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Facile synthesis of thiazoles via an intramolecular thia-Michael strategy☆

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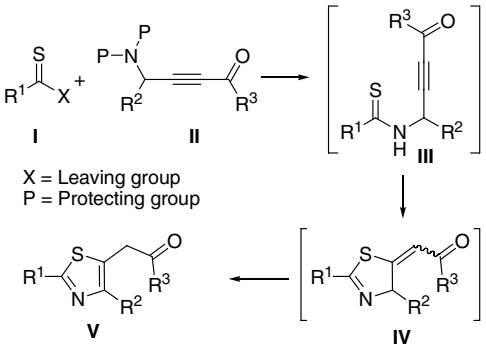
Abstract—A mild and efficient method for the synthesis of substituted thiazoles is reported via one-pot *N*-desilylation, thioacylation/oxythioacylation/thiothioacylation followed by thia-Michael cycloisomerisation. This method has a general applicability to introduce various oxo and thio functionalities including aliphatic and aromatic moieties, especially at the C2-position of thiazoles.

Thiazoles play a prominent role in Nature. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids.[1] Various pesticides possessing a thiazole nucleus are well known in agriculture. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory,[2] anti-tumour,[3] anti-hyperlipidemic,[4] anti-hypertensive[5] and several other biological properties.[6] Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry. Several methods[7] for the synthesis of thiazole derivatives were developed by Hantzsch, Tcherniac, Cook–Heilbron, Gabriel and several other groups, amongst which the most widely used method is Hantzsch's synthesis[7,8] (reaction between α-halocarbonyl compounds and thioamides, thioureas or thiocarbamic acid derivatives or dithiocarbamic acid derivatives). Relatively, newer methods involve cycloaddition of TosMIC to thione derivatives,[9] oxidation of thiazoline/thiazolidine ring systems,[10] Ugi reaction[11] and others.[12] Recently, palladium-mediated coupling processes (Suzuki coupling,[13] Stille reaction[14] and Negishi coupling[15]) have emerged as powerful tools to introduce various aryl and olefinic moieties into the thiazole ring systems. Nucleophilic reactions of lithiothiazole[16] also afford substituted thiazoles. Despite these procedures, novel methods for thiazole synthesis are still in demand. We were interested in developing a general protocol to synthesise thiazoles which could accommodate various *C*-, *O*-, *S*- and *N*- functionalities, especially at the C2 position of the thiazole ring. Towards this purpose, we envisioned an intramolecular thia-Michael strategy (Scheme 1), where intermediate **III** will eventually give thiazole **V** with or without the help of any additives via the intermediacy of **IV**.

Initially we used the HCl salt of ethyl 3-aminoprop-1-yn-1-carboxylate **1a**[17] and then ethyl 4-*N*,*N*-bis(trimethylsilyl)aminobut-2-ynoate **1b**[18] and *N*,*N*-dimethyl 4-*N*′,*N*′-bis(trimethylsilyl)aminobut-2-yne amide **1c**[18a] as amino compounds (Fig. 1).

For the thione counterparts, we used different benzotriazolylthione derivatives as the benzotriazole anion is



Scheme 1.

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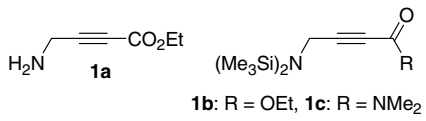


Figure 1.

an excellent leaving group and its derivatives are non-hazardous, easy to handle and are quite stable for long periods of time. Thus, compounds **2**–**5** were prepared (Scheme 2) following a standardised four-step protocol viz., acylation of 2-nitroaniline, $NiCl_2$–$NaBH_4$-mediated reduction[19] of the nitro group, conversion of the amide to a thioamide followed by benzotriazole formation using Rapoport chemistry.[20]

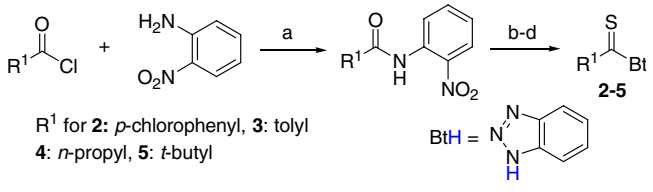
Initially, compound **2** was reacted with amine **1a** in THF in the presence of triethylamine and according to our expectation thiazole **14** (see Table 3) was obtained in 81% yield. While preparing **1a** from **1b**,[17] we observed *N*-desilylation of compound **1b** in different solvents containing traces of alcohol. In alcoholic solvent, this desilylation was much faster. This observation suggested the use of trimethylsilyl protected amines (**1b** and **1c**) directly in our subsequent studies as it reduces by one step, the overall synthesis.

To understand better the effect of the alcohol solvent in the desilylation process and in subsequent thiazole synthesis, we studied the concentration effect of MeOH, as well as the effect of different alcohols on the rate of reaction between **2** and **1b** in THF (Tables 1 and 2).

We observed that higher concentrations of MeOH accelerated the rate of reaction and also, as expected, higher homologues of MeOH slowed down the desilylation process and hence the rate of reaction. Based on these studies, we used a combination of 10 equiv of MeOH in THF in our subsequent one-pot approach for thiazole synthesis.

Accordingly, benzotriazolylthione derivatives **2**–**5** were treated with silyl protected amines **1b**–**c** and the results are summarised in Table 3. In all cases, cycloisomerisation was spontaneous and the corresponding thiazoles[21] were obtained in good to excellent yields. Amines **1b** and **1c** both behaved in a similar fashion in these reactions.

We next investigated this methodology with di-benzotriazolylmethanethione **6**,[22] and gratifyingly we obtained thiazole **20** in 85% yield from amine **1b** (entry



Scheme 2. Reagents and conditions: (a) pyridine, 0 °C to rt, 4 h; (b) $NiCl_2{\cdot}6H_2O$ (2 equiv), $NaBH_4$ (4 equiv), MeOH, 0 °C to rt, 2 h; (c) P_4S_{10} (0.5 equiv), Na_2CO_3 (0.5 equiv), THF, rt, 3 h; (d) $NaNO_2$ (1.5 equiv), 70% aq HOAc, 0 °C to rt, 1 h.

Table 1. Concentration effect of MeOH on the rate of reaction between **2** and **1b** in THF (0.2 M with respect to **2**) to synthesise thiazole **14**

Entry	MeOH (equiv)	Reaction time
1	0	>2 d
2	1	4 h
3	2	2 h
4	5	1 h 20 min
5	10	1 h
6	20	30 min
7	Only MeOH as solvent	10 min

Table 2. Effect of different alcohols on the rate of reaction between **2** and **1b** in THF (0.2 M with respect to **2**) to synthesise thiazole **14**

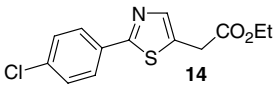
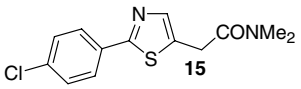
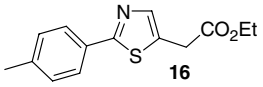
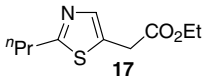
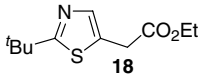
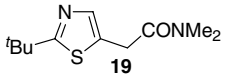
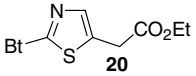
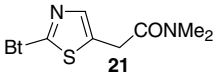
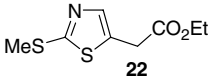
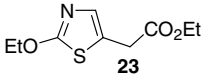
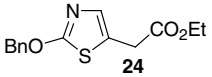
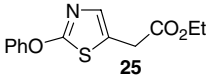
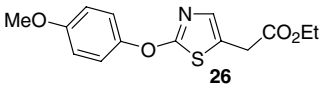
Entry	Alcohol (10 equiv)	Reaction time
1	MeOH	1 h
2	EtOH	1 h 20 min
3	*n*-PrOH	1 h 40 min
4	*i*-PrOH	2 h
5	*t*-BuOH	6 h

8) and thiazole **21** in 75% yield from amine **1c** (entry 9). According to our knowledge, this is, so far, the fastest method available to synthesise compounds such as **20** and **21**. Encouraged by these results, we then studied related substrates like benzotriazole carbothioates, benzotriazole carbodithioates and benzotriazolylaminomethanethione systems, most of which (compounds **8**–**13**) were prepared following Katritzky's protocol[23] (Scheme 3).

Once in hand, compound **7**[24] and compounds **8**–**13** were then reacted with amines **1b**–**c** and the results are shown in Table 3. We observed that in the case of the thiomethyl derivative **7** (entry 10) and alkoxy derivatives **9** and **10** (entries 12 and 13), Bt (benzotriazolyl) acts as a leaving group, whereas, in the case of the thiophenoxy derivative **8** (entry 11), the Bt group was retained in the thiazole product eliminating thiophenoxy as the leaving group. In the case of phenoxy derivative **11** (entry 14), there was leaving group competition between Bt and OPh. As a result, 2-phenoxythiazole derivative **25** and compound **20** were obtained in 26% and 60% yields, respectively. As expected, *p*-methoxyphenoxy derivative **12** (entry 15) gave relatively more 2-aryloxythiazole **26** (40%) along with thiazole **20** (45%), as the methoxy group reduces the leaving group capacity of the aryloxy moiety. In the case of compound **13**, inconclusive results were obtained.[25] The electronic effect of different substituents on the final outcome of cycloisomerisation needs special mention. In the case of both alkoxy and aryloxy substituents, addition of Et_3N facilitates the cyclisation process from the initially formed intermediates whereas, in all other cases, cyclisation was almost spontaneous and the base was introduced to ensure that the cycloisomerisation–aromatisation process took place. Overall, in all the cases, thiazole synthesis was very easy as indicated in Table 3.[26]

Mechanistically, it can be postulated that initially intermediate **A** is formed which after *N*-desilylation generates

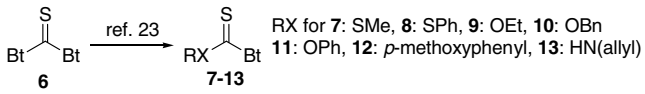
Table 3.

Entry	Substrate[a]	Amine[b]	Conditions[c]	Time[d] (h)	Product	Yield[e] (%)
1	**2**	**1a**	A	1.5	 **14**	81
2	**2**	**1b**	B	1	**14**	80
3	**2**	**1c**	B	4	 **15**	74
4	**3**	**1b**	B	1.5	 **16**	78
5	**4**	**1b**	B	5	 **17**	93
6	**5**	**1b**	B	3.5	 **18**	74
7	**5**	**1c**	B	6	 **19**	78
8	**6**	**1b**	B	0.5	 **20**	85
9	**6**	**1c**	B	1.5	 **21**	75
10	**7**	**1b**	B	8	 **22**	70
11	**8**	**1b**	B	3	**20**	82
12	**9**	**1b**	B	5	 **23**	74
13	**10**	**1b**	B	3	 **24**	93
14	**11**	**1b**	B	2	 **25**	26
15	**12**	**1b**	B	3	 **26**	40

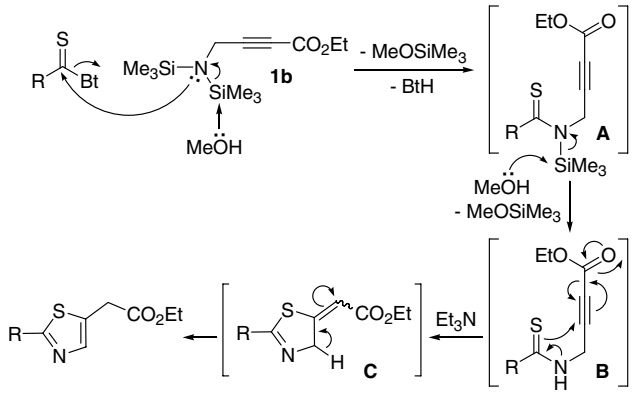
[a] Concentration of substrate is 0.2 M in THF.
[b] Amine (1.5 equiv) was used.
[c] Reaction conditions: (A) THF, Et_3N (1.5 equiv); (B) THF, MeOH (10 equiv), Et_3N (1.0 equiv).
[d] Time required for the starting material to disappear before addition of Et_3N.
[e] Pure isolated yield.

intermediate **B** (Scheme 4). Intermediate **B** subsequently undergoes, spontaneously or in the presence of a base, cycloisomerisation–aromatisation to give thiazoles via the intermediacy of **C**. It should be noted that intermediates **A** and **C** were not observed by TLC, whereas intermediate **B** was observed in TLC and in some cases could be isolated by column chromatography.

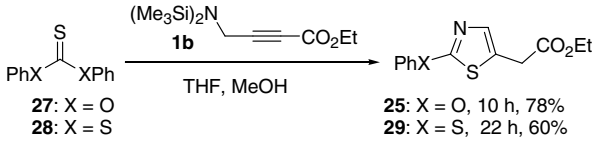
As we obtained poor yields in the cases of aryloxy and thio-aryloxy thiazoles (see entries 11, 14 and 15 in Table



Scheme 3.



Scheme 4.



Scheme 5.

3), we decided to apply this method to di-aryloxy thione and di-thioaryloxy thione systems. According to our expectations, when compounds **27** and **28** were treated with amine **1b** (Scheme 5), the desired thiazoles **25** and **29** were obtained in good yields.

In conclusion, we have demonstrated a novel method for the synthesis of thiazoles via one-pot *N*-desilylation, thioacylation/oxythioacylation/thiothioacylation followed by cycloisomerisation in an intramolecular thia-Michael fashion. The beauty of this method lies in the fact that it is very mild, simple, highly efficient and can introduce various oxo and thio functionalities including aliphatic and aromatic moieties, especially at the C2 position of thiazole derivatives. There is a huge scope to expand this approach. Currently, we are preparing different *N*-trimethylsilyl protected 1-alkyl/aryl-substituted propargyl amines with various electron withdrawing groups on the acetylenic moiety for the synthesis of 2,4,5-trisubstituted thiazole libraries, details of which will be published in due course.

Acknowledgements

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25. Even after a couple of days, more than half of the starting material remained unreacted. Optimised reaction conditions for this class of compounds will be published in due course.
26. In a typical experiment, the thione (1.0 mmol) was dissolved in THF (0.2 M) under an inert atmosphere. To the solution at room temperature was added amine (1.5 equiv) followed by MeOH (10 equiv). The reaction mixture was stirred at the same temperature until the disappearance of starting material, as checked by TLC. Et_3N (1.0 equiv) was added and the reaction mixture stirred for 30 min. The reaction mixture was diluted with ethyl acetate and the organic layer was successively washed with 5% aq Na_2CO_3 solution, water and brine and dried ($MgSO_4$). Concentration and chromatographic purification afforded the desired thiazole derivatives.