Solid-Phase Synthesis of Thiazolo[4,5-*b*]pyridine Derivatives Using Friedländer Reaction

Taeho Lee,*,† Doohyun Lee,† Ill Young Lee,† and Young-Dae Gong‡

Center for High Throughput Synthesis Platform Technology, Korea Research Institute of Chemical Technology, P.O. Box 107, Singseongno, Yuseong-gu, Daejeon 305-600, Korea, and Department of Chemistry, Science College, Dongguk University, 26 Pildong 3-ga, Jung-gu, Seoul 100-715, Korea

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Traceless solid-phase synthesis of 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridine derivatives is described. Thorpe−Ziegler type cyclization of solid supported cyanocarbonimidodithioate with α-halo ketones afforded thiazole resin, which were converted to the desired thiazolopyridine resin by the Friedländer protocol under microwave irradiation conditions. After oxidation of sulfides to sulfones, nucleophilic desulfonative substitution with amines gave the target thiazolo[4,5-*b*]pyridine derivatives in good overall yields.

Introduction

The thiazole and fused-thiazole heterocycles are important structural components of bioactive molecules, and, as a result, they serve as attractive targets for combinatorial library construction via solution- and solid-phase synthesis.[1,2] Because of their pharmaceutical importance in the area of drug discovery, we have been interested in developing an efficient protocol to prepare fused-thiazole scaffolds such as 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridines **1** and recently reported a facile and rapid traceless linker based solid-phase strategy for the preparation of a small molecule library based on the thiazoles,[3a] thiazolo[4,5-*c*][1,2]thiazin-4(3*H*)one-2,2-dioxide,[3b] and thiazolo[4,5-*d*]pyrimidine-5,7-dione[3c] (Figure 1).

Thiazolo[4,5-*b*]pyridine derivatives (**1**, Figure 1) exhibit a wide range of biological properties.[4] For example, thiazolo[4,5-*b*]pyridines have demonstrated activities as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors,[4a] as metabotropic glutamate receptor 5 (mGluR5) antagonists for various CNS disorders,[4b] as serine protease factor Xa (fXa) inhibitors for thrombosis,[4c] as histamine H_3-receptor antagonists for epilepsy and Alzheimer's disease,[4d] and as cAMP phosphodiesterase (PDE) III inhibitors for congestive heart failure.[4e]

Thus, many synthetic methods for thiazolo[4,5-*b*]pyridine derivatives have been well documented.[5] In addition, Kirsch and co-workers reported a solution-phase synthesis of 7-amino-thiazolo[4,5-*b*]pyridine derivatives[5a] as well as fused-pyridine derivatives such as the selenopheno[2,3-*b*]pyridines[6a] and thiopheno[2,3-*b*]pyridines[6b] using the Friedländer reaction. However, to the best of our knowledge, there is no report which describes the synthesis of thiazolo[4,5-*b*]pyridine derivatives on solid support. Herein, we wish to represent our recent progress on this project which includes the first solid-phase synthetic protocol for the preparation of 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridines **1** (see Figure 1), which is applicable to high throughput construction of drug-like compound libraries.

Results and Discussion

In preliminary studies, the initial synthetic route began with the conversion of the known thiazole **2**[7] to thiazolo[4,5-*b*]pyridine **4** via the Friedländer reaction using microwave (MW) irradiation with cyclohexanone **3** that serve as one diversity element (Table 1).[5a,6,8] Recently, microwave irradiation has been shown to be a powerful tool for various solution- or solid-phase chemical reactions.[9]

First, two reaction parameters (amounts of $AlCl_3$ and MW irradiation time) were examined for the reaction of thiazole **2a** and **3** (Table 1, entries 1−4). Under these conditions, MW irradiation (15 min) and $AlCl_3$ (3.0 equiv.) gave the best result with a high yield (91%) of thiazolo[4,5-*b*]pyridine **4a** (entry 4). Under conventional heating conditions (entry 5), product **4a** was obtained with an 85% yield. The Friedländer reaction was attempted with $FeCl_3$,[8a] LiBr,[8b] or TsOH[8c] instead of $AlCl_3$ in acetonitrile using MW irradiation (entries 6−8). The conditions with $FeCl_3$ led to a poor yield (36%) of thiazolo[4,5-*b*]pyridine **4a**, whereas the cases of LiBr and TsOH were unsuccessful. In trials for expansion of diversity in the target thiazolo[4,5-*b*]pyridines **1** (entries 9−11), the desired thiazolo[4,5-*b*]pyridine derivatives **4b**,

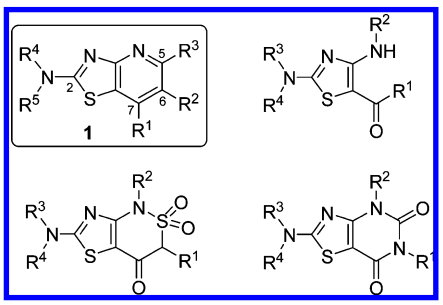

Figure 1. Structure of the thiazole and fused-thiazoles.

* To whom correspondence should be addressed. E-mail: taeholee@krict.re.kr. Phone: 82-42-860-7693. Fax: 82-42-860-7698.
† Korea Research Institute of Chemical Technology.
‡ Dongguk University.

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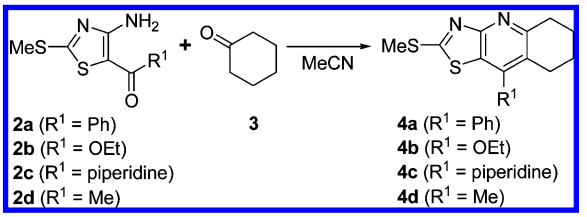
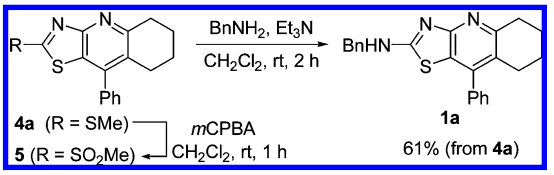
Table 1. Synthesis of Thiazolo[4,5-*b*]pyridine **4** under the Friedländer Reaction[a]



entry	reactant	reagent	reaction condition	product	yield (%)[b]
1	**2a**	$AlCl_3$ (1.5 equiv)	MW (5 min)	**4a**	72
2	**2a**	$AlCl_3$ (0.5 equiv)	MW (5 min)	**4a**	23[c]
3	**2a**	$AlCl_3$ (3.0 equiv)	MW (5 min)	**4a**	86
4	**2a**	$AlCl_3$ (3.0 equiv)	MW (15 min)	**4a**	91
5	**2a**	$AlCl_3$ (3.0 equiv)	reflux, 12 h	**4a**	85
6	**2a**	$FeCl_3$ (3.0 equiv)	MW (15 min)	**4a**	36[c]
7	**2a**	LiBr (3.0 equiv)	MW (15 min)	**4a**	N.R.[d]
8	**2a**	TsOH (3.0 equiv)	MW (15 min)	**4a**	N.R.[d]
9	**2b**	$AlCl_3$ (3.0 equiv)	MW (15 min)	**4b**	N.R.[d]
10	**2c**	$AlCl_3$ (3.0 equiv)	MW (15 min)	**4c**	N.R.[d]
11	**2d**	$AlCl_3$ (3.0 equiv)	MW (15 min)	**4d**	N.R.[d]

[a] All reactions, unless otherwise noted, were performed on **2** (0.2 mmol) and **3** (0.4 mmol) using MW irradiation at 150 °C. [b] Isolated yield. [c] Starting material **2a** was recovered. [d] No reaction.

Scheme 1. Synthesis of Thiazolo[4,5-*b*]pyridine **1a**



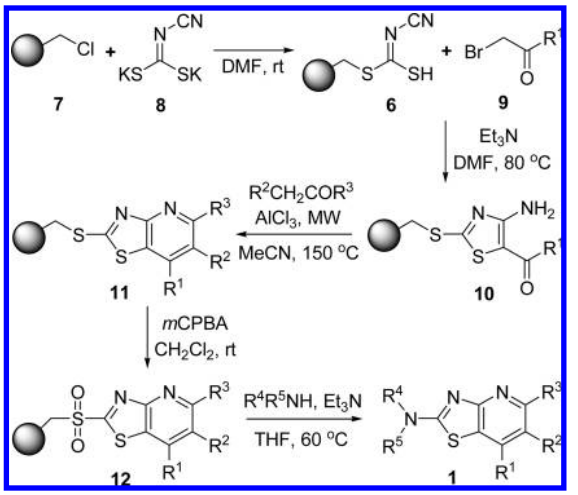
4c, and **4d** were not obtained under MW irradiation with $AlCl_3$ from **2b**, **2c**, and **2d**, respectively.

With optimized Friedländer reaction conditions for the formation of **4a**, the stage progressed to the corresponding thiazolo[4,5-*b*]pyridines **1a** (Scheme 1). The resulting thiazolo[4,5-*b*]pyridine **4a** was oxidized to form sulfone **5** by treatment with *m*CPBA in CH_2Cl_2. The sulfone group in **5** without additional purification was displaced by benzylamine in CH_2Cl_2 to produce the target thiazolo[4,5-*b*]pyridine derivative **1a** (61% yield from **4a**). This product was characterized by using ESI-LC-MS as well as ^1H and ^{13}C NMR spectroscopy.[10] Overall, this efficient and practical solution-phase synthetic route is available for solid-phase synthesis of 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridine derivatives **1**.

The solid-phase synthetic route for preparation of thiazolo[4,5-*d*]pyridine derivatives utilizes appropriate α-bromoacetophenones, ketones, and amines as key building blocks and diversity elements. The sequence began with the formation of the known solid supported cyanocarbonimidodithioate **6**[3] through the reaction of Merrifield resin **7** with dipotassium cyanodithioimidocarbonate **8**[11] (Scheme 2).

The resin **6** were first swollen in DMF and then treated with α-bromoacetophenone **9** (the first diversity element) and triethylamine at 80 °C to give the corresponding thiazole resin **10** via the Thorpe−Ziegler cyclization.[3,7] The reaction progress (R^1 = Ph) was monitored by using ATR-FTIR (Attenuated Total Reflection Fourier Transform Infrared) which showed the disappearance of the nitrile stretching band at 2170 cm^{-1} and the appearance of the ketone carbonyl stretching band at 1600 cm^{-1} and the NH_2 stretching bands

Scheme 2. Solid-Phase Synthesis of Thiazolo[4,5-*b*]pyridine Derivatives **1**



at 3469 and 3321 cm^{-1} (Figure 2). The thiazole resin **10** were then reacted under the Friedländer reaction condition with a ketone ($AlCl_3$ and MW irradiation). The progress of this process, which efficiently produced the thiazolo[4,5-*d*]pyridine resin **11** (R^1 = Ph, R^2 and R^3 = $-(CH_2)_4-$) and introduced the second potential diversity element R^2 and R^3, was monitored by using ATR-FTIR (specifically, the disappearance of the ketone carbonyl stretching band at 1600 cm^{-1} and the NH_2 stretching bands at 3469 and 3321 cm^{-1}). Treatment of resin **11** with *m*CPBA in CH_2Cl_2 provided the resin-bound sulfone intermediate **12**. Although this reaction is not amenable to ATR-FTIR monitoring, solid- and solution-phase thiazole synthetic studies are well-known.[3,12]

Finally, the sulfone group in resin **12** was displaced by a desulfonative substitution reaction with the corresponding amines (benzylamine for **1a**), serving as a third diversity element in THF.[13] This process, which is accompanied by

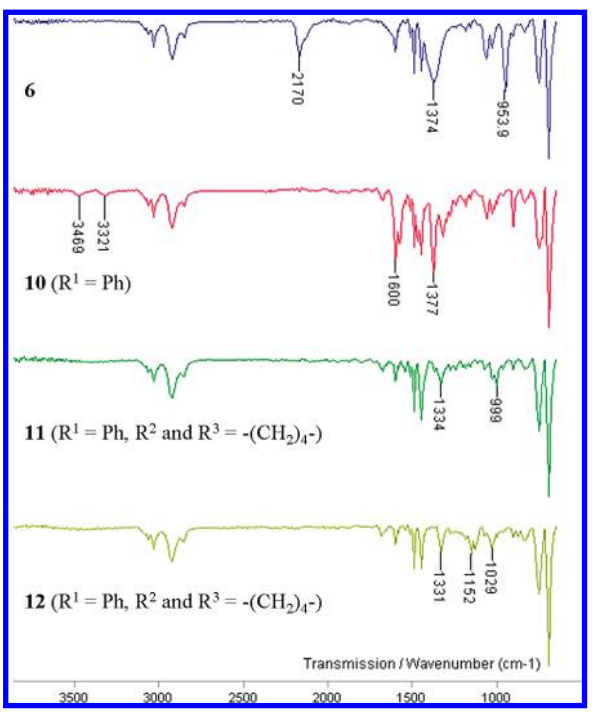
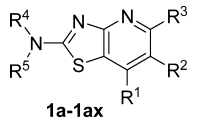


Figure 2. ATR-FTIR spectra of resins **6**, **10**, **11**, and **12** (R^1 = Ph, R^2 and R^3 = $-(CH_2)_4-$).

Table 2. Thiazolo[4,5-*b*]pyridine Derivatives**1** Using the Solid-Phase Synthetic Route[a]



1a-1ax

entry	products	R^1	R^2 R^3	R^4R^5N	yield (%)[b]
1	**1a**	Ph	-$(CH_2)_4$-	BnNH	32
2	**1b**	Ph	-$(CH_2)_4$-	4-MeO-BnNH	29
3	**1c**	Ph	-$(CH_2)_4$-	n-PrNH	35
4	**1d**	Ph	-$(CH_2)_4$-	$C_6H_{11}CH_2NH$	27
5	**1e**	Ph	-$(CH_2)_4$-	Et_2N	27
6	**1f**	Ph	-$(CH_2)_4$-		29
7	**1g**	Ph	-$(CH_2)_4$-		33
8	**1h**	Ph	-$(CH_2)_4$-		31
9	**1i**	Ph	-$(CH_2)_3$-	BnNH	16
10	**1j**	Ph	-$(CH_2)_3$-	4-MeO-BnNH	21
11	**1k**	Ph	-$(CH_2)_3$-	n-PrNH	19
12	**1l**	Ph	-$(CH_2)_3$-		13
13	**1m**	Ph	-$(CH_2)_3$-		17
14	**1n**	Ph	-$(CH_2)_5$-	BnNH	50
15	**1o**	Ph	-$(CH_2)_5$-	4-MeO-BnNH	43
16	**1p**	Ph	-$(CH_2)_5$-	n-PrNH	48
17	**1q**	Ph	-$(CH_2)_5$-		34
18	**1r**	Ph	-$(CH_2)_5$-		37
19	**1s**	Ph	Me Et	BnNH	24
20	**1t**	Ph	Me Et	4-MeO-BnNH	31
21	**1u**	Ph	Me Et	n-PrNH	39
22	**1v**	Ph	Me Et		33
23	**1w**	Ph	Me Et		26
24	**1x**	Ph	-$CO(CH_2)_3$-	BnNH	23
25	**1y**	Ph	-$CO(CH_2)_3$-	4-MeO-BnNH	24
26	**1z**	Ph	-$CO(CH_2)_3$-	n-PrNH	20
27	**1aa**	Ph	-$CO(CH_2)_3$-		18
28	**1ab**	Ph	-$CO(CH_2)_3$-		16
29	**1ac**	4-MeO-Ph	-$(CH_2)_4$-	BnNH	37
30	**1ad**	4-MeO-Ph	-$(CH_2)_4$-	n-PrNH	48
31	**1ae**	4-MeO-Ph	-$(CH_2)_4$-		32
32	**1af**	4-MeO-Ph	-$(CH_2)_4$-		34
33	**1ag**	4-MeO-Ph	-$(CH_2)_5$-	BnNH	40
34	**1ah**	4-MeO-Ph	-$(CH_2)_5$-	n-PrNH	49
35	**1ai**	4-MeO-Ph	-$(CH_2)_5$-		44
36	**1aj**	4-MeO-Ph	-$(CH_2)_5$-		38
37	**1ak**	4-MeO-Ph	Me Et	BnNH	30
38	**1al**	4-MeO-Ph	Me Et	n-PrNH	38
39	**1am**	4-MeO-Ph	Me Et		33
40	**1an**	4-MeO-Ph	Me Et		29
41	**1ao**	4-NO_2-Ph	-$(CH_2)_4$-	BnNH	39
42	**1ap**	4-NO_2-Ph	-$(CH_2)_4$-	4-MeO-BnNH	45
43	**1aq**	4-NO_2-Ph	-$(CH_2)_4$-	n-PrNH	41
44	**1ar**	4-NO_2-Ph	-$(CH_2)_4$-		35
45	**1as**	4-NO_2-Ph	-$(CH_2)_4$-		37
46	**1at**	4-NO_2-Ph	-$(CH_2)_3$-	BnNH	24
47	**1au**	4-NO_2-Ph	-$(CH_2)_3$-	4-MeO-BnNH	27
48	**1av**	4-NO_2-Ph	-$(CH_2)_3$-	n-PrNH	31
49	**1aw**	4-NO_2-Ph	-$(CH_2)_3$-		28
50	**1ax**	4-NO_2-Ph	-$(CH_2)_3$-		19

[a] All reactions were performed on 150−200 mg scale of resin **12**. [b] Five-step overall isolated yield from Merrifield resin **7** (loading capacity = 0.94 mmol/g).

concurrent cleavage from the resin, furnished the final thiazolo[4,5-*d*]pyridine derivative **1a** (32% over five steps, from Merrifield resin **7**)[14] which was purified by column chromatography. The ^{1}H NMR spectrum of thiazolo[4,5-*d*]pyridine **1a** matched that of material produced by using the solution-phase synthetic route.

By using the new solid-phase synthetic route, we were able to prepare a number of thiazolo[4,5-*d*]pyridine derivatives displayed in Table 2 starting from Merrifield resin **7** and appropriate α-bromoacetophenones (R^1COCH_2Br), ketones ($R^2CH_2COR^3$), and amines (R^4R^5NH).

When the R^1 is phenyl, 4-methoxyphenyl, or 4-nitrophenyl, the corresponding thiazolo[4,5-*d*]pyridines are formed in good overall yields (Table 2: for Ph, entries 1−8, 27−35%; for 4-MeO-Ph, entries 29−32, 32−48%; and for 4-NO_2−Ph, entries 41−45, 35−45%). In cases where the R^2 and R^3 substituents are cyclized moieties, the yield of target product **1** is high in accordance with the ring size of cycloalkanone (R^1 = Ph: cyclopentanone, entries 9−13, 13−21%; cyclohexanone, entries 1−8, 27−35%; and cycloheptanone, entries 14−18, 34−50%). Also, in cases where the R^2 and R^3 substituents are non-cyclized moiety from 3-pentanone, the

products **1** are obtained in moderate yields (entries 19−23 and entries 37−40). However, when the R^2 and R^3 substituents are from cyclohexan-1,3-dione, the overall yields are lower (entries 24−28, 16−24%). Among the R^4R^5NH series, desulfonative nucleophilic substitution takes place smoothly with benzyl, primary aliphatic, and secondary amines (entries 1−8). The isolated overall yields for thiazolo[4,5-*d*]pyridines ranged from 13 to 50% for the five step linear pathway from the Merrifield resin **7**, indicating that the average yield for each step is 67 to 87%). Moreover, the target compounds are furnished in high purities following column chromatography [>95% as judged from LC-MS traces (integration of diode array 200−400 nm traces)] and characterized by using MS, as well as ^{1}H NMR spectroscopy.

In summary, this investigation has led to the development of the first traceless solid-phase synthetic route that efficiently generated 2,5,6,7-tetrasubstituted thiazolo[4,5-*b*]pyridine derivatives, which is one of the fused-thiazole scaffolds. The sequence contains four diversity sites that are introduced in reactions involving α-bromoacetophenones (R^1), ketones (R^2 and R^3), and amines (R^4R^5N). The strategy, based on an efficient solution-phase sequence, allows for a ready access to a large library and is potentially applicable to the preparation of other drug-like fused-thiazole ring systems. Further studies in this area are underway, the results of which will be reported in due course.

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Supporting Information Available. Full experimental procedures, analytical data of compounds, copies of ^{1}H NMR and LC-MS spectra of compounds **1a**-**1ax** and **4a**, and ^{13}C NMR spectra of compounds **1a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Spectroscopic data of compound **1a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (m, 2H), 1.88 (m, 2H), 2.54 (t, J = 6.3 Hz, 2H), 3.03 (t, J = 6.5 Hz, 2H), 4.66 (s, 2H), 5.87 (br s, 1H), 7.27−7.38 (m, 7H), 7.39−7.48 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.1, 23.2, 27.2, 33.1, 48.8, 123.0, 123.2, 127.7,

127.8, 128.0, 128.3, 128.7, 128.8, 137.5, 138.6, 142.9, 155.1, 161.5, 168.5; LC-MS (ESI) *m/z* 372 ($[M+1]^+$).

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(13) When CH_2Cl_2 was used as a solvent, the product **1a** was obtained with a poor yield (13%). To optimize the final desulfonative substitution reaction and cleavage, various reaction conditions were screened in CH_2Cl_2, chloroform, THF, or dichloroethane from room temperature to higher temperatures. Treatment of THF at 60 °C gave the best result for product **1a** (32% yield).

(14) In the case of a compound **1a**, the crude purity is 52% as judged from LC-MS traces.

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