Domino alkylation-cyclization reaction of propargyl bromides and thioureas: a new facile synthesis of 2-aminothiazoles and 5*H*-thiazolo[3,2-*a*]pyrimidin-5ones.

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The 2-aminothiazole ring system is an useful structural element in medicinal as well as agricultural chemistry and has found a broad application in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, and bacterial and HIV infections.[1] A few methods for the synthesis of 2-aminothiazoles have been reported so far.[2-3] Among them the Hantzsch synthesis[2] which consists in the condensation of α-haloketones or haloacetaldehydes with monosubstituted thioureas still remains the widely used method for the preparation of 2-aminothiazoles. However, the difficulties that can be found in the preparation and isolation of not always commercially available α-haloketones together with their well known lacrimatory properties might represent a serious limitation to the Hantzsch approach. As a consequence, it seems reasonable that the development of a new, easy and fast procedure for the synthesis of 2-aminothiazole ring system is higly desiderable. Herein, the synthesis of 2-aminothiazoles with general structure **A** (Figure 1) through a domino alkylation-cyclization reaction between propargylbromides and thioureas was reported. This synthetic route was particularly attractive in light of the large availability of alkynes and constitutes a valid alternative to the classical use of α-haloketones in Hantzsch synthesis. In addition, the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5ones with general structure **B** (Figure 1) was also reported. These latter compounds could be considered as the bicyclic analogues of 2-aminothiazoles and represent attractive scaffolds in medicinal chemistry endowed with interesting antiulcer and anti-inflammatory activity after oral admistartion.[4] Moreover, due to our synthetic and biological experience in the field of antiviral agents such as the highly active S-DABO compounds,[5] we reasoned that the new methodology could be applied for the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5ones **C** (Figure 1). These latter compounds could be considered as the bicyclic analogues of S-DABOs and, as a consequence, could be evaluated for their anti-HIV activity.

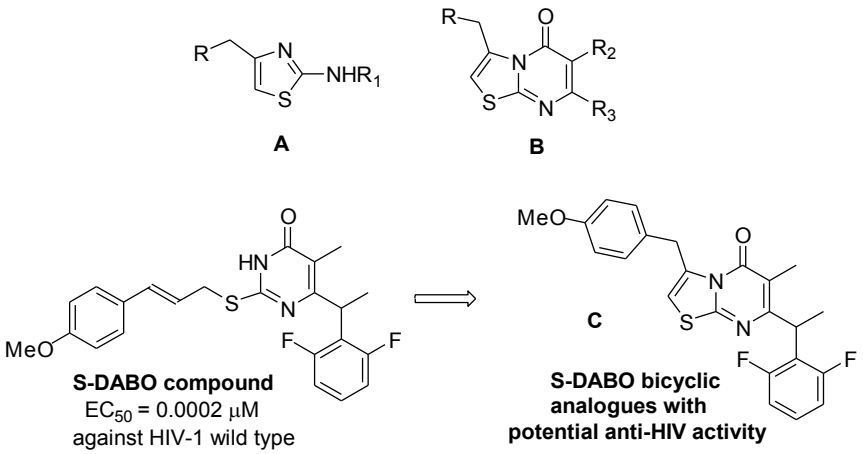
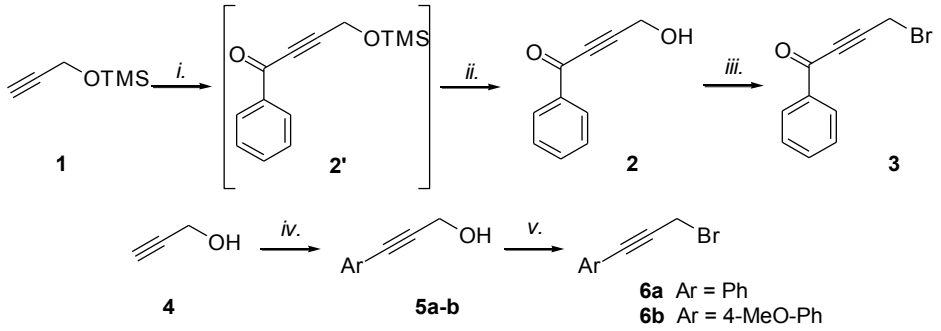


Figure 1.

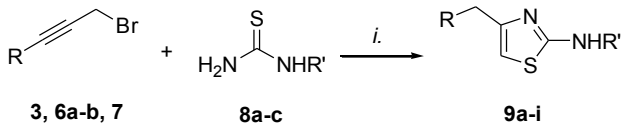
A series of propargyl bromides precursors was first synthesised. Alkyne **1** was reacted with benzoyl chloride through Sonogashira coupling affording compound **2'** which was directly converted into the deprotected propargyl alcohol **2** after chromatographic purification on silica gel. Alcohol **2** was then converted into bromide **3** derivative through a two step one pot mesylation-bromination procedure.[6] Sonogashira coupling of alkyne **4** with the appropriate iodide (phenyliodide and iodoanisole) led to alcohols **5a-b** which were in turn converted into bromide **6a-b** using the mesylation-bromination protocol described above. (Scheme 1).



Scheme 1. Reagents and conditions: *i.* PhCOCl, Et_3N, CuI, $PdCl_2(PPh_3)_2$, DMF. *ii.* Silica gel chromotography. *iii.* a) MsCl, Et_3N, DCM, then b) LiBr, THF. *iv.* ArI, Et_3N, CuI, $PdCl_2(PPh_3)_2$, DMF. *v.* a) MsCl, Et_3N, DCM, then b) LiBr, THF.

The commercially available propargyl bromide **7** and the bromides **3** and **6a-b** were then used as substrates for the domino alkylation-cyclization synthesis of 2-aminothiazoles **9**. Alkynes **3**, **6a-b**, **7** were reacted with thioureas **8a-c** at 130 °C in the presence of stechiometric amount of K_2CO_3 and

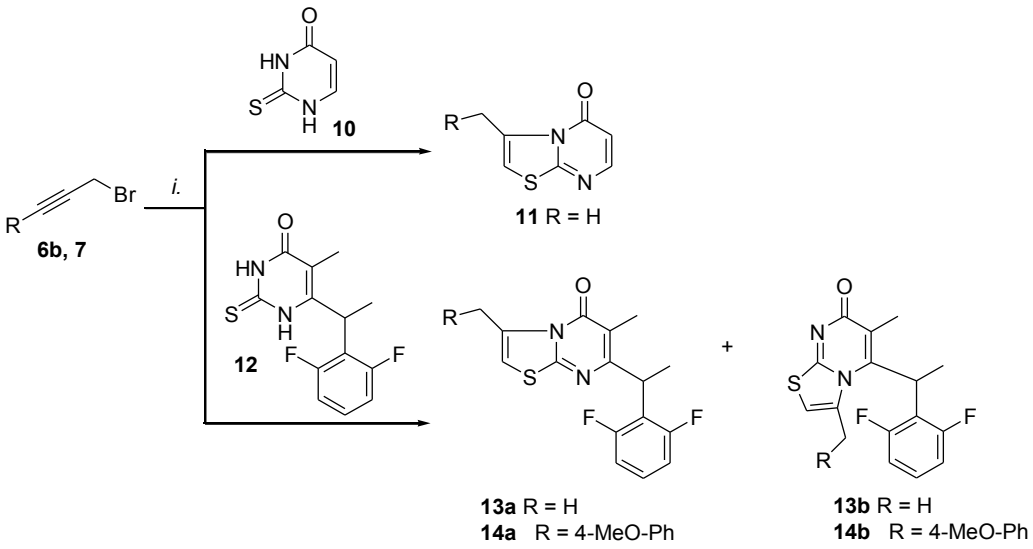
under microwave irradiation (Scheme 2) leading in only 10 minutes (2 runs, 5 minutes each) to 2-aminothiazoles **9a-i** (*Entries 1-9*).[7] Yields are reported in Table 1.



3, 6a-b, 7 **8a-c** **9a-i**

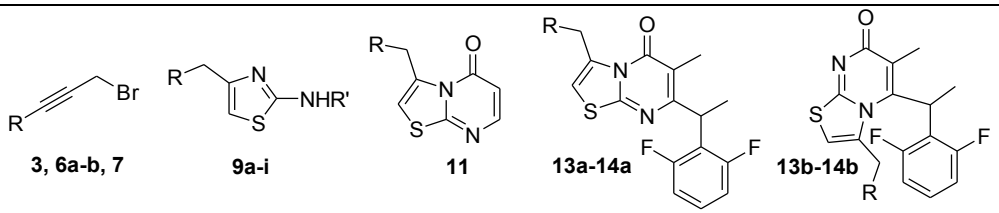
Scheme 2. Reagents and conditions: *i.* K_2CO_3, DMF, μW, 2 x 5min., 130 °C.

The reaction of propargyl bromide **7** with thiopyrimidinones was then investigated. Propargylbromide **7** was first reacted with thiouracyl **10** leading to derivative **11** as the only product and in high yield (*Entry 10*). The reaction of propargyl bromide **7** with the S-DABO compound **12**[5] led to a mixture of two isomers **13a-b** which were isolated in a 2:1 ratio (*Entry 11*). On the contrary reaction of alkyne **6b** with S-DABO **12** led to the formation of compound **14a** together with traces of its isomers **14b** (*Entry 12*). The observed regioselectivity might be due to the steric hyndrance of p-MeO-Ph moiety on the alkyne **6b** which could reduce the rate of formation of **14b** over **14a** during the thiazole cyclization step. Structures of compounds **11**, **13** and **14** were confirmed by 2D-NOESY experiments and are in agreement with spectroscopic data reported in the literature for similar compounds.[4b-8] Reaction yields are summarized in Table 1.



Scheme 3. Reagents and conditions: *i.* K_2CO_3, DMF, μW, 2 x 5min., 130 °C.

Table 1.

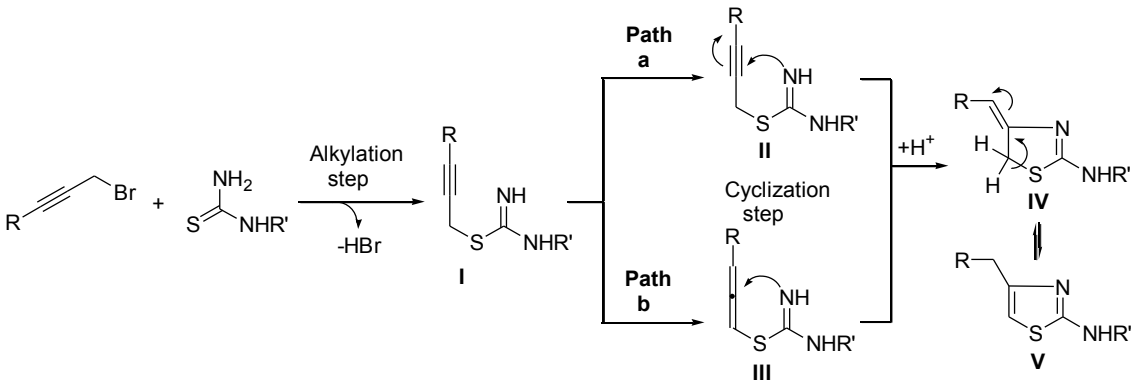


3, 6a-b, 7 | 9a-i | 11 | 13a-14a | 13b-14b

Entry	Propargyl bromide	R	Product	R^1	Yield (%)[a]
1	**3**	Bz	**9a**	H	61
2	**3**	Bz	**9b**	Me	65
3	**6a**	Ph	**9c**	H	70
4	**6a**	Ph	**9d**	Me	73
5	**6b**	4-MeO-Ph	**9e**	H	78
6	**6b**	4-MeO-Ph	**9f**	Me	75
7	**7**	H	**9g**	H	90
8	**7**	H	**9h**	Me	83
9	**7**	H	**9i**	Allyl	87
10	**7**	H	**11**		62
11	**7**	H	**13a/13b**		56 : 32
12	**6b**	4-MeO-Ph	**14a/14b**		77 : traces

a) Isolated yields were reported.

The proposed mechanism for the domino alkylation-cyclization reaction of propargyl bromides and thioureas is described in Scheme 4. The first alkylation step is supposed to be the alkylation of thiourea resulting in the formation of the intermediate **I**. Two possible pathways could then explain the cyclization step: (i) the nucleophilic imino group undergoes a 5-*exo*-dig cyclization directly on the triple bond leading to intermediate **IV** which isomerizes into the final product **V** (**path a**). (ii) The alkaline enviroment promotes the isomerization of the triple bond into allene **III**. Then the imino group attacks on the central carbon of **III** leading to **IV** which isomerizes into final aminothiazole **V** (**path b**). We hypothesised that the reaction proceeds following the **pathway a**. In fact, the isomerization of the triple bond into allene is generally promoted by strong bases such as ^{t}BuOK or EtONa. It seems reasonable to think that K_2CO_3 is a too weak base to favour the formation of allene intermediate **III** and it is higly probable that carbonate is consumed in the alkylation step by the quenching of the formed HBr.



Scheme 4. Proposed mechanism for the tandem alkylation-cyclization reaction of propargyl bromides with thioureas.

In conclusion, a new approach for the synthesis of 2-aminothiazoles **9a-i** and 5*H*-thiazolo[3,2-*a*]pyrimidin-5ones **11**, **13** and **14** starting from different substituted propargylbromides and thioureas/thiopyrimidinones was developed.[9-11] All the compounds were obtained in good-high yields in a few minutes, through a domino alkylation-cyclization reaction under microwave irradiation. The new methodology represents an effective and versatile method for the synthesis of 2-aminothiazoles in addition to Hantzsch synthesis. Finally the synthesis of bicyclic S-DABOs analogues **13-14** was reported. Biological evaluation of **13-14** as HIV inhibitors is currently in progress.

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7. Reaction of alkyne **7** with thiourea **8a** was also carried out under the same reaction condition but in the absence of K_2CO_3. No traces of aminothiazole **9g** were detected in this case and only side products, whose characterization resulted to be difficoult, were isolated.
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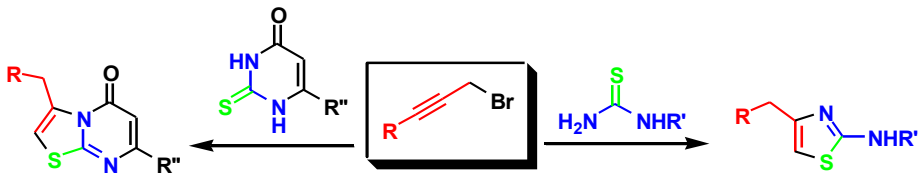
9. Synthesis of 2-aminothiazoles **9a-i**. General procedure. Alkyne **3-6-7** (1.0 mmol) and the appropriate thiourea **8a-c** (1.0 mmol) were suspended in anhydrous DMF (1.0 mL) in a 10 mL glass vial equipped with a small magnetic stirring bar. K_2CO_3 (1.0 mmol) was then added to this solution and the mixture was irradiated under microwaves for 2 x 5 minutes at 130 °C, using an irradiation power of 300 W. Microwave irradiations were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The mixture was then poured into water (10 mL) and then extracted with AcOEt (2 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by flash column chromatography (SiO_2) using 1:1 AcOEt/hexanes as the eluent, to yield the 2-aminothiazoles **9a-i** as tan oils.
10. Characterization of **13a**: ^{1}H NMR ($CDCl_3$): δ 7.54 (s, 1H, S*CH*CHCH$_3$) 7.08-7.06 (m, 1H, Ph), 6.75-6.71 (m, 2H, Ph), 4.56-4.54 (m, 1H, CH$_3$*CH*Ph), 2.34 (s, 3H, NC*CH$_3$*), 1.94 (s,

3H, *CH₃*), 1.58 (d, 3H, CH*CH₃*) ppm. ^{13}C-NMR ($CDCl_3$): δ 162.61, 160.13, 159.36, 128.10, 124.85,119.38, 117.84, 111.64, 111.39, 34.27, 17.88, 13.47, 10.35 ppm. MS (ESI) *m/z* 321 $[M+H]^+$, 343 $[M+Na]^+$. Characterization of **13b**: ^{1}H NMR ($CDCl_3$): δ 7.08-7.04 (m, 1H, Ph), 6.76-6.72 (m, 2H, Ph), 6.27 (s, 1H, S*CH*CHCH₃), 4.54-4.49 (m, 1H, CH₃*CH*Ph), 2.70 (s, 3H, NC*CH₃*), 1.89 (s, 3H, *CH₃*), 1.58 (d, 3H, CH*CH₃*) ppm. ^{13}C-NMR ($CDCl_3$): δ 162.63, 162.24, 160.14, 135.98, 128.09, 119.37, 112.86, 111.38, 105.68, 34.07, 18.56, 17.77, 10.23 ppm. MS (ESI) *m/z* 321 $[M+H]^+$, 343 $[M+Na]^+$.

11. Characterization of **14**: ^{1}H NMR ($CDCl_3$): δ 7.11-7.04 (m, 3H, Ph), 6.81-6.72 (m, 4H, Ph), 5.97 (s, 1H, S*CH*), 4.54-4.49 (m, 1H, CH₃*CH*Ph), 3.71 (s, 3H, O*CH₃*), 1.91 (s, 3H, *CH₃*), 1.59 (d, 3H, CH*CH₃*) ppm. ^{13}C-NMR ($CDCl_3$): δ 162.60, 161.85, 158.61, 140.31, 130.62, 129.99, 114.38, 113.84, 111.77, 111.30, 107.22, 106.19, 55.40, 37.06, 33.96, 17.80, 10.77 ppm. MS (ESI) *m/z* 427 $[M+H]^+$, 449 $[M+Na]^+$.

Graphical Abstract



Keywords: Domino reaction, 2-aminothiazole, thiazolopyrimidinone, microwave synthesis, antiviral agents.

Abstract

A new synthesis of 2-aminothiazoles and 5*H*-thiazolo[3,2-*a*]pyrimidin-5ones was developed by a domino alkylation-cyclization reaction of propargylbromides and thioureas/thiopyrimidinones. Domino reactions were performed under microwave irradiation leading to desired compounds in a few minutes and high yields.