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Graphical Abstract

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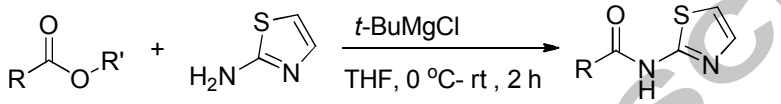

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ABSTRACT

A facile and efficient method has been developed for the synthesis of novel thiazolylcarboxamide derivatives by direct reaction of corresponding esters and 2-aminothiazole. Treatment of 2-aminothiozole with various carboxylic esters in the presence of *t*-butylmagnesium chloride provides the biologically significant thiazolylcarboxamide derivatives in good to excellent yields.

Amidation is a highly useful synthetic strategy used by nature as exemplified by proteins, peptides and many other naturally occurring substances[1]. The reaction also occupies a prominent position in many fields of chemical industry including material science and drug development.[2] It is noteworthy that more than 25% of known drug molecules possess amide groups.[3] Numerous amidation protocols have been extensively explored and developed[1-3] and in principle most amides are synthesized by the reaction between amines with activated carboxylic acid derivatives.[4]

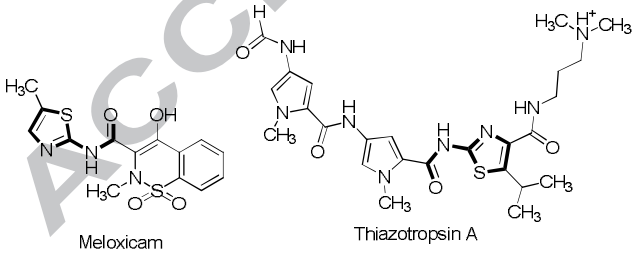
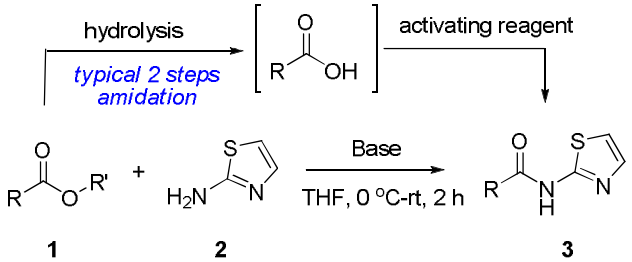


Figure 1. Representative drugs possessing a thiazole amide.

Thiazolyl carboxamides, the amides of 2-aminothiazoles are very important structural motifs used by drug discovery chemists and found in many important disease-intervening substances. For example, Meloxicam is a selective cyclooxygenase-2 inhibitor called as non-steroidal, anti-inflammatory drug (NSAID)[5] and Thiazotropsin A is binding to the minor groove of duplex DNA[6] (Figure 1). Despite significant progress made in peptide coupling strategies, however, chemists still are seeking after an optimized synthetic protocol for thiazolyl carboxamides since most of the known methods require activation of carboxylic acids by using stoichiometric amount of coupling reagent and often tedious workup procedures.[7] Moreover, due to the weak nucleophilicity of the amino group in 2-aminothiazole, the reaction suffers from undesirably long reaction time and low yields. Thus, facile formation of thiazolyl carboxamides has remained as a major hurdle in medicinal chemist's compound design. We herein report a novel and direct coupling method between 2-aminothiazole and unactivated esters that yields thiazolyl carboxamides atom-economically and in high yields.



Scheme 1. Direct amidation strategy

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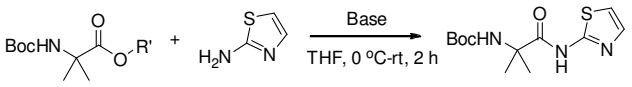
Table 1. Optimization of the transamidation reaction[a]



1a **2** **3a**

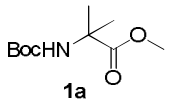
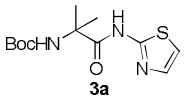
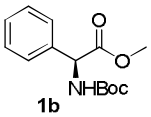
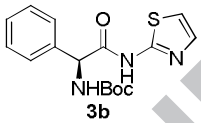
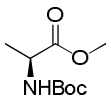
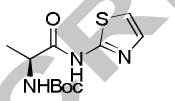
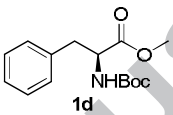
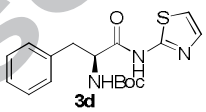
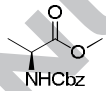
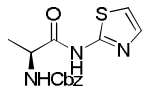
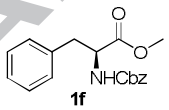
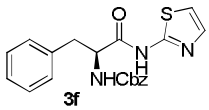
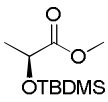
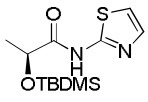
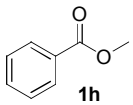
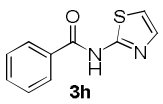
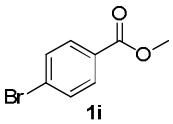
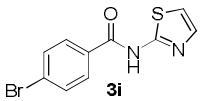
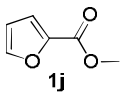
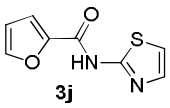
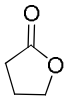
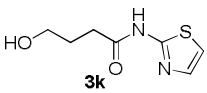
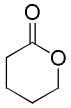
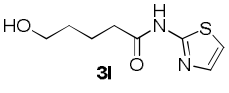
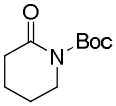
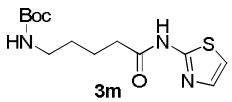
Entry	2-Aminothiazole (equiv.)	Base (equiv.)	Yield[b] (%)[b]
1	1.0	*t*-BuMgCl (1.0)	38
2	2.0	*t*-BuMgCl (1.0)	43
3	**2.0**	***t*-BuMgCl (2.0)**	**81**
4	3.0	*t*-BuMgCl (1.0)	50
5	2.0	*i*-PrMgCl (2.0)	64
6	2.0	*i*-PrMgCl (1.0)	31

[a] Unless otherwise stated, all the reaction were conducted in 1.0 equiv of ester **1a**, 2-aminothiazole **2**, and the base (as mentioned above equivalence) were stirred at 0 ºC then rt for 2 h. [b] isolated yields.

Issues arise in the general amidation reactions owing to the onerous formation of activated esters (electrophiles) and low reactivity of 2-aminothiazole (nucleophile). In order to overcome the issues, we turned our attention to generating an activated nucleophile instead. Inspired by the Merck's procedure developed for the synthesis of Weinreb amides,[8] we were prompted at using the magnesium amidate of 2-aminothiazole. As a touchstone for the utility of the magnesium amidate in amidation, we designed a highly challenged coupling reaction as an initial study. The study was performed with the ester **1a** (1.0 equiv) and 2-aminothiazole **2** (1.0 equiv) in the presence of the base *t*-butylmagnesiumchloride (*t*-BuMgCl, 1.0 equiv) in THF at 0 ºC. The highly sterically-challenged neopentyl position of **1a** was successfully elaborated by the amidate and afforded the desired thiazolyl amide **3a** in 38% yield as shown in Table 1.(entry 1) Encouraged by this result, we screened several reaction conditions to optimize the amidation. We were pleased to find that the desired product **3a** was obtained in 81% yield when the reaction was performed with 2 euiv. of **2** and 2 euiv. of the base (Table 1, entry 3). When *i*-PrMgCl was used as base, relatively low yields of the desired product were obtained. (entry 5 and 6). [9] It is worth to note that the amide coupling with the corresponding acid of **1a** under the conventional protocols utilizing EDC, HATU, and HOBt afforded the desired product **3a** in less than 30% yield.[10]

The scope of this application was investigated by using 2-aminothiazole and different carboxylic ester derivatives, which proved to be widely applicable. Smooth conversion to the corresponding amidation products was observed all through the tested reactions in good to excellent yields, as shown in Table 2.[12] We subjected various *N*-protected α-amino acid methyl ester and TBDMS-protected methyl-L-lactate substrates to this reaction protocol and all of them were successfully converted to the corresponding products in good yields. We were particularly delighted to find that there was no sign of racemization in forming **3b** even though enantiomerically-rich phenylglycines are often highly prone to racemization during their peptide bond formations.[11] The **1h-m** substrates (entry 8 to 13) did not require an additional stoichiometry and yielded the corresponding thiazolyl carboxamides by using 1.0 equiv of 2-aminothiazole and 1.0 equiv of *t*-BuMgCl. No variation in reaction conditions was necessary for handling the aryl ester substrates like **1h-j**.

Table 2. Transamidation of 2-aminothiazole with various esters[a]

Entry	Substrate	Product	Yield[c] (%)[c]
1	 **1a**	 **3a**	81.0
2	 **1b**	 **3b**	69.4
3	 **1c**	 **3c**	70.8
4	 **1d**	 **3d**	73.6
5	 **1e**	 **3e**	69.6
6	 **1f**	 **3f**	65.7
7	 **1g**	 **3g**	71.3
8[b]	 **1h**	 **3h**	83.2
9[b]	 **1i**	 **3i**	79.0
10[b]	 **1j**	 **3j**	74.2
11[b]	 **1k**	 **3k**	83.2
12[b]	 **1l**	 **3l**	87.4
13[b]	 **1m**	 **3m**	77.6

[a] Unless otherwise stated, all the reaction were conducted in 2.0 equiv of 2-aminothiazole, 1.0 equiv of ester, 2.0 equiv of, *t*-butylmagnesiumchloride stirred at 0 ºC for 2 h. [b] 1.0 equiv of 2-aminothiazole, 1.0 equiv of ester, 1.0 equiv of *t*-butylmagnesiumchloride stirred at 0 ºC to rt for 2 h. [c] isolated yields

The lactones and lactam **1k-m** were also well tolerated in this reaction conditions and the ring opening proceeded smoothly in all cases furnishing functionalized thiazolylcarboxamides in good to excellent yields.

In summary, we have developed a novel and direct formation of thiazolyl carboxamides via utilizing the magnesium amidate of 2-aminothiazole. We hope this method would become a very useful tool for synthetic or medicinal chemists performing amidation reactions. We believe the presented new methodology offers distinguished advantages over the conventional methods especially for sterically or electronically challenged peptide bond formations.

Acknowledgments

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References and notes

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8. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.;Dolling, Ulf-H.; Grabowski, J. J. *Tetrahedron Lett.* **1995**, *36*, 5461
9. The reason why the use of *i*-PrMgCl afforded **3a** in relatively low yield is unclear at the present time.
10. When the conventional carbodiimides-based amidation protocols were used, the oxazolone was obtained as a major byproduct. For an example of the amide coupling between the carboxylic acid and the substituted 2-aminothiazole, see: Forster, C. J.; Kwak, Y.-S.; Nakajima, K; Wang, B. PCT Int. Appl. 2010007046
11. See the supporting information for the general procedure and spectral data.
12. No racemization occurred. (2% <)

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.