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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Kodam Sujatha & Rajeswar Rao Vedula (2018): Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three-component reaction under solvent free conditions, Synthetic Communications, DOI: 10.1080/00397911.2017.1399422

To link to this article: https://doi.org/10.1080/00397911.2017.1399422

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https://doi.org/10.1080/00397911.2017.1399422

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Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three-component reaction under solvent free conditions

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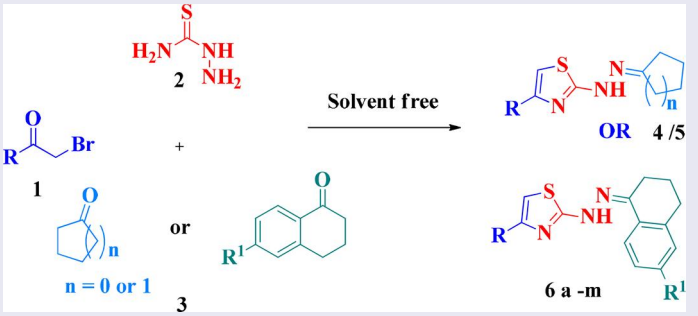
ABSTRACT

An expeditious one pot method has been developed for the synthesis of 2,4-disubstituted thiazoles under solvent free conditions via a multicomponent approach. Substituted thiazoles were synthesized with high yields by the reaction of cyclic ketones, thiosemicarbazide, and phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in a shorter reaction time with high purity via simple purification technique.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 6 September 2017

KEYWORDS
2,4-Disubstituted thiazoles; cyclic ketones; cyclocondensation; multicomponent reactions; phenacyl bromides; thiosemicarbazone

Introduction

Multicomponent reactions are simple efficient,[1] convergent, diversity oriented reactions,[2,3] in which three are more reactants come together in a single reaction operation to form a desired novel product in which all the reactants are incorporated into the product. One-pot multicomponent approach is the best method of synthesis of complex heterocyclic molecules,[4,5] it involves minimum number of steps, there is no isolation of intermediate, without use of noxious solvents, shorter reaction time, easy work up procedure to give good to excellent yields.

Coumarins are important pharmacophores in medicinal chemistry and have biological activities,[6] such as cytotoxic, anti-inflammatory,[7] antituberculosis,[8] antibacterial,[9] antiviral,[10] herbicidal,[11] anti-HIV agent,[12] and antioxidant.[13] Significantly coumarin

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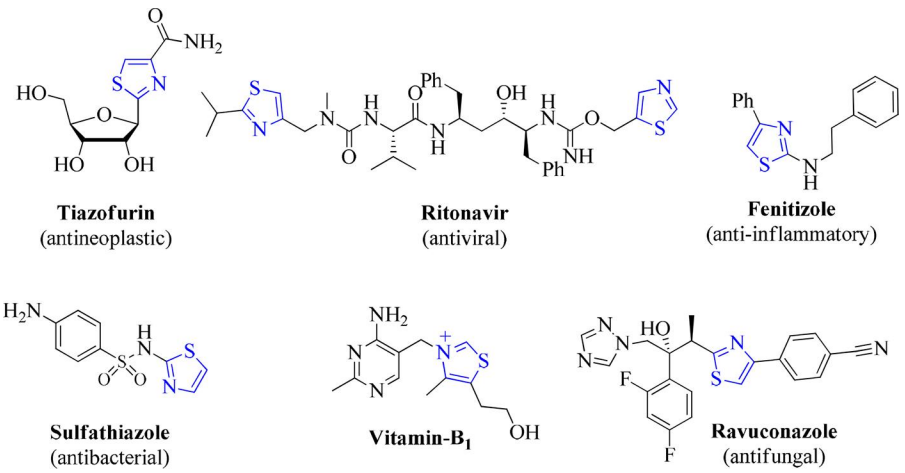


Figure 1. Some of the representative examples of biologically potent compounds bearing thiazole scaffold.

derivatives are used as luminescent materials,[14] inhibition of platelet aggregation,[15] allosteric MEK1 inhibitor[16] and also acts as free radical scavengers.[17]

In the recent years, thiazole[18,19] and its derivatives attained considerable interest due to their wide variety of biological and pharmacological activities,[20], such as antiproliferative,[21] anticancer,[22] antimalarial,[23] anti-HIV,[24] antimicobacterial,[25] anti-inflammatory[26] and antihypertensive agents. Moreover thiazole and its derivatives being a structural framework in variety of biologically important natural, semi-synthetic, and synthetic drugs[27] (Fig. 1). Besides, actinomycete member's producing complex naturally occurring antibiotics which are thiazole embedding secondary metabolites.[28]

In view of various physiological activities associated with coumarins and thiazoles, our current studies are focused on the development of new routes for the synthesis of thiazoles incorporating both aryl and coumarin moieties. We have developed a one-pot multicomponent reaction for the synthesis of title compounds assuming that the resulting compounds may possess good biological activities.

2,4-Disubstituted thiazoles were generally synthesized by various methods. The most common method involves the Hantzsch thiazole synthesis. This involves condensation of α -halogeno ketones with thiourea or thioamides.[29,30] King and co-workers[31–33] synthesized 2,4-disubstituted thiazoles by replacing α -halogenoketones with ketone and halogen. Despite of this modification, the method of King and co-workers is cumbersome and time taking process (24–25 h).

Results and discussion

By considering the importance of the heterocyclic moieties and in continuation of our earlier work on the development of biologically important heterocyclic compounds containing nitrogen and sulfur atoms,[34,35] we designed synthesis of novel 2,4-disubstituted thiazoles, using a multicomponent approach involving modified Hantzsch thiazole synthesis at room temperature. An equimolar mixture of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one, thiosemicarbazide and cyclic ketone

was stirred for 5 min at room temperature to afford the corresponding 2,4-disubstituted thiazoles (**4, 5**, and **6a–m**) with good to excellent yields (85–95%) (Table 1).

In the one step solvent free synthesis (Scheme 1, method 1), it is believed that the phenacyl bromides or 3-(2-bromoacetyl) coumarins react with thiosemicarbazide to give the corresponding intermediate 2-hydrazino-4-substituted thiazoles followed by the reaction with cyclic ketones to afford the target compounds (**4, 5**, and **6**).

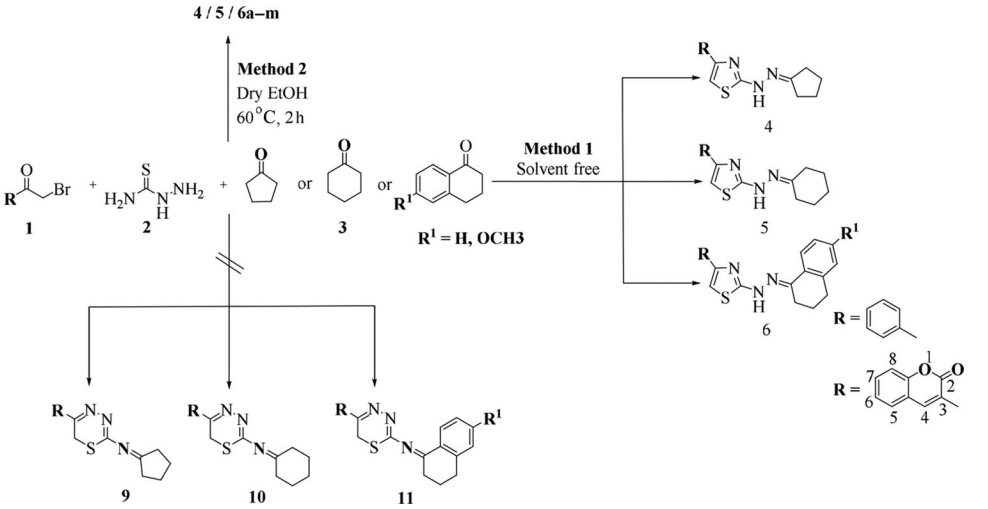
We have synthesized compounds **4, 5**, and **6** by a one pot condensation of three reactants in ethanol at 60 °C (method 2) and also we have performed the synthesis of **4, 5**, and **6** by unambiguous method (Scheme 2, method 3). In the method 3, condensation of various phenacyl bromides or 3-(2-bromoacetyl) coumarins with thiosemicarbazide to give corresponding 2-hydrazino-4-substituted thiazoles (**8**). These on treatment with cyclic ketones resulted in the formation of **4, 5**, and **6** through a two-step process. The products obtained by all the three methods were found to be identical by their mixed melting point measurements, co-TLC, and IR spectra. In the present investigation, method 1 was used as it has more advantages, such as higher yields, shorter reaction times, milder reaction conditions, one pot, solvent free and easy reaction workup. In method 2 the overall yields were 75–85% and this method was not used for the synthesis of title compounds. The intermediates 2-hydrazino-4-aryl thiazoles and 2-hydrazino-4-coumarinyl thiazoles were synthesized by following the literature procedures.[36,37]

Method 3

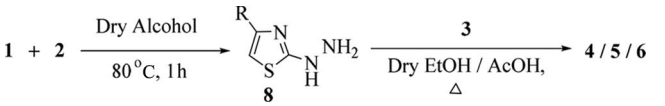
Reaction between phenacyl bromide or 3-(2-bromoacetyl) coumarin, thiosemicarbazide and cyclic ketone is expected to give the compound **4/5/6** or corresponding *N*-cyclopentylidine (**9**), cyclohexylidene (**10**), and 3,4-dihydronaphthalene-1(2*H*)-ylidene-5-substituted-6*H*-1,3,4-thiadiazines (**11**) or both depending on the mode of cyclization and reaction conditions used. In the present investigation the reaction between 1 and 2 proceeds selectively in such a way that the thioamide of 2 undergoes cyclization to give only 2,4-disubstituted thiazoles. The reaction conditions played a crucial role in the selective hetero cyclization. The alternate products **9, 10**, and **11** can be rejected on the basis of spectral studies (IR, NMR, ^{13}C, and Mass).

Table 1. Synthesis of compounds (**4**, **5**, and **6a–m**) and their corresponding yields.

Entry	R	R1	Yields (%) (method 1)
4	Phenacyl	—	95
5	6,8-Dibromo-3-coumarinyl	—	95
6a	Phenacyl	H	96
6b	4-Bromo phenacyl	H	91
6c	4-Chloro phenacyl	H	90
6d	2,4-Dichloro phenacyl	H	96
6e	4-Nitro phenacyl	H	95
6f	6-Bromo-3-coumarinyl	H	96
6g	6,8-Dibromo-3-coumarinyl	H	93
6h	8-Methoxy-3-coumarinyl	H	92
6i	Phenacyl	6-OCH_3	97
6j	4-Chloro phenacyl	6-OCH_3	93
6k	4-Nitro phenacyl	6-OCH_3	95
6l	6,8-Dibromo-3-coumarinyl	6-OCH_3	92
6m	6-Bromo-8-methoxy-3-coumarinyl	6-OCH_3	85

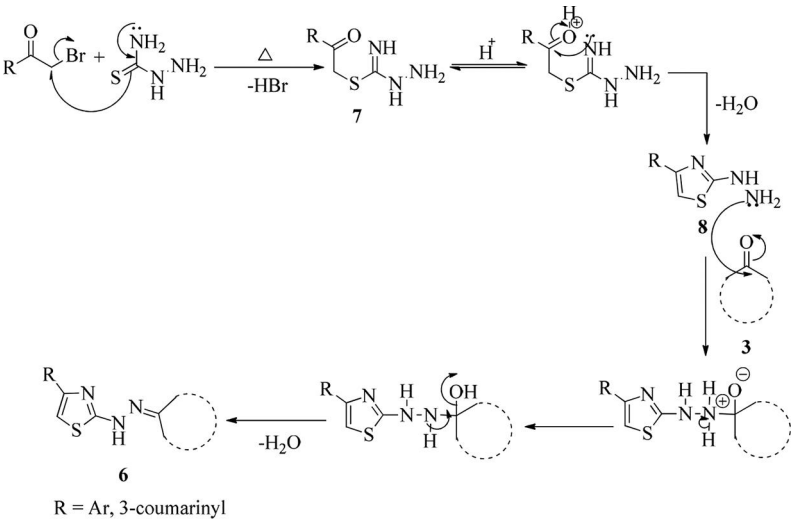


Scheme 1. Synthesis of 2,4-disubstituted thiazoles via multicomponent approach.



Scheme 2. Unambiguous synthesis of 2,4-disubstituted thiazoles.

The formation of the products (**4, 5**, and **6**) can be explained (Scheme 3), by the intra molecular cyclization of α-thioketone (**7**) to give 2-hydrazino-4-substituted thiazole (**8**). This intermediate undergoes intermolecular condensation reaction with cyclic ketone to give final compounds (**4, 5**, and **6**).



Scheme 3. Plausible mechanism for the synthesis of 2,4-disubstituted thiazoles.

All the structures of newly synthesized compounds have been confirmed by their spectral data. The IR spectrum of compound **6c** shows prominent peaks at 3450–3030 cm^{-1} (b, m to different NH stretchings), 1609 cm^{-1} (C=N–) stretching vibrations, respectively. The ^{1}H-NMR spectrum of compound **6c** gave prominent peaks for three CH_2 protons of tetralone at δ 2.04 (t, $J = 5.2$ Hz, 2H), 2.82 (s, 2H) and 2.91 (t, $J = 6.0$ Hz, 2H), respectively. Thiazole proton appeared as singlet at δ 6.77. The NH proton appeared at δ 12.34. The peaks of the remaining aromatic protons were observed in the usual region. ^{13}C NMR spectrum of **6c** shows three non-equivalent methylene carbons of tetralone ring at δ 21.74, 26.51, and 29.32 ppm respectively and thiazole carbon appeared at δ 105.37 ppm. Whereas the remaining aromatic carbons were observed in the usual region. The mass spectrum of **6c** exhibited $[M+H]^+$ peak at *m/z* 354 as base peak.

Experimental section

All the chemicals which were used in the present study were purchased from commercial sources and used further without any purification. Melting points were determined in open capillaries with a Stuart melting point apparatus (Mumbai, India) and were uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100S spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker WM-400 spectrometer in δ ppm using TMS as the standard, ESI-MS spectra were recorded on JEOL JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer, compounds purity was checked by TLC plates (E Merck, Mumbai, India). The supplemental materials contain ^{1}H and ^{13}C NMR spectra of products **4, 5**, and **6**.

General procedure for the synthesis of 2,4-disubstituted thiazoles (method 1)

An equimolar amount of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one, thiosemicarbazide and cyclopentanone/cyclohexanone/tetralone were taken in a round bottom flask and stirred at room temperature for about 5 min. The progress of the reaction was monitored through TLC using ethyl acetate and *n*-hexane (40%). After completion of the reaction, the separated solid was filtered, washed with ether to remove unreacted cyclic ketone and dried. The product was purified by recrystallization from methanol.

2-(2-Cyclopentylidenehydrazinyl)-4-phenylthiazole (4)

Phenacyl bromide (199 mg, 1 mmol), thiosemicarbazide (91 mg, 1 mmol), and cyclopentanone (0.5 mL, 4 mmol) were stirred at room temperature for 5 min. The solid separated was filtered and washed with ether to remove unreacted cyclic ketone. The product was recrystallized from methanol. Black solid; mp 142–143 °C; yield (95%); IR (KBr, ν_{max}, cm^{-1}): 3437–3053 (b, m to different NH stretching), 1628 (–C=N–); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80–1.87 (m, 2H), 1.90–1.96 (m, 2H), 2.5–2.57 (m, 4H), 6.74 (s, 1H), 7.38–7.42 (m, 1H), 7.44–7.48 (m, 2H, ArH), 7.74 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.83, 24.95, 29.91, 33.28, 101.67, 125.60, 129.13, 129.33, 129.79, 143.69, 168.90, 169.27. ESI-MS, *m/z* (%): 258 $(M+H)^+$; anal. calcd for $C_{14}H_{15}N_3S$, C, 65.34; H, 5.87; N, 16.33; S, 12.46%. Found: C, 65.30, H, 5.84; N, 16.39; S, 12.42.

6,8-Dibromo-3-(2-(2-cyclohexylidenehydrazinyl) thiazol-4-yl)-2h-chromen-2-one (5)

6,8-Dibromo-3-(2-bromoacetyl)-2*H*-chromen-2-one (425 mg, 1 mmol), thiosemicarbazide (91 mg, 1 mmol) and cyclohexanone (0.5 mL, 4 mmol) were stirred at room temperature for 5 min. The solid separated was filtered and washed with ether to remove unreacted cyclic ketone. The product was recrystallized from methanol. Yellow solid; mp 172–173 °C; yield (95%); IR (KBr, ν_{max}, cm^{-1}): 3448–3061 (b, m to different NH stretching vib.), 1733 (C=O of lactone), 1609 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.59–1.64 (m, 6H), 2.26 (s, 2H), 2.45 (s, 2H), 7.74 (s, 1H), 8.11 (s, 2H), 8.40 (s, 1H), 10.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.19, 25.33, 26.91, 34.86, 110.42, 116.96, 121.98, 122.50, 123.63, 131.29, 136.86, 138.63, 144.95, 147.07, 148.92, 158.23, 175.30. ESI- MS, *m/z* (%): 498 $(M+H)^+$; anal. calcd for $C_{18}H_{15}Br_2N_3O_2S$, C, 43.48; H, 3.04; Br, 32.14; N, 8.45; S, 6.45%. Found: C, 43.53; H, 3.12; Br, 32.19; N, 8.49; S, 6.41.

2-(2-(3,4-Dihydronaphthalen-1(2h)-ylidene)hydrazinyl)-4-phenylthiazole (6a)

Phenacyl bromide (199 mg, 1 mmol), thiosemicarbazide (91 mg, 1 mmol) and tetralone (0.5 mL, 4 mmol) were stirred at room temperature for 5 min. The solid separated was filtered and washed with ether to remove unreacted cyclic ketone. The product was recrystallized from methanol. Black solid; mp 157–159 °C; yield (96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89–1.95 (m, 2H), 2.57 (t, $J = 6.8$ Hz, 2H), 2.76 (t, $J = 6.0$ Hz, 2H), 6.92 (s, 1H), 7.15 (d, $J = 4.4$ Hz, 1H), 7.27–7.29 (m, 3H), 7.33 (d, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.82 (d, $J = 7.6$ Hz, 2H), 8.16 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.41, 25.68, 29.41, 103.58, 124.62, 125.96, 126.57, 127.96, 128.44, 128.76, 128.92, 132.12, 134.34, 139.32, 147.23, 150.58, 170.17. Anal. calcd for $C_{19}H_{17}N_3S$, C, 71.44; H, 5.36; N, 13.15; S, 10.04%. Found: C, 71.49; H, 5.31; N, 13.19; S, 10.14.

Conclusion

In conclusion, we have successfully synthesized a novel 2,4-disubstituted thiazole derivatives through a multi component approach under solvent free reaction conditions. The method had the advantages of mild reaction conditions, better to excellent yields, one pot operational simplicity.

Acknowledgments

The authors are thankful to the Director, National Institute of Technology, Warangal, Telangana, India for providing the facilities. K. S. thanks to the MHRD, India for fellowship.

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