

# Microwave-Assisted Asinger Synthesis of Thiazolines <sup>†</sup>

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**Abstract:** An array of 2,4-disubstituted thiazolines was obtained through Asinger reaction approach from the straightforward treatment of diverse aldehydes/ketones with 1-mercaptopropan-2-one, in the presence of NH<sub>3</sub> assisted by microwave irradiation, displaying similar and sometimes higher yields, as well as shorter reaction times that traditional Asinger reaction conditions at room and lower temperatures.

**Keywords:** thiazoline; Asinger reaction; microwave irradiation

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## 1. Introduction

Thiazolines are five-membered heterocycles that contain both nitrogen and sulfur, belonging to 1,3-azole heterocycles group. Compared with other azole rings, the thiazoline moiety is relatively less studied, in spite of the growing interest raised by this heterocycle, as a component of many natural products and synthetic compounds displaying a wide range of biological activities [1]. In this regard, diverse synthetic protocols for thiazolines were developed from condensations of thioamides and derivatives [2–6], as well as cysteine and other amino acids [7–9].

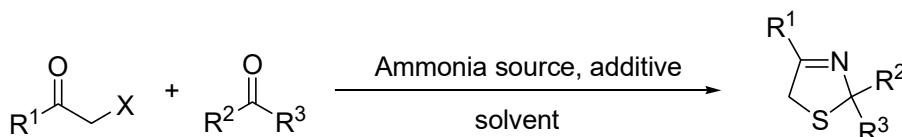
On the other hand, since its discovery in the late fifties [10–12], Asinger reaction showed the distinctive advantages provided by multicomponent reactions applied to the synthesis of cyclic compounds [13–17]. However, these apparent benefits were missed probably due to the few starting materials reported in the literature, which are compatible (and sometimes soluble) with aqueous ammonia, in addition to reaction temperatures close to ambient conditions or lower [18,19].

These facts motivated us to explore alternative conditions for the Asinger Reaction, in order to incorporate structurally diverse feedstock, keeping the attractive characteristics of this process and inherent multicomponent reaction approach. In this report, we disclose our first findings in this area.

## 2. Results and Discussion

Initial experiments were carried out following a four-component reaction approach, according to the literature [18,19], through a simultaneous mixing of a 2-bromoketone, an

ammonia source, NaSH, and a ketone under diverse reaction conditions, which are summarized in Scheme 1 and Table 1. Preliminary results represented in entries 1–3 showed poor yields of thiazoline, as a consequence of incompatibility of aqueous ammonia with the other components, especially 2-bromoketone, affording some degradation products related to competition in nucleophilic substitution on 2-bromoketones, which resulted in it being sensitive to ammonia. This behavior was kept with the introduction of other solvents (entries 4–7) at different temperatures (entries 8–10), as well as diverse ammonia sources (entries 11–18).



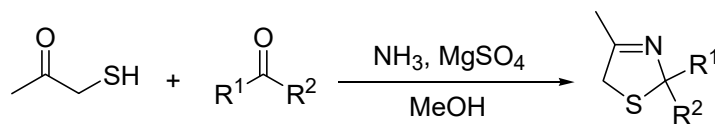
**Scheme 1.** Preparation of thiazolines from a four-component reaction.

**Table 1.** Synthesis of thiazoline 4 catalyzed by phenylacetylide 1.

Entry	R1	R2	R3	X	Ammonia Source	Solvent	Additive	Reaction Temperature (°C)	Reaction Time (h)	%Yield
1	Me	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	-	NaSH	R. T.	24	<5
2	Ph	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	-	NaSH	R. T.	24	0
3	Me	Ph	Ph	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	-	NaSH	R. T.	24	0
4	Me	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	MeOH	NaSH	R. T.	24	0
5	Me	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	Acetone	NaSH	R. T.	24	0
6	Me	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	NaSH	R. T.	24	0
7	Me	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	THF	NaSH	R. T.	24	0
8	Me	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	MeOH	NaSH	Reflux	24	0
9	Ph	Me	Me	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	MeOH	NaSH	Reflux	24	0
10	Me	Ph	Ph	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	MeOH	NaSH	Reflux	24	0
11	Ph	Me	Me	Br	NH <sub>4</sub> OAc	Acetone	NaSH	R. T.	48	0
12	Me	Me	Me	Br	NH <sub>4</sub> OAc	Acetone	NaSH	R. T.	48	0
13	Me	Me	Me	Br	NH <sub>4</sub> OAc	MeOH	NaSH	R. T.	48	0
14	Ph	Me	Me	Br	NH <sub>4</sub> OAc	MeOH	NaSH	R. T.	48	0
15	Ph	Me	Me	Br	NH <sub>4</sub> OAc	MeOH	NaSH	Reflux	24	0
16	Me	Ph	Ph	Br	NH <sub>4</sub> OAc	AcOH	NaSH	100	24	0
17	Me	Ph	Ph	Br	NH <sub>4</sub> OAc	DMF	NaSH	100	24	0
18	Me	Ph	Ph	Br	NH <sub>4</sub> OAc	Toluene	NaSH	100	24	0
19	Me	4-ClC <sub>6</sub> H <sub>4</sub>	H	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	-	NaSH	R. T.	24	8
20	Me	4-ClC <sub>6</sub> H <sub>4</sub>	H	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	MeOH	NaSH	R. T.	24	12
21	Me	4-ClC <sub>6</sub> H <sub>4</sub>	H	Br	NH <sub>4</sub> OH/H <sub>2</sub> O	MeOH	NaSH	R. T.	24	<5
22	Me	4-ClC <sub>6</sub> H <sub>4</sub>	H	Br	NH <sub>3</sub> /MeOH	MeOH	NaSH	R. T.	24	20
23	Me	4-ClC <sub>6</sub> H <sub>4</sub>	H	Br	NH <sub>3</sub> /MeOH	MeOH	NaSH, MgSO <sub>4</sub>	R. T.	24	35
24	Me	4-ClC <sub>6</sub> H <sub>4</sub>	H	SH	NH <sub>3</sub> /MeOH	MeOH	MgSO <sub>4</sub>	R. T.	24	64
25	Me	cyclohexanone	SH	SH	NH <sub>3</sub> /MeOH	MeOH	MgSO <sub>4</sub>	R. T.	24	68

The change of a ketone by an aldehyde in Asinger Reaction slightly improved thiazoline yields up to 20%, using the ammonia solution in methanol described by Silvani et al. [14]. According to these authors, anhydrous conditions using MgSO<sub>4</sub> also contributed to yield optimization, however, a radical change in reaction yield was observed when 1-mercapto-propan-2-one was used instead of the 2-bromoketone/NaSH system, avoiding secondary nucleophilic substitutions. This reactivity pattern was corroborated through the use of cyclohexanone giving the corresponding thiazoline in 68% yield. Hence, the components reduction in the Asinger reaction was compensated by a substantial yield increase.

From these improvements, a general three-component synthetic protocol was developed via straightforward reaction of 1-mercapto propan-2-one and ammonia/MeOH, and was modulated by an aldehyde (Scheme 2). Results in Table 2 show the procedure scope covering distinct substituents in the aldehyde component, giving yields ranged from 33% to 90%.



**Scheme 2.** Preparation of thiazolines from a three-component reaction at room temperature and under microwave irradiation.

**Table 2.** Thiazoline yields obtained at room temperature and under microwave irradiation.

Compound	R <sup>1</sup>	R <sup>2</sup>	%Yield at R.T.	%Yield under MW
1	4-ClC <sub>6</sub> H <sub>4</sub>	H	64	71
2	2-ClC <sub>6</sub> H <sub>4</sub>	H	77	47
3	Ph	H	33	50
4	4-OHC <sub>6</sub> H <sub>4</sub>	H	55	65
5	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	69	49
6	2,3-(OCH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	69	75
7	(3-OCH <sub>3</sub> -4-OH)C <sub>6</sub> H <sub>3</sub>	H	90	70
8	(2-OCH <sub>2</sub> C≡CH)C <sub>6</sub> H <sub>4</sub>	H	88	73
9	cyclohexanone		68	75

Based on our previous experiences on microwave-assisted reactions [20], we considered that these conditions could be extended to the Asinger reaction. Thus, early investigations revealed thiazoline formation from the last studied three-component reaction treated under microwave irradiation. The best yields were obtained at 40 °C (200 W), which is comparable to, and in some cases higher than those observed at room temperature (see Table 2), but showed shorter reaction times. To the best of our knowledge, this was the first report about the synthesis of thiazolines from Asinger reaction using microwave irradiation as an alternative energy source.

The above examples demonstrate the feasibility of this methodology, and future studies are envisioned to broaden the applications of thiazolines in the synthesis of biologically active molecules, potential drugs, and ligands for catalysis.

### 3. Experiment

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were distilled before use. Silica plates of 0.20 mm thickness were used for thin layer chromatography. The melting points were determined with a Krüss Optronic melting point apparatus and they were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using a Bruker Avance 300-MHz; the chemical shifts (δ) are given in ppm relative to TMS as the internal standard (0.00). For analytical purposes, the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (m/z) were reported. IR spectra were recorded on a Bruker Tensor 27 equipment. The microwave-assisted reactions were performed using a CEM Discover microwave unit (constant factor of the microwave 1.214). The temperature was monitored with an IR temperature sensor. In all experiments, the microwave temperature was held constant. Reactions were carried out in 5-mL glass vessels, which were sealed with a cap septum. The specific reaction time corresponded to the total irradiation time.

#### 3.1. Synthesis of Thiazolines under Conventional Conditions—General Procedure

The appropriate aldehyde or ketone (1 mmol) and anhydrous MgSO<sub>4</sub> (0.360 g, 3 mmol) were added to a ~13 M ammonia solution in MeOH (1 mL), and the mixture was stirred for 1 h at room temperature. Mercaptoacetone (0.099 g, 1.1 mmol) was added dropwise, over 5 min. The resulting mixture was stirred for 24 h at room temperature. The mixture was filtered through celite. The solvent was removed under reduced pressure and the final product was purified by column chromatography (SiO<sub>2</sub>, hexane/AcOEt 8:2).

### 3.2. Synthesis of Thiazolines under Microwave Irradiation Conditions—General Procedure

A 5-mL microwave vial was charged with the corresponding aldehyde or ketone (1 mmol),  $\text{MgSO}_4$  (0.360 g, 3 mmol) and a ~13 M ammonia solution in MeOH (1 mL) and a cylindrical magnetic stirring bar. The vessel was sealed with a septum, placed into the microwave cavity of a CEM Discover microwave unit and irradiated to heat the reaction mixture at 40 °C. The total heating time was 10 min at 200 W, 40 °C. After the first cycle, mercaptoacetone (0.099 g, 1.1 mmol) was added and the mixture was irradiated with same parameters for 10 min. When the reaction was completed, the vial was cooled to room temperature. The vial was then opened and the mixture was filtered through celite. The solvent was removed under reduced pressure and the final product was purified by column chromatography ( $\text{SiO}_2$ , hexane/AcOEt 8:2).

### 3.3. 2-(4-Chlorophenyl)-4-methyl-2,5-dihydrothiazole **1**

4-Chlorobenzaldehyde and 1-mercaptopropan-2-one afforded 2-(4-chlorophenyl)-4-methyl-2,5-dihydrothiazole **1** as white solid. Yields: 135.0 mg (64% at room temperature conditions) and 149.8 mg (71% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  2922, 1489, 1089, 828  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.3 (d,  $J$  = 6 Hz, 2H), 7.2 (d,  $J$  = 6 Hz, 2H), 6.56 (s, 1H), 4.09 (dd,  $J$  = 5 Hz,  $J$  = 16 Hz, 1H), 3.98 (dd,  $J$  = 3 Hz,  $J$  = 16 Hz, 1H), 2.23 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 140.5, 133.6, 128.7, 128.2, 83.8, 47.3, 19.5. MS [ $\text{EI}^+$ ]  $m/z$  (%): 211 [ $\text{M}]^+$  (10).

### 3.4. 2-(2-Chlorophenyl)-4-methyl-2,5-dihydrothiazole **2**

2-Chlorobenzaldehyde and 1-mercaptopropan-2-one afforded 2-(2-chlorophenyl)-4-methyl-2,5-dihydrothiazole **2** as the white solid. Yields: 162.4 mg (77% at room temperature conditions) and 99.2 mg (47% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  2916, 1469, 1036, 740  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.17 (m, 4H), 6.9 (s, 1H), 3.89 (s, 2H), 2.25 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 140.0, 132.3, 129.4, 128.8, 127.4, 127.1, 81.0, 46.6, 19.7. MS ( $\text{EI}^+$ )  $m/z$  (%): 211 [ $\text{M}]^+$  (5).

### 3.5. 4-Methyl-2-phenyl-2,5-dihydrothiazole **3**

Benzaldehyde and 1-mercaptopropan-2-one afforded 4-methyl-2-phenyl-2,5-dihydrothiazole **3** as white solid. Yields: 58.4 mg (33% at room temperature conditions) and 88.5 mg (50% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  2915, 1662, 1421  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42–7.25 (m, 5H), 6.62 (bs, 1H), 4.10 (dd,  $J$  = 5 Hz,  $J$  = 15 Hz, 1H), 3.98 (dd,  $J$  = 3 Hz,  $J$  = 15 Hz, 1H), 2.23 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 141.9, 128.6, 128.41, 127.9, 126.8, 84.5, 47.2, 19.5. MS ( $\text{EI}^+$ )  $m/z$  (%): 177 [ $\text{M}]^+$  (15).

### 3.6. 4-(4-Methyl-2,5-dihydrothiazol-2-yl)phenol **4**

4-Hydroxybenzaldehyde and 1-mercaptopropan-2-one afforded 4-(4-methyl-2,5-dihydrothiazol-2-yl)phenol **4** as white solid. Yields: 106.1 mg (55% at room temperature conditions) and 125.4 mg (65% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  3065, 2900, 1663, 1514  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 8.69 (bs, 1H, -OH), 7.12 (d,  $J$  = 9 Hz, 2H), 6.79 (d,  $J$  = 9 Hz), 6.53 (bs, 1H), 4.10 (dd,  $J$  = 5 Hz,  $J$  = 16 Hz, 1H), 3.96 (dd,  $J$  = 3 Hz,  $J$  = 16 Hz, 1H), 2.22 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 156.9, 132.6, 127.9, 115.48, 84.3, 47.0, 19.4. MS ( $\text{EI}^+$ )  $m/z$  (%): 193 [ $\text{M}]^+$  (5).

### 3.7. 4-Methyl-2-(*p*-tolyl)-2,5-dihydrothiazole **5**

4-Methylbenzaldehyde and 1-mercaptopropan-2-one afforded 4-methyl-2-(*p*-tolyl)-2,5-dihydrothiazole **5** as white solid. Yields: 131.7 mg (69% at room temperature conditions) and 93.5 mg (49% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  2916, 1662, 817  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (d,  $J$  = 9 Hz, 2H), 7.13 (d,  $J$  = 9 Hz, 2H), 6.59 (bs, 1H), 4.11 (dd,  $J$  = 6 Hz,  $J$  = 15 Hz, 1H), 3.98 (dd,  $J$  = 6 Hz,  $J$  = 15 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.7, 138.7, 137.3, 128.9, 126.3, 84.1, 46.9, 29.4, 20.8, 19.2. MS ( $\text{EI}^+$ )  $m/z$  (%): 191 [ $\text{M}]^+$  (10).

### 3.8. 2-(2,3-Dimethoxyphenyl)-4-methyl-2,5-dihydrothiazole 6

2,3-Dimethoxy-benzaldehyde and 1-mercaptopropan-2-one afforded 2-(2,3-dimethoxyphenyl)-4-methyl-2,5-dihydrothiazole **6** as white solid. Yields: 163.5 mg (69% at room temperature conditions) and 177.7 mg (75% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  2935, 2834, 1665, 1478, 1263  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.02 (dd,  $J = 9$  Hz,  $J = 6$  Hz, 1H), 6.94 (bs, 1H), 6.84 (dd,  $J = 3$  Hz,  $J = 6$  Hz, 1H), 6.76 (dd,  $J = 3$  Hz,  $J = 6$  Hz, 1H), 4.05 (dd,  $J = 6$  Hz,  $J = 15$  Hz, 1H), 3.98 (dd,  $J = 6$  Hz,  $J = 15$  Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.26 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.2, 150.9, 144.3, 134.6, 122.5, 117.0, 110.3, 59.4, 54.2, 45.2, 18.1. MS (EI+)  $m/z$  (%): 237 [ $\text{M}$ ] $^+$  (20).

### 3.9. 2-Methoxy-4-(4-methyl-2,5-dihydrothiazol-2-yl)phenol 7

4-Hydroxy-3-methoxy-benzaldehyde and 1-mercaptopropan-2-one afforded 2-methoxy-4-(4-methyl-2,5-dihydrothiazol-2-yl)phenol **7** as white solid. Yields: 200.7 mg (90% at room temperature conditions) and 156.1 mg (70% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  3101, 2920, 1595, 1368, 1270  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.85–6.82 (m, 3H), 6.55 (bs, 1H), 5.73 (bs, 1H), 4.11 (dd,  $J = 3$  Hz,  $J = 16$  Hz, 1H), 3.98 (dd,  $J = 3$  Hz,  $J = 16$  Hz, 1H), 3.88 (s, 3H), 2.24 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 146.5, 145.4, 133.7, 119.9, 114.3, 109.4, 84.5, 55.9, 47.2, 19.6. MS (EI+)  $m/z$  (%): 223 [ $\text{M}$ ] $^+$ .

### 3.10. 4-Methyl-2-(2-(prop-2-yn-1-yloxy)phenyl)-2,5-dihydrothiazole 8

2-Prop-2-ynyloxy-benzaldehyde and 1-mercaptopropan-2-one afforded 4-methyl-2-(2-(prop-2-yn-1-yloxy)phenyl)-2,5-dihydrothiazole **8** as white solid. Yields: 203.2 mg (88% at room temperature conditions) and 168.3 mg (73% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  3285, 2918, 2120, 1663, 1487, 1220, 751  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25–7.23 (m, 1H), 7.21–7.19 (m, 1H), 6.99–6.95 (m, 1H), 6.93 (bs, 1H), 4.75 (s, 2H), 4.03 (dd,  $J = 3$  Hz,  $J = 9$  Hz, 1H), 3.94 (dd,  $J = 1.5$  Hz,  $J = 9$  Hz, 1H), 2.52 (s, 1H), 2.26 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.1, 131.6, 128.6, 126.8, 121.6, 112.0, 78.8, 78.5, 75.5, 56.2, 46.4, 19.7. MS [EI+]  $m/z$  (%): 231 [ $\text{M}$ ] $^+$  (5).

### 3.11. 3-Methyl-1-thia-4-azaspiro[4.5]dec-3-ene 9

Cyclohexanone and 1-mercaptopropan-2-one afforded 3-methyl-1-thia-4-azaspiro[4.5]dec-3-ene **9** as white solid. Yields: 114.9 mg (68% at room temperature conditions) and 126.7 mg (75% under microwave conditions). IR (ATR)  $\nu_{\text{max}}$  2927, 1691, 1444, 894  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.77 (s, 2H), 2.10 (s, 3H), 2.04–1.16 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  165.7, 95.4, 44.3, 40.9, 24.8, 24.1, 19.8. MS [EI+]  $m/z$  (%): 169 [ $\text{M}$ ] $^+$  (10).

## 4. Conclusions

Thiazolines are readily available from microwave assisted Asinger reaction through a synthetic procedure that takes advantage of joining both, a multicomponent reaction approach and microwave irradiation methods. The simplicity of this methodology suggests that this route to thiazolines can have widespread application.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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