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Microwave-Assisted Domino Reactions of Propargylamines with Isothiocyanates: Selective Synthesis of 2-Aminothiazoles and 2-Amino-4-methylenethiazolines

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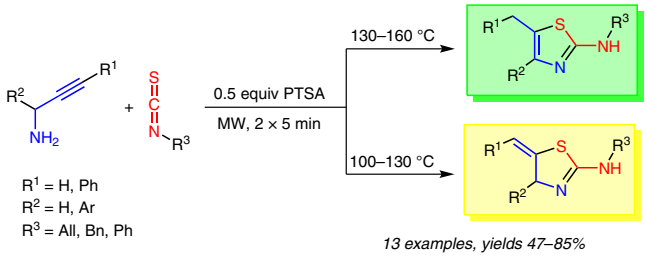

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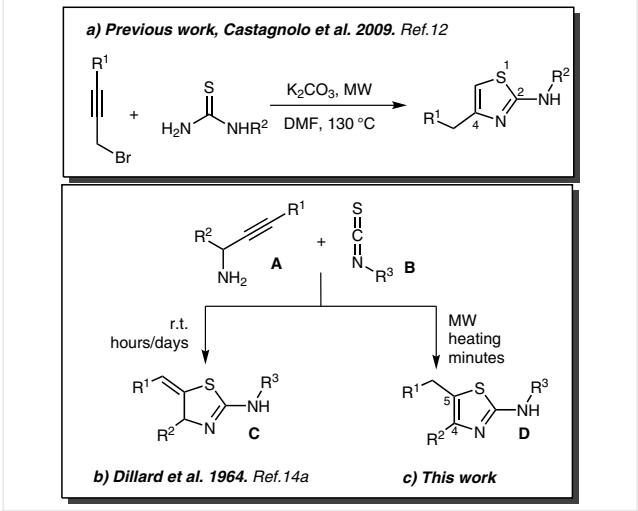
Abstract A simple and versatile microwave-assisted protocol for the synthesis of 2-aminothiazoles has been developed. The domino reaction of propargylamines and isothiocyanates in the presence of catalytic PTSA leads to the selective synthesis of 2-aminothiazoles at temperatures above 130 °C and in a few minutes. The same reaction carried out at lower temperatures leads to the formation of the tautomeric 2-amino-4-methylenethiazolines.

Key words 2-aminothiazole, thiazoline, propargylamine, isothiocyanate, microwave chemistry, imidazol-thione

The 2-aminothiazole ring is an important heterocyclic nucleus that has found broad application in organic and medicinal chemistry. Thiazole and aminothiazole scaffolds have been recognised as privileged structural motifs in medicinal chemistry. Several drug candidates endowed with potent biological activity against hypertension, allergies, inflammation, schizophrenia, cancer, bacterial, and viral infections contain a 2-aminothiazole moiety.[2] As a consequence, a number of methodologies for the synthesis of 2-aminothiazole derivatives has been developed,[3] including the Hantzsch[4] and the Cook–Heilborn syntheses.[5] The Hantzsch synthesis still represents the most widely used method for preparing aminothiazoles, despite the limitations arising from the low availability of hazards associated with the lachrymatory α-haloketone starting materials. Improvements of the Hantzsch synthesis have been recently reported and are based on the in situ generation of the α-halo carbonyl reagents from ketones.[6] Other protocols for the synthesis of aminothiazole derivatives include the use of catalysts such as iodine,[7] silica chloride,[8] 1,3-di-*n*-butylimidazolium tetrafluoroborate,[9] and cyclodextrins.[10,11] Recently, a microwave domino alkylation–cyclization reaction of propargyl bromides with thioureas leading to a variety of 2-aminothiazoles substituted at the C4 position was described by our group[12] (Scheme 1).

In continuation of our work on the development of novel, atom economical methods for the synthesis of heterocyclic compounds, and due to our experience in propargylamine chemistry and microwave synthesis,[12,13] we became interested in studying the reaction of propargylamines **A** with isothiocyanates **B** with the aim to develop a one-pot approach to substituted 2-aminothiazoles **D** (Scheme 1).

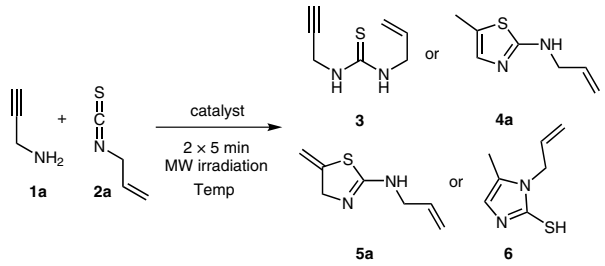


Scheme 1 Different approaches to 2-aminothiazoles and 2-amino-4-methylenethiazolines

Dillard and coworkers in 1964, and later Eloy and Deryckere,[14] first reported that the reaction of propargylamines and isothiocyanates led to 2-amino-4-methylenethiazolines **C** under mild temperature conditions in basic medium after extended reaction times (Scheme 1). More

recently, this approach has been adopted by Clausen and coworkers as an efficient conjugation method in aqueous medium.[15] In all cases, the thiazoline **C** was obtained as the only reaction product, whilst no traces of the corresponding thiazole **D** were detected. We reasoned that, under microwave irradiation and using an appropriate catalyst, the thiazoline **C** could tautomerise leading to the formation of the corresponding thiazole **D** in a one-pot process. Herein, a novel microwave domino amine nucleophilic addition–cyclization approach to 2-aminothiazole from propargylamines is described (Scheme 1).

Table 1 Reaction of Propargylamine **1a** with Allyl Isothiocyanate **2a**



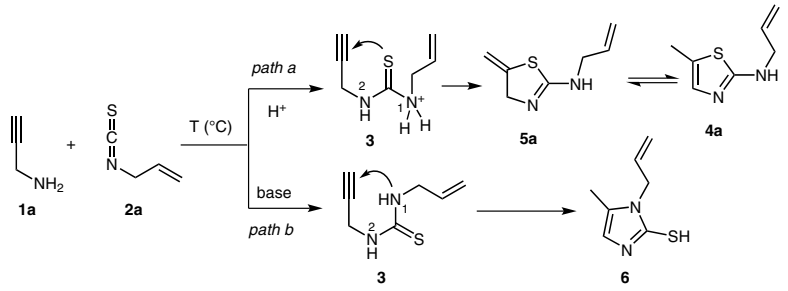
Entry	Acid/base catalyst (equiv)	Additive (equiv)	Solvent	Temp (°C)	Ratio[a] **3**/**4a**/**5a**/**6** (yield, %)[b]
1	K_2CO_3 (1)		DMF	130	100/0/0/0 (82)
2	K_2CO_3 (1)		DCE	100	100/0/0/0 (78)
3	K_2CO_3 (1)	–	DMF	160	0/48/0/52
4	DIPEA (1)	–	DMF	160	0/68/0/32
5	PTSA (1)	–	DMF	160	0/89/0/11
6	–	$ZnCl_2$ (1)	DMF	160	0/89/0/11
7	–	CuI (1)	DMF	160	0/80/0/20
8	–	$FeCl_3$ (1)	DMF	160	0/75/0/25
9	PTSA (0.5)	–	DMF	160	0/90/0/10
10	PTSA (0.1)	–	DMF	160	0/85/0/15
11	PTSA (0.5)	–	DCE	130	0/100/0/0 (78)
12	PTSA (0.5)	–	DCE	100	0/0/100/0 (85)
13	PTSA (0.5)	–	MeCN	100	0/0/100/0

[a] Calculated by ^{1}H NMR integration.
[b] Isolated yields are reported.

The reaction of propargylamine **1a** with allylisothiocyanate **2a** under microwave irradiation at different temperatures and in the presence of different catalysts was first investigated (Table 1). According to our previous method,[12] **1a** and **2a** were reacted at 130 °C in DMF and in the presence of a stoichiometric amount of K_2CO_3. The reaction was carried out under microwave irradiation for 2 × 5 min, leading to the formation of the thiourea **3** as the only product (Table 1, entry 1). The same product was isolated when the reaction was carried out at lower temperature and in a different solvent (Table 1, entry 2). Heating the mixture at 160 °C in DMF led to the cyclization of the thiourea **3** and to the formation of two products in 1:1 ratio (Table 1, entry 3). ^{1}H NMR analysis of the reaction mixture revealed the formation of the desired 2-aminothiazole **4a**, showing the characteristic NH broad peak at δ = 5.79 ppm, together with the imidazole derivative **6**, showing the SH broad singlet at δ = 11.44 ppm. The structures of **4a** and **6** were determined by ^{1}H NMR, ^{13}C NMR, and MS analyses. When DIPEA was used as a base under the same reaction conditions, a mixture of isomers **4a** and **6** was also obtained in a 2:1 ratio. Interestingly, the replacement of K_2CO_3 with a stoichiometric amount of *p*-toluenesulfonic acid (PTSA) led to **4a** as the major isomer (Table 1, entry 5). Only a small amount of **6** was detected by ^{1}H NMR analysis. In the presence of the Lewis acid $ZnCl_2$ (1 equiv) the desired thiazole **4a** was obtained, again as the major reaction product (Table 1, entry 6), whilst a 4:1 and a 3:1 mixture of **4a**/**6** was obtained when **1a** and **2a** were reacted in the presence of CuI and $FeCl_3$, respectively (Table 1, entries 7 and 8). The use of a catalytic instead of stoichiometric amount of PTSA did not affect the outcome of the reaction, leading to **4a**/**6** in 9:1 ratio (Table 1, entries 9 and 10). In a further attempt to reduce the amount of the imidazole **6**, the compounds **1a** and **2a** were reacted at lower temperature. When the reaction was carried out in the presence of catalytic PTSA at 130 °C in DCE (Table 1, entry 11), the thiazole **4a** was obtained as the only product. On the other hand when the temperature was lowered to 100 °C, using both DCE or MECN as solvent, no traces of **4a** were detected whilst the 2-allylamino-4-methylenethiazoline **5a** was isolated as single product (Table 1, entries 12 and 13).

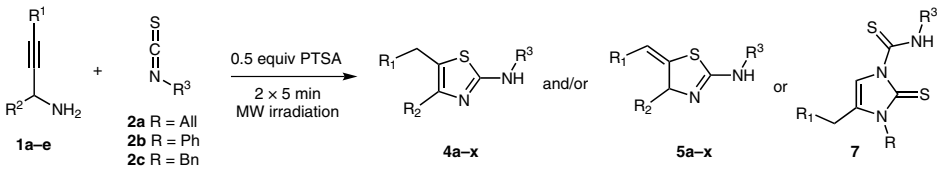
The proposed mechanism for the formation of the three isomers **4a**, **5a**, and **6** is outlined in Scheme 2. The propargylamine **1a** reacts almost instantaneously with the isocyanate **2a** leading to the formation of the thiourea intermediate **3**. The latter can then undergo a 5-*exo*-dig cyclization through two different pathways.[14a] In basic medium and at high temperatures, the thiourea N1 nitrogen preferably acts as the nucleophile, attacking the alkyne and leading to the imidazole **6** (Scheme 2, path b). On the other hand, in acidic medium, the N1 nitrogen of the thiourea intermediate is likely to be protonated leaving the sulfur to act as the nucleophile and leading at 100 °C to the formation of **5a**. Upon heating at 130 °C, **5a** can tautomerise, leading to thiazole **4a** (Scheme 2, path a). When the reaction is carried out in the presence of base at high temperatures (Table 1, entry 3), it is likely that both pathways occur due to a combination of catalytic and heating effects, thus leading to a mixture of **4a** and **6**.

On the basis of these results, the reaction of propargylamine **1a**–**e**[16,13a] with different isothiocyanates **2a**–**c** was further investigated. The results are reported in Table 2.



Scheme 2 Proposed mechanism for the formation of 2-aminothiazoles and imidazoles

Table 2 Synthesis of 2-Aminothiazoles 4 and 2-Amino-4-methylenethiazoline 5



Entry	Amine	R^1	R^2	RNCS	Solvent	Temp (°C)	Product	Ratio[a] **4**/**5**/**7** (yield, %)[b]
1	**1a**	H	H	Ph	DCE	130	**4b**	100/0/0 (74)
2		H	H	Ph	MeCN	100	**4b**/**5b**	20/80/0 (12/57)
3		H	H	Bn	DCE	130	**4c**	100/0/0 (78)
4		H	H	Bn	MeCN	100	**4c**/**5c**	25/75/0 (18/60)
5	**1b**	H	Ph	All	DCE	130	**4d**/**5d**	32/68/0
6		H	Ph	All	DMF	160	**4d**	100/0/0 (47)
7		H	Ph	Bn	DMF	160	**4e**	100/0/0 (56)
8	**1c**	H	4-ClC_6H_4	All	DCE	130	**4f**/**5f**	50/50/0
9		H	4-ClC_6H_4	All	DMF	160	**4f**	100/0/0 (55)
10	**1d**	H	2,4-$Cl_2C_6H_3$	All	DCE	130	**5g**	0/100/0 (60)
11		H	2,4-$Cl_2C_6H_3$	All	DMF	160	**4g**	100/0/0 (62)
12		H	2,4-$Cl_2C_6H_3$	Bn	DMF	160	**4h**	100/0/0 (62)
13	**1e**	Ph	H	All	DCE	130	**7i**	0/0/100 (31)[d]
14		Ph	H	All	MeCN	130	**7i**	0/0/100 (27)[d]
15		Ph	H	Bn	MeCN	130	**7j**	0/0/100 (22)[d]
16		Ph	H	Ph	MeCN	130	**7k**	0/0/100 (24)[d]
17		Ph	H	All	DMF	160	**7i**	0/0/100 (33)[d]
18		Ph	H	Ph	DMF	160	**7j**	0/0/100 (21)[d]
19		Ph	H	Bn	DMF	160	**7k**	0/0/100 (15)[d]
20		Ph	H	All	MeCN	reflux[c]	**7i**	0/0/100 (28)[d]

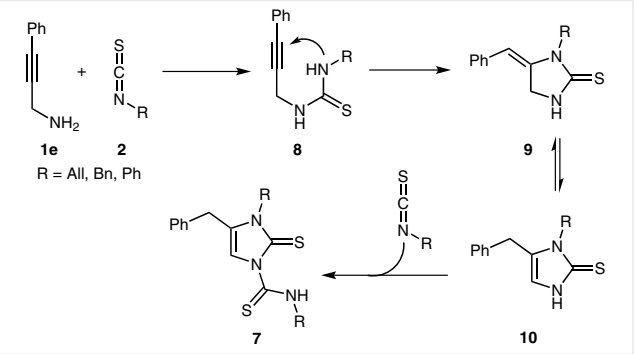
[a] Calculated by ^{1}H NMR integration.
[b] Isolated yields are reported.
[c] The reaction was carried out in an oil bath and refluxing MeCN for 12 h and in the presence of 1 equiv of K_2CO_3.
[d] Unreacted starting material (45–50% yield) **1e** was recovered from the reaction mixture.

When propargylamine **1a** was reacted with phenylisothiocyanate **2b** and benzylisothiocyanate **2c** at 130 °C in DCE and in the presence of catalytic PTSA, the thiazoles **4b** and **4c** were isolated as the only products in high yields (Table 2, entries 1 and 3). On the other hand, when the same reaction was carried out in MeCN at 100 °C, the thiazolines **5b** and **5c** were obtained as major products in good yields

together with a lesser amount of the corresponding thiazoles **4** (Table 2, entries 2 and 4).

The introduction of a phenyl ring onto the propargylamine backbone proved to affect the selectivity of the reaction. In fact, when 1-phenylpropargylamine **1b** and the allyl isothiocyanate **2a** were reacted in DCE at 130 °C a mixture of **4d** and **5d** in a 1:2 ratio was unexpectedly obtained (Table 2, entry 5). However, heating the mixture to 160 °C in DMF led to **4d**[17] as a single product (Table 2, entry 6). No traces of **5d** or the corresponding imidazole derivative were observed. Similarly, compound **4e**[18] was obtained as a single product when **1b** and **2c** were reacted in DMF at high temperatures (Table 2, entry 7). A similar trend was observed when **1c** was reacted with **2a** leading to a mixture of thiazole/thiazoline **4f**/**5f** at 130 °C; whilst **4f** was selectively obtained at higher temperatures (Table 2, entries 8 and 9). When 1-(2,4-dichlorophenyl)propargylamine (**1d**) was used as substrate and reacted with **2a**, the thiazoline **5g** was formed as the sole product at 130 °C (Table 2, entry 10); whilst at 160 °C only **4g** was isolated (Table 2, entry 11). Thiazole **4h** was also obtained as a single isomer when the reaction was carried out at 160 °C in DMF (Table 2, entry 12). It is clear that the aryl substituent on the propargylamine affects the outcome of the reaction, probably due to a combination of steric and electronic effects. In general, higher temperatures favour the tautomerisation of **5** into **4**. Intrigued by the effect of the aromatic ring on the outcome of the reaction, we then focused on the reaction of the 3-phenylpropargylamine **1e** with different isothiocyanates. When **1e** was reacted with **2a**–**c** at 130 °C, the imidazolethione derivatives **7i**–**k** were obtained as the only reaction products.[19] No traces of the thiazole/thiazoline **4** and **5** were detected (Table 2, entries 13–16). At higher temperature the imidiazolethiones **7i**–**k** were also recovered as the only products (Table 2, entries 17–19). A substantial amount of starting material **1e** was also recovered from all the reaction mixtures. Finally, amine **1e** was reacted with **2a** under standard heating conditions (reflux in oil bath) at 130 °C in the presence of one equivalent of K_2CO_3 and, in this case, the imidazoline **7i** was also recovered as the sole product together with starting material **1e**.

Interestingly, Dethe and coworkers recently described the formation of imidazolethiones from propargylamines under basic conditions at room temperature.[19] However, at high temperature we observed the cyclization of **1e** and formation of imidazolethiones **7** both in acidic and basic medium. The proposed mechanism for the formation of **7** is outlined in Scheme 3. The reaction of **1e** with isothiocyanates leads to the thiourea intermediate **8**. The presence of a phenyl ring on the alkyne moiety seems to favour the attack of the nitrogen leading to the tautomeric imidazoline intermediates **9** and **10** that upon reaction with an additional isothiocyanate equivalent, lead to the final product **7**.



Scheme 3 Proposed mechanism for the formation of imidazolthiones **7**

In conclusion, an efficient and versatile microwave method for the synthesis of 2-aminothiazole and 2-aminothiazolines from propargylamines has been developed.[20–22] A set of compounds **4** and **5** has been synthesised in short reaction times and high yields. The formation of thiazoline derivatives **5** occurs when propargylamines and isothiocyanates are reacted in the temperature range 100–130 °C, depending on the substrate. At higher temperatures the selective formation of the 2-aminothiazoles **4** is favoured. The effect of aromatic substituents on the propargylamine substrate has been also investigated, showing that the presence of a phenyl ring on the propargylamine backbone affects the selectivity of the reaction.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561985.

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(1) Most of this work has been carried out at Northumbria University Newcastle (UK), Department of Applied Sciences, before DC relocated to King's College London (UK), Institute of Pharmaceutical Science, 150 Stamford Street, SE1 9NH, London, UK.

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(20) **General Procedure for the Synthesis of 2-Aminothiazoles 4 and 2-Amino-4-methylenethiazolines 5**
Propargylamine **1a**–**e** (1.0 mmol) and the appropriate isothiocyanate **2a**–**c** (1.0 mmol) were suspended in an appropriate solvent (DCE, MeCN, DMF, 1.0 mL) in a 10 mL glass vial equipped with a small magnetic stirring bar. PTSA (0.5 mmol) was then added to this solution, and the mixture was irradiated under microwave conditions at the appropriate temperature (see Tables 1 and 2) for 2 × 5 min, using an irradiation power of 300 W. The mixture was then poured into $NaHCO_3$ solution (10 mL) and then extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried over Mg_2SO_4, filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography (SiO_2; hexanes–EtOAc, 4:1), to yield the desired products as tan-coloured oils.
(21) **2-Aminothiazole 4a**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 5.95–5.85 (m, 1 H), 5.79 (br s, 1 H), 5.30–5.25 (d, 1 H, *J* = 20 MHz), 5.17–5.14 (d, 1 H, *J* = 12 MHz), 3.82 (d, 2 H, *J* = 4 MHz), 2.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 135.5, 134.1, 121.1, 116.8, 48.2, 12.0 ppm. ESI-MS: *m/z* = 155 $[M + H]^+$, 177 $[M + Na]^+$.
(22) **2-Amino-4-methylenethiazoline 5a**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92–5.83 (m, 1 H), 5.24–5.19 (d, 1 H, *J* = 20 MHz), 5.14–5.08 (m, 3 H), 4.68 (m, 2 H), 3.89–3.88 (d, 2 H, *J* = 4 MHz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 148.8, 134.3, 116.5, 102.5, 67.0, 46.6 ppm. ESI-MS: *m/z* = 155 $[M + H]^+$, 177 $[M + Na]^+$.