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Recent progress in the synthesis of five-membered heterocycle boronic acids and esters

Nicolas Primas [a], Alexandre Bouillon [b], Sylvain Rault [a,*]

[a] Centre d'Etudes et de Recherche sur le Médicament de Normandie, CERMN, UPRES EA 4258, FR CNRS 3038, Boulevard Becquerel Université de Caen Basse Normandie, 14032 Caen Cedex, France
[b] BoroChem S.A.S., Immeuble Emergence, 7 rue Alfred Kastler, 14000 Caen, France

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* Corresponding author. Tel.: +33 2 31 56 68 01; fax: +33 2 31 56 68 03; e-mail address: sylvain.rault@unicaen.fr (S. Rault).

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1. Introduction

The use of cross-coupling reactions for the preparation of new alkylated or arylated heteroaromatic compounds has increased tremendously over the past two decades. Among all of these transition metal-catalyzed reactions, the Suzuki–Miyaura reaction, which uses boronic acids or esters remains the method of choice. There is therefore great interest in studying the synthesis and the reactivity of new boronic species especially in heterocyclic chemistry in order to create new focused libraries, which are now mandatory in medicinal chemistry. In this context, this review brings together the bibliographic elements concerning the synthesis of five-membered ring boronic acids and esters. Among them, some are well known and extensively used, as is the case for thiophene or furan, for example, whiles on the other hand, others, especially those derived from diazoles, oxazole or thiazole, the synthesis of which is often more difficult, are not yet commonly used. This review will focus on the synthesis of these latter compounds, which are of great interest for modern medicinal chemists.

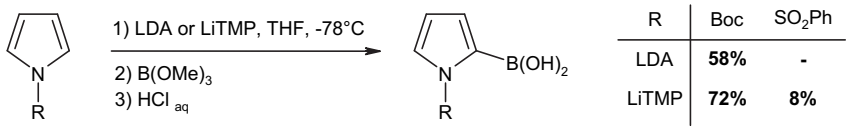
2. Pyrrole

The first studies on pyrrole boronic derivatives were carried out in the early 1990s. Except in a few cases where direct boronation is used, the nitrogen atom of the pyrrole ring must be protected by groups, such as *tert*-butyloxycarbonyl (Boc), triisopropylsilyl (TIPS) or phenylsulfonyl (SO_2Ph).

2.1. Synthesis of boronic acids and esters in the 2-position of pyrrole

In 1991, Martina described for the first time a direct lithiation of *N*-Boc-pyrrole using LiTMP followed by the action of trimethyl borate and then by an acidic hydrolysis to give the *N*-Boc-pyrrol-2-ylboronic acid in 40% yield.[1] Two years later, Kelly and Snow's team described the same access to this compound in 82% yield.[2] More recently, other groups starting from the same substrate and using LDA[3] or LiTMP[4] for the direct lithiation step, followed by the boronation/acidic hydrolysis sequence, provided the *N*-Boc-pyrrol-2-ylboronic acid in 58 and 72% yield, respectively (Scheme 1).

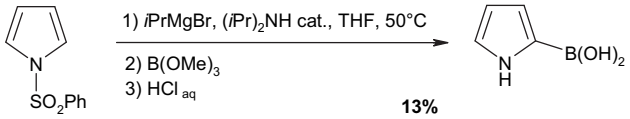
Using a different protecting group, the lithiation with LDA performed on the *N*-phenylsulfonylpyrrole followed by treatment with trimethyl borate and acidic hydrolysis afforded the *N*-protected boronic acid with a yield of only 8% (Scheme 1).[5]



R	Boc	SO_2Ph
LDA	**58%**	-
LiTMP	**72%**	**8%**

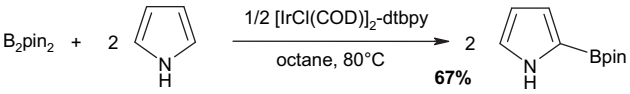
Scheme 1.

More recently, using the same substrate, but via the formation of a Grignard reagent, isopropylmagnesium bromide, in the presence of diisopropylamine, the sequence boronation/acidic hydrolysis led to the *N*-deprotected boronic acid, but with a low yield (13%) (Scheme 2).[6]



Scheme 2.

Direct iridium-catalyzed borylations were first developed by Miyaura[7] and his team.[8] The reaction occurs on the unprotected pyrrole with bis(pinacolato)diborane (B_2pin_2), the iridium catalyst (dimer of chloro-1,5-cyclooctadiene iridium (I)), and a ligand (4,4′-di-*tert*-butyl-2,2′-bipyridine), leading to 2-pyrrolylboronic acid pinacol ester in 67% yield (Scheme 3).



dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine

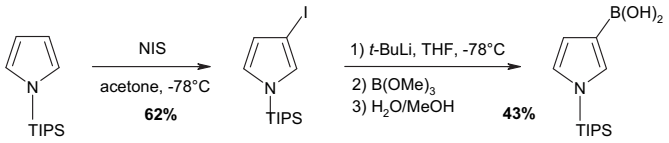
Scheme 3.

The use of pinacolborane (HBpin) instead of bis(pinacolato) diborane (B_2pin_2) for this reaction is also possible, but the yield of the reaction is significantly lower (42%).[9] The major drawback in this direct borylation reaction is the use of a large excess of substrate, namely 10 equiv of pyrrole in the first case and 30 equiv with HBpin. It is necessary to use these excess amounts in order to prevent the formation of di-boronated products. This attractive methodology therefore as its limitations and is not as simple and effective as had been previously announced.

2.2. Synthesis of boronic acids and esters in the 3-position of pyrrole

In 1992, Alvarez and his team[10] have synthesized 3-pyrrolyl-*N*-TIPS-boronic acid. Indeed, the TIPS protecting group, due to its large

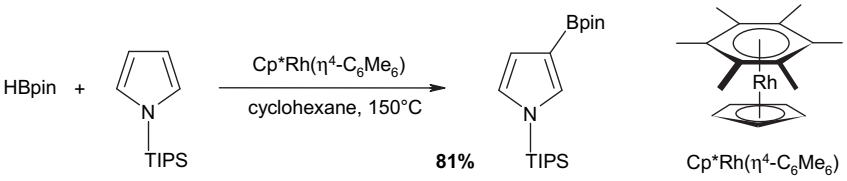
steric hindrance, orients the iodination into the 3-position of pyrrole. By using an iodine–lithium exchange with *tert*-butyllithium, the so-formed lithio intermediate was trapped by trimethyl borate and, finally, the hydrolysis of the intermediary salt leads to the 3-pyrrolyl-*N*-TIPS-boronic acid in 43% yield (Scheme 4).



Scheme 4.

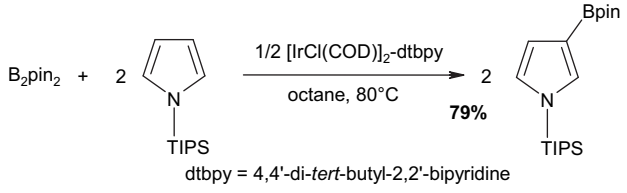
Following the same reaction pathway, Nadeau realized the halogen–metal exchange starting with 3-bromo-*N*-TIPS-pyrrole and *n*-butyllithium and, by subsequently performing the treatment described in Scheme 4, obtained the *N*-TIPS protected boronic acid with 50% yield.[11]

In 2001, Smith and his team described the direct borylation of *N*-TIPS-pyrrole with pinacolborane (HBpin) using a rhodium complex catalyst.[12] Again, the TIPS group hinders the 2-position and thus directs the borylation onto the 3-position of pyrrole, which is freely accessible. The protected boronic ester is obtained in 81% yield (Scheme 5). This process has been patented by Smith in 2003.[13]



Scheme 5.

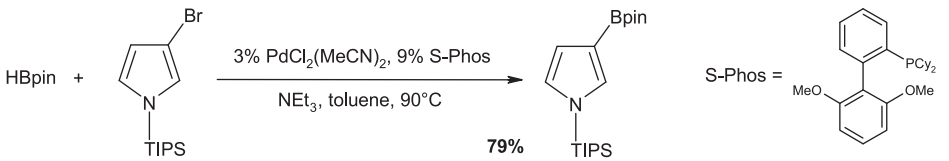
Using the same starting material and B_2pin_2 with iridium as catalyst, Miyaura obtained the boronic ester with a yield of 79% (Scheme 6).[7]



Scheme 6.

The Boc protecting group was also suitable to prepare pyrrol-3-ylboronic esters via iridium-catalyzed C–H borylation of *N*-Boc-pyrrole in good yields using HBpin as the source of boron.[14]

The Buchwald team in three publications, have described a synthesis of the same pinacol ester, by metal-catalyzed coupling with palladium, from 3-bromo-*N*-TIPS-pyrrole and pinacolborane in the presence of *S*-Phos and triethylamine (Scheme 7).[15] They have also achieved the same coupling by changing the protecting group to Boc and benzyl, but observed poor yields of 30 and 24%, respectively.

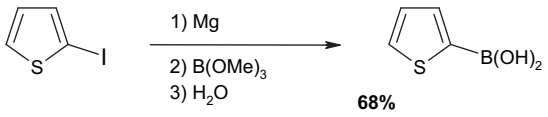


Scheme 7.

3. Thiophene

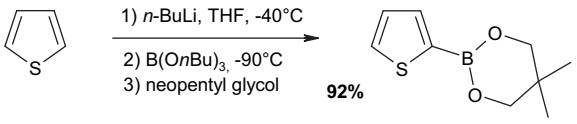
3.1. Synthesis of boronic acids and esters in the 2-position of thiophene

3.1.1. Synthesis by metalation. Early work on thiophene was carried out in 1932 by Krause, who described the synthesis of 2-thienylboronic acid by the action of boron trifluoride on 2-thienylmagnesium bromide in ether.[16] In 1938, Johnson modified the synthesis by reacting trimethyl borate with the Grignard reagent, itself previously prepared from 2-iodothiophene.[17] In 1983, a similar method using 2-thienylmagnesium iodide has been described by Kabalka, providing the boronic acid with a yield of 68% (Scheme 8).[18]



Scheme 8.

Using organolithium derivatives, several methods have been described to prepare either acids[19]or esters according to the different alcohols used in the final transesterification step. The boronic ester of neopentyl glycol, for example, is obtained in 92% yield (Scheme 9).[20]

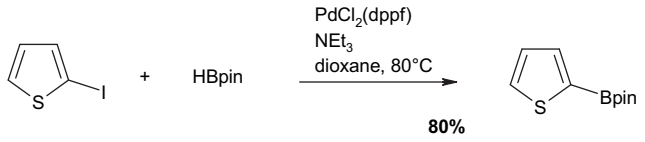


Scheme 9.

The synthesis of the boronic pinacol ester has recently been described with an excellent yield by performing a direct lithiation reaction of thiophene using *n*-butyllithium at −78 °C in THF followed by the action of isopropoxypinacolborane (^{i}PrOBpin), which leads to the desired boronic ester with a yield of 95%.[21]

3.1.2. Synthesis by metal-catalyzed coupling or direct borylation. The synthesis of the boronic pinacol ester using a metal-catalyzed coupling reaction has been described by Murata in 2000 from 2-iodothiophene with pinacolborane (Scheme 10).[22] Other teams have also described the same reaction by changing the nature of the catalyst[23] or the source of boron (B_2pin_2).[24]

The direct borylation catalyzed by iridium has been described for the first time in 2002 by Tagaki using thiophene and B_2pin_2, providing the boronic ester with 83% yield.[7] Other teams have also performed the same reaction using pinacolborane as the source of

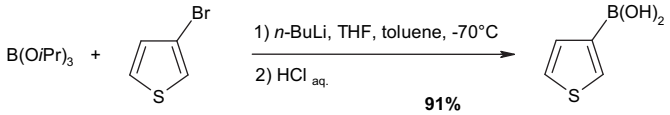


Scheme 10.

boron.[9] In 2008, Smith's team used the direct borylation reaction to obtain boronic esters of thiophene variously substituted with halogens, silyl groups, ketones or esters.[25]

3.2. Synthesis of boronic acids and esters in the 3-position of thiophene

The first synthesis of 3-thienylboronic acid was described by Lawesson in 1957. 3-Bromothiophene is subjected to halogen–metal exchange using *n*-butyllithium in ether at −60 °C, and the anion formed is trapped by tri-*n*-butyl borate. Acidic hydrolysis followed by an acid–base treatment provided the boronic acid with 59% yield.[26] In 2002, Li[27] applied the technique of trapping in situ to form the boronic acid. In this process, *n*-butyllithium is added directly to a mixture of 3-bromothiophene and triisopropy lborate. The final acid hydrolysis provided the expected product with 91% yield. This process greatly improved the traditional technique of successive additions, which gave only 51% yield (Scheme 11). This in situ procedure was reproduced in 2005 by Denton with the same result.[28]



Scheme 11.

The synthesis of boronic pinacol ester was mentioned in 2006 by Xie, but without experimental details.[29]

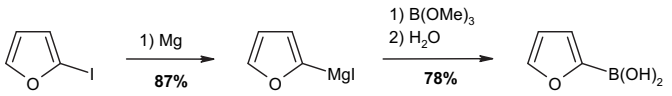
Derivatives in position 3 of unsubstituted thiophene are not accessible by direct borylation. In fact, the regioselectivity of this reaction does not allow this substitution, and it always takes place in position 2. If positions 2 and 5 are occupied, however it becomes possible to functionalize the thiophene in position 3 by a boronic ester of pinacol.[25] If the substituents in positions 2 and 5 are not the same, this reaction leads to mixtures (Scheme 12).

The pinacol boronic ester in the 3-position can also be prepared by a metal-catalyzed coupling reaction of 3-chlorothiophene. Buchwald's group have described its preparation using B_2pin_2[30] (Scheme 13) and HBpin[15c] with yields of 76 and 59%, respectively.

4. Furan

4.1. Synthesis of boronic acids and esters in the 2-position of furan

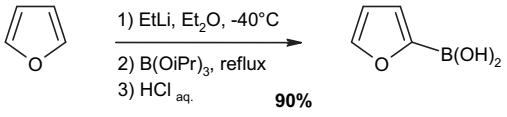
Furan-2-boronic acid was prepared for the first time in 1938 by Johnson from 2-iodofuran via the formation of furan-2-yl magnesium iodide followed by treatment with trimethy lborate (Scheme 14).[17]



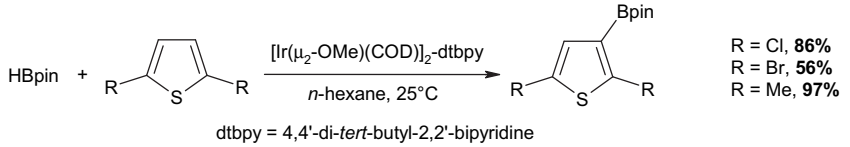
Scheme 14.

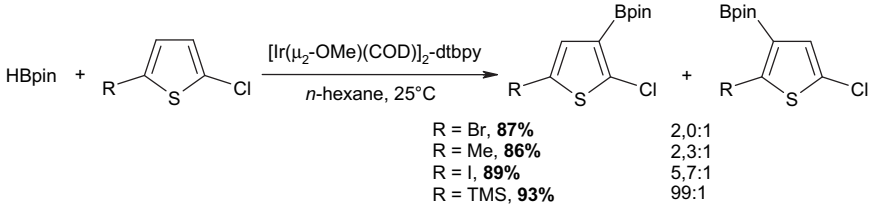
It was not until 1975 that Roques proposed a synthesis by direct metalation of furan using ethyllithium in ether at −40 °C followed by treatment with tri-*n*-butyl borate at reflux temperature.[31] The yield was equivalent. Thompson, by using triisopropyl borate, however was able to improve this yield to up to 90% (Scheme 15).[32]

More recently, a patent has described the access to this acid using a different procedure, which consists of reacting lithium metal on 2-chlorofuran in THF at −40 °C before treatment with

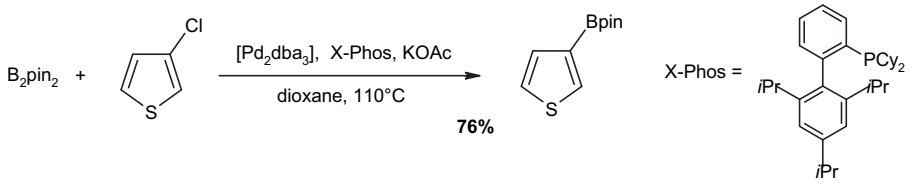


Scheme 15.



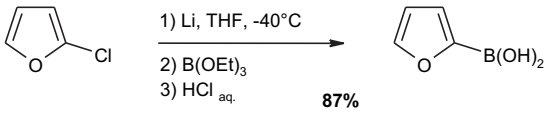


Scheme 12.



Scheme 13.

triethyl borate. A final acid hydrolysis gives furan-2-boronic acid with a yield of 87% (Scheme 16).[33]

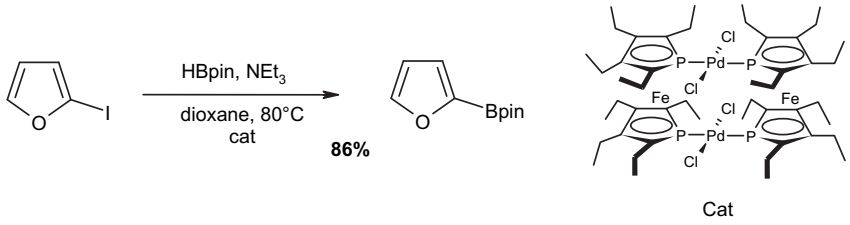


Scheme 16.

Through a pallado-catalyzed coupling reaction, Melaimi described the synthesis of furan-2-boronic acid pinacol ester with a yield of 86% (Scheme 17).[23b]

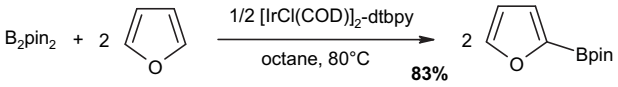
Access to furan-3-boronic acid pinacol ester has been described by a metal-catalyzed coupling reaction from 4-bromo-2-furancarboxaldehyde protected as its dioxolan and HBpin in toluene at 80 °C with a yield of 60% (Scheme 20).[34]

Using direct boronation, Chotana synthesized boronic acid pinacol esters in the *ortho* position relative to a nitrile function carried by aromatic or heteroaromatic rings. From 5-methyl-2-furonitrile, the direct boration using HBpin gave, in a global 97% yield, a mixture of the 2 *ortho* and *meta* isomers in a proportion of 85/15 (Scheme 21). The authors did not describe the separation of these isomers.[35]



Scheme 17.

Takagi described in 2002 a new method of synthesis of this ester by a direct boration catalyzed with iridium from furan using B_2pin_2, with a yield of 83% (Scheme 18).[7]

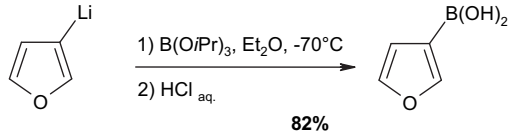


dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine

Scheme 18.

4.2. Synthesis of boronic acids and esters in the 3-position of furan

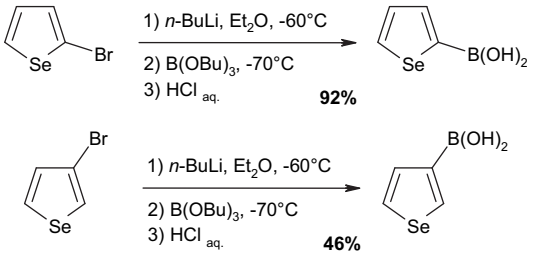
Furan-3-boronic acid has been described for the first time by Roques et al. in 1975.[31] This acid was obtained from 2-bromofuran under the action of ethyllithium and tri-*n*-butyl borate followed by acid hydrolysis. In 1984, Thompson realized a new synthesis by adding directly 3-furyllithium to a solution of triisopropyl borate in ether at −70 °C. After acid hydrolysis, the yield was 82% (Scheme 19).[32]



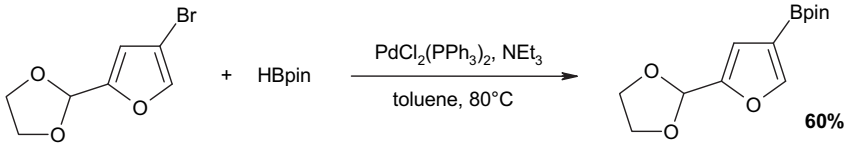
Scheme 19.

5. Selenophene

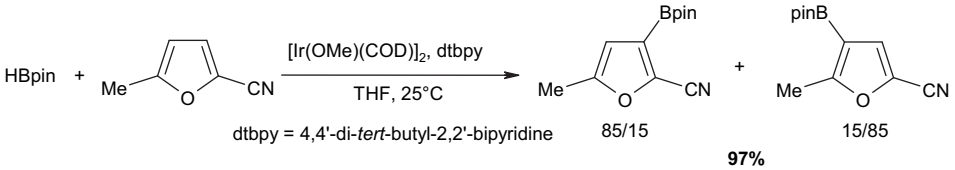
There are only few references concerning the synthesis and use of selenopheneboronic acids or esters. The first description of a boronic acid of selenophene was reported in 1971 by Morel et al..[36] They realized a halogen–metal exchange with *n*-butyllithium at −60 °C starting with 2-bromoselenophene. The rapid addition of tri-*n*-butyl borate followed by acidic hydrolysis led to 2-selenylboronic acid with a high yield (Scheme 22). Applying the same methodology on 3-bromoselenophene, the corresponding acid was obtained with 46% yield. A ^{1}H NMR study of these compounds was performed in the same year.[37]



Scheme 22.



Scheme 20.

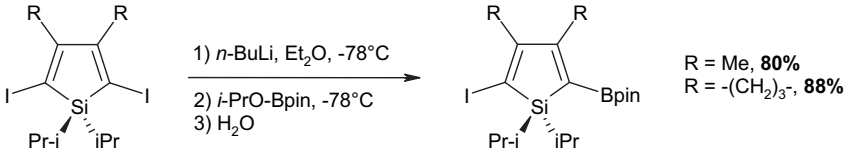


dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine

Scheme 21.

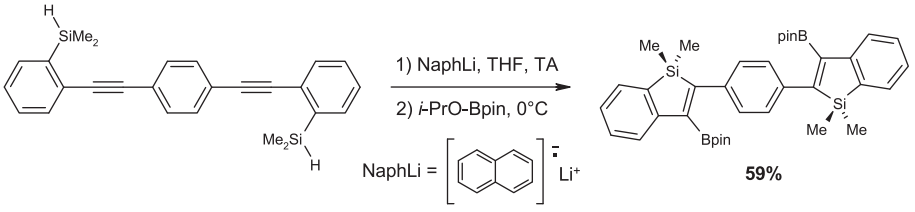
6. Silole

In 1998, Yamaguchi described the synthesis of boronic pinacol esters in the 2-position of siloles (or silacyclopentadienes) variously substituted using a halogen–metal exchange with *n*-butyllithium followed by a treatment with isopropoxypinacolborane (Scheme 23).[38] A patent was filed later in Japan by the same authors on the synthesis of these derivatives including boronic diacids in positions 2 and 5 of silole.[39]



Scheme 23.

Boronic esters in the 3-position of silole are only known on silaindene derivatives with the 2-position substituted. Their synthesis occurs by intramolecular cyclization of (*ortho*-silylphenyl)acetylene by the action of naphthyllithium and isopropoxypinacolborane as electrophile (Scheme 24).[40]



Scheme 24.

7. Imidazole

Imidazole possesses one NH group that needs to be protected if metalation conditions are used. The most frequently used protective groups are benzyl, methoxymethyl (MOM), 2-(trimethylsilyl)ethoxymethyl (SEM) and tetrahydropyranyl (THP).

7.1. Synthesis of boronic acids and esters in the 2-position of imidazole

To date, there is only one example of the preparation of a boronic ester in the position 2 of imidazole. A 2003 patent describes its synthesis by metal-catalyzed coupling borylation with palladium between 2-bromo-1-methylimidazole and B_2pin_2. The boronic ester so obtained was not further purified, the spectral data were not reported and it was directly engaged in the crude form in a Suzuki cross-coupling reaction with a very poor yield of 5% (Scheme 25).[41]

Scheme 25.

7.2. Synthesis of boronic acids and esters in the 5-position of imidazole

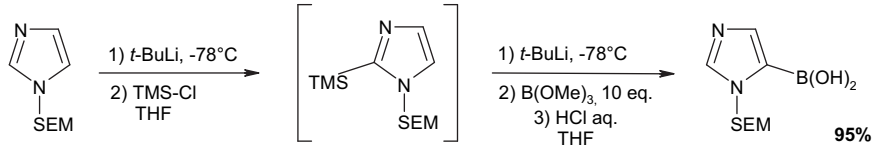
Early work dealing with imidazoleboronic acids dates from 1998. Han reported the synthesis of 1-SEM-imidazol-5-ylboronic acid by direct lithiation at the 5-position followed by trapping of the resulting anion with trimethyl borate.[42] It is necessary to ensure an efficient protection at the 2-position in order to complete the lithiation at C-5 because H-2 is more acidic than H-5 and reacts with strong bases. Han chose a temporary protection by performing a first lithiation on the 2-position followed by the action of trimethylsilyl chloride (TMS/Cl) to install a TMS group, thus allowing a second lithiation at C-5. The two successive lithiations were conducted without isolating the intermediates. The TMS group is finally cleaved after the boronation step by an acidic hydrolysis to provide the boronic acid in 95% yield (Scheme 26). A major drawback of this method is that it appears necessary to use 10 equiv of trimethyl borate in the boronation step.

In the same year, Kawasaki realized a lithiation of 1-SEM-2-thiophenylimidazole followed by the action of trimethyl borate. 2-Thiophenylimidazole-5-boronic acid was not isolated, but was directly engaged in a Suzuki cross-coupling reaction. The yield was poor without final deprotection (Scheme 27).[43]

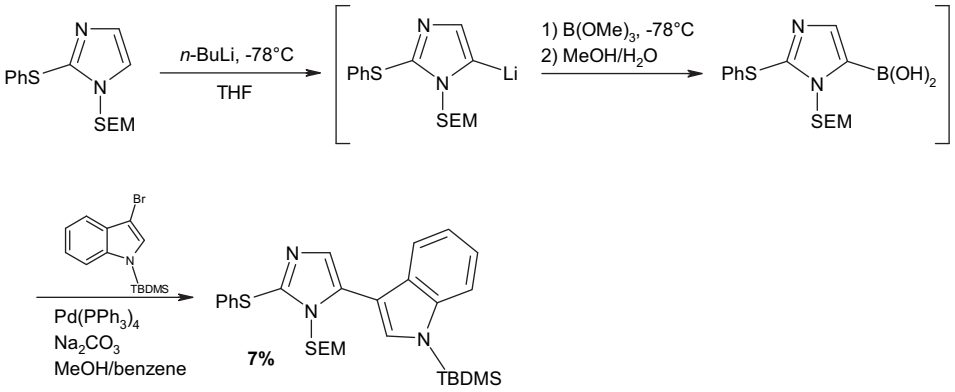
In 2008, starting again with an imidazole blocked at the 2-position by a thiophenyl group but, N-protected with a methoxymethyl (MOM) group, the sequence, lithiation/boronation/acidic hydrolysis, gave the boronic acid in 50% yield (Scheme 28).[44] This latter compound was then engaged in a variety of Suzuki cross-coupling reactions.

Direct borylation at the 5 position of 1-benzylimidazole and 1-methylimidazole variously substituted in position 2 was described by Smith's team (Scheme 29).[45] It must be pointed out that the position 2 was blocked with substituents.

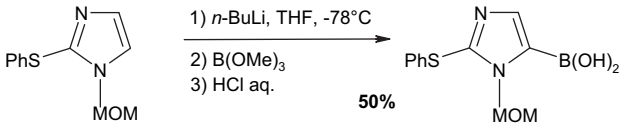
In 2008, Rault's team have described the access to *N*-THP-5-imidazolyl-boronic acid pinacol ester from 2-chloro-1-THP-imidazole[46] by using a lithiation/boronation sequence and then a dechlorination step by catalytic hydrogenation (Scheme 30).[47]



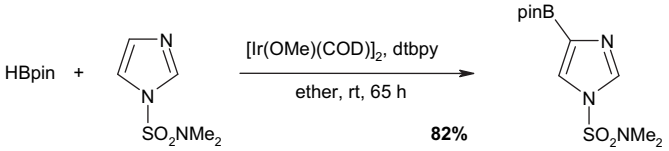
Scheme 26.



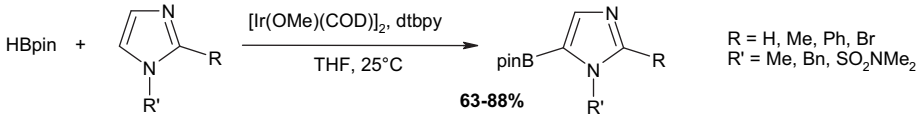
Scheme 27.



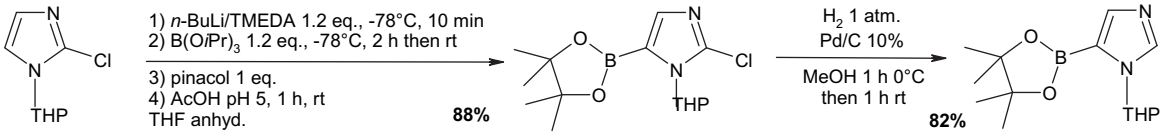
Scheme 28.



Scheme 32.



Scheme 29.



Scheme 30.

7.3. Synthesis of boronic acids and esters in the 4-position of imidazole

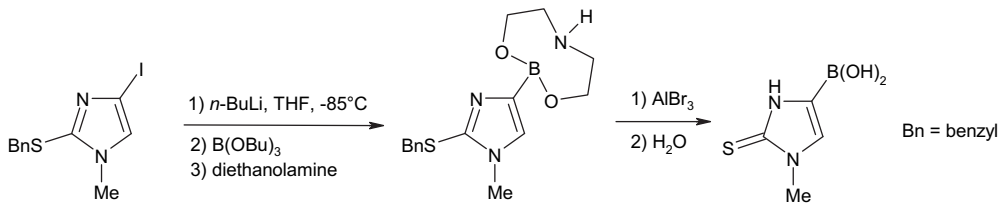
A halogen–metal exchange is performed on 4-iodo-1-methyl-2-thiobenzylimidazole with *n*-butyllithium followed by the action of tri-*n*-butyl borate and a final transesterification using diethanolamine gave the desired ester, which gave finally the 2-thioxoboronic acid by treatment with aluminum tribromide, which also cleaved the benzyl group (Scheme 31).[48] The yield of this reaction sequence is not specified.

It is noteworthy that, in several publications, several authors have used 4(5)-imidazolyl-boronic acid, but its synthesis has not been reported in the literature.[49]

8. Thiazole

8.1. Synthesis of boronic acids and esters in the 2-position of thiazole

There are only a few references that relate to derivatives in the boronic thiazole series. In one report, in 1998, Marcuccio described

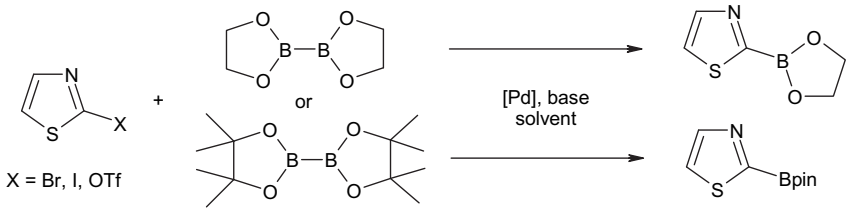


Scheme 31.

Recently, Smith's team have described the access to an *N*-protected imidazol-4-ylboronic ester via an Ir-catalyzed C–H direct borylation (Scheme 32).[14]

in a patent the access to thiazole-2-boronic acid pinacol or neopentyl glycol esters.[50] He only mentioned a palladium-catalyzed coupling reaction between a halogenated substrate and a tetraalkoxydiborane

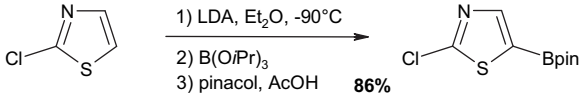
without details concerning the procedure and the boronic derivatives obtained (Scheme 33).



Scheme 33.

8.2. Synthesis of boronic acids and esters in the 5-position of thiazole

Stanetty has reported in 2006 a synthesis of 2-chlorothiazole-5-boronic pinacol ester, starting from 2-chorothiazole.[51] Because position-2 was blocked by a chlorine atom, there was no problem of regioselectivity during the lithiation done directly with LDA. The action of triisopropyl borate followed by a transesterification with pinacol led to the expected product in 86% yield (Scheme 34).



Scheme 34.

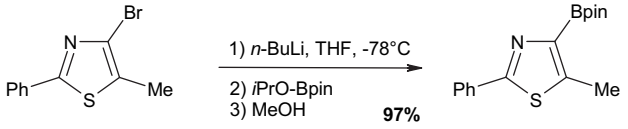
Stanetty only managed to synthesize the boronic ester and, indeed, the corresponding acid was found to be too sensitive and could not be isolated. Moreover, the work up procedure requires an anhydrous protocol to ensure satisfactory yields.[52]

This boronic ester has proved to be a poor coupling partner in the Suzuki reaction, despite various attempts to optimize the experimental conditions.

In 2009, Rault's team have performed the synthesis of thiazole-5-boronic acid, as well as its pinacol and neopentyl glycol esters.[53] A C-5 lithiation was carried out, starting from 2-trimethylsilylthiazole, followed by a boronation step using triisopropyl borate. Transesterification of the intermediate was achieved by treatment with pinacol followed by an adjustment of the pH to 5 using acetic acid. The reaction led directly to the corresponding stable pinacol ester of thiazole itself because the trimethylsilyl group was cleaved during the last stage of the work up. The neopentyl glycol ester is obtained in a similar fashion with a comparable yield. Without transesterification in the final stage, it is possible to isolate the thiazole-5-boronic acid with a moderate yield (Scheme 35).

8.3. Synthesis of boronic acids and esters in the 4-position of thiazole

Only one example of thiazol-4-ylboronic acid pinacol ester was published in 2007 by Nakashima. Starting from 4-bromo-2-phenyl-5-methylthiazole, he performed a halogen–metal exchange followed by the action of isopropoxypinacolborane. The boronic pinacol ester was obtained in excellent yield (Scheme 37).[54]



Scheme 37.

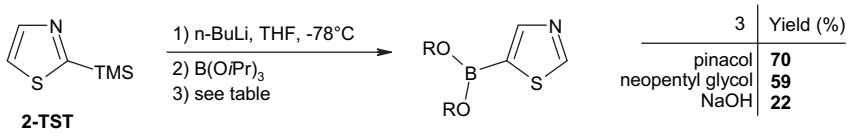
9. Oxazole

9.1. Synthesis of boronic acids and esters in the 2-position of oxazole

A 2005 Japanese patent deals with the synthesis of a boronic acid in the 2-position of the oxazole ring.[55] A lithiation in the 2-position was performed by LDA at −70 °C in THF on oxazole bearing an *n*-octyl group at the 4-position. Trimethyl borate was then added to trap the anion formed and a final acidic hydrolysis provided the corresponding boronic acid in 80% yield. This latter compound was engaged in a Suzuki cross-coupling reaction and yielded the coupling product in good yield (Scheme 38).

9.2. Synthesis of boronic acids and esters in the 5-position of oxazole

In 2008, Inoue described the synthesis of boronic acids in position 5 bearing diverse substituents (alkyl or aryl) at C-2 or C-4.[56]

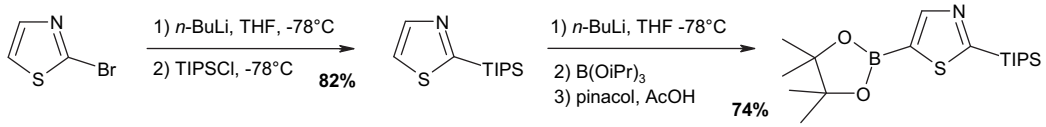


3	Yield (%)
pinacol	70
neopentyl glycol	59
NaOH	22

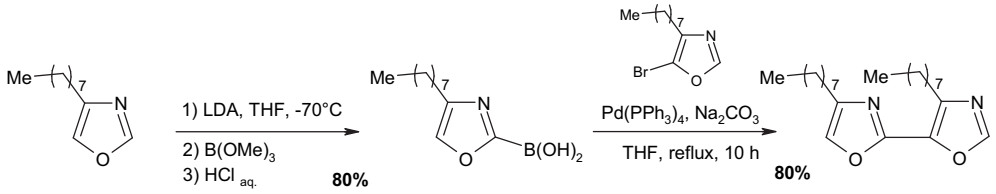
Scheme 35.

Contrary to the above results, starting from 2-TIPS-thiazole obtained from 2-bromothiazole, the silylated group is not cleaved during the lithiation process and it is possible to isolate in good yield the 2-TIPS-5-thiazoleboronic acid pinacol ester either by a boronation of 2-TIPS-thiazole via a direct metalation or via a halogen–metal exchange of 5-bromo-2-TIPS-thiazole, itself obtained from 2-TIPS-thiazole (Scheme 36).

The boronic acids or esters are synthesized either by direct lithiation at −15 °C in THF or by bromine–lithium exchange at −78 °C, followed by the action of a trialkyl borate. Hydrolysis with acetic acid or transesterification with a diol derivative provided the corresponding acid or ester. Some derivatives are also obtained by



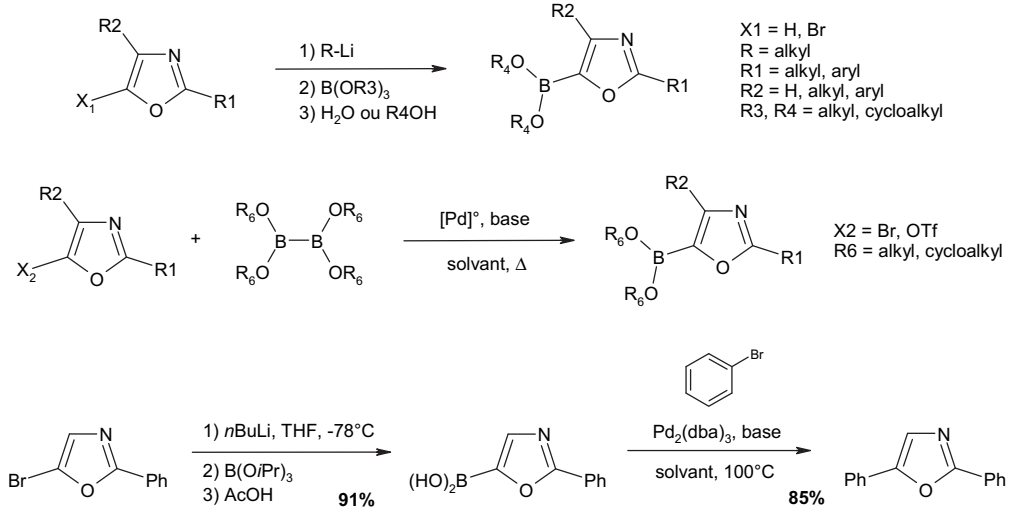
Scheme 36.



Scheme 38.

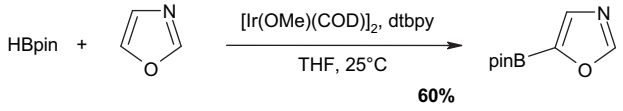
metal-catalyzed coupling with palladium with tetraalkoxydiborane as B_2pin_2. These boronic derivatives are satisfactorily engaged in Suzuki cross-coupling reactions with 30–89% yield (Scheme 39).

When this boronic ester was engaged in a Suzuki cross-coupling reaction, the 2-TIPS protecting group was cleaved during the reaction, affording directly the 5-aryloxazole (Scheme 42).



Scheme 39.

The same year, Smith described in a patent 5-oxazolylboronic acid pinacol ester using his C–H activation method, as he had applied to imidazole derivatives (Scheme 40).[45]



Scheme 40.

Flynn has used this boronic ester as a partner in a Suzuki cross-coupling reaction.[57] The yield, however, was not specified.

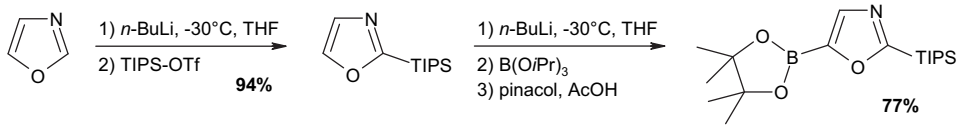
Rault et al. have recently reported the synthesis of 2-TIPS-5-oxazolylboronic acid pinacol ester by using a lithiation/boronation/transesterification sequence in a good overall yield.[58] The boronic acid so prepared is unstable, is rapidly degraded at room temperature and must therefore be prepared and used extemporaneously (Scheme 41).

9.3. Synthesis of boronic acids and esters in the 4-position of oxazole

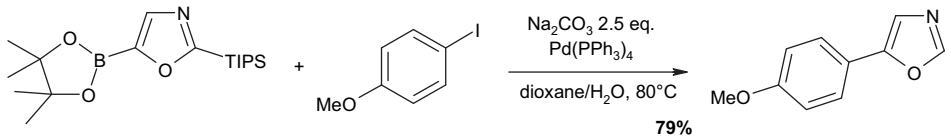
The first examples of the synthesis of 4-oxazolylboronic acid pinacol esters were described in 2006 by Araki, either by direct borylation via a metal-catalyzed coupling reaction of 2-phenyl-4-[(trifluoromethyl)sulfonyl]oxazole with B_2pin_2 or by performing a sequence lithiation/boronation/transesterification via a halogen–metal exchange starting from 4-bromo-5-methyl-2-phenyloxazole (Scheme 43).[59] This whole procedure and the synthesized compounds have been patented in 2007.[60]

10. Pyrazole

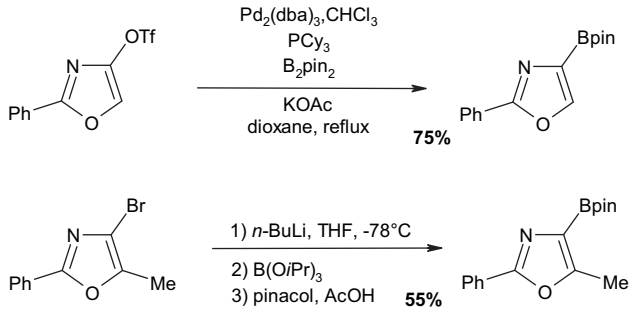
In 1962, Matteson was the first to obtain pyrazolylboronic acids by 1,3-dipolar cycloaddition between diazo compounds and akyl alkynylboronates.[61] Thus, ethyl diazoacetate and dibutyl ethynylborate react slowly via a [3+2] cycloaddition leading, after a final



Scheme 41.



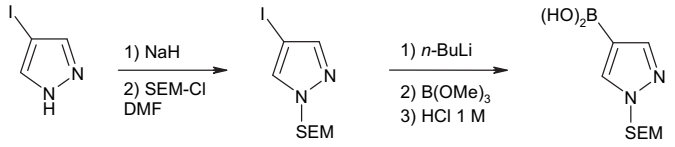
Scheme 42.



Scheme 43.

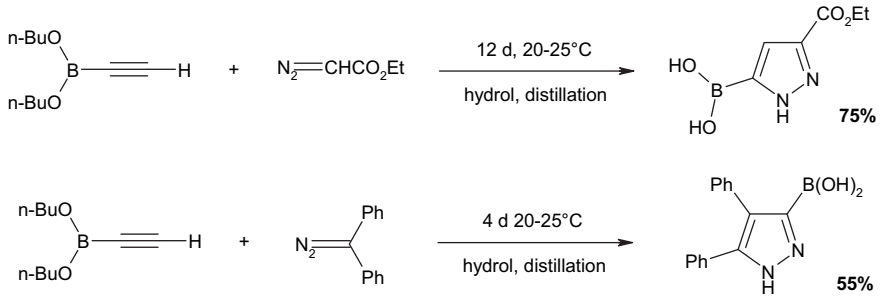
hydrolysis, to 3-carbethoxypyrazol-5-ylboronic acid. Diazomethane is too reactive and decomposes instantly in contact with the boronate derivative. However, diphenyldiazomethane reacts with dibutyl ethynylborate and provides 4,5-diphenylpyrazol-3-ylboronic acid after hydrolysis (Scheme 44).

This coupling method has been re-used by Cosford starting from 3-(4-bromo-1*H*-pyrazol-1-yl) benzonitrile and B_2pin_2 without a specified yield.[64] The following year, Wendt et al.[65] synthesized *N*-SEM-pyrazol-4-ylboronic acid by performing a halogen–metal exchange from *N*-SEM-4-iodopyrazole followed by the action of trimethyl borate and a final acidic hydrolysis. However, the operating conditions and the yield were not communicated (Scheme 47).



Scheme 47.

Ivachtchenko and his team have conducted numerous studies on the synthesis of *N*-substituted-pyrazole-4-boronic acids and esters via lithiation reactions.[66] Thus, at very low temperature (−80 to −90 °C), only the lithio derivative in the 4-position is obtained. It

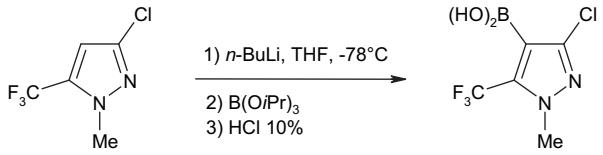


Scheme 44.

Although very little work has been published concerning the pyrazole series between 1962 and 2000, the number of references has considerably increased since 2000, confirming the interest of the chemical community in these molecules.

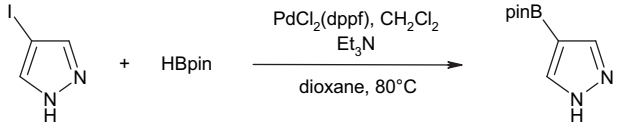
10.1. Synthesis of boronic acids and esters in the 4-position of pyrazole

In 1994, Chupp synthesized 3-chloro-5-trifluoromethyl-1-methylpyrazole-4-boronic acid by a direct ortholithiation in the 4-position (Scheme 45). The yield of this synthesis was not, however, communicated.[62]



Scheme 45.

In 2000, Marcuccio et al. synthesized 1*H*-pyrazole-4-boronic acid pinacol ester using a palladium-catalyzed coupling between 4-iodopyrazole and HBpin in the presence of triethylamine. Again, the yield of the reaction was not specified (Scheme 46).[63]



Scheme 46.

is trapped by trimethyl borate to yield the corresponding boronic acid after final hydrolysis. At higher temperatures (−45 to −50 °C), this reaction leads to mixtures (Scheme 48).

The same team found that the boronic acids were less stable than the corresponding pinacol esters. For this reason, the acids were converted into pinacol esters in the presence of the diol and molecular sieves in 70–90% yield (Scheme 49).

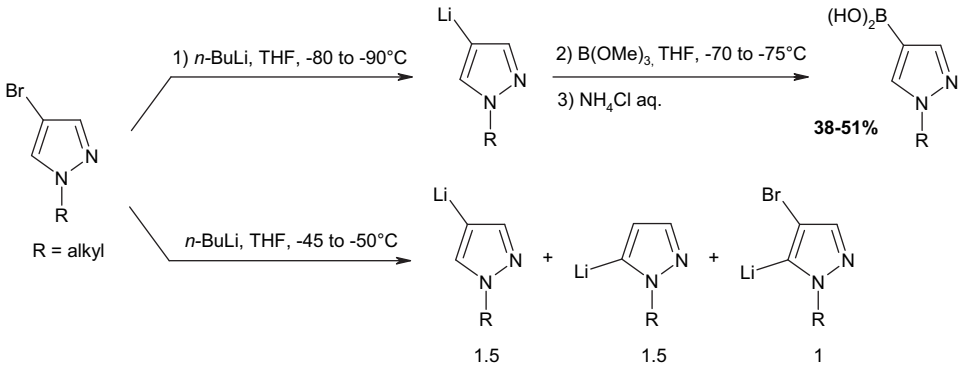
In 2007, Browne et al.[67] described the access to pyrazole-4-boronic acid pinacol ester by a cycloaddition between sydnones and alkynylboronates. The reaction occurred by heating to reflux the two components in-high-boiling point non-polar solvents like mesitylene, dichlorobenzene or xylenes. With carbon/unsubstituted sydnones, the reaction was quasi-regioselective with the phenylacetyleneboronic pinacol ester and gave the 1-methyl-3-phenyl pyrazole-4-boronic acid pinacol ester with a satisfactory yield; in other cases, this reaction gave mixtures of isomers. With carbon substituted sydnones, the cycloaddition takes place in 59–75% yield, depending on the acetylenic derivative and the sydnone substituents (Scheme 50).

In 2008, Gutierrez and his team have synthesized via a metal-catalyzed coupling 3-methylpyrazole-4-boronic acid pinacol ester in 70% yield, starting from the corresponding 4-iodopyrazole (Scheme 51).[68]

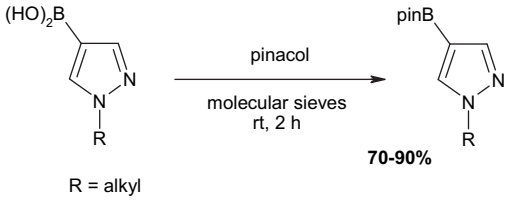
Recently, Smith et al. have described the synthesis of *N*-Boc-pyrazol-4-ylboronic ester through a direct borylation reaction (Scheme 52).[14] The protecting group could be cleaved by thermal deprotection, affording the pyrazol-4-ylboronic pinacol ester in good yield.

10.2. Synthesis of boronic acids and esters in the 5-position of pyrazole

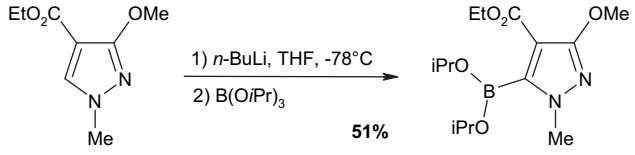
In 1998, Han described the synthesis of 1-SEM-pyrazole-5-boronic acid from *N*-SEM protected pyrazole via a lithiation/



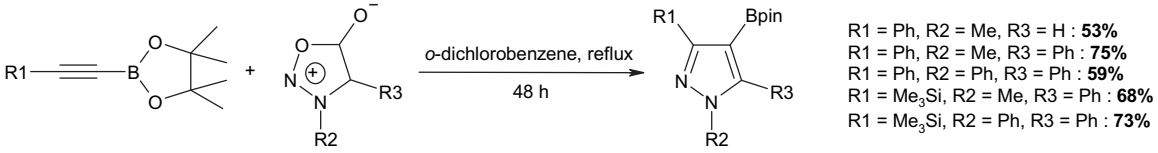
Scheme 48.



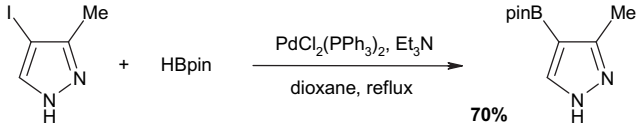
Scheme 49.



Scheme 54.



Scheme 50.

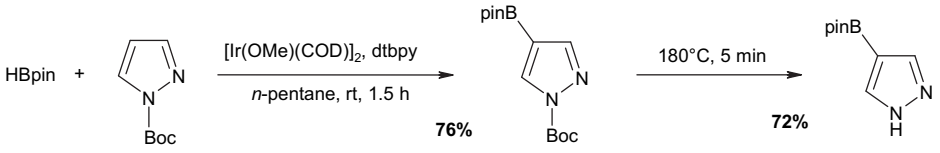


Scheme 51.

protecting group is cleaved during the final acid hydrolysis. The resulting yield remained modest (Scheme 55).[70]

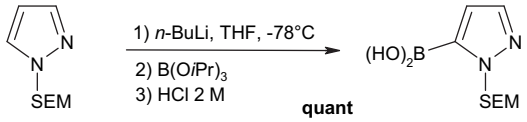
Ivachtchenko has also synthesized by lithiation some 1-alkyl-pyrazol-5-ylboronic acids and esters and studied their stability (Scheme 56).[66]

Rault's team synthesized *N*-SEM-pyrazole-5-boronic acid.[71] Facing the difficulties of purifying this acid, it was recommended to prepare and use its pinacol ester. The same team has also syn-



Scheme 52.

boronation sequence. The final acidic hydrolysis provided the expected boronic acid with a quantitative yield (Scheme 53).[42]



Scheme 53.

In 2002, Cottineau described the synthesis of a 1,3,4-tri-substituted-pyrazole-5-boronic ester by a direct ortholithiation reaction followed by a boronation step using triisopropyl borate (Scheme 54).[69]

Later, Young et al. published the synthesis of the pyrazole-5-boronic acid, starting from the *N*-THP-protected pyrazole. The THP

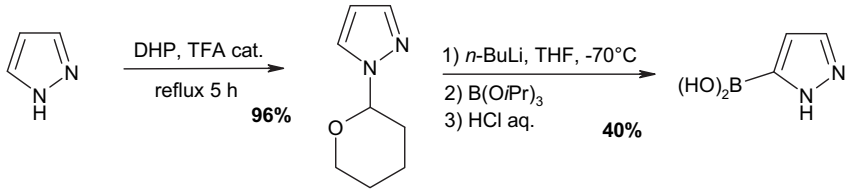
thesized with excellent yield the 1-THP-pyrazol-5-ylboronic acid pinacol ester (Scheme 57).

Smith has patented the access, by iridium-catalyzed direct borylation, to 4-bromo-1-methylpyrazole-5-boronic acid pinacol ester in 68% yield, starting from 4-bromo-1-methylpyrazole (Scheme 58).[45]

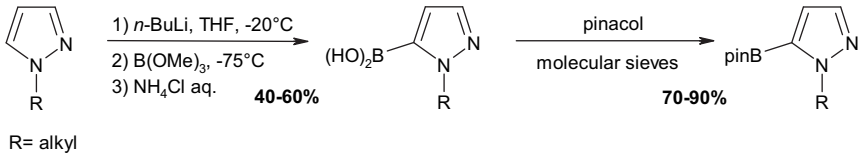
Very recently, Harrity et al. have published the synthesis of a pyrazol-5-ylboronic pinacol ester via a halogen–metal exchange reaction. This boronic ester was isolated in 60% yield (Scheme 59).[72]

11. Isothiazole

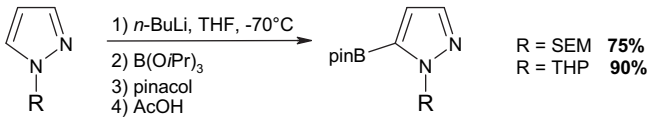
There are only a few references concerning isothiazole boronic derivatives and nothing is known about those with boronic acid in the 3-position to date.



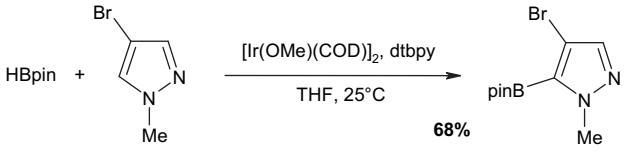
Scheme 55.



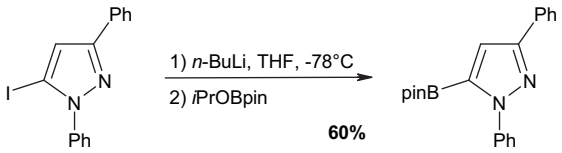
Scheme 56.



Scheme 57.



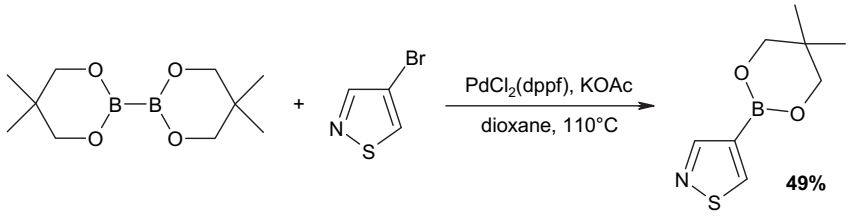
Scheme 58.



Scheme 59.

11.1. Synthesis of boronic acids and esters in the 4-position of isothiazole

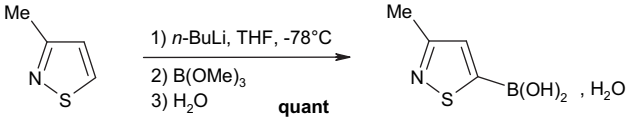
Only one patent refers to an isothiazol-4-ylboronic acid neopentylgycol ester. This boronic ester is obtained in 49% yield by a metal-catalyzed coupling between the corresponding tetraalkoxydiborane and the 4-bromoisothiazole in the presence of $PdCl_2$(dppf) and potassium acetate in dioxane (Scheme 60).[73]



Scheme 60.

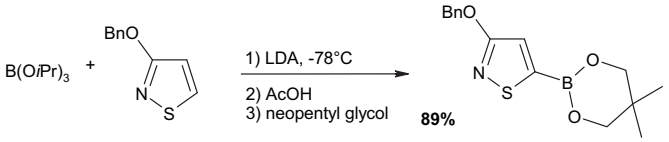
11.2. Synthesis of boronic acids and esters in the 5-position of isothiazole

Collins reported in 1998, the synthesis of an isothiazole-5-boronic acid by using an ortholithiation reaction on 3-methylisothiazole with the action of *n*-BuLi, followed by trapping the anion with trimethyl borate. A final hydrolysis led to the boronic acid hydrate with a quantitative yield (Scheme 61).[74]



Scheme 61.

In 2004, Kaae and his team have also described, via a lithiation, the synthesis of an isothiazole-5-boronic acid obtained from the 3-benzyloxyisothiazole.[75] The starting material is added to a solution of LDA and triisopropyl borate in ether at −78 °C. The temperature then rose to room temperature and, finally, acetic acid and neopentyl glycol are added successively. After treatment, the boronic ester is isolated in 89% yield (Scheme 62).



Scheme 62.

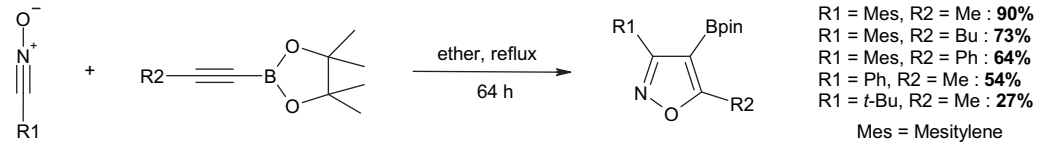
12. Isoxazole

As for isothiazole, boronic derivatives in the 3-position are not known. The references on isoxazole, however, outnumber those on its sulfur counterpart.

12.1. Synthesis of boronic acids and esters in the 4-position of isoxazole

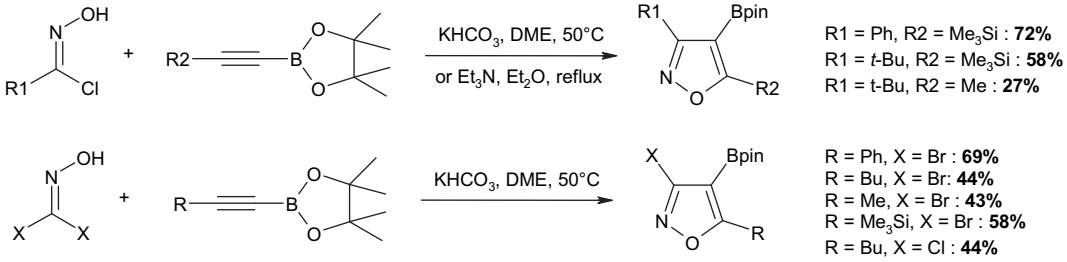
The first isoxazole-4-boronic esters have been described by Davies et al. via a [3+2] cycloaddition between alkynylboronic

esters and nitrile *N*-oxides.[76] The reaction is regiocontrolled, depending on the nature of alkynylboronic esters used. Indeed, if a terminal alkyne is used, the cycloaddition leads mainly to the isoxazole-5-boronic ester (see next Section 12.2), while substituted alkynes lead to isoxazol-4-ylboronic esters (Scheme 63).



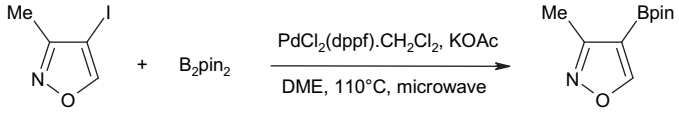
Scheme 63.

This team has also worked on the same type of cycloaddition, but using iminoyl halides as substrates in the presence of base (Scheme 64).[77]



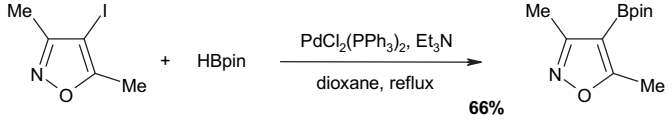
Scheme 64.

A 2008 patent reported the synthesis of the 3-methylisoxazole-4-ylboronic acid pinacol ester by a metal-catalyzed coupling from the corresponding 4-iodo substrate and B_2pin_2.[78] The spectral characteristics of this boronic ester are not mentioned, however, and it was directly engaged in a Suzuki coupling without details concerning the result (Scheme 65).



Scheme 65.

The same year, Gutierrez and his team have also described, by palladium coupling, the synthesis of 3,5-dimethylisoxazole-4-boronic acid pinacol ester in 66% yield using HBpin the a source of boron (Scheme 66).[68]



Scheme 66.

12.2. Synthesis of boronic acids and esters in the 5-position of isoxazole

In 1966 Bianchi has described the access to 3-arylisoxazol-5-ylboronic acid by a cycloaddition of arylnitrile *N*-oxides with acetylene dibutyl boronate (Scheme 67).[79] Access to 5-boronic derivatives of isoxazole cannot be achieved via a halogen–metal exchange, because it is not possible to obtain the Grignard reagent from 5-halogeno isoxazoles.[80]

In 2001, Davies has re-investigated this work by studying the regioselectivity of the cycloaddition reaction.[76] As mentioned in the previous section, substituted alkylnylboronates lead to the formation of isoxazol-4-ylboronic esters. With terminal alkylnylboronates, as already shown by Bianchi,[79] the cycloaddition led to isoxazol-5-ylboronic derivatives. A non-negligible proportion of the 4-isomer is formed (Scheme 68), however, and the separation of these isomers is possible by chromatography on silica gel.

Sáez and his team have conducted a theoretical study on the regioselectivity of 1,3-dipolar cycloadditions between alkynylboronates and nitrile *N*-oxides.[81] Davies et al.[76] and Moore et al.[77] also performed the cycloaddition of terminal alkynylboronates with iminoyl chlorides (Scheme 69).

13. Triazole

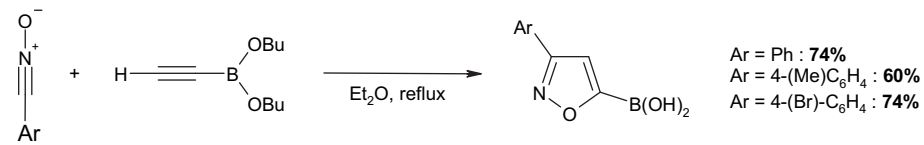
There is currently only one reference describing triazole boronic derivatives, either on 1,2,3-or on 1,2,4-triazole.

13.1. Synthesis of boronic acids and esters in the 4-position of 1,2,3-triazole

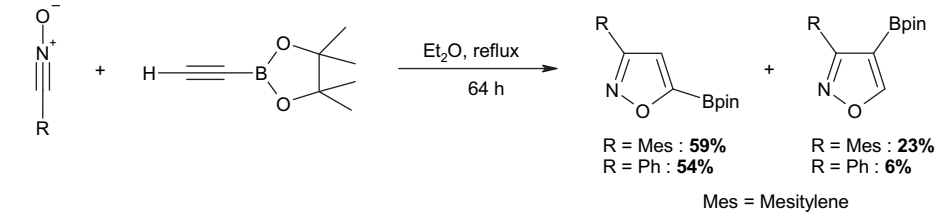
Recently, Harrity et al. have published the synthesis of 1,2,3-triazole boronic esters by thermal cycloaddition of alkylnylboronates with azides.[82] They have shown that a trimethylsilylalkyne boronic derivative underwent a cycloaddition with benzyl azide by heating the two components in dichlorobenzene at 150 °C for 24 h, leading to the corresponding triazole as a single regioisomer in a very good yield. They noted a significant difference in the regioselectivity and product stability, however, depending on the nature of the starting alkynylboronates nature (Scheme 70).

Finally, in order to overcome this stability problem, the authors have developed a sequential cycloaddition-Suzuki cross-coupling reaction without isolation of the sensitive triazole boronic species. In this way, they prepared a library of trisubstituted triazoles.

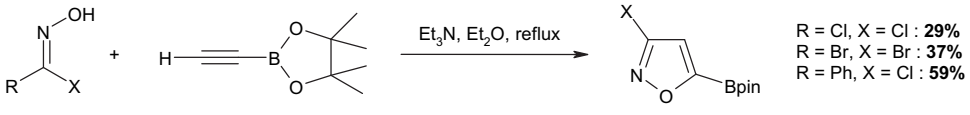
Very recently, Gérard during her thesis, worked on the synthesis of such derivatives in Rault's team.[83] The first step was the protection



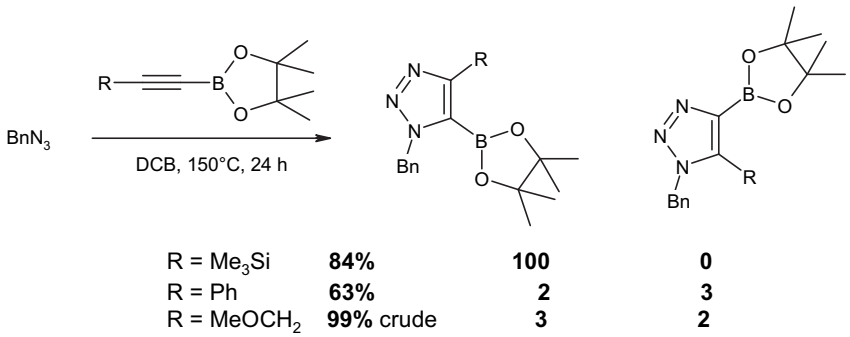
Scheme 67.



Scheme 68.

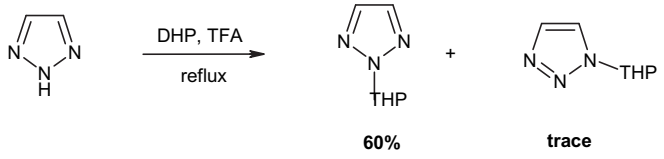


Scheme 69.



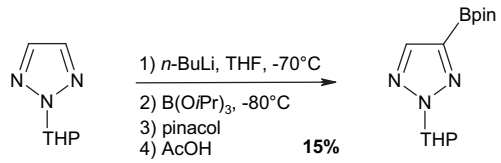
Scheme 70.

of 1,2,3-triazole. Thus, the action of dihydropyran in the presence of a catalytic amount of trifluoroacetic acid on the triazole leads mainly to 2-THP-2*H*-1,2,3-triazole in 60% yield. The isomer protected in the 1-position is only produced in trace amounts (Scheme 71).



Scheme 71.

The 2-THP-triazole is then engaged in a direct ortholithiation reaction with *n*-BuLi at −70 °C and the lithio intermediate is trapped by triisopropyl borate at −80 °C. The transesterification is carried out at 0 °C by pinacol and acetic acid to lead in 15% yield to the expected 2-THP-1,2,3-triazol-4-ylboronic acid pinacol ester (Scheme 72). The structure of this new boronic ester was confirmed by an X-ray crystallography diffraction study.



Scheme 72.

All attempts to perform Suzuki cross-coupling reactions using this boronic ester of triazole have been unsuccessful to date.

13.2. Synthesis of boronic acids and esters in the 3-position of 1,2,4-triazole

1,2,4-Triazole has been protected in the same manner as above in quantitative yield, leading to the 2-THP-2*H*-1,2,4-triazole. Despite several attempts at a lithiation/boronation sequence, no boronic species could be isolated.[83]

14. Synthesis of boronic acids and esters of thiadiazoles

A 1997 patent mentions 1,2,5-thiadiazole-4-boronic acid, but, after reading the procedure, it appears that the authors have synthesized an organozinc derivative, which is not described and directly involved in a Negishi coupling.[84] These authors have extended the same procedure to 5-phenyl-[1,2,4]thiadiazol-3-ylboronic acid, which turns out, after reading the patent, also to bean organozinc compound.[85] Finally, in neither of these patents are boronic thiadiazole actually described.

15. Synthesis of boronic acids and esters of oxadiazoles

To the best of our knowledge, no syntheses of oxadiazole boronic derivatives have been reported to date. The 5-methyl-[1,2,4]-oxadiazol-3-ylboronic acid is cited in a publication to be engaged in a Suzuki cross-coupling reaction, but it is more likely that it was the corresponding stannane that was used. No details are provided in the publication of the substrate used.[86]

16. Synthesis of boronic acids and esters of tetrazole

To the best of our knowledge, no syntheses of tetrazole boronic derivatives have been reported to date. Yi and Yoo had tried in vain to obtain tetrazol-5-ylboronic acid from 1-benzyltetrazole.[87] Gérard also tried lithiation/boronation sequences on the *N*-THP- or *N*-benzyl-protected tetrazole or direct lithiation by lithium–iodine exchange with no satisfactory results so far.[83]

17. Conclusions

Many boronic acids and esters are now well known in the five-membered heterocyclic series. Their syntheses are very varied,

depend on the reactivity of their supports and often require the introduction of protective groups on nitrogen or carbon atoms. Their stability and their reactivity are also variable, although a great majority of them can be engaged in metallo-catalyzed cross-coupling reactions and this ability makes them of great value to constitute new heterocyclic libraries of interest in medicinal chemistry.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.001.

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Biographical sketch

Nicolas Primas was born in Lorient, France, in 1983. He received his Master's research degree in 2006 from the Institute of Pharmaceutical Chemistry Albert Lespagnol at the University of Lille. He performed a training course under the supervision of Prof. Sylvain Rault at the University of Caen Lower-Normandy in order to synthesize new tetracycles via cyclization reactions from 3-amino-β-carboline. He completed his Ph.D. degree under the supervision of Prof. Sylvain Rault in the same laboratory (2006–2009), where he developed the synthesis of new boronic acids and esters in the imidazole, thiazole, and oxazole series. He also studied their reactivity toward the Suzuki cross-coupling reaction in order to produce 5-aryl-1,3-azole libraries.

Sylvain Rault was born in Casablanca, Morocco, in 1950. He studied pharmacy at the Faculty of Pharmacy of Caen (France). After receiving his 'Diplôme d'Etat de Pharmacien' in 1975 he was awarded the position of lecturer at the University of Caen. He completed his 'Thèse d'Etat' in Organic Chemistry at the Faculty of Sciences of the same university in 1982 under the supervision of Prof. Noël Lozac'h and then performed postdoctoral studies with Prof. Max Robba. He obtained the position of assistant professor of medicinal chemistry in 1986 in Caen and then left this university to work in Paris at the Ministry of Environment. For a period of two years, he was in charge of the file on the protection of the ozone layer. Upon his return to his lab, he pursued research activities in the field of heterocyclic chemistry. He was subsequently appointed professor in 1988, Dean of Faculty (1988–1998) and Director of CERMN in 1998. He is currently professor of 'classe exceptionnelle'. He has directed more than 50 Ph.D. students and is co-author of more than 300 international articles. His research interests are mainly in the field of medicinal chemistry and drug design, new methodologies in heterocyclic chemistry, creation, and development of new chemical libraries, and exploration of new areas in the chemical space.

Alexandre Bouillon was born in France in 1976. His undergraduate research concerned the oxidation of β-cyclodextrin and aldehyde synthesis. In 1999, he joined Wirzbicki's team where he developed new methodologies for the synthesis of 2-(2-halomethylphenyl)-acetonitriles or use in polycyclic construction. In the same year, he obtained his Engineering degree from the National Institute of Applied Sciences (Rouen, France). He joined Rault's team in 2000, were he obtained his Ph.D. degree in therapeutic chemistry from the University of Caen on the design, synthesis, and physico chemical study of boronic acids and esters of nitrogen-containing heterocycles. He received an award from the National Academy of Pharmacy for the excellence of his research works. In 2005, Dr. Bouillon founded BoroChem. This company is involved in many research programs dealing with the design and synthesis of novel boronated compounds. His collaborations with Dr. Carboni, Prof. Molander and Prof. Rault have the same goal: to obtain a better understanding of boronated compounds and to make them available for all chemists.