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Microwave-Assisted Asinger Synthesis of Thiazolines †

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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 presence of NH_3 assisted by microwave irradiation, displaying similar and sometimes higher yields as well as shorter reaction times that traditional Asinger rection conditions at room and lower temperatures.

Keywords: thiazoline; Asinger reaction; microwave irradiation

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, thiazoline moiety has been 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 have been developed from condensations of thioamides and derivatives [2–6], as well as cysteine and other amino acids [7–9].

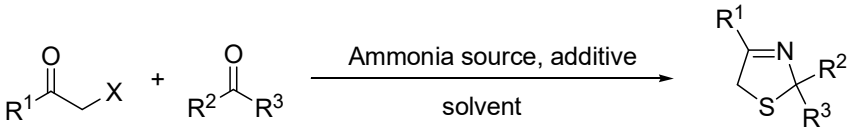
On the other hand, since its discovery in the late fifties [10–12], Asinger reaction has showed the distinctive advantages provided by multicomponent reactions applied to the synthesis of cyclic compounds [13–17], however, these apparent benefits are missed probably due to the few starting materials reported in 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 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 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 thiazoline poor yields as a consequence of

incompatibility of aqueous ammonia with the other components, specially 2-bromoketone, affording some degradation products related to competition in nucleophilic substitution on 2-bromoketones which resulted 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).



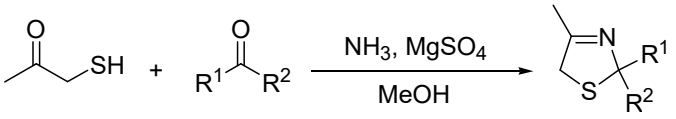
Scheme 1. Preparation of thiazolines from a four-component reaction.

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_4OH/H_2O	-	NaSH	R. T.	24	<5
2	Ph	Me	Me	Br	NH_4OH/H_2O	-	NaSH	R. T.	24	0
3	Me	Ph	Ph	Br	NH_4OH/H_2O	-	NaSH	R. T.	24	0
4	Me	Me	Me	Br	NH_4OH/H_2O	MeOH	NaSH	R. T.	24	0
5	Me	Me	Me	Br	NH_4OH/H_2O	Acetone	NaSH	R. T.	24	0
6	Me	Me	Me	Br	NH_4OH/H_2O	CH_2Cl_2	NaSH	R. T.	24	0
7	Me	Me	Me	Br	NH_4OH/H_2O	THF	NaSH	R. T.	24	0
8	Me	Me	Me	Br	NH_4OH/H_2O	MeOH	NaSH	Reflux	24	0
9	Ph	Me	Me	Br	NH_4OH/H_2O	MeOH	NaSH	Reflux	24	0
10	Me	Ph	Ph	Br	NH_4OH/H_2O	MeOH	NaSH	Reflux	24	0
11	Ph	Me	Me	Br	NH_4OAc	Acetone	NaSH	R. T.	48	0
12	Me	Me	Me	Br	NH_4OAc	Acetone	NaSH	R. T.	48	0
13	Me	Me	Me	Br	NH_4OAc	MeOH	NaSH	R. T.	48	0
14	Ph	Me	Me	Br	NH_4OAc	MeOH	NaSH	R. T.	48	0
15	Ph	Me	Me	Br	NH_4OAc	MeOH	NaSH	Reflux	24	0
16	Me	Ph	Ph	Br	NH_4OAc	AcOH	NaSH	100	24	0
17	Me	Ph	Ph	Br	NH_4OAc	DMF	NaSH	100	24	0
18	Me	Ph	Ph	Br	NH_4OAc	Toluene	NaSH	100	24	0
19	Me	4-ClC_6H_4	H	Br	NH_4OH/H_2O	-	NaSH	R. T.	24	8
20	Me	4-ClC_6H_4	H	Br	NH_4OH/H_2O	MeOH	NaSH	R. T.	24	12
21	Me	4-ClC_6H_4	H	Br	NH_4OH/H_2O	MeOH	NaSH	R. T.	24	<5
22	Me	4-ClC_6H_4	H	Br	NH_3/MeOH	MeOH	NaSH	R. T.	24	20
23	Me	4-ClC_6H_4	H	Br	NH_3/MeOH	MeOH	NaSH, $MgSO_4$	R. T.	24	35
24	Me	4-ClC_6H_4	H	SH	NH_3/MeOH	MeOH	$MgSO_4$	R. T.	24	64
25	Me	cyclohexanone		SH	NH_3/MeOH	MeOH	$MgSO_4$	R. T.	24	68

The change of a ketone by an aldehyde in Asinger Reaction slightly improved thiazoline yields up 20% using ammonia solution in methanol described by Silvani and coworkers [14]. According to these authors, anhydrous conditions using $MgSO_4$ also contributed to yield optimization, however, a radical change in reaction yield was observed when 1-mercaptopropan-2-one was used instead of 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 Asinger reaction is 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, ammonia/MeOH and modulated by an aldehyde (Scheme 2). Results in Table 2 show the procedure scope covering distinct substituents in 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^1	R^2	%Yield at R.T.	%Yield under MW
1	4-ClC_6H_4	H	64	71
2	2-ClC_6H_4	H	77	47
3	Ph	H	33	50
4	4-OHC_6H_4	H	55	65
5	4-$CH_3C_6H_4$	H	69	49
6	2,3-$(OCH_3)_2C_6H_3$	H	69	75
7	(3-OCH_3-4-OH)C_6H_3	H	90	70
8	(2-$OCH_2C{\equiv}CH)C_6H_4$	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 Asinger reaction. Thus, early investigations revealed thiazoline formation from last studied three-component reaction treated under microwave irradiation. Best yields were obtained at 40 °C (200 W) comparable, and in some cases higher than those observed at room temperature (see Table 2) but showing shorter reaction times. To the best of our knowledge, this is 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. Experimental

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. Melting points were determined with a Krüss Optronic melting point apparatus and they are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance 300-MHz; the chemical shifts (δ) are given in ppm relative to TMS as 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*) are 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 corresponds to the total irradiation time.

3.1. Synthesis of Thiazolines under Conventional Conditions; General Procedure

The appropriate aldehyde or ketone (1 mmol) and anhydrous $MgSO_4$ (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_2, 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), $MgSO_4$ (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 a 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 (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) νmax 2922, 1489, 1089, 828 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 170.8, 140.5, 133.6, 128.7, 128.2, 83.8, 47.3, 19.5. MS [EI+] *m*/*z* (%): 211 [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 white solid. Yields: 162.4 mg (77% at room temperature conditions) and 99.2 mg (47% under microwave conditions). IR (ATR) νmax 2916, 1469, 1036, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (m, 4H), 6.9 (s, 1H), 3.89 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 140.0, 132.3, 129.4, 128.8, 127.4, 127.1, 81.0, 46.6, 19.7. MS (EI^+) *m*/*z* (%): 211$[M]^+$ (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) νmax 2915, 1662, 1421 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 170.3, 141.9, 128.6, 128.41, 127.9, 126.8, 84.5, 47.2, 19.5. MS (EI^+) *m*/*z* (%): 177 $[M]^+$ (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) νmax 3065, 2900, 1663, 1514 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 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}C NMR (75 MHz, $CDCl_3$) δ 169.6, 156.9, 132.6, 127.9, 115.48, 84.3, 47.0, 19.4. MS (EI^+) *m*/*z* (%): 193 $[M]^+$ (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) νmax 2916, 1662, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 169.7, 138.7, 137.3, 128.9, 126.3, 84.1, 46.9, 29.4, 20.8, 19.2. MS (EI+) *m*/*z* (%): 191 [M]+ (10).

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

2,3-Dimethox-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) νmax 2935, 2834, 1665, 1478, 1263 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 [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) νmax 3101, 2920, 1595, 1368, 1270 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 [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) νmax 3285, 2918, 2120, 1663, 1487, 1220, 751 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 [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) νmax 2927, 1691, 1444, 894 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 2H), 2.10 (s, 3H), 2.04-1.16 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 95.4, 44.3, 40.9, 24.8, 24.1, 19.8. MS [EI+] *m*/*z* (%): 169 [M]+ (10).

4. Conclusions

Thiazolines are readily available from microwave assisted Asinger reaction by a synthetic procedure which takes the advantages of joining both multicomponent reaction approach and microwave irradiation methods. The simplicity of this methodology suggests that this route to thiazolines will enjoy widespread application.

Author Contributions: Conceptualization, E.C.-Y.; methodology, R.E.G.-C., L.G.-R., M.C.-R. and N.Z.-S.; formal analysis, N.Z.-S.; investigation, R.E.G.-C., N.Z.-S., E.C.-Y., B.A.F.-U., M.A.G.-E. and M.V.B.U.; resources, B.A.F.-U. and E.C.-Y.; data curation, N.Z.-S., M.A.G.-E. and M.V.B.U.; writing—original draft preparation, E.C.-Y.; writing—review and editing, E.C.-Y.; supervision, E.C.-Y., M.A.G.-E. and M.V.B.U.; project administration, E.C.-Y.; funding acquisition, B.A.F.-U. and E.C.-Y. All authors have read and agreed to the published version of the manuscript.

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

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