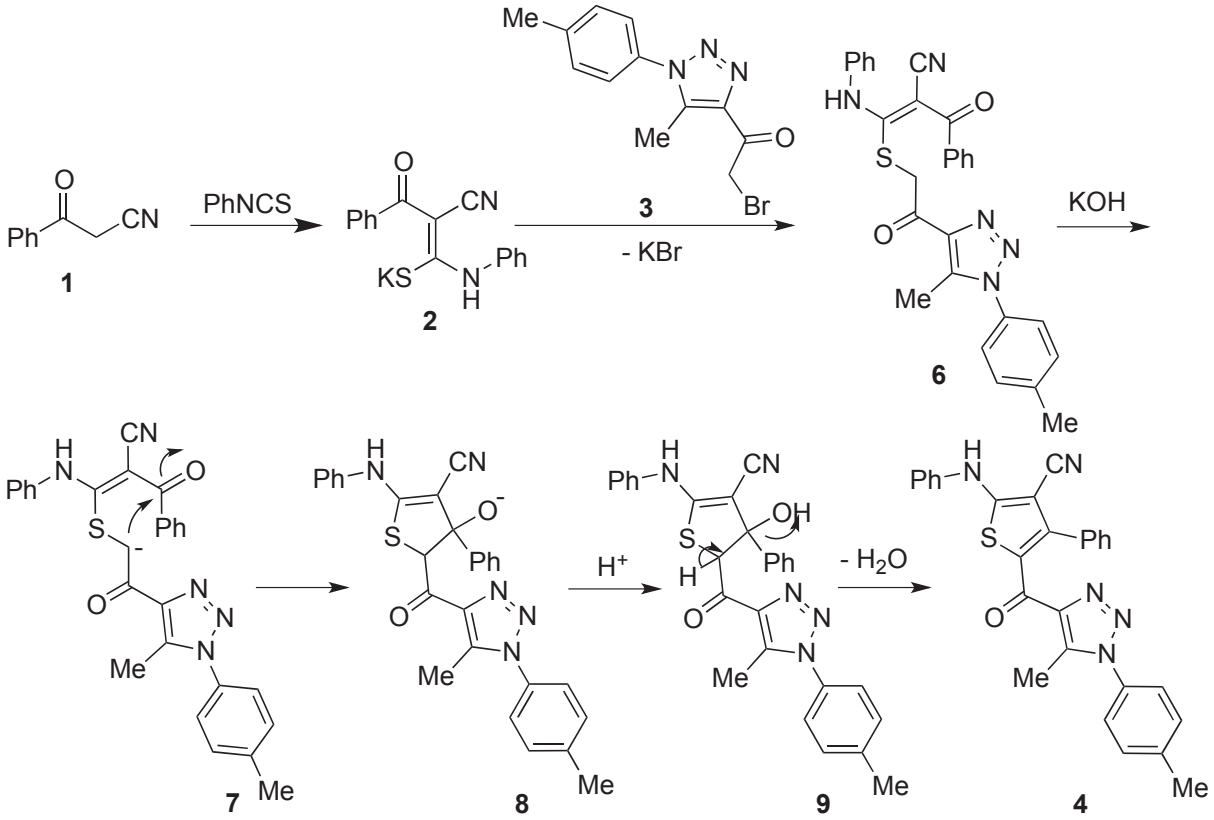
Chemistry

A mixture of molar equivalents of phenyl isothiocyanate, 3-oxo-3-phenylpropanenitrile (**1**) and potassium hydroxide were stirred in dimethylformamide (DMF) at room temperature for 4 h to afford potassium 2-cyano-3-oxo-3-phenyl-1-(phenylamino)prop-1-ene-1-thiolate (**2**) *in-situ*. Intermediate **2** has not be isolated and has been allowed to react, at room temperature, with a molar equivalent of 2-bromo-1-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone (**3**) and the mixture was stirred for 12 h. Following work-up, 2-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazole-4-carbonyl)-4-phenyl-2-(phenylamino)-thiophene-3-carbonitrile (**4**; Scheme 1) was obtained in 73% yield after purification. There was no evidence for the formation of the expected product, (3-amino-4-benzoyl-5-(phenylamino)thiophen-2-yl)-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)methanone (**5**; Scheme 1).

A suggested mechanism for the formation of product **4** is shown in Scheme 2. The mechanism involves formation of intermediate **6**, produced from reaction potassium salt **2** with **3**, which under basic condition (KOH) provided anionic intermediate **7**. Cyclization of **7** gave anionic intermediate **8** which on protonation gave intermediate **9**. Elimination of a water molecule from **9** gave the product **4** (Scheme 2).

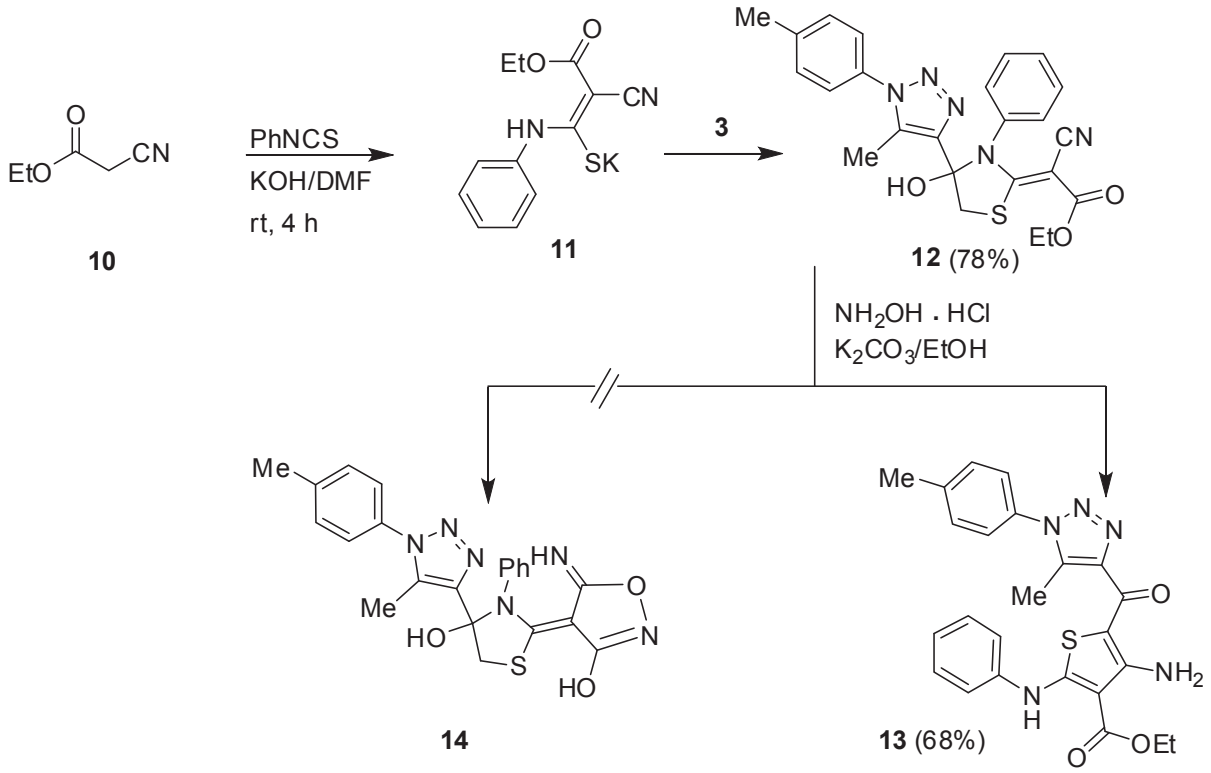


Scheme 1. One-pot synthesis of thiazole **4**



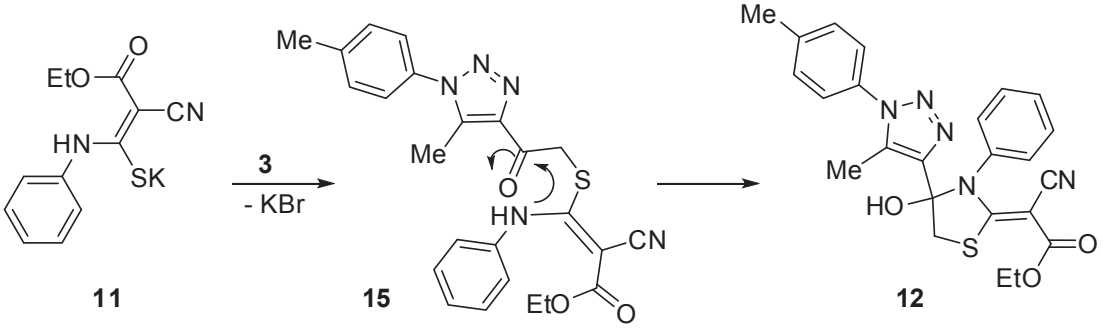
Scheme 2. A proposed mechanism for the production of **4**

Reaction of ethyl 2-cyanoacetate **10** and phenyl isothiocyanate in the presence of dried potassium hydroxide gave potassium salt **11** (Scheme 3). Treatment of **11** with **3** gave ethyl 2-cyano-2-(4-hydroxy-4-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)-3-phenylthiazolidin-2-ylidene)acetate (**12**) in 78% yield (Scheme 2). Reaction of thiazolidine **12** with hydroxylamine hydrochloride in the presence of anhydrous potassium carbonate in dry ethanol under reflux for 4 h afforded ethyl 4-amino-5-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazole-4-carbonyl)-2-(phenylamino)thiophene-3-carboxylate (**13**) in 68%. There was no evidence for the formation of the expected isoxazole **14** (Scheme 3).



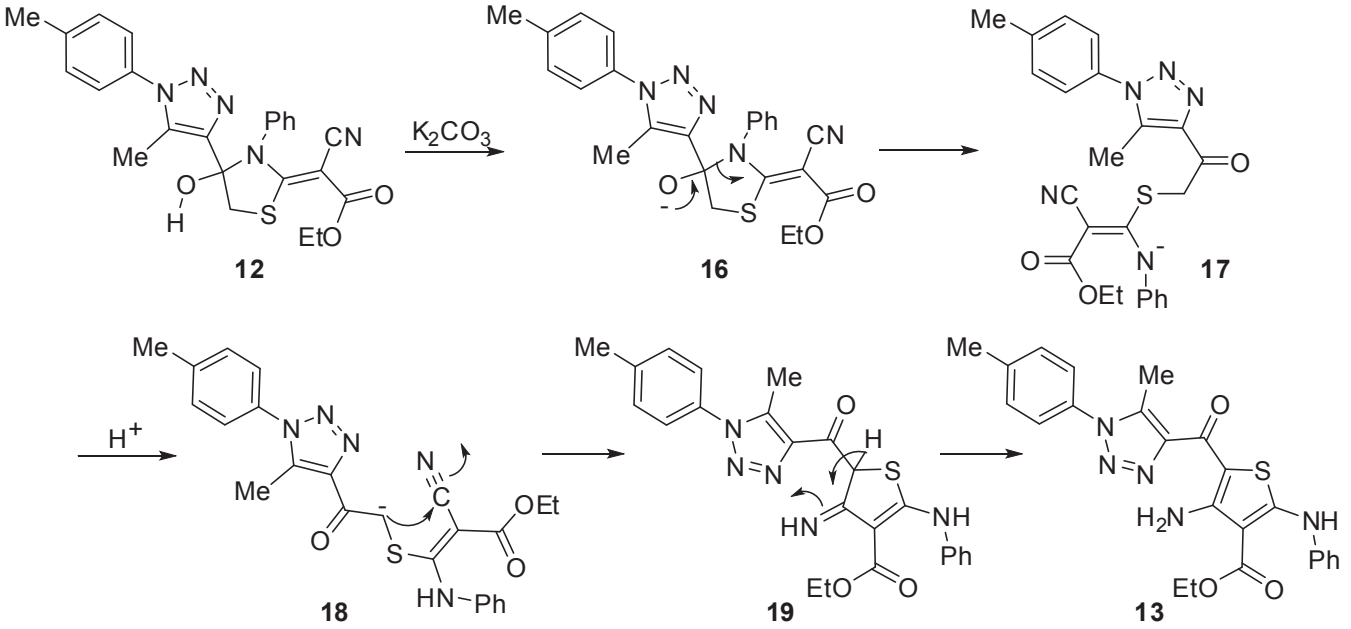
Scheme 3. One-pot synthesis of **13**

The mechanism for the production of thiazolidine compound **12** is suggested in Scheme 4. It involves reaction of **11** with equimolar equivalent of **3** to give the intermediate **15**, ethyl 3-(2-oxoethylthio)-2-cyano-3-(phenylamino)acrylate (Scheme 4). The nucleophilic attack of the NH nitrogen at the carbonyl carbon affords **12**.



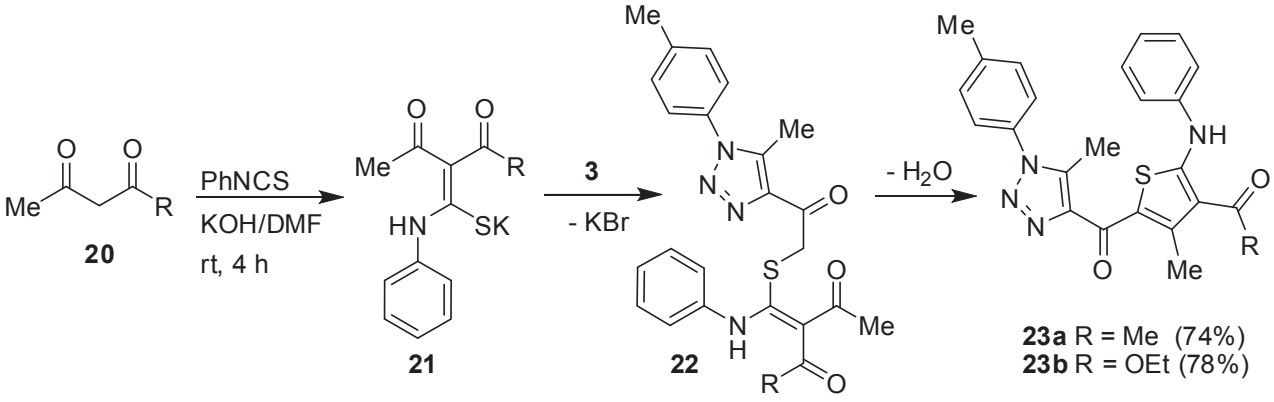
Scheme 4. A proposed mechanism for the production of **12**

The mechanism for the conversion of thiazole **12** to thiophene **13** is depicted in Scheme 5. It involves formation of anionic intermediate **16** under basic condition (K_2CO_3) as a result of deprotonation at hydroxyl group in compound **12**. Intermediate **16** would give the enolate **18** through the open form **17**. Intermediate **18** would react toward the cyano group to give the imine structure **19**. Finally, the protonation of **19** during work-up and isomerization from imine gave the product **13** (Scheme 5).



Scheme 5. A proposed mechanism for the production of **13**

Phenyl isothiocyanate are very reactive toward nucleophilic attack.[21–23] Thus, pentane-2,4-dione (**20a**, R = Me) or ethyl 3-oxobutanoate (**20b**, R = OEt) was treated with phenyl isothiocyanate in the presence of potassium hydroxide in DMF gave the corresponding 3-oxo-1-(phenylamino)but-1-ene-1-thiolate **21a,b** as an intermediate. Reactions of **21a,b** with **3** gave the corresponding intermediate **22a,b**, respectively. Elimination of water from **22a,b** afforded the target thiophenes **23a,b** (Scheme 6) in 74 and 76% yields, respectively.



Scheme 6. Synthesis of **23a,b**

The products structures were confirmed by spectral and analytical data. For example, the IR spectrum of compound **4** showed three peaks that resonate at ν 1624, 2217 and 3263 cm^{-1} corresponding to the $C{=}O_{str.}$, carbonitrile and $N\text{-}H_{str.}$, respectively. In the IR spectrum of compound **12** there are three peaks that resonate at 1685, 2212 and 3491 cm^{-1} corresponding to the $C{=}O_{str.}$, carbonitrile and $OH_{str.}$, respectively. The ^1H NMR spectrum of **12** shows the two thizolidine protons as a doublet and a double doublet that resonated at 3.58 and 4.44 ppm, respectively. The ^1H NMR spectrum of **13** shows a singlet exchangeable signal corresponding to the NH_2 protons that resonate at δ 10.17 ppm. The structures of **4** and **12** were confirmed further by the X-ray crystallography (Figure 3).

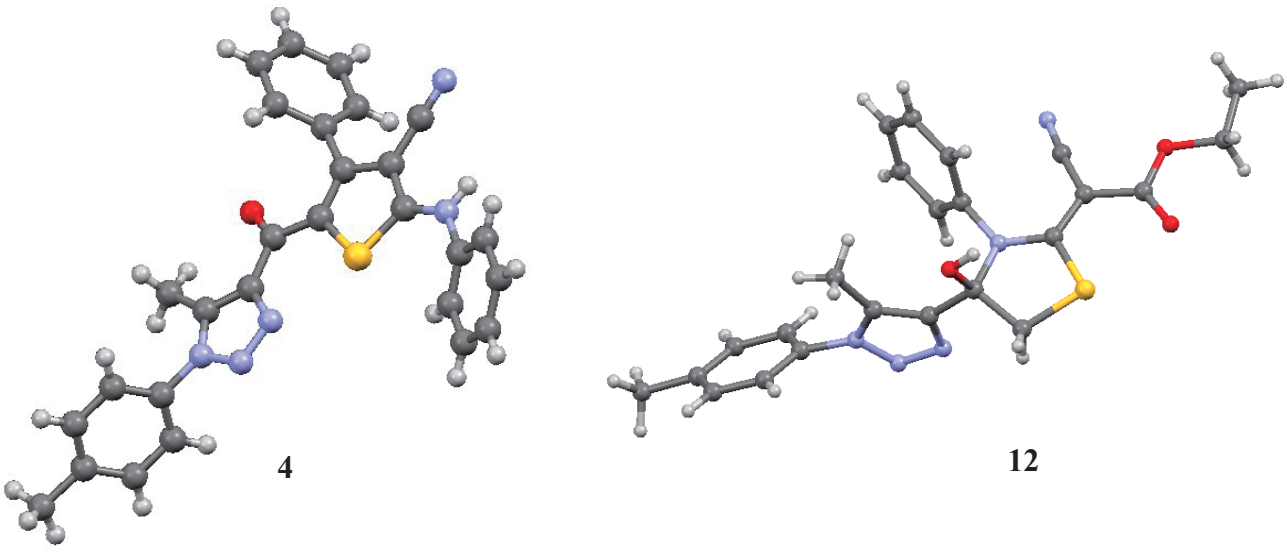


Figure 3. The X-ray structures for compounds **4** and **12**

Antimicrobial Evaluation

The antibacterial efficacy of the tested compounds was studied *versus* three Gram positive bacteria, *Staphylococcus aureus* (ATCC29213), *Bacillus subtilis* (ATCC6633) and *Bacillus megaterium* (ATCC9885) and three Gram negative bacteria, *Klebseilla peneumoniae* (ATCC13883), *Pseudomonas aeruginosa* (ATCC27953) and *Escherichia coli* (ATCC25922). Two yeasts were used as *Saccharomyces cerevisiae* and *Candida albicans* (NRRL Y-477). Ciprofloxacin was used a standard antibiotic. Clotrimazole was used as a standard antifungal agent. The results obtained are recorded in Tables 1 and 2. The synthesized compounds showed good antimicrobial activity against the tested microbes. Compound **23a** exhibited the highest activity against all tested microorganisms with an inhibition zones from 19 to 25 mm and a minimum inhibitory concentrations (MIC) of 200 μg/mL. Compound **4** exhibited an excellent activity with inhibition zones of 28 to 30 mm with a MIC of 50 μg/mL (Tables 1 and 2).

Table 1. The inhabitation zone (mm) for the synthesized compounds using diffusion assay[a]

Product	Gram positive bacteria			Gram negative bacteria			Yeast	
	S. aureus	*B. subtilis*	*B. megaterium*	*K. peneumoniae*	*P. aeruginosa*	*E. coli*	*S. cerevisiae*	*C. albicans*
4	19	20	21	19	19	18	30	28
12	19	15	17	14	18	18	22	20
13	17	21	20	13	19	19	18	16
23a	25	22	20	20	20	21	20	21
23b	21	22	22	20	22	22	19	20
Ciprofloxacin	20	22	24	25	24	23	—	—
Clotrimazole	—	—	—	—	—	—	30	29

[a] The experiments were performed in triplicate and the average zone of inhibition was calculated.

Table 2. The MIC (mg/mL) for the synthesized compounds using two fold serial dilution method[a]

Product	Gram positive bacteria			Gram negative bacteria			Yeast	
	S. aureus	*B. subtilis*	*B. megaterium*	*K. peneumoniae*	*P. aeruginosa*	*E. coli*	*S. cerevisiae*	*C. albicans*
4	200	200	200	200	200	200	50	50
12	200	—	200	—	200	200	100	200
13	200	200	200	—	200	200	200	200
23a	200	200	200	200	200	200	—	—
23b	200	200	200	200	—	200	—	—
Ciprofloxacin	25	25	25	25	25	25	—	—
Clotrimazole	—	—	—	—	—	—	25	25

CONCLUSION

Novel thiophenes and thiazoles have been synthesized from one-pot reaction involving phenyl isothiocyanate, active methylene compound and potassium hydroxide. The process provides some unexpected products as has been confirmed by the single X-ray crystal structures. The synthesized products showed good antimicrobial activities against the tested microorganisms compared to standard antimicrobial agents.

EXPERIMENTAL

Melting points have been measured using the open glass capillaries Gallenkamp melting point apparatus and are uncorrected. The IR spectra (KBr disks) were recorded on the Perkin-Elmer GX Spectrometer. The NMR spectra were recorded on JEOL 600 MHz Spectrometer using TMS as internal reference (δ in ppm and J in Hz). Mass spectra were performed using the Varian MAT, CH-5 Spectrometer at 70 eV. 2-Bromo-1-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)ethanone was synthesized according to the literature procedure.[24] The crystallographic data for products **4** and **12** have been deposited at the Cambridge Crystallographic Data Center (CCDC) as CCDC1515222 and CCDC1515223, respectively. Free copies of the data can be obtained *via* www.ccdc.cam.ac.uk.

Synthesis of thiazolidines 4 and 12 and thiophene 23; general procedure: A mixture of appropriate active methylene compound (**1**, **10**, **20a** or **20b**; 0.05 mol) and anhydrous KOH powder (0.05 mol) in DMF (20 mL) was stirred for 1 h at room temperature. Phenyl isothiocyanate (0.05 mol) was added dropwise and the mixture was stirred for 4 h. Compound **3** (0.05 mol) was added the resulting mixture and the stirring was continued for 12 h. The mixture was poured into an ice-water mixture and the solid produced was filtered, dried and crystallized from DMF.

5-(5-Methyl-1-(4-tolyl)-1*H*-1,2,3-triazole-4-carbonyl)-4-phenyl-2-(phenylamino)thiophene-3-carbonitrile (4): Yield 73%; Mp 222–223 °C. IR (KBr) ν_{max}/cm^{-1} 1600 (C=C), 1624 (C=O), 2217 (CN), 3263 (NH); ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.34–7.48 (m, 15H, NH, Ar-H). ^{13}C NMR (DMSO-d_6) δ 9.65, 20.77, 115.50, 119.12, 119.41, 121.34, 125.13, 127.89, 128.32, 128.92, 129.01, 129.73, 130.12, 132.53, 133.30, 138.41, 139.65, 139.96, 142.90, 144.39, 144.60, 186.49.

Ethyl 2-cyano-2-(4-hydroxy-4-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)-3-phenylthiazolidin-2-ylidene)acetate (12): Yield 78%; Mp 210–212 °C. IR (KBr) ν_{max}/cm^{-1} 1592 (C=C), 1685 (C=O), 2212 (CN), 3213 (NH). ^{1}H NMR (DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.58 (d, J = 12.5 Hz, 1H, thiazololidine), 4.09 (q, J = 7.2 Hz, 2H, CH_2), 4.44 (dd, J = 7.5, 7.8 Hz, 1H, thiazololidine), 7.17–7.44 (m, 9H, Ar-H), 8.04 (s, exch., 1H, OH). ^{13}C NMR (DMSO-d_6) δ 88.67, 14.40, 20.75, 60.16, 97.45, 114.07, 125.28, 128.26, 128.46, 129.50, 129.84, 130.12, 130.75, 132.89, 134.21, 136.59, 139.76, 141.86, 166.47, 171.06. MS *m/z* (%): 463 ([M^+ + 2], 18), 462 ([M^+ + 1], 18), 461 (M^+, 18), 91 (100). Anal. Calcd for $C_{24}H_{23}N_5O_3S$ (461.54): C, 62.46; H, 5.02; N, 15.17%. Found: C, 62.63; H, 5.19; N, 15.27.

1-(4-Methyl-5-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazole-4-carbonyl)-2-(phenylamino)thiophen-3-yl)-ethanone (23a): Yield 74%; Mp 222–224 °C; IR (KBr) ν_{max}/cm^{-1} 1601 (C=C), 1691 (C=O), 3162 (NH). ^{1}H NMR (DMSO-*d*$_6$) δ 1.23 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.22–7.54 (m, 9H, Ar-H), 11.45 (s, exch., 1H, NH). ^{13}C NMR (DMSO-*d*$_6$) δ 10.04, 17.59, 20.79, 28.89, 120.32, 121.09, 122.39, 125.16, 125.33, 129.86, 130.15, 132.61, 139.12, 140.04, 142.88, 143.29, 148.47, 165.81, 178.37, 196.75. MS *m/z* (%): 432 ([M^+ + 2], 5), 431 ([M^+ + 1], 24), 430 (M^+, 21), 132 (100). Anal. Calcd for $C_{24}H_{22}N_4O_2S$ (430.52): C, 66.96; H, 5.15; N, 13.01%. Found: C, 67.81; H, 5.23; N, 13.17.

Ethyl 4-methyl-5-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazole-4-carbonyl)-2-(phenylamino)thiophene-3-carboxylate (23b): Yield 76%; Mp 198–200 °C. IR (KBr) ν_{max}/cm^{-1} 1612 (C=C), 1668 (C=O), 3276 (NH). ^{1}H NMR (DMSO-*d*$_6$) δ 1.34 (t, 3H, *J* = 7.2 Hz, CH_3), 2.41 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.34 (q, *J* = 7 Hz, 2H, CH_2,), 7.23–7.52 (m, 9H, Ar-H), 10.20 (s, exch., 1H, NH). ^{13}C NMR (DMSO-*d*$_6$) δ 10.03, 14.19, 17.12, 20.78, 60.48, 109.61, 115.79, 121.53, 125.26, 125.32, 129.81, 130.14, 132.61, 139.04, 139.93, 140.03, 149.49, 164.38, 165.35, 177.95, 180.71. MS *m/z* (%): 462 ([M^+ + 2], 6), 461 ([M^+ + 1], 24), 460 (M^+, 22), 132 (100). Anal. Calcd for $C_{25}H_{24}N_4O_3S$ (460.55): C, 65.20; H, 5.25; N, 12.17%. Found: C, 65.33; H, 5.36; N, 12.31.

Ethyl 4-amino-5-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazole-4-carbonyl)-2-(phenylamino)thiophene-3-carboxylate (13): A mixture of **12** (0.46 g, 1.0 mmol), hydroxylamine hydrochloride (0.07 g, 1.0 mmol) and anhydrous potassium carbonate (0.14 g, 1.0 mmol) in anhydrous EtOH (20 mL) was heated under reflux for 4 h. The mixture was cooled down to room temperature and poured into ice-water mixture. The solid obtained was filtered and recrystallized from DMF. Yield 68%; Mp 210 °C. IR (KBr) ν_{max}/cm^{-1} 1605 (C=C), 1701, 1695 (2 C=O), 3350–3190 (NH_2, NH). ^{1}H NMR (DMSO-*d*$_6$) δ 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.39 (q, *J* = 7.2 Hz, 2H, CH_2), 7.30–7.52 (m, 9H, Ar-H), 9.50 (s, exch., 1H, NH), 10.17 (s, exch., 2H, NH_2).^{13}C NMR (DMSO-*d*$_6$) δ 9.93, 14.44, 20.78, 60.37, 93.31, 117.82, 122.40, 123.22, 125.28, 129.74, 130.10, 132.90, 136.01, 138.00, 138.40, 139.30, 139.91, 145.89, 159.91, 164.39. MS *m/z* (%): 463 ([M^+ + 2], 5), 462 ([M^+ + 1], 28), 461 (M^+, 34), 91 (100). Anal. Calcd for $C_{24}H_{23}N_5O_3S$ (461.54): C, 62.46; H, 5.02; N, 15.17%. Found: C, 62.60; H, 5.16; N, 15.23.

ANTIMICROBIAL ACTIVITY

The antimicrobial activities of the products were examined against various types of bacteria and fungi. A standard procedure was used based on the agar well diffusion method.[25] The MIC was calculated based on the two fold serial dilution style.[26] The solution concentrations were 500, 250, 125 and 65 μg/mL.

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