Tetrahedron 71 (2015) 3367–3377

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient solid-phase synthesis of 2,4-disubstituted 5-carbamoyl-thiazole derivatives using a traceless support

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ARTICLE INFO

Article history:
Received 3 December 2014
Received in revised form 25 March 2015
Accepted 26 March 2015
Available online 1 April 2015

Keywords:
5-Carbamoyl-thiazole
Solid-phase synthesis
Combinatorial chemistry
Traceless support
Heterocycles

ABSTRACT

An efficient protocol for the solid-phase synthesis of 2,4-disubstituted 5-carbamoyl-thiazole derivatives has been developed. After the reaction scopes were investigated in solution-phase, the polymer-supported synthesis route was progressed using a sulfide linker in a traceless manner. The solid-phase synthetic protocol started with the Thorpe-Ziegler type cyclization of 2-chloroacetamide and polymer-bound cyanocarboimidodithioate, which is derived from Merrifield resin. The resulting 5-carbamoyl-thiazole was introduced to one substitution by N-acylation. After the oxidation of sulfides to sulfones for subsequent cleavage, nucleophilic desulfonative substitution with amines and thiols gave the target 2,4-disubstituted 5-carbamoyl-thiazole derivatives in good purities and overall yields.

1. Introduction

The thiazole scaffold and its fused-heterocycles play an important role in the area of drug discovery and medicinal chemistry.[1,2] For example, 2-aminothiazoles have been developed as β-site APP-cleaving enzyme 1 (BACE1) inhibitor,[1a] cyclin dependent kinase (CDK) inhibitor,[1b,c] and voltage-gated sodium channel (VGSC) blockers.[1d] Thiazolopyrimidine derivatives have shown activities such as phosphatidylinositol 3-kinase β (PI3K-β) selective inhibitor,[2a] melanin-concentrating hormone receptor 1 (MCH R1) antagonist,[2b] epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor,[2c] and growth hormone secretagogue receptor type 1a (GHS-R1a) antagonist.[2d] As an attractive target, the thiazole scaffold has been developed as the core heterocycle of drug-like chemical libraries in combinatorial chemistry. Combinatorial chemistry, either solid- or solution-phase synthetic approaches, provides small organic chemical libraries using high-speed and efficient synthesis methods.[3] Although several combinatorial solution- and solid-phase synthesis methods for thiazole derivatives have been described,[4,5] the solid-phase synthesis of 5-carbamoyl-thiazole derivatives **1** (Fig. 1) has not been reported.

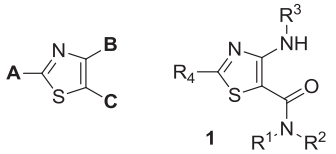

Fig. 1. Structures of thiazole and 5-carbamoyl-thiazole **1**.

Previously, we reported a facile and rapid solid-phase synthetic strategy for the preparation of a small-molecule library based on the thiazole and fused-thiazole scaffolds.[6] As an extension of the previous studies, we report the first solid-phase synthetic protocol for 2,4-disubstituted 5-carbamoyl-thiazole derivatives **1** using a traceless linker, which may be an efficient approach for the construction of drug-like compound libraries in a high-throughput manner.

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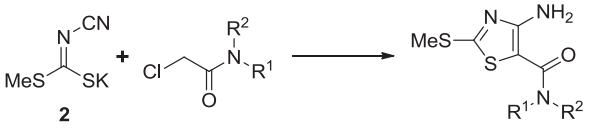
http://dx.doi.org/10.1016/j.tet.2015.03.104
0040-4020/

2. Result and discussion

In preliminary studies, the reaction scopes and conditions for the solution-phase synthesis of 5-carbamoyl-thiazole derivatives **1** were investigated. The initial synthetic route began with the Thorpe–Ziegler type cyclization of the known mono-methyl cyanocarbonimidodithioate **2**[4a,7] with 2-chloroacetoamides **3**[8] (Table 1). The 2-chloroacetoamides **3** were prepared from 2-chloroacetyl chloride and the corresponding amines. First, different bases were screened for the thiazole formation from **2** and **3** (entries 1–5). Under these conditions, DBU in DMF at room temperature afforded **4a** in a moderate yield (53%; entry 2), and sodium ethoxide in refluxing ethanol gave 5-carbamoyl-thiazole **4a** in a good yield (71%; entry 5). Because of the difficulty encountered in high-temperature solid-phase synthesis, the solvent was changed to acetone and triethylamine and DBU were screened (entries 6 and 7). The highest yield (86%) of **4a** was obtained using DBU and acetone at room temperature (entry 7). Because compound **2** is more soluble in acetone than DMF, thiazole **4a** was obtained with excellent yield in acetone at room temperature. In the trials to expand the diversity of the target 5-carbamoyl-thiazoles **1** (entries 8 and 9), the secondary amide product **4b** was not obtained from **3b** (entry 8),[5f,9] whereas the non-cyclic tertiary amide product **4c** was obtained from **3c** (entry 9) in 79% yield under the optimal reaction conditions.

Table 1
Synthesis of 5-carbamoyl-thiazole **4** under Thorpe–Ziegler reaction conditions[a]

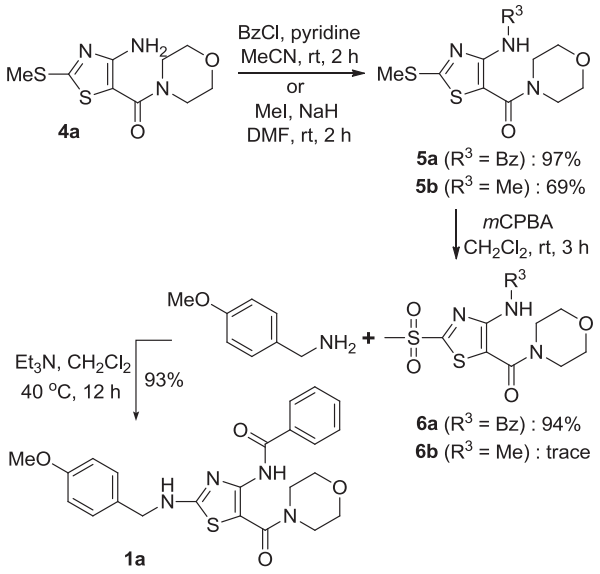


Entry	Reactant	Base	Reaction conditions	Product	Yield[b] (%)
1	**3a**	Et_3N	DMF, rt to 80 °C, 1 d	**4a**	42
2	**3a**	DBU	DMF, rt, 1 d	**4a**	53
3	**3a**	DABCO	DMF, rt, 1 d	**4a**	33
4	**3a**	KO^{t}Bu	DMF, rt, 1 d	**4a**	Trace
5	**3a**	NaOEt	EtOH, reflux, 12 h	**4a**	71
6	**3a**	Et_3N	Acetone, rt, 1 d	**4a**	24
7	**3a**	DBU	Acetone, rt, 1 h	**4a**	86
8	**3b**	DBU	Acetone, rt, 1 h	**4b**	Trace
9	**3c**	DBU	Acetone, rt, 1 h	**4c**	79

[a] All the reactions were performed using **2** (0.2 mmol), **3** (0.3 mmol), and base (3.0 equiv).
[b] Isolated yield.

With the optimized Thorpe–Ziegler type thiazole formation conditions for 5-carbamoyl-thiazole **4a**, diverse substituents (R^3 and R^4) were introduced to obtain the desired 2,4-disubstituted 5-carbamoyl-thiazoles **1** (Scheme 1).

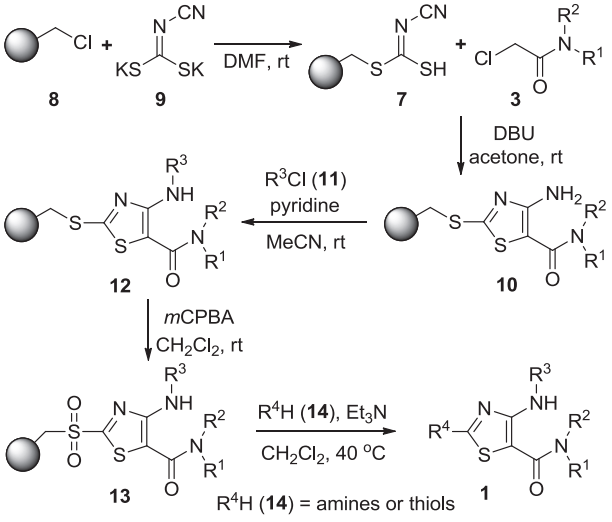
Attempts to promote the N-substitution reactions of **4a** for R^3 diversity in **1** under several reaction conditions (pyridine/MeCN for acylation and NaH/DMF for alkylation) were successful. The acylation of **4a** afforded 5-carbamoyl-thiazole **5a** in an excellent yield (97%) and alkylation product **5b** was obtained in 69% yield. The resulting 5-carbamoyl-thiazoles **5** were oxidized to form the corresponding sulfones **6** by reacting with *m*-CPBA in CH_2Cl_2. Although acyl derivative **5a** was successfully converted to sulfone **6a** (94%), alkyl derivative **5b** did not afford sulfone **6b** (traces). The sulfone **6b** (R^3=Me) was not obtained by over-oxidation of thiazole **5b** such as *N*-oxide formation, and the sulfone **6a** (R^3=Bz) was produced because of the low over-oxidation rate by a influence of electron-withdrawing acyl group in the 2-aminothiazole **5a** (R^3=Bz).[2c,6,7b] The sulfone group in



Scheme 1. Solution-phase synthesis of 5-carbamoyl-thiazole **1a**.

6a was substituted by 4-methoxybenzylamine in CH_2Cl_2 to produce the target 2,4-disubstituted 5-carbamoyl-thiazole **1a**. This product was characterized using ESI-LC–MS and ^1H and ^{13}C NMR spectroscopy. Overall, this solution-phase synthetic protocol is efficient, practical, and available for the solid-phase synthesis of 2,4-disubstituted 5-carbamoyl-thiazole derivatives **1**.

Based on these successful solution-phase reaction conditions, appropriate diversity elements such as of 2-chloroacetoamides, acyl chlorides, and amine/thiol building blocks were used for the solid-phase synthesis of 5-carbamoyl-thiazoles **1**. The reaction sequence began with polymer-bound cyanocarbonimidodithioate **7**,[6] which was obtained by the reaction of Merrifield resin **8** and dipotassium cyanodithioimidocarbonate **9**[10] (Scheme 2).



Scheme 2. Solid-phase synthesis of 2,4-disubstituted 5-carbamoyl-thiazole **1**.

Resin **7** was first swollen in acetone and then treated with 2-chloroacetoamides **3** (Fig. 2; the first diversity element) and DBU at room temperature to give the corresponding 5-carbamoyl-thiazole resin **10** via the Thorpe–Ziegler cyclization. The reaction progress (**10a**; NR^1R^2=morpholine) was monitored using attenuated total reflection Fourier transform infrared (ATR-FTIR), which showed the disappearance of the nitrile stretching band at 2161 cm^{-1} and the appearance of the amide carbonyl stretching band at 1582 cm^{-1} and