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Rapid Access to Pyrimido[5,4-*c*]isoquinolines via a Sulfur Monoxide Extrusion Reaction

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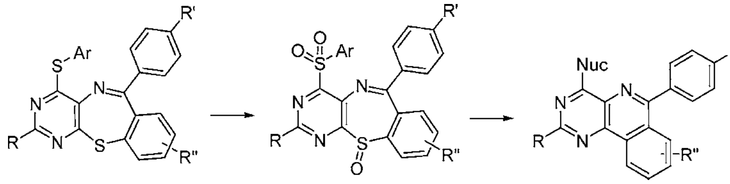
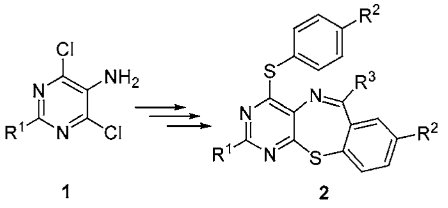
ABSTRACT



The scope of a sulfur monoxide extrusion reaction of pyrimido[4,5-*b*][1,4]benzothiazepines leading to pyrimido[5,4-*c*]isoquinolines was investigated. Thus, selective oxidation followed by nucleophilic displacement of the oxidized side chain sulfur group and subsequent extrusion reaction of sulfur monoxide in the ring, which can be conducted in a two-step sequence or in a one-pot procedure, produced novel pyrimido[5,4-*c*]isoquinolines, a class of compounds with potential biological and pharmaceutical applications.

Isoquinoline derivatives are well-known to exhibit diverse biological activities.[1] Consequently, there is a continuing interest in developing efficient methodologies to access pyrimidine-fused heterocyclic scaffolds both by our laboratory[2] and by others. [3] Previously, we reported that arylthiopyrimido[4,5-*b*][1,4]benzothiazepines **2** could be prepared from a simple pyrimidine building block **1** via Bischler−Napieralski-like reactions (Scheme 1).[2e] To expand the scope of applications, it is envisioned that pyrimido[5,4-*c*]isoquinolines **5** should be readily accessible from benzothiazepines **2** following a synthetic strategy outlined in Scheme 2. This new strategy entails the selective oxidation of the aryl sulfide substituent in 4-arylthiopyrimido[4,5-*b*][1,4]benzothiazepines **2** to its corresponding sulfone, whereas the ring sulfur is oxidized to the sulfoxide. This is then followed by a one-pot transformation to the final pyrimido[5,4-*c*]isoquinoline derivatives **5** via displacement of the newly oxidized side chain sulfur with various nucleophiles and sulfoxide extrusion to contract the central ring. This strategy complements a previous report on the preparation of pyrimido[5,4-*c*]isoquinolines via sulfur monoxide extrusion of 4-aminopy-

Scheme 1. Synthesis of Pyrimido[4,5-*b*][1,4]benzothiazepines



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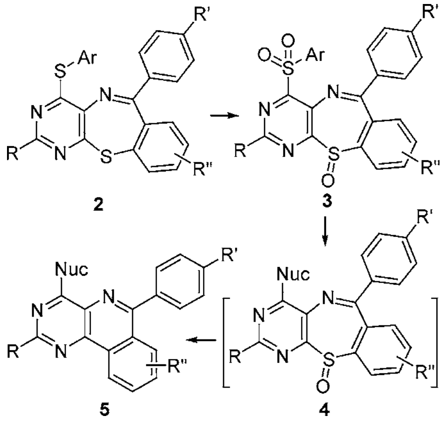
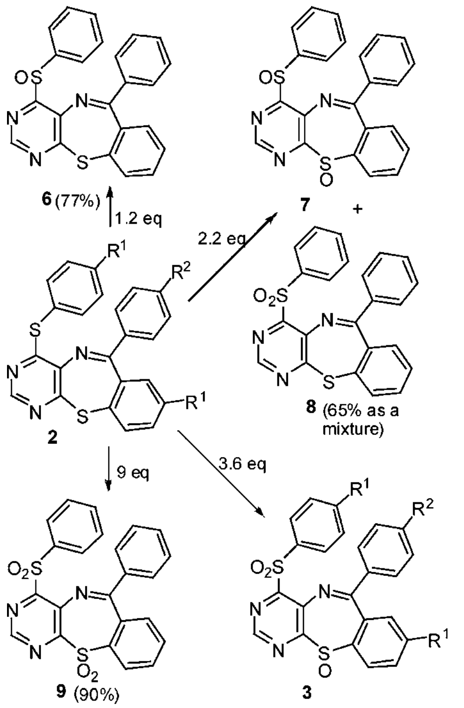
Scheme 2. Strategy to Access Pyrimido[5,4-*c*]isoquinolines



Scheme 3. Sequential Selective Oxidation of Pyrimido[4,5-*b*][1,4]benzothiazepines **2** by *m*-CPBA



rimidothiazepines.[4] It is recognized that the scope of this sulfur monoxide extrusion reaction was not fully explored, especially with regard to a one-pot variation of the reaction. Sulfur extrusion reactions are often reported for organic sulfides, sulfoxides, and sulfones, and only a few complex molecules were prepared through their applications.[5] On the other hand, direct extrusions of sulfur monoxide[6] are less common, compared to the well-documented extrusion reactions of sulfide and sulfur dioxide.[7] Herein, we report the details of our investigation on the scope of the nucleophilic aromatic substitution−sulfur monoxide extrusion approach to pyrimido[5,4-*c*]isoquinolines outlined in Scheme 2.

The existence of two sulfur atoms in compounds **2** presents a challenge for selective or sequential oxidation of the 4-sulfide group and the ring sulfur atom. Previously, we demonstrated that the arylsulfide group in 4-phenylthiopyrimido[4,5-*b*][1,4]benzothiazepine **2** could be selectively oxidized to its corresponding sulfoxide **6** (Scheme 3) in good yield.[2e] To explore the feasibility of sequential selective oxidation, various oxidation conditions were applied to **2.1** ($R^1 = R^2 = H$) as outlined in Scheme 3. Compound **2.1** could be selectively converted to **6**, **7**, **8**, **3.1**, and **9** by controlling the stoichiometry of *m*-CPBA and the reaction temperature. Treatment of compound **2.1** with 1.2 equiv of *m*-CPBA at 0 °C provided the side chain sulfoxide **6** in 77% yield. Increasing *m*-CPBA to 2.2 equiv and elevating the reaction temperature to ambient gave a mixture of two compounds (**7** and **8**) which could not be separated via flash column chromatography. Further increase of *m*-CPBA to 3.6 equiv at room temperature resulted in sulfone−sulfoxide **3.1** in 60% isolated yield. Sulfone−sulfone product **9** could be

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obtained in high yield by employment of a large excess (9 equiv) of *m*-CPBA The conditions identified for the selective conversion of **2.1** to **3.1** were applied to other substrates (**2.2**−**2.7**) and gave the corresponding sulfone−sulfoxides **3.2**−**3.7** in good yields (Table 1).

Table 1. Conversion of Compounds **2** to **3**

entry	2	R^1	R^2	3	yield (%)
1	**2.1**	H	H	**3.1**	60
2	**2.2**	Me	H	**3.2**	55
3	**2.3**	Cl	H	**3.3**	55
4	**2.4**	MeO	H	**3.4**	53
5	**2.5**	H	Me	**3.5**	59
6	**2.6**	H	F	**3.6**	52
7	**2.7**	Me	Me	**3.7**	55

The introduction of a sulfoxide or a sulfone substituent at the 4-position in compounds **3**, **6**, and **9** enables the introduction of various nucleophiles in the final scaffold of pyrimido[5,4-*c*]isoquinoline thus providing a diversification point. To test the feasibility of sequential displacement of the oxidized side chain sulfur followed by sulfur extrusion to form the desired pyrimidoisoquinoline skeleton, *n*-butyl amine was selected as the nucleophile. Both side chain sulfoxide and sulfones in compounds **3**, **6**, and **9** could be replaced by *n*-butylamine to give desired products **4**, **10**, and **11** in excellent yields when the substrate was treated with 3 equiv of *n*-butylamine in methylene chloride at room temperature (Scheme 4). With substrates **4**, **10**, and **11** in hand, the sulfur extrusion reactions were explored (Scheme 4). First, the sulfide extrusion reaction of **10** was investigated because several examples were reported for the conversion of benzothiazepines to quinolines most likely via the well-known Eschenmoser sulfur extrusion reaction mechanism.[5a,8] Under thermal conditions (such as prolonged refluxing in toluene or xylene), no sulfur extrusion was observed for sulfide **10**. Addition of triphenylphosphine was shown to promote the Eschenmoser sulfur extrusion reactions,[5g,8] but it did not help the sulfur extrusion in **10**. Next, the sulfoxide **4.1** was subjected to the thermal sulfur extrusion reaction conditions (refluxing in toluene), and to our delight, it was smoothly converted to the desired pyrimidoquinoline **5.1** in excellent yield (entry 1, Table 2). This thermal sulfur monoxide extrusion condition was applied to other sulfoxides **4.2**−**4.6** and produced pyrimidoquinolines **5.2**−**5.6** in excellent yields (Table 2). The extrusion of sulfur monoxide was surprisingly facile. For example, sulfoxide **4.1** underwent extrusion even at room temperature, albeit at a slower rate. A solution of **4.1** in chloroform standing at room temperature after 2 days generated about 50% of **5.1**. Encouraged by the successful extrusion reactions of **4.1**−**4.6**, sulfone **11** was subjected to the same reaction conditions, but like sulfide **10**, it also proved to be unsuitable for the extrusion reaction even after prolonged heating (Scheme 4).

Scheme 4. Exploration of Stepwise Nucleophilic Substitution−Sulfur Extrusion Reactions

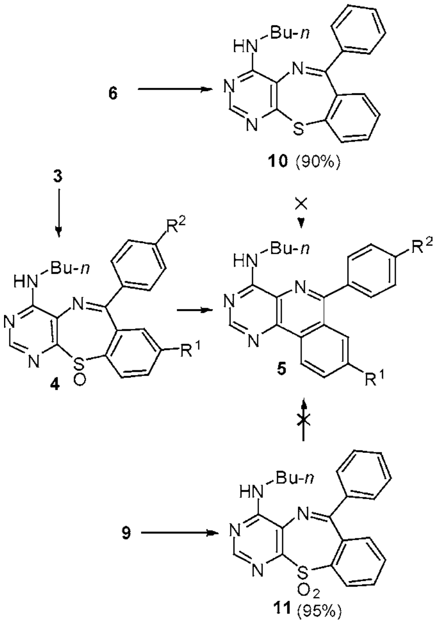

Table 2. Stepwise Preparation of Pyrimido[4,5-*b*][1,4]benzothiazepines from Sulfoxide **3**

entry	3	R^1	R^2	4[a]	yield (%)	5[b]	yield (%)
1	**3.1**	H	H	**4.1**	90	**5.1**	94
2	**3.2**	Me	H	**4.2**	85	**5.2**	92
3	**3.3**	Cl	H	**4.3**	80	**5.3**	80
4	**3.4**	MeO	H	**4.4**	80	**5.4**	82
5	**3.5**	H	Me	**4.5**	88	**5.5**	90
6	**3.6**	H	F	**4.6**	92	**5.6**	90[c]

[a] Reactions were conducted in CH_2Cl_2 with 3 equiv of *n*-$BuNH_2$ at room temperature. [b] Reactions were conducted in refluxing toluene under nitrogen for 0.3 h unless otherwise noted. [c] Reaction was run for 24 h.

It is logical to explore a one-pot procedure by combining the nucleophilic replacement and sulfoxide extrusion because one-pot procedures are often developed for efficient synthesis of various heterocycles.[9] When substrate **3** was subjected to an excess (3 equiv) of the corresponding nucleophiles in refluxing toluene, the desired substituted pyrimidoisoquinolines **5** were obtained. As demonstrated by the results in Table 3, all the employed amines (NH_3, primary and secondary amines, even those with demanding steric properties) worked quite well in this one-pot procedure to give the desired heterocycles. The reaction proceeded faster, and yields were even higher when strong nucleophiles were used

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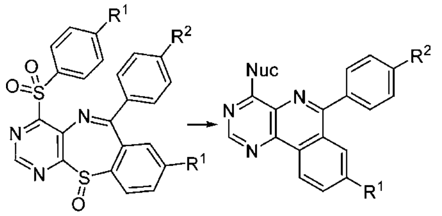
Table 3. One-Pot Preparation of Pyrimido[5,4-*c*]isoquinolines[a]



3 5

entry	5	R^1	R^2	nucleophile	time (h)	yield (%)
1	**5.1**	H	H	*n*-BuNH	0.3	94
2	**5.7**	H	H	BnNH	0.3	93
3	**5.8**	H	H	*i*-PrNH	0.3	90
4	**5.9**	H	H	PhNH	3	55
5	**5.10**	H	H	NH_2	0.3	80[b]
6	**5.11**	H	H	pyrrolidin-1-yl	0.3	82
7	**5.12**	H	H	BnS	4	27
8	**5.12**	H	H	BnS	3.5	66[c]
9	**5.13**	H	H	*n*-BuO	6	0
10	**5.13**	H	H	*n*-BuO	4	21[d]
11	**5.2**	Me	H	*n*-BuNH	0.3	93
12	**5.14**	Me	H	BnNH	0.3	90
13	**5.15**	Me	H	*i*-PrNH	0.3	88
14	**5.16**	Me	H	PhNH	4	60
15	**5.17**	Me	H	pyrrolidin-1-yl	0.3	83
16	**5.3**	Cl	H	*n*-BuNH	0.3	89
17	**5.18**	Cl	H	*i*-PrNH	0.3	83
18	**5.19**	Cl	H	NH_2	0.3	93[b]
19	**5.4**	MeO	H	*n*-BuNH	0.3	91
20	**5.20**	MeO	H	BnNH	0.3	92
21	**5.21**	MeO	H	*i*-PrNH	0.3	85
22	**5.22**	MeO	H	pyrrolidin-1-yl	0.3	88
23	**5.23**	Me	Me	BnNH	0.3	92
24	**5.24**	Me	Me	*i*-PrNH	0.3	88
25	**5.25**	Me	Me	PhNH	4	68
26	**5.26**	Me	Me	BnS	5	32
27	**5.26**	Me	Me	BnS	4	69[c]

[a] Reactions were conducted in refluxing toluene with 3 equiv of nucleophiles under nitrogen. [b] Ammonia saturated methanol was utilized. [c] 20 equiv of pyridine was used as the base. [d] Reactions were conducted in refluxing butan-1-ol with 20 equiv of pyridine as the base.

(entries 1−3, 5, 6, 11−13, and 15−24, Table 3) compared to weak nucleophiles such as, for example, aromatic amines (entries 4, 14, and 25, Table 3). Although other weak nucleophiles were also used to test the scope of the reaction, such as phenylmethanethiol (entries 7, 8, 26, and 27, Table 3) or butan-1-ol (entries 9 and 10, Table 3), the reactions were more difficult. In these cases, pyridine has been added as the base catalyst to promote the nucleophilic substitution. Therefore, other alkoxides and sulfides could be assumed to give the expected pyrimidoisoquinoline analogues under the same conditions.

In summary, an efficient strategy for the conversion of 4-arylthiopyrimido[4,5-*b*][1,4]benzothiazepines to pyrimido-[5,4-*c*]isoquinoline derivatives was demonstrated. Keys to this synthesis of pyrimido[5,4-*c*]isoquinolines are selective oxidation of the two sulfur atoms present in 4-arylthiopyrimido[4,5-*b*][1,4]benzothiazepines and one-pot conversion of selective displacements of the 4-arylsulfonyl groups and a sulfur monoxide extrusion reaction. This synthetic strategy expands the scope of 4-arylthiopyrimido[4,5-*b*][1,4]benzothiazepines to access novel heterocyclic scaffolds of pyrimido[5,4-*c*]isoquinoline. Moreover, various nucleophiles were readily introduced via the displacement of the 4-arylsulfonyl groups thereby generating additional structural diversification. It is demonstrated herein that this new strategy provides a convenient methodology to access these biologically interesting scaffolds of pyrimido[5,4-*c*]isoquinolines with high structural diversity.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR and LC-MS-ELSD spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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