A convenient synthesis of 2-acyl benzothiazoles/thiazoles from benzothiazole/ thiazole and N,N'-carbonyldiimidazole activated carboxylic acids

Tonghui Huang, Xin Wu, Yongbo Yu, Lin An, Xiaoxing Yin

PII: S0040-4039(19)30487-3
DOI: https://doi.org/10.1016/j.tetlet.2019.05.043
Reference: TETL 50815

To appear in: *Tetrahedron Letters*

Received Date: 5 March 2019
Revised Date: 16 May 2019
Accepted Date: 21 May 2019

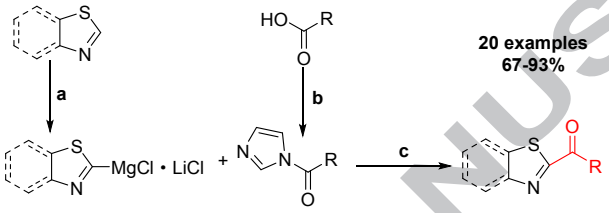
Please cite this article as: Huang, T., Wu, X., Yu, Y., An, L., Yin, X., A convenient synthesis of 2-acyl benzothiazoles/ thiazoles from benzothiazole/thiazole and N,N'-carbonyldiimidazole activated carboxylic acids, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.05.043

Graphical Abstract

A convenient synthesis of 2-acyl benzothiazoles/ thiazoles from benzothiazole/thiazole and N,N'-carbonyldiimidazole activated carboxylic acids

Leave this area blank for abstract info.

Tonghui Huang [a,b], Xin Wu [a], Yongbo Yu [a], Lin An [a], Xiaoxing Yin [a,*]



Conditions : (a) *i*-PrMgCl·LiCl, THF, -10 °C, 30 min. (b) N,N'-carbonyldiimidazole, THF, r.t., 1 h. (c) THF, -10 °C to r.t., 3 h.

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A convenient synthesis of 2-acyl benzothiazoles/thiazoles from benzothiazole/thiazole and N,N'-carbonyldiimidazole activated carboxylic acids

Tonghui Huang [a,b], Xin Wu [a], Yongbo Yu [a], Lin An [a], Xiaoxing Yin [a,*]

[a] *Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, Xuzhou Medical University, Xuzhou, Jiangsu 221000, PR China*
[b] *Xuzhou Medical University Science Park, Xuzhou, Jiangsu 221006, PR China*

* Corresponding author. e-mail: yinxx@xzhmu.edu.cn (X. Yin).

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-acyl thiazoles
2-acyl benzothiazoles
Grignard reagents
Acylation

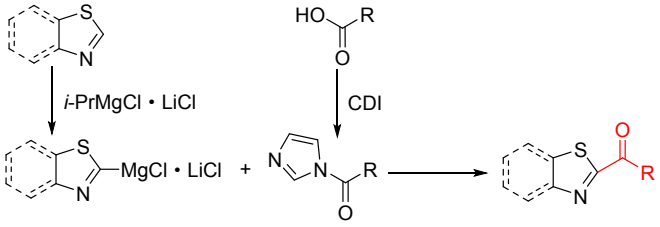
ABSTRACT

A convenient and efficient strategy for the synthesis of 2-acyl benzothiazoles/thiazoles has been developed. The treatment of benzothiazole/thiazole with allylic Grignard reagents readily generates the corresponding 2-Grignard reagents, which is followed by a reaction with N,N'-carbonyldiimidazole activated carboxylic acids to afford various 2-acyl benzothiazoles/ thiazoles products. The synthetic method is applicable to a wide array of carboxylic acids and allows easy access to 2-acyl benzothiazoles/thiazoles with considerable yields under mild reaction conditions.

Introduction

Benzothiazole is a privileged heterocyclic scaffold with its derivatives frequently found in diverse pharmacological agents,[1] natural products,[2] as well as synthetic intermediates.[3] Studies on benzothiazoles suggest they have various pharmacological effects, exhibiting anticancer,[4] anti-inflammatory,[5] antimicrobial,[6] and antifungal activities.[7] In particular, 2-acyl benzothiazoles have attracted significant attention due to their highly effective therapeutic activities and favorable pharmaceutical properties.[8] In our previous work, we also designed a series of 2-acyl benzothiazoles, which could serve as a potential inhibitor toward the herbicidal target D1 protease (CtpA).[9] The extensive biological activities of 2-acyl benzothiazoles have provided a strong motive to achieve synthesis of this series of compounds.

In the past decades, a number of approaches have been developed for the preparation of 2-acyl benzothiazoles, mainly including: (1) nucleophilic addition of metallized benzothiazoles with electrophiles;[10] (2) direct acylation of benzothiazoles with carbonyl sources;[11] (3) coupled oxidation/heterocyclization of 2-aminothiophenols with diverse substrates.[12] However, these synthetic strategies remain less than ideal with some inevitable drawbacks. For example, due to the highly reactive of lithium salts, a very low temperature is imperative for the metallation of benzothiazoles with *n*-butyllithium or other lithium reagents, as well as the following reaction with suitable electrophiles. To the I_2/KOH synergistically promoted direct ring-opening acylation of benzothiazoles,[11a] $FeCl_3 \cdot 6H_2O$ or copper (I) iodide catalyzed acylation of benzothiazoles,[11b, 11c] only aryl ketones can serve as carbonyl sources, which greatly limited the application of them. In contrast, a multipathway coupled domino strategy demonstrated the ability to synthesize 2-acyl benzothiazoles from multiform substrates including arylethenes, arylacetylenes, 2-hydroxy-aromatic ketones, and 1-arylethanol; whereas it is worth noting that only 2-aroyl benzothiazoles were obtained via this method.[12a] Moreover, harsh reaction conditions like high reaction temperature, long reaction times and/or tedious workup procedure are indispensable for the coupled oxidation/heterocyclization of 2-aminothiophenols with substrates such as phenylacetaldehydes,[12b] α,α-dihaloketones,[12c] and aromatic ketones.[12d, 12e] Thus, it is worthwhile to develop a concise and practical approach that capable of synthesizing both alkyl benzothiazoyl ketones and aryl benzothiazoyl ketones.



Scheme 1. The synthetic method for 2-acyl benzothiazoles/thiazoles.

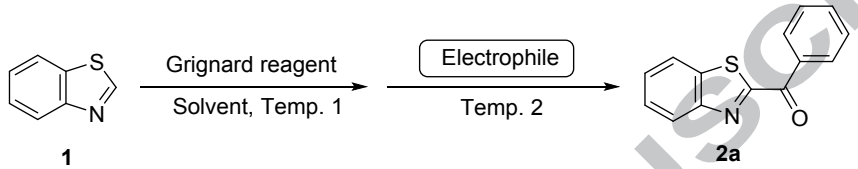
Herein, we report a convenient and efficient approach for the synthesis of 2-acyl benzothiazoles/thiazoles via treatment of benzothiazole/thiazole (1.2 equiv) with *i*-PrMgCl·LiCl (1.3 equiv), followed by reaction with N,N'-carbonyldiimidazole (CDI, 1 equiv) activated carboxylic acids (Scheme 1). The present method is applicable to a wide range of substrates and allows easy access to desired products with considerable yields under mild reaction conditions.

Results and disscussion

Motivated by the effective preparation of 2-acyl oxazoles through the reactions of Grignard oxazole reagents with iminium

reagents or Weinreb amides,[13] it was postulated that the 2-Grignard benzothiazole reagents might react with carboxylic acid derivatives in a similar fashion to yield 2-acyl benzothiazoles. Hence, benzothiazole, *i*-PrMgCl, and N-Methoxy-N-methylbenzamide were chosen as model substrates to initiate this study (Table 1). Fortunately, the treatment of benzothiazole (1.2 equiv) with *i*-PrMgCl (1.3 equiv) at -10 °C in THF, followed by reaction with the Weinreb amide of benzoic acid (1 equiv) at room temperature for 3 h, provided the desired product **2a** in 70% yield (Table 1, entry 1). Encouraged by this initial success, attention was focused on determining an alternative electrophile, and benzoyl chloride, ethyl benzoate, benzoic acid anhydride, benzonitrile, (1H-imidazol-1-yl)(phenyl)methanone, and HATU activated benzoic acid were investigated (Table 1, entry 2−7). The optimization results revealed that (1H-imidazol-1-yl)(phenyl)methanone was the best electrophile to provide **2a** in a yield of 83% (Table 1, entry 6), whereas only a trace amount of **2a** were observed in the other five reactions. Based on this research, an appropriate approach to generate (1H-imidazol-1-yl)(phenyl)methanone was also designed (Table 1, entry 8). The CDI activated benzoic acid can directly react with 2-Grignard benzothiazole without purification and provided **2a** in a comparable yield (80%).

Table 1
Optimization of reaction conditions.[a]



1 **2a**

Entry	Electrophile	Solvent	Temp. 1 (°C)	Temp. 2 (°C)	Grignard reagent	Yield (%)[b]
1	N-methoxy-N-methylbenzamide	THF	-10	r.t.	*i*-PrMgCl	70
2	benzoyl chloride	THF	-10	r.t.	*i*-PrMgCl	Trace
3	ethyl benzoate	THF	-10	r.t.	*i*-PrMgCl	Trace
4	benzoic acid anhydride	THF	-10	r.t.	*i*-PrMgCl	Trace
5	benzonitrile	THF	-10	r.t.	*i*-PrMgCl	Trace
6	(1H-imidazol-1-yl)(phenyl)methanone	THF	-10	r.t.	*i*-PrMgCl	83
7	benzoic acid + HATU	THF	-10	r.t.	*i*-PrMgCl	Trace
8	benzoic acid + CDI	THF	-10	r.t.	*i*-PrMgCl	80
9	benzoic acid + CDI	diethyl ether	-10	r.t.	*i*-PrMgCl	40
10	benzoic acid + CDI	toluene	-10	r.t.	*i*-PrMgCl	Trace
11	benzoic acid + CDI	THF	0	r.t.	*i*-PrMgCl	58
12	benzoic acid + CDI	THF	-10	60	*i*-PrMgCl	30
13	benzoic acid + CDI	THF	-20	r.t.	*i*-PrMgCl	78
14	benzoic acid + CDI	THF	-10	-10	*i*-PrMgCl	70
15	benzoic acid + CDI	THF	-10	r.t.	EtMgCl	43
16	benzoic acid + CDI	THF	-10	r.t.	*n*-BuMgCl	64
17	benzoic acid + CDI	THF	-10	r.t.	TMPMgCl·LiCl	73
18	benzoic acid + CDI	THF	-10	r.t.	*i*-PrMgCl·LiCl	90
19[c]	benzoic acid + CDI	THF	-10	r.t.	*i*-PrMgCl·LiCl	63
20[d]	benzoic acid + CDI	THF	-10	r.t.	*i*-PrMgCl·LiCl	65
21	methyl benzoyl-L-prolinate	THF	-10	r.t.	*i*-PrMgCl·LiCl	25
22	phenyl(pyrrolidin-1-yl)methanone	THF	-10	r.t.	*i*-PrMgCl·LiCl	Trace

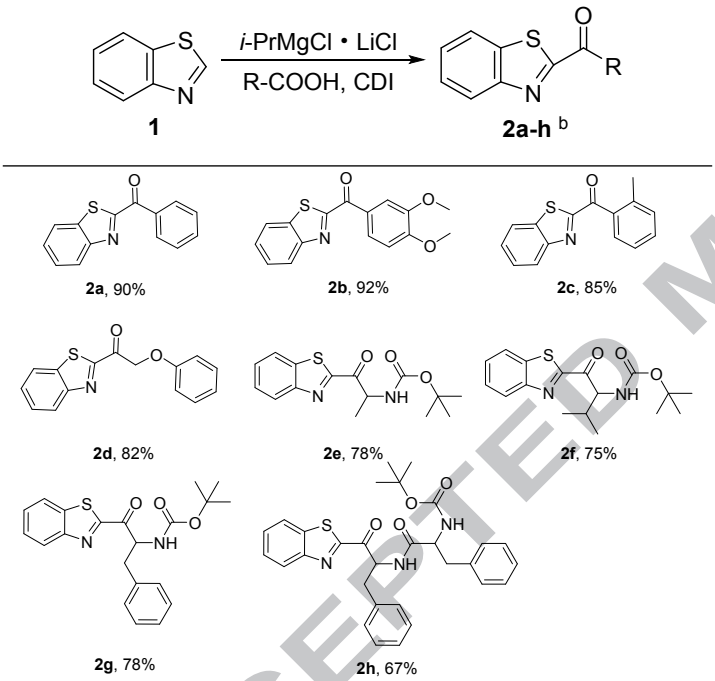
[a] Reaction conditions: **1** (1.2 mmol), Grignard reagent (1.3 mmol) in solvent (8 mL) at -10 °C for 30 min, followed by electrophile (1 mmol) at r.t. for 3 h.
[b] Isolated yield.
[c] *i*-PrMgCl·LiCl (2 equiv) was used.
[d] 8 h.

With this preliminary result, the effects of different solvents on the reaction, including THF, diethyl ether, and toluene, were investigated. Among them, THF was the most appropriate due to its relatively high solubility (Table 1, entry 8−10). Attempts to increase reaction temperatures accelerated the reaction rate with increased by-product formation and lower yields (Table 1, entry 11−12), while decreasing reaction temperatures led to a reduction in the reaction rate (Table 1, entry 13−14). A slight decrease in yield was observed when utilizing EtMgCl, *n*-BuMgCl or TMPMgCl·LiCl to generate 2-Grignard benzothiazole (Table 1, entry 15−17), whereas a better yield (90%) was obtained with *i*-PrMgCl·LiCl (Table 1, entry 18). Furthermore, either increasing

the amount of *i*-PrMgCl·LiCl or prolonging the reaction time led to the formation of by-products, which are unfavorable to the yield (Table 1, entry 19−20).

With the optimized reaction conditions in hand (Table 1, entry 18), attention was turned to enlarging the substrate scope. As shown in Table 2, benzoic acid derivatives (**2a**−**2c**) tolerated the reaction well and afforded the expected 2-acyl benzothiazoles in good to excellent yields (85−92%). Moreover, a yield of 82% was achieved when phenoxyacetic acid was utilized (**2d**), suggesting this approach is appropriate for various aromatic carboxylic acids. Subsequently, investigations of amino acids were conducted, which determined the Boc-protected amino acids were adept in efficiently furnishing the corresponding products in moderate yields (**2e**−**2g**, 75−78%). To our satisfaction, the Boc-protected dipeptide, namely Boc-Phe-Phe-OH, could also provide the desired product **2h**, albeit with a slightly lower yield (67%).

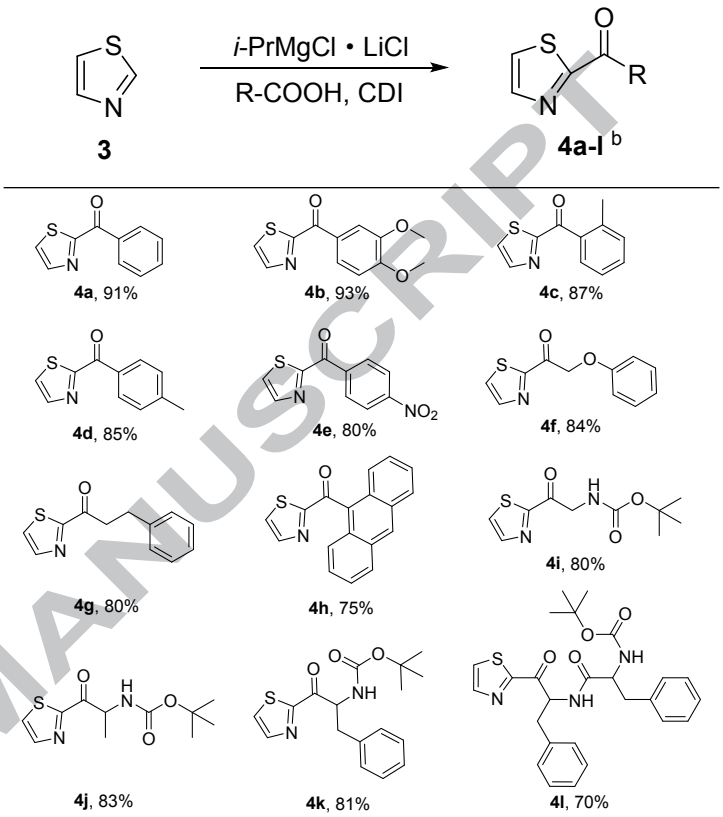
Table 2
Substrate scope of carboxylic acids for synthesis of 2-acyl benzothiazoles.[a]



[a] Reaction Conditions: **1** (1.2 mmol), *i*-PrMgCl·LiCl (1.3 mmol) in THF (8 mL) at -10 °C for 30 min, followed by imidazole carboxamide derivatives that obtained under the activation of CDI (1 equiv) at r.t. for 3 h.
[b] Isolated yield.

In view of the similar chemical properties between thiazole and benzothiazole, it was hypothesized that 2-acyl thiazoles could also be successfully obtained from thiazole under optimized reaction conditions. As illustrated in Table 3, benzoic acids bearing electron-neutral (4-H, 2-Me, 4-Me), electron-rich (3,4-OMe), and electron-deficient (4-NO_2) groups all participated in the reaction well to produce the expected 2-acyl thiazoles in moderate to excellent yields (**4a**−**4e**, 80−93%). These results revealed this method is not sensitive to the electronic effects and steric effect of substituents. Other aromatic carboxylic acids such as phenoxyacetic acid (**4f**, 84%) and 3-phenylpropanoic acid (**4g**, 80%) were both able to effectively provide the corresponding products. It is noteworthy that anthracene-9-carboxylic acid afforded the target product **4h** in a moderate yield (75%), suggesting polycyclic aromatic carboxylic acids might also accommodate this reaction. Moreover, the Boc-protected amino acids and dipeptide (**4i**−**4l**) all reacted well under optimized reaction conditions, giving the target products in 70%−83% yields. In general, the yields of 2-acyl thiazoles were higher than the corresponding 2-acyl benzothiazoles.

Table 3
Substrate scope of carboxylic acids for synthesis of 2-acyl thiazoles.[a]



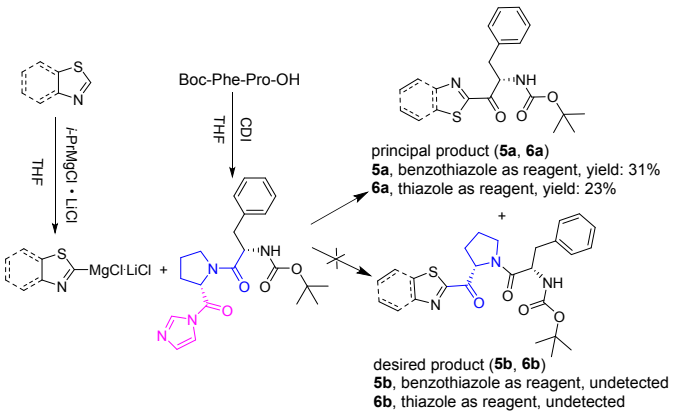
[a] Reaction Conditions: **3** (1.2 mmol), *i*-PrMgCl·LiCl (1.3 mmol) in THF (8 mL) at -10 °C for 30 min, followed by imidazole carboxamide derivatives that obtained under the activation of CDI (1 equiv) at r.t. for 3 h.
[b] Isolated yield.

A major surprise during the investigation of the substrate scope was the reaction of CDI activated Boc-Phe-Pro-OH with 2-Grignard benzothiazole/thiazole generated unexpected principal products (**5a**/**6a**), while the desired products (**5b**/**6b**) were not detected (Scheme 2). A possible explanation is the L-proline derivatives activated carboxylic acids could also react with Grignard benzothiazole/thiazole reagents to afford corresponding 2-acyl benzothiazoles/thiazoles. To demonstrate this hypothesis, phenyl(pyrrolidin-1-yl)methanone and methyl benzoyl-L-prolinate were used as electrophiles to participate in the synthesis of **2a**, respectively (Table 1, entry 21 & 22). The methyl benzoyl-L-prolinate provided **2a** in a yield of 25%, with the phenyl(pyrrolidin-1-yl)methanone gave a trace amount of **2a**, demonstrating that L-proline derivatives activated carboxylic acids could complement the electrophiles of this reaction.

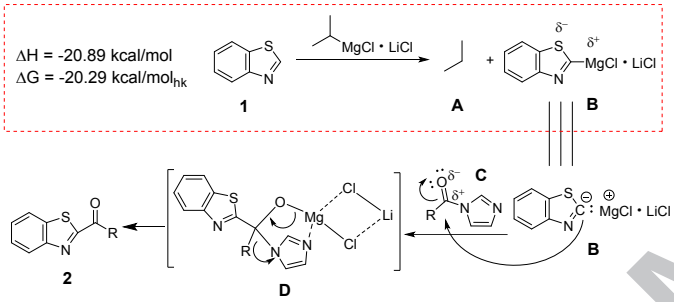
In order to evaluate the practicability of this approach, a scale-up synthesis was conducted under the standard conditions with benzoic acid (10 mmol, 1.23 g) and benzothiazole (12 mmol, 1.62 g) as the substrate. The target product **2a** was obtained in a moderate yield (81%), suggesting this method is practical for the synthesis of 2-acyl benzothiazoles/thiazoles.

Based on the above experimental results, a plausible mechanism for the reaction was proposed (Scheme 3). Initially, benzothiazole reacted with *i*-PrMgCl·LiCl to generate 2-Grignard benzothiazole **B**. The negative Gibbs free energy change (ΔG) and enthalpy change (ΔH) suggested the generation of **B** is

spontaneously and exothermic (Scheme 3). Subsequently, **B** interacted with CDI activated carboxylic acids (**C**) through the nucleophilic addition to provide the cyclic intermediate **D**, which finally yield the desired product **2**.



Scheme 2. Reactions with Boc-Phe-Pro-OH as the reagent.



Scheme 3. Proposed mechanism.

Conclusion

In conclusion, we have developed a convenient and efficient approach for the synthesis of 2-acyl benzothiazoles/thiazoles via treatment of benzothiazole/thiazole with *i*-PrMgCl·LiCl, followed by a reaction with CDI activated carboxylic acids. Various substituted carboxylic acids effectively provided the desired products in moderate to excellent yields under mild reaction conditions. This offers an alternative approach to access 2-acyl benzothiazoles/thiazoles and supplements the acylation methods of benzothiazole/thiazole. Further exploration of carbonyl sources and a thorough understanding of the mechanism of this reaction are underway in our lab.

Acknowledgments

We are grateful to the Natural Science Foundation of Jiangsu Province (BK20171184), Jiangsu Planned Projects for Postdoctoral Research Funds (1701132C), Technology Plan Projects of Xuzhou (KC17091) and Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX18-2203).

A. Supplementary

References

1. (a) Keri RS, Patil MR, Patil SA, Budagumpi S. *Eur J Med Chem.* 2015;89:207-251;
(b) Tariq S, Kamboj P, Amir M. *Arch Pharm (Weinheim).* 2019;352:e1800170.
2. Kanie S, Nakai R, Ojika M, Oba Y. *Bioorg Chem.* 2018;80:223-229.
3. Day JJ, Neill DL, Xu S, Xian M. *Org Lett.* 2017;19:3819-3822.
4. (a) Hegde M, Vartak SV, Kavitha CV, et al. *Sci Rep-UK.* 2017;7:2533-2546;
(b) El-Damasy AK, Lee JH, Seo SH, Cho NC, Pae AN, Keum G. *Eur J Med Chem.* 2016;115:201-216;
(c) Ma H, Zhuang CL, Xu XG, et al. *Eur J Med Chem.* 2017;133:174-183;
(d) Shao H, Li XK, Moses MA, et al. *J Med Chem.* 2018;61:6163-6177.
5. (a) Shafi S, Alam MM, Mulakayala N, et al. *Eur J Med Chem.* 2012;49:324-333;
(b) Kharbanda C, Alam MS, Hamid H, et al. *Bioorgan Med Chem.* 2014;22:5804-5812;
(c) Tariq S, Kamboj P, Alam O, Amir M. *Bioorg Chem.* 2018;81:630-641.
6. (a) Maddili SK, Li ZZ, Kannekanti VK, et al. *Bioorg Med Chem Lett.* 2018;28:2426-2431;
(b) Haroun M, Tratrat C, Kositzi K, et al. *Curr Top Med Chem.* 2018;18:75-87;
(c) Zha GF, Leng J, Darshini N, et al. *Bioorg Med Chem Lett.* 2017;27:3148-3155;
(d) Alborz M, Jarrahpour A, Pournejati R, et al. *Eur J Med Chem.* 2018;143:283-291.
7. (a) Luo B, Li D, Zhang AL, Gao JM. *Molecules.* 2018;23:2457-2472;
(b) Zhao SZ, Zhao LY, Zhang XQ, et al. *Eur J Med Chem.* 2016;123:514-522;
(c) Al-Talib M, Al-Soud YA, Abussaud M, Khshashneh S. *Arab J Chem.* 2016;9:S926-S930.
8. (a) Spadaro A, Frotscher M, Hartmann RW. *J Med Chem.* 2012;55:2469-2473;
(b) Thanigaimalai P, Konno S, Yamamoto T, et al. *Eur J Med Chem.* 2013;65:436-447;
(c) Thanigaimalai P, Konno S, Yamamoto T, et al. *Eur J Med Chem.* 2013;68:372-384;
(d) Duchene D, Colombo E, Desilets A, et al. *J Med Chem.* 2014;57:10198-10204.
9. Huang T, Sun J, An L, Zhang L, Han C. *Bioorg Med Chem Lett.* 2016;26:1854-1859.
10. (a) Zhou CY, Garcia-Calvo M, Pinto S, et al. *J Med Chem.* 2010;53:7251-7263;
(b) Tang G, Nikolovska-Coleska Z, Qiu S, Yang CY, Guo J, Wang S. *J Med Chem.* 2008;51:717-720;
(c) Spadaro A, Frotscher M, Hartmann RW. *J Med Chem.* 2012;55:2469-2473;
(d) Wunderlich SH, Knochel P. *Chem-Eur J.* 2010;16:3304-3307;
(e) Harn NK, Gramer CJ, Anderson BA. *Tetrahedron Lett.* 1995;36:9453-9456;
(f) Myllymaki MJ, Saario SM, Kataja AO, et al. *J Med Chem.* 2007;50:4236-4242;
(g) Zhu XY, Etukala JR, Eyunni SV, Setola V, Roth BL, Ablordeppey SY. *Eur J Med Chem.* 2012;53:124-132.
11. (a) Gao Q, Wu X, Jia F, et al. *J Org Chem.* 2013;78:2792-2797;
(b) Feng Q, Song QL. *Adv Synth Catal.* 2014;356:2445-2452;
(c) Liu SW, Chen R, Chen H, Deng GJ. *Tetrahedron Lett.* 2013;54:3838-3841;
(d) Yang K, Chen XY, Wang YQ, et al. *J Org Chem.* 2015;80:11065-11072;
(e) Hua M, Wang CQ, Liu QX, Chen DY, Fu H, Zhou HF. *Heterocycles.* 2018;96:1226-1237;
(f) Wu XF, Anbarasan P, Neumann H, Beller M. *Angew Chem Int Edit.* 2010;49:7316-7319.
12. (a) Zhu YP, Jia FC, Liu MC, Wu AX. *Org Lett.* 2012;14:4414-4417;
(b) Fan XS, He Y, Wang YY, Xue ZK, Zhang XY, Wang JJ. *Tetrahedron Lett.* 2011;52:899-902;
(c) Jiang J, Zou HX, Dong QZ, et al. *J Org Chem.* 2016;81:51-56;
(d) Meng X, Bi XR, Yu CY, et al. *Green Chem.* 2018;20:4638-4644;
(e) Mali JK, Mali DA, Telvekar VN. *Tetrahedron Lett.* 2016;57:2324-2326;

(f) Fan XS, He Y, Guo SH, Zhang XY. *Aust J Chem.* 2011;64:1568-1573;
(g) Fan XS, He Y, Zhang XY, Guo SG, Wang YY. *Tetrahedron.* 2011;67:6369-6374.
13. Pippel DJ, Mapes CM, Mani NS. *J Org Chem.* 2007;72:5828-5831.

Graphical Abstract

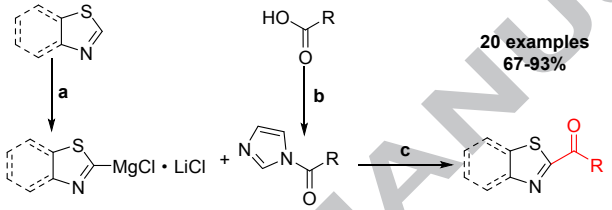
Highlights

1. Synthesis of 2-acyl benzothiazoles/thiazoles from various carboxylic acids.
2. Appropriate for Boc-protected amino acids and dipeptide.

A convenient synthesis of 2-acyl benzothiazoles/ thiazoles from benzothiazole/thiazole and N,N'-carbonyldiimidazole activated carboxylic acids

Leave this area blank for abstract info.

Tonghui Huang [a,b], Xin Wu [a], Yongbo Yu [a], Lin An [a], Xiaoxing Yin [a,*]



Conditions : (a) *i*-PrMgCl·LiCl, THF, -10 °C, 30 min. (b) N,N'-carbonyldiimidazole, THF, r.t., 1 h. (c) THF, -10 °C to r.t., 3 h.

3. Moderate to excellent yields under mild reaction conditions.