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Original article

Sodium fluoride as an efficient catalyst for the synthesis of 2,4-disubstituted-1,3-thiazoles and selenazoles at ambient temperature

Janardhan Banothu [a], Krishnaiah Vaarla [a], Rajitha Bavantula [a,*], Peter A. Crooks [b]

[a] Department of Chemistry, National Institute of Technology, Warangal 506004, India
[b] Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, AR 72205, USA

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ABSTRACT

Sodium fluoride was found to be a simple, mild and efficient catalyst for the synthesis of 2,4-disubstituted 1,3-thiazoles and selenazoles utilizing phenacyl bromides/3-(2-bromoacetyl)-2*H*-chromen-2-one and thiourea/phenylthiourea/selenourea in aqueous methanol at ambient temperature. Analytically pure products are formed within 1–3 min in excellent yields.

1. Introduction

Thiazole is a core structural motif present in a variety of natural products, such as vitamin B_1 (thiamine) and penicillin. Thiazole derivatives also exhibit a broad spectrum of medicinal and biological properties, such as antibacterial, antifungal [1], anti-inflammatory [2], antiviral [3], antimalarial [4] and anti-HIV activities [5]. Thiazole analogs have also been reported as ligands at estrogen receptors [6], neuropeptide Y5 [7], adenosine receptors [8], and act as inhibitors of human platelet aggregation factor [9], urokinase [10] and poly (ADP-Ribose) polymerase-1 [11]. Selenazoles have been reported to possess antibacterial [12], and superoxide anion scavenging activity [13], and exhibit cytotoxicity and DNA fragmentation effects in human HT-1080 fibrosarcoma cells [14]. The structures of sulfathiazole, meloxicam, and selenazofurin and their pharmacological activities are given in Fig. 1.

In view of the importance of thiazole and selenazole derivatives in medicinal chemistry, several methods for their synthesis have been reported utilizing various catalytic systems, such as ammonium-12-molybdophosphate [15], β-cyclodextrin [16], $CuPy_2Cl_2$ [17], HMCM-41 [9], and also under different solvent systems, such as ionic liquid/water [18], PEG-400 [19], glycerin [20] and water [21]. However, most of these reported methods suffer from drawbacks, such as harsh reaction conditions, unsatisfactory yields, longer reaction times and critical isolation procedures, and use of hazardous and expensive catalysts. Therefore, to overcome the above limitations we have developed a simple, mild and highly efficient protocol for the synthesis of thiazoles and selenazoles utilizing sodium fluoride (NaF) as a catalyst in aqueous methanol.

2. Experimental

Melting points were recorded on Stuart SMP30 apparatus and are uncorrected. Analytical thin layer chromatography was performed on F_{254} silica-gel precoated sheets using hexane/ethyl acetate (8:2) as eluent, and visualized with UV light and iodine vapor. Products were characterized by comparison with authentic samples, and by spectral data (IR, ^{1}H NMR and mass spectrometry). IR spectra were recorded on a Perkin-Elmer 100S spectrophotometer using a KBr disk. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed on a Carlo Erba modal EA1108 unit, and the values obtained are within ±0.4% of the theoretical values. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

* Corresponding author.
E-mail addresses: rajitabhargavi@yahoo.com, rajitha_nitw@yahoo.com (R. Bavantula).

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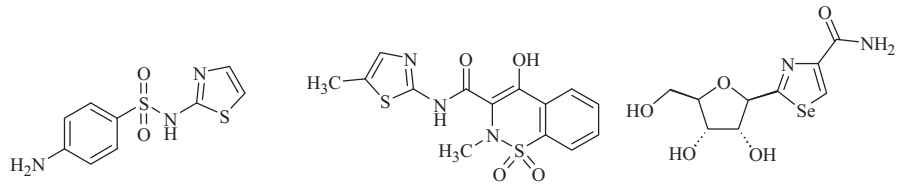
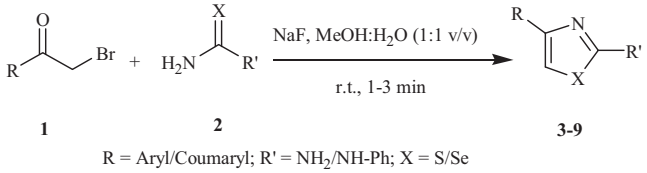


Fig. 1. Biologically active thiazole and selenazole derivatives.



Scheme 1. Synthesis of 1,3-thiazoles and 1,3-selenazoles.

2.1. General procedure for the synthesis of 1,3-thiazoles and selenazoles (**3–9**):

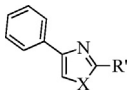
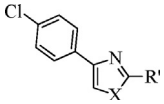
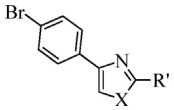
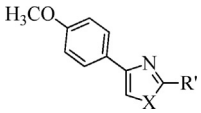
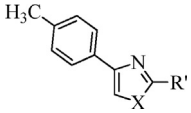
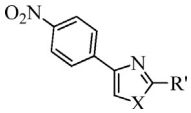
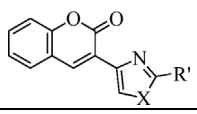
The appropriate phenacylbromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol) and either thiourea, phenylthiourea or selenourea (1 mmol) were dissolved in 2 mL of methanol, water (2 mL) containing 0.02 g of NaF added and the mixture stirred at room temperature for the appropriate time. After completion of

Table 1
Comparison of the catalytic activity of NaF with other catalysts in the synthesis of 4-(4-chlorophenyl)thiazol-2-amine (**4a**).

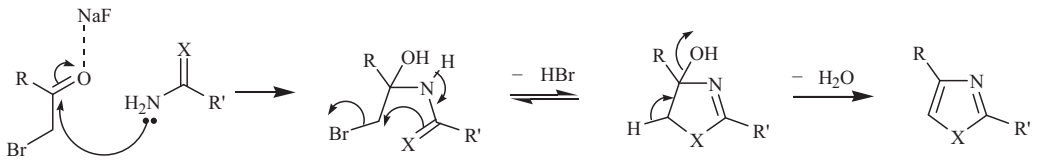
Entry[a]	Catalyst (0.02 g)	Time (min)	Yield[b] (%)
1	NaF	1	99
2	KF	5	94
3	$CuCl_2$	5	90
4	$AlCl_3$	5	88
5	$SnCl_2$	10	86
6	$BaCl_2$	10	85
7	PCl_5	5	82
8	$CuPy_2Cl_2$	5	88
9	$CoPy_2Cl_2$	5	87

$CuPy_2Cl_2$, Dipyridine copper chloride; $CoPy_2Cl_2$, Dipyridine cobalt chloride.
[a] Reaction conditions: 4-chlorophenacyl bromide (1 mmol), thiourea (1 mmol), catalyst (0.02 g), methanol:water (1:1 v/v), stirring at ambient temperature.
[b] Isolated yields.

Table 2
NaF-catalyzed synthesis of substituted 1,3-thiazoles and 1,3-selenazoles.

Entry[a]	Product		X	R'	Time (min)	Yield[b] (%)	Melting point (°C)	
							Found	Lit. [Ref.]
1		**3a**	S	NH_2	1	98	150–152	150–151 [21]
		3b	S	NH-Ph	1	98	134–136	135–136 [21]
		3c	Se	NH_2	2	97	132–134	132 [16]
2		**4a**	S	NH_2	1	99	166–168	167–168 [19]
		4b	S	NH-Ph	1	98	145–146	144–146 [19]
		4c	Se	NH_2	1	97	154–156	157 [16]
3		**5a**	S	NH_2	1	96	182–184	176–177 [23]
		5b	S	NH-Ph	1	98	230–232	–
		5c	Se	NH_2	1	98	177–178	132 [16]
4		**6a**	S	NH_2	3	93	204–206	206–207 [21]
		6b	S	NH-Ph	2	95	137–138	138–139 [21]
		6c	Se	NH_2	3	94	194–195	173 [16]
5		**7a**	S	NH_2	2	97	135–136	–
		7b	S	NH-Ph	1	98	102–103	–
		7c	Se	NH_2	2	98	166–168	167 [16]
6		**8a**	S	NH_2	2	97	284–286	–
		8b	S	NH-Ph	1	97	206–207	–
		8c	Se	NH_2	2	98	269–271	250 [16]
7		**9a**	S	NH_2	1	99	228–229	–
		9b	S	NH-Ph	1	98	188–190	–
		9c	Se	NH_2	1	98	217–218	280 [17]

[a] Reaction conditions: phenacyl bromide/3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol), thiourea/phenylthiourea/selenourea (1 mmol), methanol:water (1:1 v/v), stirring at ambient temperature.
[b] Isolated yields.



Scheme 2. Proposed mechanism.

the reaction, 10 mL of water was added and the solid that separated out was filtered off and washed with water, affording analytically pure substituted 1,3-thiazoles or 1,3-selenazole derivatives in excellent yields.

Associated characterization data can be found in Supporting information.

3. Results and discussion

In continuation of our studies toward the synthesis of biologically active molecules [22], we now report the synthesis of substituted 1,3-thiazoles and 1,3-selenazoles from the reaction of ω-bromoacetophenones and 3-(ω-bromoacetyl)coumarin with thiourea, phenylthiourea and selenourea utilizing NaF as catalyst in 1:1 (v/v) methanol/water at ambient temperature. Under these conditions excellent yields and rapid reaction times were obtained (Scheme 1).

In order to determine optimal conditions, initially, a model reaction between 4-chlorophenacyl bromide and thiourea was carried out in methanol by varying the amount of NaF catalyst. A maximum yield of 92% was obtained with 0.02 g of NaF within 5 min. Increasing amount of NaF led to no change in product yield or reaction time. Several similar synthetic methodologies have been reported utilizing water as solvent [21]; hence we carried out the reaction in 1:1 (v/v) water/methanol utilizing 0.02 g of NaF. To our surprise, under these conditions the reaction was completed within 1 min and afforded analytically pure 4-(4-chlorophenyl)thiazol-2-amine (**4a)** in 99% yield. We also carried out the reaction in pure water, but these conditions required a longer reaction time (25 min) for complete conversion. For authenticity, the structure of **4a** was confirmed on the basis of IR, ^{1}H NMR and mass spectral data and comparison with a literature report [19].

To investigate the unique catalytic activity of NaF, the above reaction was also carried out utilizing different inorganic and organometallic catalysts. These results clearly showed that, NaF is a unique and efficient catalyst for the synthesis of thiazoles at ambient temperature (Table 1).

After optimizing the reaction conditions, we examined the scope and generality of the method utilizing other substrates, *i.e.*, a variety of phenacyl bromides, 3-(2-bromoacetyl)-2*H*-chromen-2-one, and thiourea, phenylthiourea and selenourea. All the products from these reactions were obtained within 1–3 min in excellent yields. The results are presented in Table 2.

The proposed reaction pathway for the NaF-catalyzed formation of 2,4-disubstituted-1,3-thiazoles and selenazoles is shown in Scheme 2. In the presence of NaF, the electrophilicity of the carbonyl carbon of substituted 2-bromo ethanones is enhanced due to coordination of the carbonyl oxygen with NaF. Amination followed by cyclization and dehydration affords the desired thiazole or selenazole.

4. Conclusion

In conclusion, we have developed a facile method for the synthesis of substituted 1,3-thiazoles and 1,3-selenazoles by the reaction of ω-bromoacetophenones and 3-(ω-bromoacetyl)-coumarin with thiourea, phenylthiourea, and selenourea in the presence of NaF as a catalyst at ambient temperature. This methodology offers several advantages over other procedures, including higher yields, shorter reaction times, easy work-up procedure, and analytically pure products. We believe that, this methodology is superior over other reported methods, and may have industrial utility in the synthesis of substituted 1,3-thiazoles and 1,3-selenazoles at ambient temperature.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.10.001.

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