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Convenient one-pot formation of highly functionalized 5-bromo-2-aminothiazoles, potential endocannabinoid hydrolase MAGL inhibitors

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ABSTRACT

Highly functionalized 5-bromo-2-amino-1,3-thiazoles bearing various substituents could be easily prepared by a rapid and efficient one-pot method, using simple starting materials and mild conditions while avoiding the use of metal catalysts or inconvenient reagents such as elemental halogens. These useful products can serve as starting materials for other reactions or as pharmacologically interesting compounds. In our work we have shown that the resulting 5-bromothiazole compounds could lead to monoacylglycerol lipase (MAGL) inhibition in the μM range.

During an attempt to prepare substituted thiazole *N*-oxides [1] in our laboratory, we unexpectedly found that treatment of 2-aminothiazoles with *m*-chloroperoxybenzoic acid (*m*CPBA) in ethanol did not afforded the desired product **1** (Scheme 1). Spectral analyses proved that the corresponding 5-bromo-2-amino-thiazole **2** was formed instead in a very good yield (>90%).

This observation can be explained by the fact that the starting compound was, in fact, obtained as a hydrobromide salt. Thus, rapid oxidative bromination mediated by *m*CPBA occurred in the 5-position of the thiazole ring. We decided to explore this interesting transformation in more detail, especially because thiazoles are present in many natural products possessing biological activity, such as anti-mycobacterial agents [2–5]. A growing body of medicinal chemistry literature reports thiazole derivatives as candidates for the treatment of various pathologies [6–15]. These heteroaromatics have also found applications in materials science, e.g. as liquid crystals [16,17] Furthermore, halogenated thiazoles are useful synthetic intermediates for introducing this heterocyclic scaffold into more complex molecules [18]. The older method of using elemental bromine for bromination of the thiazole ring [19–21] has still occasionally been used in the recent years [22–24]. However, this approach has drawbacks such as toxicity, low atom economy, corrosiveness, handling issues and a relatively high cost. Apart from the application of *N*-halosuccinimides [25], more recent methods for thiazole halogenation include the use of copper(II) halides [26], metalations of the thiazole ring followed by quenching the reactive intermediates with electrophiles [27] and transition metal catalysis [28]. In general, despite the modern development in aromatic halogenation [29,30], there still remains a need for new procedures operating under mild conditions. Environmentally friendly and atom-economic oxidative halogenation holds a lot of promise in this respect [31].

We firstly examined the influence of the nature of the oxidant on the yield of bromothiazole **2**. The brominated compound **2** vs. non-brominated compound **3** system was chosen as the benchmark and the absolute yields of the two thiazoles were determined by LC/MS analysis. As observed from Table 1, compared to *m*CPBA (Entry 1), all the other oxidants, such as hydrogen peroxide (entry 2), sodium hypochlorite (entry 5), and sodium periodate (entry 10) gave a lower yield of **2**. Moreover, even Oxone® (entry 4), which works fine in some other oxidative halogenations [32–39], did not give satisfying results in our experiments, permitting a 6% yield on **2**.

With the evidence of *m*CPBA being the best oxidant agent, the next part of this study examined the amount of oxidant. Adding up to 1 equivalent of *m*CPBA improved the bromination ratio, but

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[1] This paper is dedicated to the memory of Mrs Sara Modaffari, a very nice and brilliant student, who passed away in March 9, 2018, aged 34.

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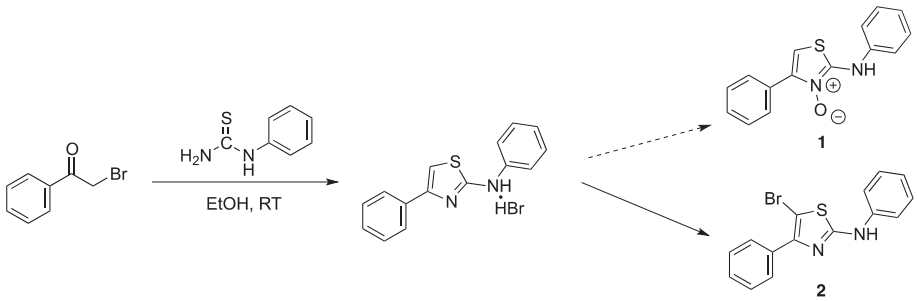
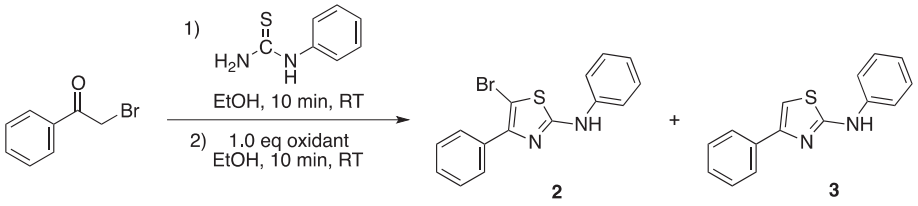


Scheme 1. *m*CPBA-mediated 5-bromo-2-amino-1,3-thiazole formation.

Table 1
Yield optimization studies for the formation of the bromothiazole 2.

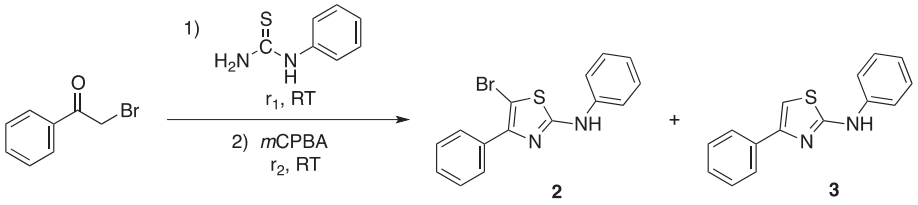


Entry	Oxidant	Equivalent	η (**2**) (%)[a]	η (**3**) (%)[a]
1	*m*CPBA	1.0	93	7
2	H_2O_2 50% aq.	1.0	6	93
3	UHP*	1.0	3	97
4	Oxone®**	1.0	6	94
5	$NaClO_2$	1.0	58	25
6	$NaBiO_3$	1.0	19	68
7	*t*-BuOOH	1.0	traces	69
8	MnO_2	1.0	12	64
9	$Na_2CO_3 \cdot 1.5\ H_2O$	1.0	traces	74
10	$NaIO_4$	1.0	77	20

*Urea hydrogen peroxide adduct.
**2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.
[a] Yields determined by LC/MS analysis.

further increase of its quantity caused a drop in yields. We secondly aimed at exploring the influence of solvent. As depicted in Table 2, polar solvents such as ethanol and DMF (Table 2, entry 1, and 7) worked best, permitting high yields (>93%). In fact, the highest yield of 5-bromo derivative **2** is obtained when using DMF (Table 2, entry 7). Using acetone, dichloromethane, 1,4-dioxane, toluene or acetonitrile lead to poor global yields (Table 2, entries 2, 4, 5, 6 and 7).

Table 2
Investigation of the solvent and the reaction times for the formation of (5-bromo-4- phenyl-thiazol-2-yl)-phenylamine **2**.



entry	solvent	Reaction time (min, r1 + r2)	η (**2**) (%)[a]	η (**3**) (%)[a]
1	EtOH	10 + 10	93	7
2	acetone	10 + 10	52	29
3	CH_2Cl_2	10 + 10	47	10
4	1,4-dioxane	10 + 10	43	22
5	toluene	10 + 10	10	12
6	MeCN	10 + 10	33	30
7	DMF	10 + 10	>99	<1
7′	DMF	5 + 5	99	1
7″	DMF	0 + 10	5	69

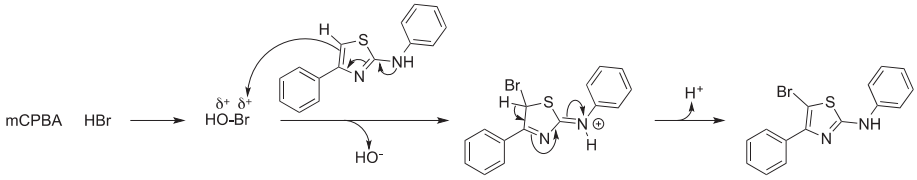
[a] Yields determined by LC/MS analysis.

Reduction of the r_1 and r_2 reaction time was also evaluated using DMF as solvent (Table 2, entry 7, 7′ and 7″). Reaction times limited at 5 min per step at room temperature is sufficient to obtain the desired compound **2** in a very good yield (99%). However, a one-pot operation adding *m*CPBA simultaneously with the α-bromoketone and thiourea (Table 2, entry 7″) caused a sharp drop in the yield of **2**, as well as in total thiazole (**2** + **3**). In most cases, a maximum of 10 min with *m*CPBA at room temperature was enough for the completion of the oxidative bromination reaction. Being more practical to handle than DMF, ethanol was chosen for all subsequent experiments and the chosen conditions were applied to probe the syntheses of a range of brominated thiazoles along with their non-brominated counterparts.

A suggested mechanism of the formation of the halogenation products includes the oxidation of halide to a reactive halogen derivative (Scheme 2) after reaction with the *m*- chloroperoxybenzoic acid. This *in situ* formed electrophilic hypobromous acid could then be attacked by the thiazole ring system in an electrophilic aromatic substitution reaction, giving the product brominated at C5 after aromatization. In fact, polarity inversion (umpolung) of the bromine is the key step for the addition-elimination reaction on the nucleophilic position of the thiazole ring. The formation of the diatomic elemental halogen X_2 with radical reaction seems to not occur due to the strict need of a stoichiometric amount of *m*CPBA to react with bromine. ^{13}C NMR studies showed easy identification thanks to a chemical shift for the carbon linked with the bromine in the brominated derivative around 90 ppm, against 115 ppm for none brominated compound. 2D NMR experiments (COSY, HSQC and HMBC) also led to the same conclusion.

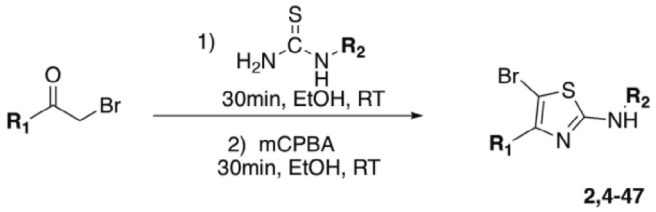
Various methods of purification were also tried. Because of the very small differences between the retention values (R_f) for the thiazole and the 5-bromo-thiazole, flash chromatography did not reveal to be successful. After several attempts, we found that the best way to obtain an easy and rapid isolation was by precipitation. Briefly, to a solution of the compounds in methanol or ethanol, addition of water led to the precipitation of the brominated derivative first. In case of mixture after precipitation, a second recrystallisation allowed to obtain the desired products in very high purity (>95%).

Finally, using standard conditions (0.3 M of all reagents in ethanol), the syntheses of a range of brominated thiazoles was undertaken (Table 3). Briefly, *m*CPBA was added and the mixture was stirred for 30 min at room temperature to allow completion of the first (Hantzsch) step reaction. Conversion rates and absolute



Scheme 2. Suggested mechanism of the 5-bromo derivatives formation.

Table 3
Outcomes of syntheses of 5-bromo-thiazoles with various substitution patterns (**Compound**, Yield[a] %).



2,4-47

R_1	R_2								
		F	F	F	Cl	Cl	Cl		
	2 63%	**4** 74%	**5** 70%	**6** 71%	**7** 71%	**8** 78%	**9** 39%	**10** 36%	**11** 82%
	12 14%	**13** 51%	**14** 47%	**15** 28%	**16** 76%	**17** 87%	**18** 91%	**19** 77%	**20** 77%
	21 25%	**22** 27%	**23** 51%	**24** 41%	**25** 60%	**26** 45%	**27** 35%	**28** 51%	**29** 55%
O_2N	**30** 45%	**31** 36%	**32** 53%	**33** 45%	**34** 61%	**35** 49%	**36** 45%	**37** 85%	**38** 85%
NC	**39** 71%	**40** 36%	**41** 53%	**42** 45%	**43** 61%	**44** 49%	**45** 45%	**46** 85%	**47** 85%

[a] Yields determined by LC/MS analysis.

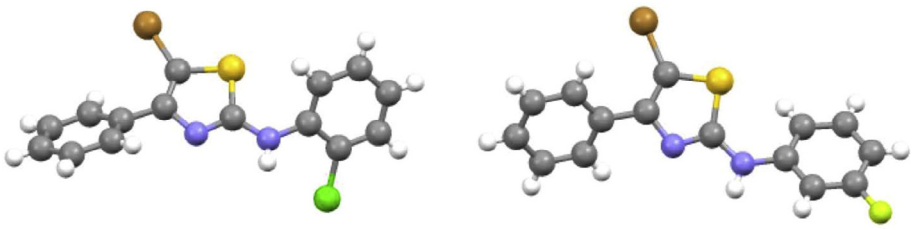


Figure 1. Solid state crystallographic structures of **5** (left) and **7** (right).

yields of the brominated vs. non-brominated derivatives were determined by LC/MS. In all cases, conversion rates proved to be quantitative with complete disparition (>99%) of the starting materials. As observed from Table 3, the absolute yields (non-optimized) ranged from 14% for **12** up to 91% for **18**, most of the transformation leading to a yield of brominated compounds >50%.

To further illustrate the scope of this reaction, the influence of electro-donating groups on R_1 and R_2 (Table 3) was also investigated. To this end, the 5-bromo-*N*-(4-methoxyphenyl)-4-phenylthiazol-2-amine **48**, the 5-bromo-*4*-(4-methoxyphenyl)-*N*-phenylthiazol-2-amine **49**, and the 5-bromo-*N,4-bis* (4-methoxyphenyl)-thiazol-2-amine **50,** containing a methoxy group on R_1 and/or R_2 were prepared and yields of, respectively, 86%, 76% and 73% were obtained, thus corroborating the versatility of this reaction.

In the case of the fluorinated (**5**) and chlorinated (**7**) compounds (see Table 3 above), crystals suitable for X-ray measurements were obtained (Fig 1). X-Ray data analysis unambiguously confirmed the structures of the newly synthesized molecules and the insertion of the bromine in the 5-position on the thiazole core.

Next, we investigated the potential of 5-bromothiazole as enzyme inhibitors. To this end, the brominated parent compound **2** was screened on various targets available in our lab and we found that this compound was interestingly a relatively potent inhibitor of the monoacylglycerol lipase (MAGL) [40] with > 60% inhibition at 100 μM. The compounds displayed in Table 3 were thus assayed on MAGL and 6 derivatives **6**, **8**, **11**, **14**, **15** and **19** proved to be more potent than the initial compound **2** with half maximal inhibitory concentration (IC_{50}) determined to be in the range of 10–55 μM [41–45]. Interestingly, the adamantyl and the phenyl on the left part of the molecules (R_1) seem better tolerated. The biological evaluation of these derivatives on MAGL can be found in the associated contents available.

In conclusion, our work describes a new, original and easy preparation of 5-bromo-thiazoles that can be synthesized efficiently following a one-pot procedure from simple starting materials, α-bromomethyl-ketones and thiosemicarbazides, and without using expensive catalysts or harsh conditions and reagents. The nature of the oxidant to perform the reaction, of the solvent and of the reaction time was evaluated. The initial compound **2** proved to be potentially interesting to target monoacylglycerol lipase (MAGL). A small library of 5-bromo-2-amino-thiazoles was thus elaborated and demonstrated promising although very preliminary inhibitory potency of MAGL.

Experimental

General information

All chemicals were purchased from Sigma or Acros Organics and used without further purification. NMR spectra were recorded on a Bruker Ultrashield Advance II 400 MHz instrument using dimethyl sulfoxide (DMSO d_6) or chloroform ($CDCl_3$) as deuterated solvent. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, q = quartet, m = multiplet, b = broad. Melting points (m.p.) were determined using an electrothermal apparatus and are reported uncorrected. LC-MS analyses were performed on an Agilent 6200 series TOF mass spectrometer equipped with ESI and APCI as ionization sources and TOF (Time Of Flight) detector, coupled with an Agilent 1200 series LC system with flux of 0.25 mL/min. High- resolution mass spectra were carried out on a Thermofisher Scientific LTQ-Orbitrap XL hybrid. X- ray diffraction datas were collected at room temperature on a Gemini Ultra (Rigaku) diffractometer using Cu Ka (1.54584) radiation.

MAGL esterase activity assay

MAGL activity was measured by following [^{3}H]-2-oleoyl glycerol ([^{3}H]-2-OG) hydrolysis, as previously described (cf ref 37, Morera, L.; et al. *Bioorganic and Medicinal Chemistry* **2012**, 20, 6260–6275). Briefly, 6 ng of pure human MAGL was preincubated during 30 min at room temperature in the presence of the inhibitor at various concentrations (Tris buffer 50 mM, BSA 0.15% w/v, pH 8.0, inhibitor dissolved in 10 μL DMSO). 2-OG (10 μM final concentration; [^{3}H]-2-OG 50,000 dpm, American Radiolabeled Chemicals; 200 μL total volume assay) was then added and the tubes were placed at 37 °C for 10 min. The reaction was stopped by adding 400 μL of a cold methanol- chloroform (1–1) mixture and, after 5 min centrifugation at 700*g*, the radioactivity was measured in the organic phase by liquid scintillation. The dpm value obtained for a blank (containing no enzyme) was systematically subtracted. Results were then expressed as percent of control activity (without inhibitor), after which GraphPad prism software was used to treat the data and to analyze the dose-response curves.

MAGL rapid dilution assay

The reversibility of MAGL inhibition by synthesized compounds was investigated using the rapid dilution assay. The enzyme (800 ng in 38 μL of a buffer containing Tris 50 mM, BSA 0.15%, pH 8.0) was incubated during 30 min at room temperature with 2 μL of compound **19** (concentration of 10^{-4} M and 10^{-5} M in the mixture) dissolved in DMSO. The enzyme-inhibitor mixture was then diluted 300-fold with the buffer. After 15 min of incubation, the enzyme activity was measured on a 150 μL aliquot (corresponding to 10 ng of enzyme) according to the above-described standard procedure.

Intermediate thioureas synthesis

To a solution of a (substituted)-phenylisothiocyanate derivative (0.6 M) in MeCN was added aqueous ammonia (25%, 1.5 eq). The solution was stirred at room temperature for 3 h. The reaction mixture was then concentrated. Purification was done by precipitation

from a mixture of *n*-hexane/ethyl acetate mixture (3/2). The pure product was recovered as a powder after filtration in a quantitative yield.

2-Amino-5-bromothiazole derivatives synthesis

To a solution of the intermediate thioureas (1 eq., 0.1 M) in EtOH was added 2-bromoacetophenone (1.25 eq). The solution was stirred at room temperature until completion of the reaction followed by TLC. Then *m*CPBA (1 eq., 3 M in EtOH) was added and the solution was stirred until completion. The reaction mixture was then concentrated. The resulting powder was dissolved in CH_2Cl_2 and extracted with water. The organic phases were combined, dried over Na_2SO_4 and evaporated. Purification by precipitation was performed: to the resulting powder was added a solution of 10% water in methanol until obtention of a cloudy solution. After cooling at 4 °C, precipitation of the product occurred over time. Filtration afforded the pure products as powders.

*5-Bromo-N,4-diphenylthiazol-2-amine **2**/N,4-diphenylthiazol-2-amine **3** system synthesis and LC/MS analysis procedure*

A mixture of the synthesized thiourea and variously substituted haloketones (0.3 mmol of each) in an appropriate solvent (900 µL) is reacted under the indicated experimental conditions. The oxidant in ethanol solution (0.3 mmol in 100 µL)) is added and the mixture is stirred. Then 1 mL of acetone is added and 20 µL of the mixture is added to 980 µL of acetonitrile. A second dilution with 20 µL of the previously prepared solution is added to 980 µL of acetonitrile to give a sample from 0 (0% yield) to 60 µM (100% yield) of either thiazole, which is then analyzed by LC/MS (measurement of UV absorption at 254 nm).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.10.055.

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