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A Synthesis of Functionalized Thiazoles and Pyrimidine-4(3*H*)-thiones from 1,1,3,3-Tetramethylguanidine, Acetylenic Esters, and Aryl Isothiocyanates

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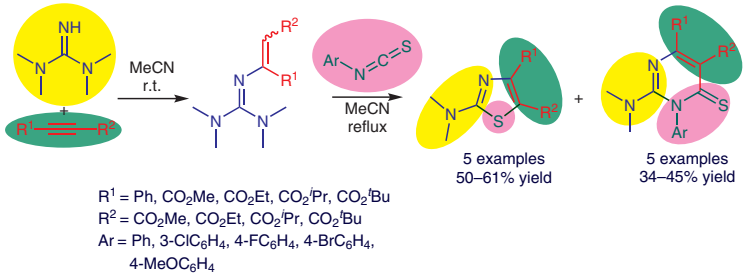

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Abstract Aryl isothiocyanates react with dialkyl 2-[[bis(dimethylamino)methylene]amino]maleates, generated from 1,1,3,3-tetramethylguanidine and acetylenic esters, to afford 2-(dimethylamino)-1,3-thiazole derivatives, functionalized 2-(dimethylamino)-6-thioxo-1,6-dihydropyrimidines, and ethyl 2-(dimethylamino)-6-[(4-nitrophenyl)imino]-4-phenyl-6*H*-1,3-thiazine-5-carboxylate, in moderate to good yields.

Key words thiazolamines, alkynoate esters, pyrimidinethiones, tetramethylguanidine, aryl isothiocyanates

Heterocyclic compounds such as pyrimidines play important roles in the fields of drugs and agrochemicals, and in many biological processes. In recent decades, many pharmacological studies have been carried out on pyrimidine and its derivatives, such as pyrimethamine.[1] An important derivative of pyrimidine is pyrimidine-2-thiol, also known as 2-mercaptopyrimidine or (in its tautomeric form) 2-thioxopyrimidine [pyrimidine-2(1*H*)-thione] (Figure 1).[2]

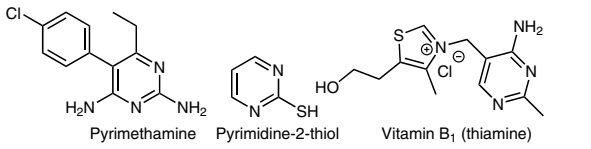


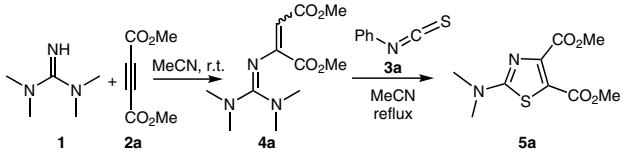
Figure 1 Examples of pharmaceuticals containing pyrimidine or thiazole moieties

Thiazoles[3] are interesting heterocyclic systems that exhibit various biological properties, such as antimicrobial,[4] antihistaminic,[5] and antiviral activities.[6] Thiazole-containing vitamin B_1 (thiamine) (Figure 1) helps in the normal functioning of the nervous system by its role in the synthesis of acetylcholine.[7] Thiazoles are usually prepared by the Hantzsch method,[8] which suffers from long reaction times, low yields, and harsh reaction conditions.[9]

Here, we report a simple procedure for the synthesis of 2-(dimethylamino)thiazole derivatives and functionalized 2-(dimethylamino)-6-thioxo-1,6-dihydropyrimidine-5-carboxylate derivatives by a three-component coupling reaction of 1,1,3,3-tetramethylguanidine (TMG), acetylenic esters, and aryl isothiocyanates.

Initially, we chose TMG (**1**) and dimethyl acetylenedicarboxylate (DMAD; **2a**) as model substrates to react with isothiocyanatobenzene (**3a**). Various solvents (EtOH, THF, and MeCN) were explored, and the results are summarized in Table 1. The reactions performed in THF or MeCN at room temperature for 48 hours gave **5a** in low yields (Table 1, entries 1 and 2). When EtOH was used as the solvent, only a reaction between EtOH and isothiocyanatobenzene

Table 1 Formation of Product **5a** under Various Reaction Conditions[a]



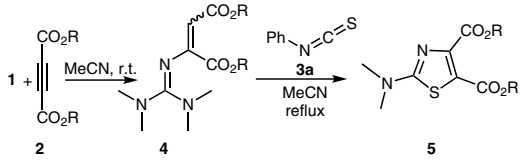
Entry	Solvent	Temp	Yield[b] (%)
1	THF	r.t.	trace
2	MeCN	r.t.	14
3	EtOH	reflux	–
4	MeCN	reflux	52

[a] Reaction conditions: **1** (0.115 g, 1 mmol), **2a** (0.142 g, 1 mmol), **3a** (0.135 g, 1 mmol), solvent (5mL).
[b] Isolated yield.

was observed (entry 3). Finally, reaction in MeCN at the reflux gave product **5a** in 52% yield (entry 4).

Therefore, the optimal reaction conditions are one equivalent each of TMG (**1**), DMAD (**2a**), and isothiocyanatobenzene (**3a**) in refluxing MeCN. By using these optimized reaction conditions and various dialkyl acetylenedicarboxylates **2**, we prepared four derivatives of 2-(dimethylamino)thiazole **5a–d** (Table 2).[10]

Table 2 Synthesis of Dialkyl 2-(dimethylamino)thiazole-4,5-dicarboxylates **5a–d**[a]



Entry	R	Product	Yield[b] (%)
1	Me	**5a**	52
2	Et	**5b**	58
3	^{i}Pr	**5c**	60
4	^{t}Bu	**5d**	61

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3a** (1 mmol), MeCN (5 mL), reflux.
[b] Isolated yield.

To extend the scope of this reaction, we used ethyl 3-phenylpropiolate (**2e**) as the acetylenic ester (Table 3). The reaction of TMG with **2e** and isothiocyanatobenzene (**3a**) gave ethyl 2-(dimethylamino)-4-phenylthiazole-5-carboxylate (**5e**)[11] together with ethyl 2-(dimethylamino)-1,4-diphenyl-6-thioxo-1,6-dihydropyrimidine-5-carboxylate (**6a**). By using a range of aryl isothiocyanates, a series of novel products **6b–e**, were prepared (Table 3).[10]

The structures of products **5a–e** and **6a–e** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra and their mass spectrometric data. Unequivocal evidence for the structures of **5e** and **6c** was obtained by single-crystal X-ray analyses.[13,14] The ORTEP diagrams of **5e** and **6c** are shown in Figure 2 and Figure 3, respectively.

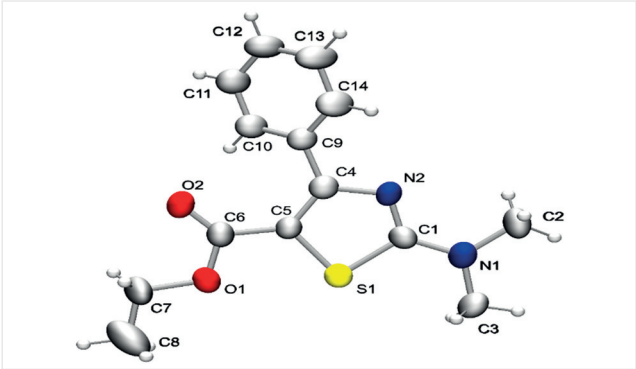


Figure 2 X-ray crystal structure (ORTEP) of **5e** with thermal ellipsoids set at the 40% probability level[14]

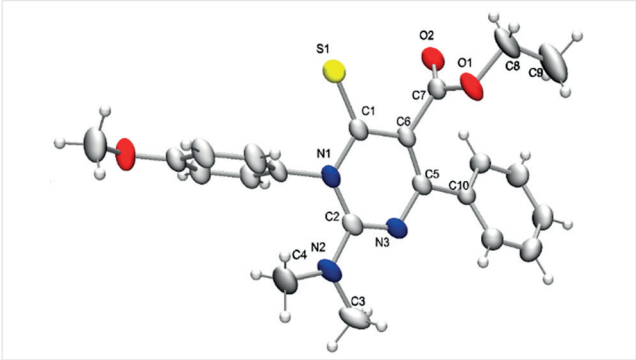
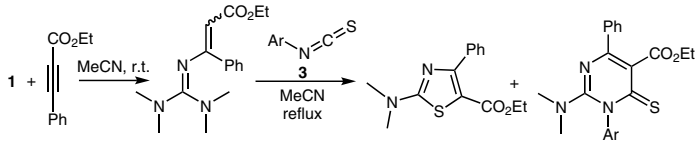


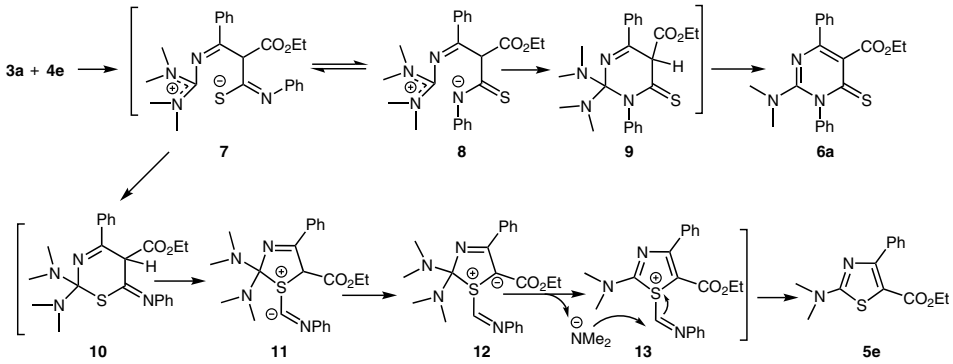
Figure 3 X-ray crystal structure (ORTEP) of **6c** with thermal ellipsoids set at the 40% probability level[14]

Table 3 Synthesis of Compounds **5e** and **6a–e**[a]



Entry	Ar	Product	Yield (%)[b]	Product	Yield[b] (%)
1	Ph	**5e**	50	**6a**	45
2	3-ClC_6H_4	**5e**	52	**6b**	36
3	4-MeOC_6H_4	**5e**	61	**6c**	34
4	4-FC_6H_4	**5e**	50	**6d**	40
5	4-BrC_6H_4	**5e**	55	**6e**	35

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), MeCN (5 mL), reflux.
[b] Isolated yield.

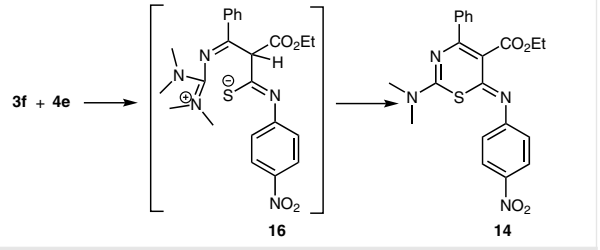


Scheme 1 A plausible mechanism for the formation of products **5e** and **6a**

On account of their similar NMR spectra, the structures **5a–d** and of **6a**, **6b**, **6d**, and **6e** were assumed to be analogous to those of **5e** and **6c** (as deduced from the crystallographic data), respectively.

A plausible mechanism for the formation of products **5e** and **6a** is shown in Scheme 1. It is conceivable that the reaction between **4e** and isothiocyanatobenzene (**3a**) affords intermediate **7**, which converts into intermediate **8**. This intermediate undergoes intramolecular nucleophilic attack by nitrogen to generate pyrimidine derivative **9**, which is then converted into the dihydropyrimidine derivative **6a** by elimination of dimethylamine. Alternatively, intermediate **7** might undergo S-alkylation to afford the 1,3-thiazine derivative **10**. This intermediate converts into the sulfur ylide **11** by 1,2-sulfur migration. The *S*-ylide **11** might then undergo tautomerism to generate the more stable S-ylide **12**, which is converted into thiazole **5e** via intermediate **13**.

In the presence of 1-isothiocyanato-4-nitrobenzene (**3f**), ethyl 2-(dimethylamino)-6-[(4-nitrophenyl)imino]-4-phenyl-6*H*-1,3-thiazine-5-carboxylate (**14**) was formed via intermediate **16** (Scheme 2). This observation suggests that the formation of product **14** is due to a lack of formation of **5e**, because the electron-withdrawing nature of the *para*-nitro group stabilizes the imine structure **16**.



Scheme 2 A plausible mechanism for the formation of product **14**

Product **14** was readily identified from its NMR spectra. In particular, in the ^{13}C NMR spectrum of **14**, there is no peak for the C=S carbon. Unequivocal evidence for the structure of **14** was obtained from single-crystal X-ray analysis.[13,14] The ORTEP diagram of **14** is shown in Figure 4.

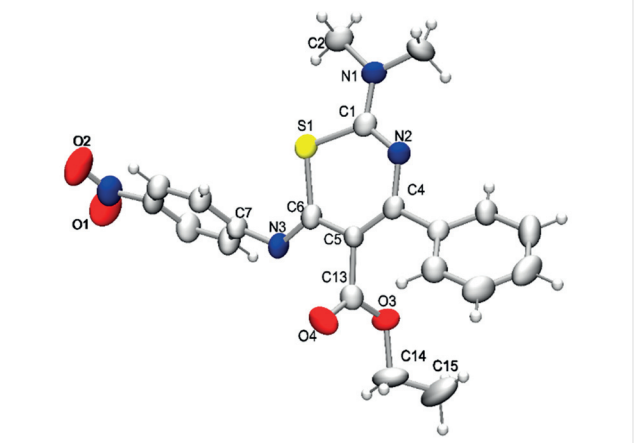


Figure 4 X-ray crystal structure (ORTEP) of **14** with thermal ellipsoids set at the 40% probability level[14]

In conclusion, we have developed a multicomponent reaction of TMG, acetylenic esters, and aryl isothiocyanates as a novel route to the synthesis of a series of 2-(dimethylamino)thiazole derivatives **5**, functionalized 2-(dimethylamino)-6-thioxo-1,6-dihydropyrimidines **6**, and ethyl 2-(dimethylamino)-6-[(4-nitrophenyl)imino]-4-phenyl-6*H*-1,3-thiazine-5-carboxylate (**14**) in moderate to good yields.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590862.

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(10) **Compounds 5, 6 and 14: General Procedure**
TMG (**1**; 0.115 g, 1 mmol) and the appropriate acetylenic ester **2** (1 mmol) were dissolved in MeCN (5 mL), and the solution was stirred for 1 h at r.t. Aryl isothiocyanate **3** (1 mmol) was added, and the mixture was stirred at the reflux until the reaction was complete [~48 h; TLC (EtOAc–hexane, 1:4)]. The mixture was then filtered and the precipitate was purified by flash column chromatography [silica gel, EtOAc–hexane (1:4)].

(11) **Ethyl 2-(Dimethylamino)-4-phenylthiazole-5-carboxylate (5e)**
Yellow crystals; yield: 0.17 g (61%); mp 111–113 °C, (Lit.[12] 115–116 °C). IR (KBr): 3382, 2975, 1697, 1566 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 3.15 (s, 6 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 7.37–7.39 (m, 3 H), 7.76 (d, *J* = 7.7 Hz, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.2 (Me), 40.2 (Me_2N), 60.6 (CH_2O), 110.4 (C), 114.2 (C), 127.6 (2 CH), 128.9 (CH), 129.9 (2 CH), 134.6 (C), 161.9 (C=O), 170.7 (C). EI-MS: *m/z* (%) = 276/09 (M^+, 100), 231 (47), 175 (50), 133 (47), 89 (65), 44 (19). Anal. Calcd for $C_{14}H_{16}N_2O_2S$ (276.35): C, 60.85; H, 5.84; N, 10.14. Found: C, 61.13; H, 5.88; N, 10.17.
Ethyl 2-(Dimethylamino)-1-(4-methoxyphenyl)-4-phenyl-6-thioxo-1,6-dihydropyrimidine-5-carboxylate (6c)
Yellow solid; yield: 0.14 g (34%); mp 116–118 °C. IR (KBr): 3438, 2929, 1685, 1617 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 2.85 (s, 6 H), 3.94 (s, 3 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 7.09 (d, *J* = 7.9 Hz, 2 H), 7.36 (d, *J* = 7.9 Hz, 2 H), 7.47–7.56 (m, 3 H), 8.89 (d, *J* = 6.7 Hz, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9 (Me), 41.6 (Me_2N), 55.6 (MeO), 61.8 (CH_2O), 114.4 (2 CH), 124.7 (C), 128.4 (2 CH), 128.5 (2 CH), 130.4 (CH), 130.7 (2 CH), 132.9 (C), 137.4 (C), 154.6 (C), 157.5 (C), 159.6 (C), 167.4 (C=O), 185.7 (C=S). EI-MS: m/z (%) = 409.15 (M^+, 100), 365 (15), 258 (22), 229 (30), 147 (28), 77 (23). Anal. Calcd for $C_{22}H_{23}N_3O_3S$ (409.50): C, 64.53; H, 5.66; N, 10.26. Found: C, 64.84; H, 5.69; N, 10.29.
Ethyl (6*Z*)-2-(Dimethylamino)-6-[(4-nitrophenyl)imino]-4-phenyl-6*H*-1,3-thiazine-5-carboxylate (14)
Yellow solid; yield: 0.31 g (73%); mp 196–198 °C. IR (KBr): 3440 and 2930 (Me), 1721 (CO_2), 1579 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.1 Hz, 3 H), 3.25 (s, 6 H), 4.17 (q, *J* = 6.9 Hz, 2 H), 7.12 (d, *J* = 8.9 Hz, 2 H), 7.49–7.50 (m, 3 H), 7.75 (d, *J* = 7.4 Hz, 2 H), 8.32 (d, *J* = 8.9 Hz, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.8 (Me), 38.8 (Me_2N), 61.6 (CH_2O), 108.5 (C), 121.1 (2 CH), 125.6 (2 CH), 128.2 (2 CH), 128.3 (2 CH), 129.7 (CH), 140.2 (C), 144.3 (C), 153.1 (C), 156.1 (C), 158.3 (C), 158.9 (C), 168.1 (C=O). EI-MS: *m/z* (%) = 424.12 (M^+, 100), 380 (14), 322 (34), 258 (21), 229 (31), 77 (23). Anal. Calcd for $C_{21}H_{20}N_4O_4S$ (424.48): C, 59.42; H, 4.75; N, 13.20. Found: C, 59.73; H, 4.78; N, 13.23.

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(13) X-ray diffraction measurements were carried out on a STOE IPDS 2T diffractometer with graphite-monochromated Mo-K_α radiation. All single crystals were obtained from CH_2Cl_2–hexane solutions and mounted on glass fibers. Cell constants and orientation matrices for data collection were obtained by least-square refinement of the diffraction data from 5045, 3838, and 3762 reflections for compounds **5e**, **6c**, and **14**, respectively. Diffraction data were collected in a series of ω scans in 1° oscillations, and integrated by using the STOE *X-AREA* software package (see Ref. 15). Multiscan absorption corrections were applied by using *WinGX-2013.3* software. The structures were solved by direct methods and subsequent difference Fourier maps, and then refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters. Atomic factors are from the *International Tables for X-ray Crystallography*. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. All refinements were performed by using the *X-STEP32*, *SHELXL-2014*, and *WinGX-2013.3* programs (see ref. 16).

(14) CCDC 1546425, 1530696, and 1530695 contain the supplementary crystallographic data for compounds **5e**, **6c**, and **14**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

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