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An efficient synthesis of thiazolo[3,2-*a*]pyrimidinones

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ABSTRACT

A series of thiazolo[3,2-*a*]pyrimidinones was synthesised in a two-step procedure, using Eaton's reagent to effect cyclisation of 2-aminothiazoles. The use of relatively low temperatures, facile product isolation and short reaction times make this cyclisation procedure a particularly attractive option over more conventional methods.

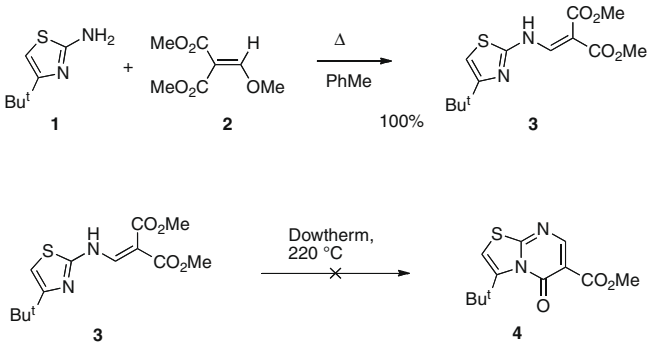
The thiazolo[3,2-*a*]pyrimidinone core is a popular motif in medicinal chemistry and has been implicated in biological activity in a variety of therapeutic areas. These include anticancer[1,2] and anti-ulcer activities,[3] and more recently as kinase inhibitors. However, there are relatively few reported methods for accessing this core structure.[4–7] As part of a medicinal chemistry programme, a series of thiazolo[3,2-*a*]pyrimidinone derivatives was required for biological testing. A typical method for their synthesis involves condensation of an aminothiazole with a malonate derivative followed by intramolecular cycloacylation. This usually requires heating for prolonged periods at high temperatures.[3,8]

The synthesis of the desired thiazolo[3,2-*a*]pyrimidinones began with 2-aminothiazole substrate **1** which was reacted with dimethyl methoxymethylenemalonate **2**; we were able to obtain the condensation product **3** in excellent yield. However, the use of conventional cyclisation methods such as heating in high boiling solvents (e.g., Dowtherm, *N*-methylpyrrolidinone, sulfolane) failed to give the desired thiazolo[3,2-*a*]pyrimidinones **4** (Scheme 1).[3] The addition of organic base also did not aid cyclisation and usually led to decomposition. Similarly, acidic conditions led to isolation of the starting material only, with no product detected.

Several explanations can be put forth for the lack of reactivity in this reaction. Mechanistically it is clear that the thiazole nitrogen needs to attack the ester carbon (Fig. 1), thus both the nucleophilicity of the nitrogen and the electrophilic nature of the ester carbon need to be considered. It is well known that an ester carbonyl is not particularly electrophilic in nature. Additionally, aromaticity is lost in the first step. Similarly, the exocyclic nitrogen is a part of a vinylogous amide leaving the thiazole nitrogen relatively electron poor and unable to initiate cyclisation. Also, an intramolecular hydrogen bond exists between the N–H and an ester carbonyl oxygen, which holds the side chain in a conformation unsuitable for cyclisation (Fig. 1).

We were made aware of the use of commercially available Eaton's reagent, a mixture of 7.7 wt % phosphorus pentoxide solution in methanesulfonic acid, for such transformations by the recent publication of Zewge and co-workers, who employed this reagent in their synthesis of 4-quinolone derivatives.[9] On applying this protocol to our substrates, for example, **3**, we were pleased to observe the formation of the desired thiazolo[3,2-*a*]pyrimidinones **4** in excellent yield (Scheme 2).

Purification of the product consisted of a simple filtration of the precipitate resulting from pouring the reaction mixture into a sufficient quantity of saturated, aqueous sodium bicarbonate and



Scheme 1. Synthesis of vinylogous amide **3** and cyclisation attempts.

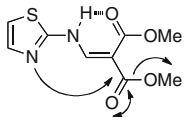


Figure 1.

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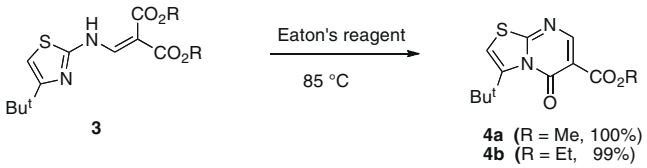


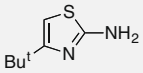
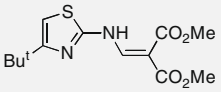
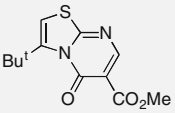
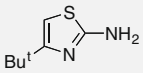
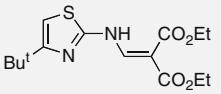
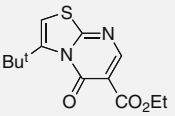
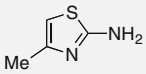
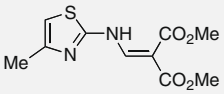
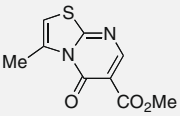
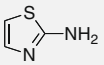
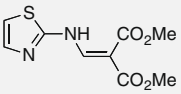
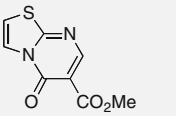
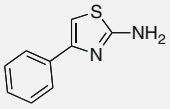
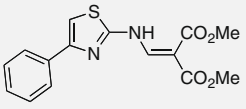
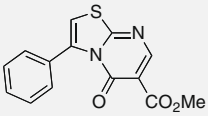
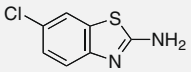
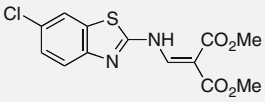
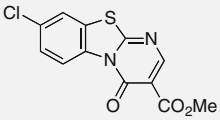
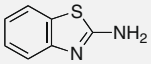
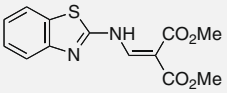
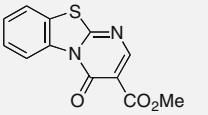
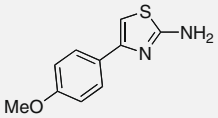
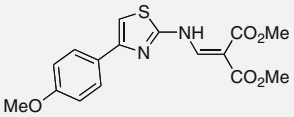
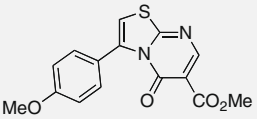
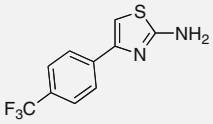
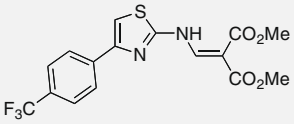
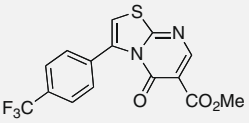
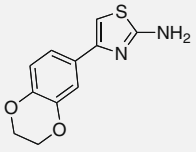
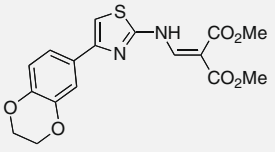
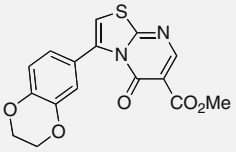
Scheme 2. Synthesis of thiazolo[3,2-*a*]pyrimidinones **4** using Eaton's reagent.

subsequent drying in air. The reaction could be scaled up to give multigram quantities of the thiazolo[3,2-*a*]pyrimidinone esters **4**.

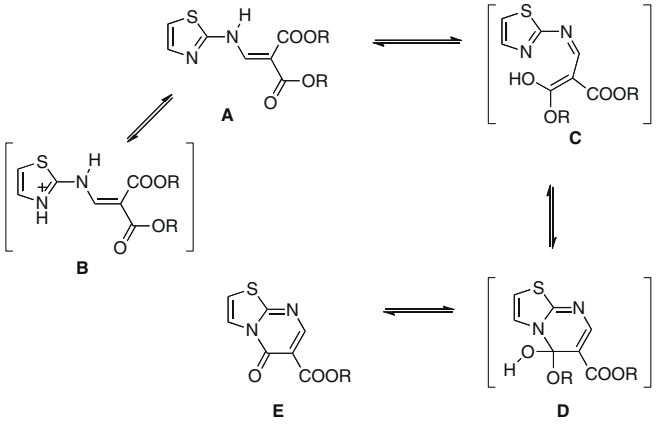
In order to determine the limits of applicability of the cyclisation reaction using Eaton's reagent, a range of substrates was employed in the two-step protocol. The results are summarised in Table 1.

Mechanistically, the presence of acid is clearly central to the cyclisation (Scheme 3). In general, the formation of amides from esters and amines is a base-catalysed process with formation of the tetrahedral intermediate being the rate-determining step.[10] Although the overall result of this cyclisation is formation of a lactam from an ester, the functional groups involved are more complex and the mechanism is not a simple aminolysis of an ester. Protonation of starting thiazole **A** can take place on the thiazole nitrogen leading to intermediate **B** which is unproductive, or on the enamide oxygen leading to **C**. This removes the double bond stereochemistry barrier to cyclisation and intermediate **C** can

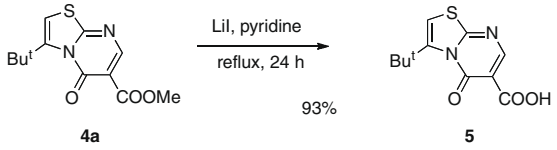
Table 1
Two-step synthesis of thiazolo[3,2-*a*]pyrimidinones from 2-aminothiazoles

Entry	Substrate	Condensation product[a] **3**[11]	Yield[b] of **3** (%)	Cyclisation product[a] **4**[12]	Yield[c] of **4** (%)
a			99		100
b			96		99
c			81		74
d			34		57
e			72		35
f			32		92
g			60		53
h			73		24
i			30		–
j			21		–

[a] All compounds were characterised by ^{1}H NMR, ^{13}C NMR and LCMS.
[b] Isolated yield after flash column chromatography.
[c] Isolated yield after purification.



Scheme 3. Proposed mechanism of cyclisation.

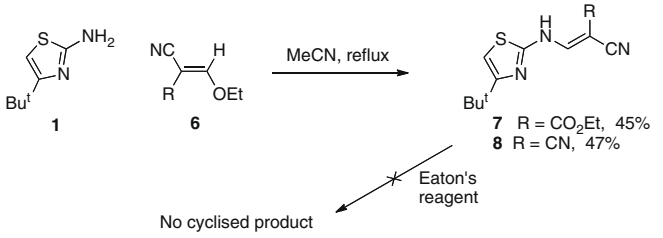


Scheme 4. Ester cleavage.

cyclise via an electrocyclic reaction to generate the tetrahedral intermediate **D**. Breakdown of this by elimination of alcohol leads to the desired product **E**. Clearly, base would lead to the deprotonation of the enamide leaving the ester carbonyl insufficiently electrophilic. On the other hand, too much acid would lead to thiazole protonation reducing the nucleophilicity of the crucial nitrogen atom. Finally, insufficient acid would not allow the formation of the key intermediate **C**. Table 1 shows that the electronic properties of the thiazole substituents affect the ease with which cyclisation takes place. Strongly electron-donating groups lead to complete protonation whilst strongly electron-withdrawing groups lead to insufficient protonation, both of which hinder the cyclisation.

In this programme, our ultimate aim was to produce a library of amides. Therefore, to further the synthesis, the carboxylic acid functionality needed unmasking by removal of the ester. This proved to be more difficult than anticipated as traditional methods such as acid hydrolysis and saponification left the ester untouched. Eventually, heating the methyl ester **4a** with lithium iodide in pyridine under reflux afforded the acid **5**, thus clearing the way for the synthesis of our library of amides (Scheme 4).

In an attempt to circumvent the ester hydrolysis step, we decided to have in place alternative functional groups which could be converted into the carboxylic acid after the key cyclisation step. To this end, two alternative cyclisation precursors, **7** and **8**, were prepared (Scheme 5) containing one and two cyano groups, respectively. Treatment with Eaton's reagent under our optimised conditions failed to give the desired cyclisation products. In these examples, the lower electrophilicity of the nitrile group appears to prevent cyclisation. The carboxylic acid, which could have resulted from in situ hydrolysis of the nitrile or ester groups, was also not detected.



Scheme 5. Reactions involving a cyano group.

In summary, we have reported a short, mild and effective protocol for the synthesis of thiazolo[3,2-*a*]pyrimidinones and related bicycles which were unattainable by previously reported methods. Further work will focus on determining which functional groups can be manipulated to undergo such cyclisations under these conditions.

Acknowledgements

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11. *Typical procedure for the synthesis of dimethyl 2-[(4-tert-buylthiazol-2-ylamino)methylene]malonate* (**3a**).
2-Amino-4-*tert*-butylthiazole (7.4 g, 48 mmol) was added to dimethyl 2-(methoxymethylene)malonate (8.4 g, 48 mmol) in dry PhMe (100 mL). The solution was heated under reflux for 16 h and then concentrated under vacuo. Purification by column chromatography (1:4 EtOAc/PE) gave the title compound as a cream-coloured solid (14.0 g, 99%); mp 92–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.31 (9H, s), 3.81 (3H, s), 3.87 (3H, s), 6.48 (1H, s), 8.70 (1H, d, *J* 12.9 Hz), 11.32 (1H, d, *J* 12.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 29.6 (CH_3), 34.9 (C), 51.7 (CH_3), 51.9 (CH_3), 95.9 (C), 104.3 (CH), 150.9 (CH), 159.7 (C), 164.3 (C), 165.3 (C), 168.7 (C); ν_{max} 1687, 1252, 1030 cm^{-1}; MS (ESI) $[M+H]^+$ 299.4.
12. *Typical procedure for the synthesis of methyl 3-tert-butyl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate* (**4a**).
Eaton's reagent (120 mL) was added to malonate derivative **3a** (14.0 g, 48 mmol) and the resulting solution was heated at 85 °C for 1.5 h. After this period, the reaction was allowed to cool, then poured onto saturated $NaHCO_3$ until pH >11. The resulting solid was filtered and dried in air to afford the title compound as a pale-yellow solid (12.5 g, 100%); mp 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.59 (9H, s, $C(CH_3)_3$), 3.92 (3H, s, OCH_3), 6.82 (1H, s, C=CH), 8.66 (1H, s, C=CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 31.0 (CH_3), 37.2 (C), 52.1 (CH_3), 107.0 (CH), 109.0 (C), 151.8 (C), 156.8 (CH), 156.8 (C), 165.0 (C), 169.9 (C); ν_{max} 1473, 1704, 1749, 3427 cm^{-1}; HRMS (ESI) found $[M+H]^+$ 267.0798, $C_{12}H_{15}N_2O_3S$ requires 267.0798.