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Letter

Multicomponent Petasis Reaction for the Synthesis of Functionalized 2-Aminothiophenes and Thienodiazepines

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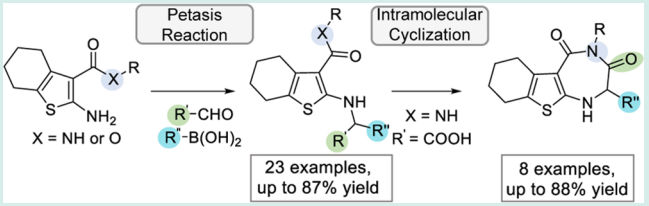
ABSTRACT: Multicomponent Petasis reaction has been widely applied for the synthesis of functionalized amine building blocks and biologically active compounds. Employing primary aromatic amines that are not typical reactive substrates contributes to expand the application scope of the Petasis reaction. In this study, we demonstrated the synthesis of functionalized 2-aminothiophenes using Gewald-reaction-derived 2-aminothiophenes as the amine substrates, whose low reactivity in the Petasis reaction was overcome using hexafluoro-2-propanol as the solvent in a mild condition. The obtained Petasis products are amenable for further transformations owing to the presence of multiple functional handles. A following intramolecular cyclization of selected Petasis products afforded substituted tricyclic heterocycles that incorporate a pharmaceutically interesting thienodiazepine moiety.



KEYWORDS: *multicomponent reaction, Petasis reaction, 2-aminothiophenes, thienodiazepines, small molecules*

Petasis borono-Mannich reaction, or Petasis reaction (PR), is a powerful multicomponent transformation of an amine, an aldehyde, and a boronic acid to afford functionalized amines via the in situ formation of a tetraboronate intermediate (Figure 1A).[1−3] Although a wide selection of carbonyl compounds and boronic acids or esters have been successfully applied in PRs, reactive amine substrates in PRs are still mainly restricted to secondary nonaromatic amines,[1−5] as shown in recent applications in peptide modification, selective bioconjugation, and DNA-encoded library synthesis.[6−9] Primary aromatic amines are typically not reactive substrates in PRs, although anilines, pyridine-2-amines, and naphthalen-2-amines have been used in a few catalyzed variants or at the expense of microwave irradiation conditions (Figure 1B).[3,10] Overall, the PR provides a versatile strategy to access highly functionalized amines that are of both synthetic and biological interest.

Aminothiophene is a common moiety in biologically active compounds and FDA-approved drugs.[11−15] For example, diverse 2-aminothiophene-containing compounds, such as RS-C-5966451/-5950331 and MD-C1-3/-C2-3, were reported as activators of latent ribonuclease and have been evaluated for their antiviral activity and applied to recruit ribonuclease to cleave an oncogenic microRNA (Figure 1C).[16,17] Olanzapine is a thienodiazepine that is used as an antipsychotic drug (Figure 1D). Furthermore, 2-aminothiophene-containing compounds have been evaluated for their anticancer activities by inhibiting kinases or bromodomain-containing protein 4.[18−20] One of the most robust methods to synthesize 2-aminothiophene is via the three-component Gewald reaction (GR) of a ketone, an α-cyanoester, and sulfur, as well as a few optimized variants.[21−24] As a part of our current efforts to evaluate scaffold-diverse small molecules as potential modulators of RNA-binding

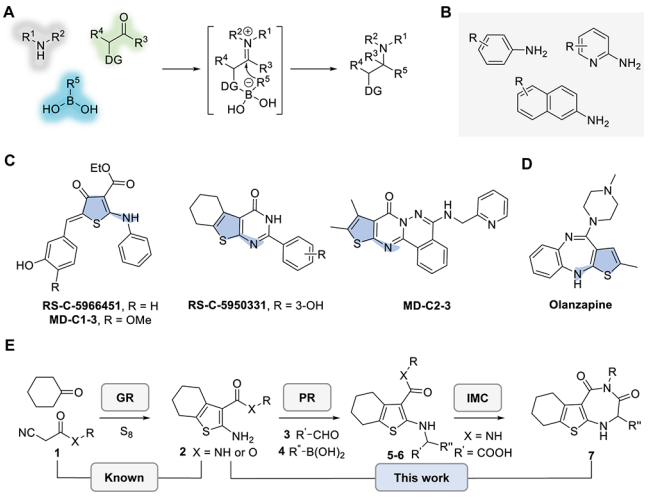


Figure 1. Background and overview. (A) Petasis reaction (PR) of an amine, an aldehyde, and a boronic acid. DG: Directing group. (B) Primary aromatic amines that have been applied in the PR under demanding conditions. (C) 2-Aminothiophene-containing molecules that were reported as activators of ribonuclease L. (D) Olanzapine is a 2-aminothiophene-containing antipsychotic drug. (E) Gewald reaction (GR)−PR−intramolecular cyclization (IMC) in this study to synthesize highly functionalized 2-aminothiophenes and thienodiazepines.

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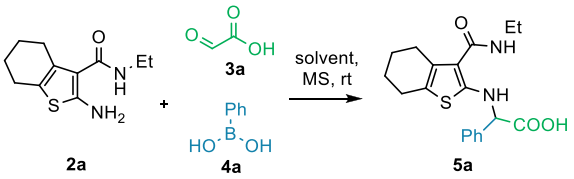
proteins, we report herein the synthesis of a series of functionalized 2-aminothiophenes via a GR−PR route, followed by an intramolecular cyclization (IMC) to afford thienodiazepines (Figure 1E).

The 2-aminothiophene-3-carboxamide **2a** was obtained by a straightforward Gewald condensation of α-cyanoamide **1a** derived from ethyl cyanoacetate and ethyl amine, cyclohexanone, and sulfur.[20] Using ethyl cyanoacetate **1b** in the Gewald condensation gave the 2-aminothiophene-3-carboxylate **2b**.[25] Then the three-component Petasis reaction of the Gewald condensation product **2a**, glyoxylic acid **3a**, and phenylboronic acid **4a** was performed to test the optimal condition to form the target phenylacetic acid **5a**. Our initial test of the reaction in dichloromethane did yield the Petasis product **5a**, although in low conversion of only 24%. Solvents of different acidity were then tested in the presence of molecular sieves (MS) for the Petasis reaction (Table 1).

Table 1. Reaction Conditions for the Three-Component Petasis Reaction Using the Gewald Reaction Product 2a



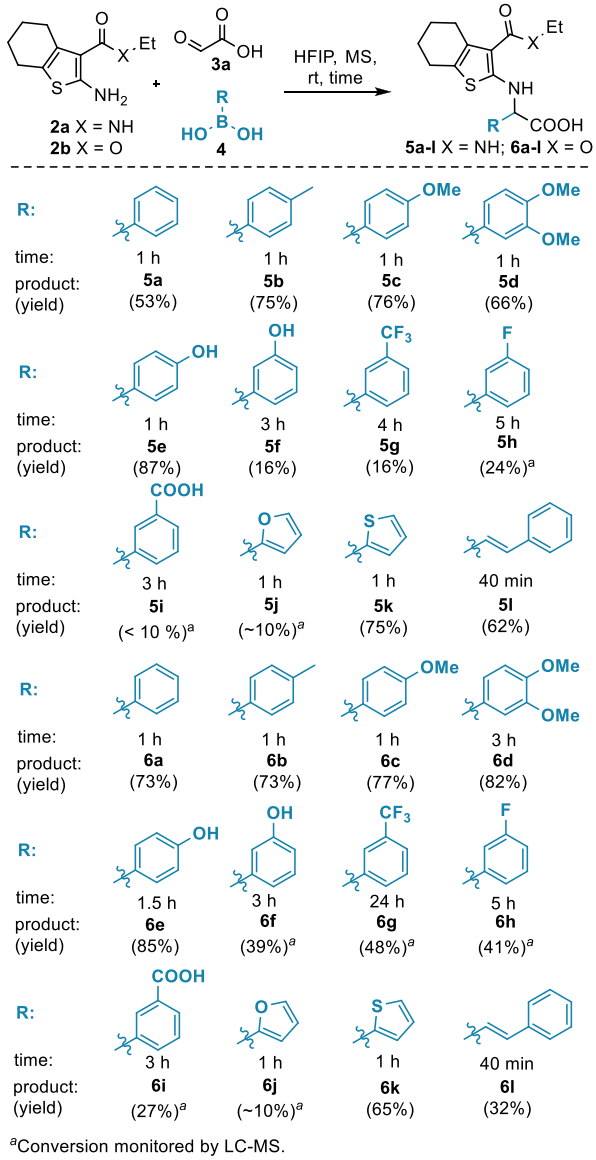
entry	solvent	time (h)	conversion (%)[a]
1[b]	CH_2Cl_2	24	24
2[b]	HFIP	1	37
3[b]	MeCN	6	13
4[b]	EtOH	12	trace
5[b]	THF	24	trace
6[c]	CH_2Cl_2	1	48
7[c]	HFIP	1	63

[a]Monitored by LC−MS. [b]Amine **2a** and aldehyde **3a** were stirred for 10 min before boronic acid **4a** was added . [c]Simultaneous addition of all three components.

Consistent with the reactivity enhancement using hexafluoroisopropanol (HFIP) in the Petasis reaction,[26−28] the use of HFIP accelerated the reaction and led to the improved conversion to the expected product **5a**. In monitoring the reaction in a duration up to 24 h, the maximum conversion was observed after 1 h. The formation of two byproducts with a combined conversion of less than 10% judged by LC−MS was also observed. It is noteworthy that sequential addition of amine **2a** and aldehyde **3a** first before adding boronic acid **4a** showed a lower conversion to **5a** in comparison with simultaneous addition of all three components (entries 2 and 7, Table 1)—an indication that both the direct migration of the phenyl group to the iminium intermediate and the migration with the formation of a tetra-coordinated boronate intermediate are likely involved, with the latter being the favored pathway.[29] HFIP presumably promotes the formation of the iminium species and stabilizes ionic transition states involved in the Petasis reaction owing to its ionizing property.[26−28,30] The condition with the best conversion of 63% in HFIP led to an isolated yield of 53% for product **5a** and was used to synthesize 2-amino-3-carbonylhydrobenzothiophene derivatives **5** and **6**.

We then investigated the scope for the Petasis reaction in terms of both boronic acids and aldehydes under the HFIP condition (Scheme 1). The Petasis reaction using carboxamide

Scheme 1. Scope of the Petasis Reaction Testing Boronic Acids



[a]Conversion monitored by LC−MS.

2a as the amine substrate tolerates a range of boronic acids, such as phenyl (**5a**) and substituted phenyl boronic acids. Most phenyl boronic acids substituted by electron-donating groups at the 4-position led to isolation of the Petasis products in good yields (**5b−d**), whereas the 3-hydroxyphenyl boronic acid only led to the Petasis product **5f** in poor yield in comparison with that of **5a**. Phenylboronic acids substituted by electron-withdrawing groups at the 3-position, such as fluoro-, trimethylfluoro-, and a carboxylic acid group, only led to less than 10% conversion, as monitored by LC−MS, even with prolonged reaction time (**5g−i**). The electron-rich 2-furanylboronic acid, which usually showed high reactivity in Petasis reactions, did not lead to **5j** in synthetically useful conversion, whereas product **5k** from 2-thienylboronic acid

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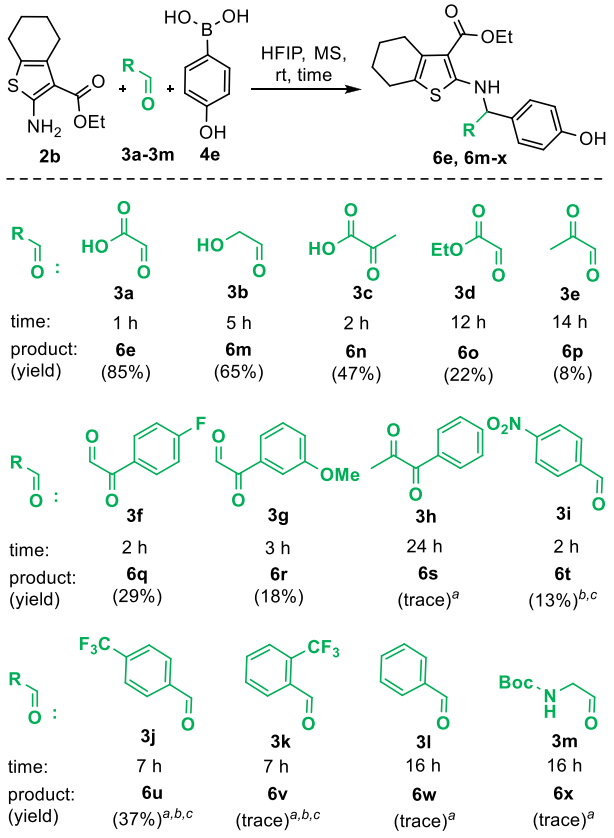
was isolated in good yield as did product **5l** from (*E*)-styrylboronic acid. Use of the carboxylate **2b** as the amine substrate showed the same tolerable profile among the same group of boronic acids, with the 4-hydroxyphenyl boronic acid affording product **6e** in the highest yield (85%).

Evaluation of the aldehyde scope revealed varied results (Scheme 2). Glyceraldehyde (dimer) **3b** led to the Petasis

Scheme 2. Scope of the Petasis Reaction Testing Aldehydes and Ketones



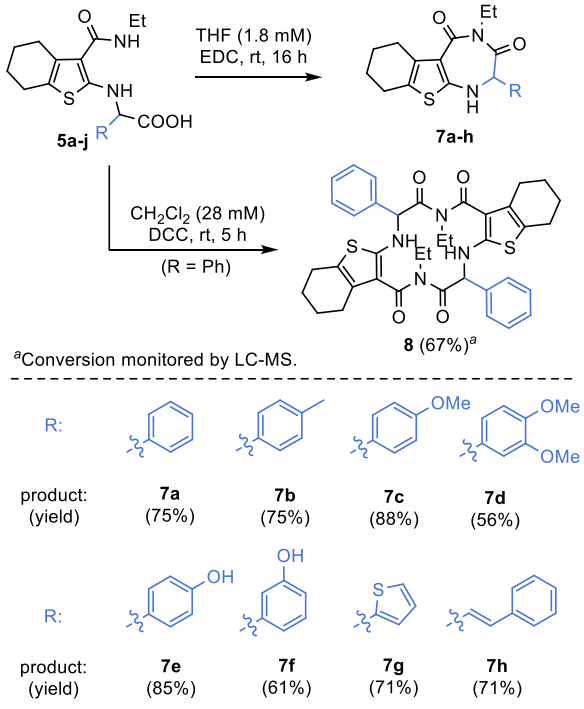
[a]Conversion monitored by LC-MS. [b]Solvent: HFIP/CH_2Cl_2 (v/v, 1/1). [c]reflux

[a]Conversion monitored by LC–MS. [b]Solvent: HFIP/CH2Cl2 (v/v, 1/1). [c]Reflux.

product **6m** in good yield but a reduced yield in comparison with that of **6e**, presumably due to the reduced electrophilicity of glyceraldehyde in comparison to that with glyoxylic acid. The fact that pyruvic acid also afforded the Petasis product **6n** showed that this reaction is tolerable to certain ketones, albeit with reduced reactivity. Ethyl glyoxylate **3d** and pyruvaldehyde **3e** only led to the corresponding products **6o** and **6p** in poor yields, which may be explained by the lack of a strong directing effect by an α-hydroxy group that can facilitate the formation of the tetraboronate intermediate. For the same assumption, phenylglyoxals **3f** and **3g** afforded the products in low yield, whereas acetylbenzoyl **3h** did not proceed with significant conversion even with prolonged reaction time. For the benzaldehydes, unless substituted by the strong electron-withdrawing nitro or trifluoromethyl group at the *para*-position (**3i** and **3j**), benzaldehydes did not lead to isolatable products (**6v** and **6w**). Additionally, *N*-Boc-2-aminoacetaldehyde **3m** did not lead to isolatable product **6x**. In summary, the results of evaluating aldehydes revealed that the low nucleophilicity of the 2-aminothiophene requires the use of an activated carbonyl component to render the 2-amine sufficiently reactive toward in situ formation of the tetraboronate intermediate. The obtained 2-amino-3-carbonylhydrobenzothiophenes **5** and **6** share several common structural moieties with reported RNase L activators, such as the tetrahydrobenzo[4,5]thieno moiety of C-5950331 and the 3-carboxylate-2-aminothiophen-3-one moiety of C-5966451 and MD-C1-3 (Figure 1C), and are thus currently being evaluated in-house for their ribonuclease-activating activity.

In addition to being potential biologically active compounds, the obtained 2-amino-3-carbonylhydrobenzothiophenes **5** and **6** feature several functional handles that are amenable for further transformations to novel scaffolds. One such scaffold could be a corresponding tricyclic thienodiazepine core after a further intramolecular cyclization step. Indeed, screening of different coupling conditions revealed EDC as the optimal coupling reagent that led to the intramolecularly cyclized thienodiazepine-3,5-diones **7a–h** from the Petasis products **5a–j** in overall good yields (56–88%). It is noteworthy to mention that a condition using DCC as the coupling reagent led to the intermolecular cyclization to afford the corresponding dimerized compound **8** (Scheme 3).

Scheme 3. Cyclization of the Petasis Products 5



[a]Conversion monitored by LC-MS.

In conclusion, a synthesis method to access highly functionalized 2-aminothiophenes has been developed using a three-component Petasis reaction employing Gewald reaction products as the amine substrates. This method converts low reactive primary aromatic amines into corresponding Petasis products under a mild and easily operational condition (no complex catalysts, microwave irradiation, or photoredox conditions) using HFIP. We obtained a collection of functionalized 2-aminothiophenes by testing the scope of the Petasis reaction, which is tolerable toward a wide range of boronic acids with yields up to 87%, although a limited selection of aldehydes led to satisfactory yields. The obtained

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2-aminothiophene products are amenable for further transformations to construct biologically interesting scaffolds, such as the formation of the new thienodiazepines **7** through an intramolecular cyclization in good yield up to 88%. This is the first report of applying 2-aminothiophenes as the amine substrate in Petasis reactions. The highly functional 2-aminothiophenes **5** and **6** and the tricyclic thienodiazepines **7** are being evaluated for their modulating activities against RNA-cleaving and -binding proteins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscombsci.0c00173.

Detailed synthetic procedures, compound characterization data, and NMR spectra of all isolated products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DCC, *N,N′*-dicyclohexylcarbodiimide; EDC, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide; GR, Gewald condensation reaction; HFIP, hexafluoroisopropanol; IMC, intramolecular cyclization; LC−MS, liquid chromatography−mass spectrometry; PR, Petasis borono-Mannich reaction

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