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A novel route to synthesize libraries of quinoxalines via Petasis methodology in two synthetic operations

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ABSTRACT

This Letter reveals an innovative and facile procedure to prepare quinoxalines in two synthetic steps. The microwave assisted Petasis reaction is followed by the acid mediated unmasking of an internal amino nucleophile, cyclodehydration and oxidation to give collections of quinoxalines in good to excellent yields.

Discovered in 1993, the Petasis reaction joined a relatively short list of Type-II multi-component reactions (MCRs) which involve only one irreversible step in their reaction mechanism.[1] Interestingly, with competition from a plethora of robust protocols that employ highly reactive organometallic reagents as nucleophilic equivalents, the Petasis reaction is probably under-utilized when one considers the complete specificity of boronic acids for the C=N bond relative to the C=O bond.[2,3] Indeed, unlike other organometallic reactions, the Petasis reaction is extremely operationally friendly, not requiring special handling, producing only relatively innocuous boric acid as a side product.[4] As such, the seminal discovery by Petasis of what is a boronic acid variant of the classical Mannich reaction has demonstrated great value for the production of libraries of small molecules. Such libraries, employing post-Petasis chemical modifications, span arrays of peptidomimetic heterocycles that include piperazinones,[5] benzopiperazinones, benzodiazepines, aza-β-lactams[6] and dihydroisoquinoline derivatives.[7] All the aforementioned strategies utilize post-Petasis modifications to rigidify the initial Petasis product. Of major significance is the application of the Petasis reaction by workers at Merck during the process development of the substance P antagonist, Apprepitant™, developed as a potential anti-depressant with a new mode of action.[8] In somewhat analogous fashion, we have been extensively involved in a number of post-MCR modifications[9] which in succint fashion lead to a variety of pharmacologically relevant scaffolds, adopted by many for the preparation of thousands of compounds in a high-through modality for file enhancement of corporate and academic screening collections alike.[10]

Herein we report a two step Petasis-deprotection–cyclodehydration–oxidation sequence that enables the preparation of quinoxaline congeners in rapid fashion. The route is even more attractive due to the easy access to numerous commercially available diverse reagents. From the perspective of biological relevance, quinoxalines exhibit a large variety of biological activities such as antibacterial,[11] antimalarial,[12] antifungal,[13] and antithrombotic.[14] Moreover quinoxaline based drugs have shown to be photochemical DNA cleaving agents making them highly attractive and promising scaffolds for anticancer therapeutics[15] In addition they have found widespread use in dyes and organic semiconductors.[16] Of particular interest to the group are reported allosteric kinase inhibitors of AKT1, that contain the diarylquinoxaline moiety made accessible through this methodology.[17]

Our initially explored model Petasis MCR comprised of reactions of *mono*-protected diamine **1**, phenylglyoxal **2** and *p*-tolyl boronic acid **3**, carried out in different media at a variety of temperatures, Scheme 1. Reaction progress was monitored by LC–MS, Table 1. Of the eight solvents and solvent combinations evaluated, dichloromethane and acetonitrile proved optimal, requiring 18 h at room temperature (>70% yield) or 15 min at 120 °C irradiated with microwaves (>90% yield) for acceptable product formation. Under the latter conditions dimethylformamide also proved to be an excellent solvent.

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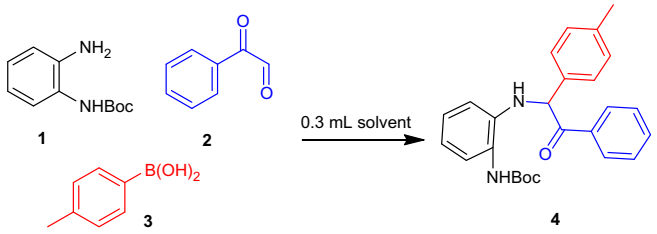
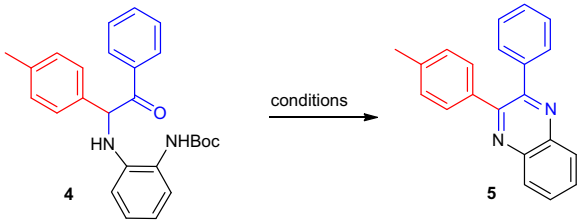


Scheme 1. Model Petasis reaction.



Scheme 2. Boc removal and cyclodehydration–oxidation.

Table 1
Optimization of the Petasis reaction[a]

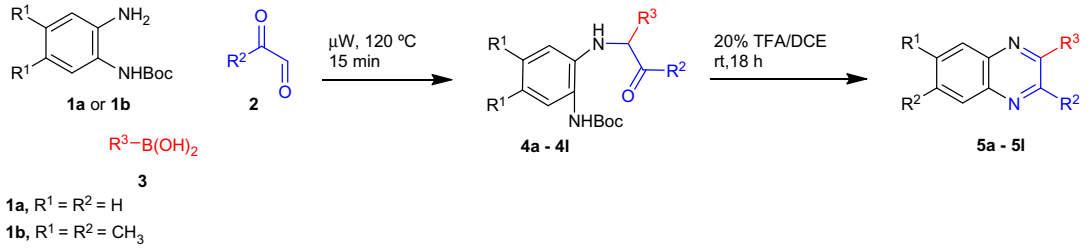
Entry	Solvent	Yield[b] (%) 0.5 h, rt	Yield[b] (%) 18 h, rt	Yield[b] (%) 15 min, 120 °C
1	DMF	<5	17	97
2	DCM	26	84	98
3	MeCN	36	72	91
4	Toluene	<5	16	31
5	THF	<5	<5	27
6	Ethanol	16	<5	<5
7	Dioxane/water (3:1)	0	<5	<5
8	MeCN/DMF (1:1)	5	24	87

[a] All the reactions were carried out at 0.1 mmol scale.
[b] LC–MS area% purity as judged by Evaporative Light Scattering (ELS).

Table 2
Optimization of reaction conditions[a]

Entry	System	Time (h)	Temp (°C)	Yield[b] (%)
1	AcOH/*i*-PrOH	18	rt	<5
2	PTSA/DCM	18	rt	18
3	PTSA/$MgSO_4$/DCM	18	rt	6
4	PTSA/TFA/DCE	18	rt	25
5	TFA/DCC/DCE	18	rt	14
6	TFA/DCE	18	rt	100
7	HCl/EtOAc	18	rt	99
8	TFA/DCE	0.25	80 °C	72

[a] All the reactions were carried out at 0.1 mmol scale.
[b] LC–MS area% purity as judged by Evaporative Light Scattering (ELS) yield.



Scheme 3. Two step sequence to quinoxalines.

Summarizing, it is clear that protic solvents whether used alone or in combination were unsuited for optimal progression of the Petasis reaction (Table 1, entries 6 and 7). Likewise toluene and tetrahydrofuran afforded only modest yields of the desired product (Table 1, entries 4 and 5), whilst DMF, dichloromethane and acetonitrile proved to be almost equally effective as solvents (Table 1, entries 1, 2, and 3). For operational ease, dichloromethane was selected as the solvent of choice for further studies.

Following optimization of the Petasis conversion, a variety of reagents were quickly screened to unmask the internal nucleophile present on the Petasis product and trigger simultaneous cyclization onto the carbonyl group derived from phenylglyoxal and oxidation to the quinoxalinone, Scheme 2. Differing combinations of dehydrating and/or drying agents and solvents were evaluated at room temperature, Table 2. Somewhat predictably both TFA/DCE and HCl/EtOAc systems resulted in excellent yields of the quinoxaline product (Table 2, entries 6 and 7). However, due to its milder nature, the TFA/DCE combination seemed to be superior since prolonged exposure of reaction mixtures to HCl/EtOAc solution resulted in disintegration of the final quinoxaline. An attempt to speed up the reaction (20% TFA/DCE, 80 °C, 15 min., microwave irradiation CEM Explorer™) proved to be counterproductive as the quinoxaline interestingly started to fragment.

Subsequently, the reaction scope in terms of substrate tolerance was explored, Scheme 3. Various glyoxaldehydes and boronic acids having different substituents (both electron withdrawing and donating groups) were screened (mainly using mono-*N*-Boc-protected *o*-phenylene-diamine as the amine equivalent). The Petasis reaction showed good to excellent yields in most examples, regardless of the electronic or steric properties of the boronic acid or glyoxaldehydes used (Table 3, entries 1–3, 5, 7, 9, and 10). Noticeably, however, using a highly hindered glyoxaldehyde (2,4,6-trimethyl glyoxaldehyde) proved to be detrimental showing no Petasis product at all (Table 3, entries 4 and 8). On the contrary, a highly sterically hindered boronic acid had much lower, if any impact on the Petasis reaction (Table 3, entry 9). Furthermore, under the conditions employed boronic acids of a non-aryl origin were seen to poorly perform in the Petasis reaction (Table 3, entry 6). Replacing *N*-Boc-protected *o*-phenylene-diamine with 3,4-dimethyl *N*-Boc-protected *o*-phenylene-diamine resulted in relatively lower yields than normal for the Petasis reaction (Table 3, entries 11 and 12), as can be seen by comparing yields of entry 9 and 12. Attempts to expand the scope of accessible chemotypes to potential pyrazines via the use of *N*-Boc-ethylene-diamine were unsatisfactory due to very low Petasis reaction yields.[18]

In contrast to the Petasis reaction the subsequent deprotection–cyclodehydration–oxidation sequence worked smoothly, furnishing products in excellent yields for nearly all examples.[19]

In conclusion, we have reported a short, convenient and robust two step procedure to prepare diversified quinoxalines. Use of

Table 3
Reactivity domain for Petasis/deprotection/cyclodehydration/oxidation protocol[a]

Entry	R^1	R^2	R^3	Yield (%) (**4a–l**)	Yield (%) (**5a–l**)
1	H	4-F-Ph	4-Me-Ph	57 (**4a**)	98 (**5a**)
2	H	4-CF_3-Ph	4-Me-Ph	49 (**4b**)	92 (**5b**)
3	H	Ph	3-F-Ph	48 (**4c**)	77 (**5c**)
4	H	2,4,6-*tri*-Me-Ph	2-MeO-Ph	0 (**4d**)	nd (**5d**)
5	H	4-CF_3-Ph	2-Naphthyl	71 (**4e**)	91 (**5e**)
6	H	Ph	*trans*-β-Styryl	39 (**4f**)	nd (**5f**)
7	H	Ph	2-MeO-Ph	63 (**4g**)	85 (**5g**)
8	H	2,4,6-*tri*-Me-Ph	4-Me-Ph	0 (**4h**)	nd (**5h**)
9	H	Ph	2,4,6-*tri*-F-Ph	83 (**4i**)	98 (**5i**)
10	H	4-CF_3-Ph	3-CF_3-Ph	87 (**4j**)	81 (**5j**)
11	CH_3	4-CF_3-Ph	2-Naphthyl	45 (**4k**)	93 (**5k**)
12	CH_3	Ph	2,4,6-*tri*-F-Ph	24 (**4l**)	35 (**5l**)

[a] All the reactions were carried out at a 1 mmol scale and isolated yields are reported. [Note: nd = not determined].

microwave makes this process more attractive since the reaction time has been considerably diminished for a usual Petasis reaction. Current efforts are focusing on optimizing the routes to additional chemotypes of pharmacological importance.

Acknowledgment

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18. Using 4-methylphenyl boronic acid, phenyl glyoxaldehyde and *N*-Boc-ethylenediamine gave a complex mixture from the Petasis reaction with a negligible amount of the desired product. Similarly in Table 3, entry 3, replacing phenyl glyoxaldehyde with methyl glyoxaldehyde showed only 23% of the desired Petasis product: none of the reactions was considered for purification or subsequent deprotection/cyclization steps.
19. *General procedure for preparation of* ***5c***: One millimolar of each diamine, glyoxaldehyde and boronic acid were taken into a microwave vial already equipped with a magnetic bar. 1 mL of dichloromethane was added to the system followed by heating it at 120 °C for 15 min. The crude Petasis product was then directly loaded to an ISCO™ purification system and using ethylacetate/hexane as eluent (0–100% gradient over 25 min) the products were purified. A weighed out amount of Petasis product (0.10–0. 30 mmol) was then subjected to 1–2 mL of 20% TFA in dichloromethane. The reaction was stirred for ~18 h at room temperature, evaporated in vacuo and crude material purified via chromatography (ISCO™) to afford the desired product (77% yield) as a white solid. *Quinoxaline* **5c**: R_f 0.55 (hexane/AcOEt 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.21 (m, 2H), 7.79–7.82 (m, 2H), 7.50–7.54 (m, 2H), 7.21–7.39 (m, 6H), 7.04–7.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 161.2, 153.1, 141.3, 140.9, 138.6, 130.3, 130.1, 129.8, 129.7, 129.6, 129.2, 129.2, 129.0, 128.4, 125.7, 116.9, 116.7, 115.9, 115.7. ESI 301 (MH^+).