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ScienceDirect
Tetrahedron 64 (2008) 4596–4601
Tetrahedron
www.elsevier.com/locate/tet

A new boronic-acid based strategy to synthesize 4(5)-(het)aryl-1*H*-imidazoles

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Received 24 January 2008; received in revised form 25 February 2008; accepted 3 March 2008
Available online 7 March 2008

Abstract

This paper describes the synthesis of a new *N*-THP protected 5-(1*H*)-imidazolyl boronic acid pinacol ester and its use in Suzuki cross-coupling reactions with a wide range of (het)aryl halides to provide 4(5)-(het)aryl-1*H*-imidazoles.

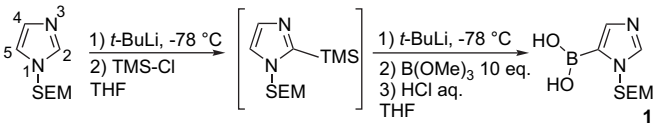
Keywords: Imidazole; Boronic ester; *N*-THP-protecting group; Suzuki cross-coupling; Aryl halides

1. Introduction

In the last decade, very much attention has been paid to the development of efficient methods for the preparation of 4(5)-aryl substituted imidazole derivatives because of their important biological and pharmacological properties. A recent review of Bellina et al.[1] reported biological properties such as antifungal activity,[2] potent β-glucosidase[3] or activin receptor-like kinase 5 (ALK5) inhibitors.[4] Relatively few methods to access the title compounds are described. Heerding et al.[5a] have described the cross-coupling reaction of 3-thienylboronic acid with 4(5)-iodoimidazole and very recently, Bellina et al.[5b] have studied the Suzuki cross-coupling reaction of 4(5)-bromoimidazole with various arylboronic acids. They obtained good yields of the expected coupling products from chloro-, methoxy- and methylenedioxy-substituted phenylboronic acid. But, they specified that this method was not effective in the presence of sensitive groups as the formyl one, for example. Sames et al.[5c] have described a C–H direct arylation of SEM-imidazoles with palladium complexes of imidazolylcarbenes. We wish to present herein a reverse methodology with a possible broader scope, which consists preparation of 4(5)-imidazolylboronic acid derivatives and use of them in Suzuki–Miyaura cross-coupling reactions towards a wide range of (het)aryl halides.

2. Results and discussion

To our knowledge, only one article relates the synthesize of an imidazolylboronic acid: 1-SEM-1*H*-imidazolyl-5-boronic acid **1** (Scheme 1), which has been engaged in one cross-coupling reaction with a bis-iodobenzyldihydroxydiazepindione with a low yield.[6] In our hands, this method, which used an expensive protecting group and required 10 equiv of trimethylborate was not applicable to produce great quantities of imidazole derivatives.



Scheme 1.

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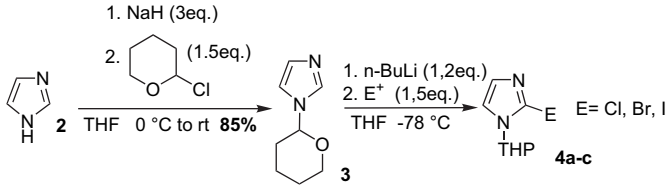
doi:10.1016/j.tet.2008.03.008

In order to improve this result, we took into account our previous work in the pyrazole series[7] in which we showed that tetrahydropyran-2-yl (THP) was an excellent pyrazole *N*-protecting group to prepare boronic acid derivatives. This *N*-protecting group was stable under Suzuki cross-coupling conditions and was then easily cleaved under acidic conditions. These good results led us to apply this methodology in imidazole series.

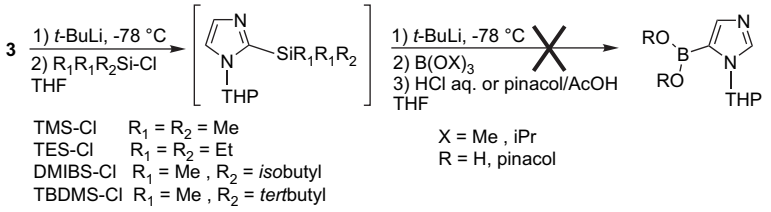
For the synthesis of the starting 1-THP-imidazole **3**, we have applied[8] the conditions described by Manfredini et al.[9] The imidazole sodium salt was treated with 2-chloro-THP[10] in THF to give **3** in good yield (Scheme 2). In a previous paper,[8] we have shown that the lithiation reaction using *n*-BuLi and an electrophile takes place at the C-2 position as for the SEM one. We easily prepared 2-halogeno-1-THP-1*H*-imidazoles **4a–c**.[8] Nevertheless, when we tried to apply the strategy of Han et al.,[6] who introduced temporarily a trimethylsilyl group at C-2 with the first lithiation of *N*-SEM-imidazole and who carried out a second lithiation at C-5 with *tert*-butyllithium followed by the action of trimethylborate to afford **1**, all our attempts conducted from 1-THP-imidazole **3** failed, and no boronic species were isolated. Carpenter and Eriksen[11,12] have reported that TMS group is very labile in imidazole series, and in our case the *N*-THP-protecting group probably still increases this instability. All the other attempts with triethylsilyl (TES),[13] dimethylisobutyl (DMIBS) or *tert*-butyldimethylsilyl group (TBDMS) also failed (Scheme 3).



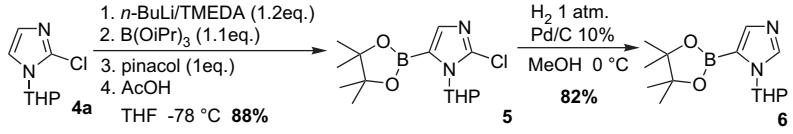
Scheme 2.

These failures prompted us to adapt the method of Begtrup,[12] which used a chlorine atom to protect the position 2 of *O*-benzyl imidazole *N*-oxide before lithiation in position 5. Starting from 2-chloro-1-THP-imidazole **4a**, a lithiation using the complex *n*-BuLi/TMEDA was carried out at −78 °C to afford 5-lithioimidazole, which was slowly quenched at −78 °C with 1.1 equiv of triisopropyl borate to give lithium isopropoxyborate, which was finally in situ transesterified using pinacol in the presence of acetic acid[14] to give the new 2-chloro-1-THP-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-imidazole **5** in 88% yield (Scheme 4). This latter transesterification was absolutely necessary to obtain a stable boronic species. Indeed a simple acidic hydrolysis did not permit to isolate the corresponding boronic acid, which seems to be very instable. To complete our study, it was necessary to remove the chlorine atom of **5** preserving the boronic ester and the THP-protecting group. After several attempts, this result was obtained by dehalogenation with Pd/C under 1 atm of hydrogen in methanol after 1 h at 0 °C and followed by another 1 h at room temperature. The new 1-THP-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-imidazole **6** was obtained in a very good yield as a stable white solid (Scheme 4). For **5** and **6**, we have not yet founded the conditions to remove the *N*-THP group while preserving the boronic ester.

Considering that THP was stable under Suzuki conditions,[7] **6** was engaged with 4-iodoanisole under standard Suzuki cross-coupling reaction conditions (DME/H_2O, K_2CO_3 2 equiv, boronic ester 1.1 equiv, halide 1 equiv, $Pd(PPh_3)_4$ 0.05 equiv),[15] but this reaction was unsuccessful. This ester being prone to deboronation.[16] We studied this side reaction and we found that the boronic ester in the presence of water and mineral base such as K_2CO_3 or $NaHCO_3$ (2 equiv) in DME was completely deboronated after 3 h at 90 °C. As a result of the instability of **6** under aqueous conditions, a water-free cross-coupling protocol was required. We initially tested K_3PO_4 in dry DMF at 90 °C with $Pd(PPh_3)_4$ (5 mol %) and 2 equiv of **6**. This reaction afforded the expected compound **7c** with a low yield (ca. 40%). The use of microwave assisted Suzuki cross-coupling[17] reactions provided a lot of by-products (deboronation, homocoupling leading to difficulties to purify the mixture). Fortunately, we finally found that CsF (2.5 equiv) as base, CuI (0.1 equiv) as co-catalyst[18] and boronic ester (1.1 equiv) in dry DMF at 90 °C were the best conditions, giving the expected **7c** with 66% yield (Table 1, Scheme 5). The use of $PdCl_2$(dppf) (0.05 equiv) instead of $Pd(PPh_3)_4$ did not increase the yield (35%).



Scheme 3.



Scheme 4.

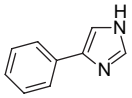
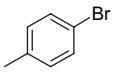
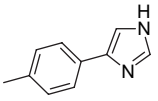
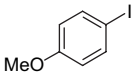
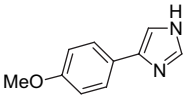
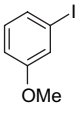
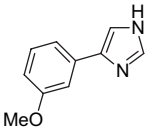
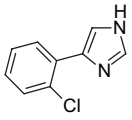
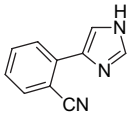
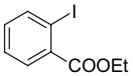
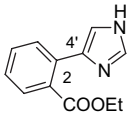
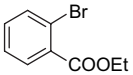
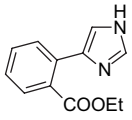
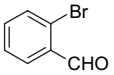
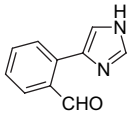
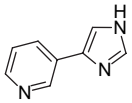
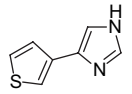
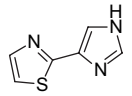
Table 1
Cross-coupling reaction optimization with 4-iodoanisole

Base (equiv)	Solvent	Heating	Yield[a] (%)
K_2CO_3 or $NaHCO_3$ (2)	DME/H_2O, 3/2	Oil bath, 90 °C, 6 h	0
K_3PO_4 (2)	DMF	Oil bath, 90 °C, 6 h	40
CsF (2.5), CuI 10%	*DMF*	*Oil bath, 90 °C, 12 h*	*66*
CsF (2.5), CuI (0.1)	Dioxane	Oil bath, 90 °C, 12 h	<10
CsF (2.5), CuI (0.1)	DMF	Micro-waves, 130 °C, 30 min	31

[a] Isolated yields were calculated after cross-coupling reaction.

The best conditions were applied to a range of (het)halides providing 1-THP-5-arylimidazoles **7**. Vis-a-vis some difficulties to isolate **7** by column chromatography, we preferred to carry out the final deprotection without purification at this stage. The THP cleavage was obtained by treatment with ethanol or dioxane (for entries **f** and **h**) HCl solution at reflux temperature for 45 min.[19] The resulting 4(5)-(het)arylimidazoles **8a–j** were isolated in good yields after an easy purification through silica gel chromatography using dichloromethane/methanol as eluent. The results summarized in Table 2 show that even in the presence of fragile groups (entries **f–h**), compound **6** is able to couple either with (het)aryl iodides or bromides. The results are, nevertheless, better with iodo derivatives. We chose to write the molecules **8a–c** as 4-arylimidazoles according to the X-ray radiocrystallographic analysis of **8g**, which clearly shows that it exists in this form in the solid state.[22]

Table 2
Cross-coupling reaction–deprotection sequence

Ar–X		Product	Yield[a] (%)
	**8a**		35
	**8b**		20
	**8c**		58
	**8d**		37
	**8e**		48
	**8f**		37
	**8g**		57
	**8g**		33
	**8h**		39
	**8i**		21
	**8j**		26
	**8k**		34

[a] Isolated yields were calculated after cross-coupling reaction and deprotection (**8g**, **8h** and **8k** are not yet described in the literature).

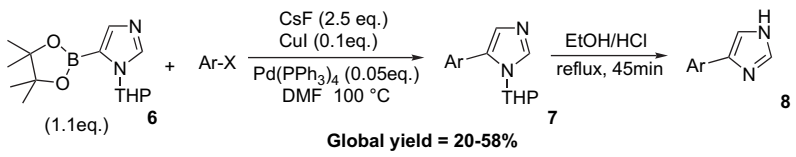
3. Conclusion

In conclusion, we have developed an efficient protocol to synthesize an *N*-THP imidazole boronic acid pinacol ester able to undergo Suzuki–Miyaura cross-coupling reaction, allowing the facile introduction of imidazole moiety on various scaffolds, including most sensitive. Considering the important biological properties of imidazole derivatives, this new methodology could be of great interest for medicinal chemists.

4. Experimental

4.1. General procedures

Commercial reagents were used as-received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer Spectrum BX FTIR System spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 Spectrometer.



Scheme 5.

Chemicals shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionizing potential of 30 eV. Thin layer chrommatographies (TLC) were performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light (234 nm) or by iodine. Column chromatographies were carried out using silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Fine' (Rouen). 2-Chlorotetrahydropyran was prepared according to the literature.[10]

4.2. 1-(Tetrahydropyran-2-yl)-1H-imidazole (**3**)[8]

To a slurry of 60% sodium hydride in oil (35.25 g, 881 mmol, 3 equiv) in dry THF (400 mL) at 0 °C under argon was slowly added imidazole **2** (20 g, 294 mmol, 1 equiv). After 30 min of stirring at this temperature was added dropwise 2-chlorotetrahydropyran (53.13 g, 440 mmol, 1.5 equiv) dissolved in 50 mL of dry THF. After this addition, the reaction was then continued at room temperature for the night. The excess of NaH was hydrolyzed by ice at 0 °C. The mixture was extracted with ether, dried over magnesium sulfate and concentrated on rotary evaporator. The resulting crude oil was purified by vacuum distillation (bp 85 °C at 0.05 mmHg) to provide the title compound **2** (33.23 g, 85%) as a white solid. IR (KBr): 3391, 3115, 2947, 2859, 1652, 1496, 1077, 1043, 992, 914, 664, 550 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.65 (s, 1H), 7.08 (s, 1H), 7.05 (s, 1H), 5.20 (dd, J=2.6, 9.5 Hz, 1H), 4.05–4.02 (m, 1H), 3.68–3.62 (m, 1H), 2.01–1.89 (m, 3H), 1.69–1.60 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 135.5, 129.2, 116.7, 83.9, 67.7, 31.3, 24.7, 22.3.

4.3. 2-Chloro-1-(tetrahydropyran-2-yl)-1H-imidazole (**4a**)[8]

Under nitrogen, a solution of **3** (18.52 g, 122 mmol) in dry THF (300 mL) was cooled to −78 °C. *n*-Butyllithium (2.5 M in hexanes) (58.5 mL, 146 mmol, 1.2 equiv) was added dropwise. After stirring for 25 min was added hexachloroethane (43.27 g, 183 mmol, 1.5 equiv) dissolved in 160 mL of THF. The resulting mixture was then stirred for 1.5 h at −78 °C and then allowed to warm at room temperature over a course of 45 min. Stirring was continued for a further 1 h. The mixture was worked up by the addition of saturated aqueous $NaHCO_3$, extraction with CH_2Cl_2, drying over $MgSO_4$ and removal of the solvents give the crude product, which was purified by vacuum distillation to afford **4a** (17.86 g, 79%) as a amber solid. Mp 40 °C. IR (KBr): 3146, 3116, 2947, 2856, 1464, 1264, 1085, 1044, 740, 668. ^1H NMR ($CDCl_3$): δ 7.12 (d, J=1.5 Hz, 1H), 6.96 (d, J=1.7 Hz, 1H), 5.27 (dd, J=2.2, 10.2 Hz, 1H), 4.12–4.09 (m, 1H), 3.71–3.64 (m, 1H), 2.05–1.60 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 131.1, 128.5, 117.6, 83.3, 68.7, 31.6, 24.7, 22.9. HRMS (EI) *m/z* calcd: 186.05597, found: 186.05648. Anal. Calcd for $C_8H_{11}N_2OCl$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.62; H, 6.09; N, 14. 89.

4.4. 2-Chloro-1-(tetrahydropyran-2-yl)-5-(4,4′,5,5′-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-imidazole (**5**)

To a stirred solution under nitrogen of **4a** (17.0 g, 91.2 mmol) in dry THF (350 mL) cooled to −78 °C were added TMEDA (16.4 mL, 109.4 mmol, 1.2 equiv) and *n*-BuLi (2.5 M) (43.8 mL, 109.4 mmol, 1.2 equiv) over a period of 20 min. After 10 min of stirring at this temperature was added triisopropyl borate (25.2 mL, 109.4 mmol, 1.2 equiv). The resulting mixture was allowed to react at this temperature for 2 h and then warmed to room temperature over a course of 1 h. After an additional stirring of 1 h, a solution of pinacol (10.77 g, 91.2 mmol, 1 equiv) in THF (30 mL) was added and after 5 min, glacial acetic acid was added until the pH reached 5. After 1 h of stirring at room temperature, the mixture was filtrated, concentrated, extracted with ether and washed with a saturated aqueous solution of $NaHCO_3$. Organic layer was dried over $MgSO_4$ and concentrated to obtain **5** (25.10 g, 88%) as a pale beige solid after washing with hexane. Mp 135 °C. IR (KBr): 2946, 2860, 1548, 1381, 1140, 856, 668, 574. ^1H NMR ($CDCl_3$): δ 7.42 (s, 1H), 5.63 (dd, J=2.7, 11.2 Hz, 1H), 4.16–4.13 (m, 1H), 3.66–3.60 (m, 1H), 2.45–2.39 (m, 1H), 2.01 (m, 1H), 1.78–1.64 (m, 3H), 1.56–1.53 (m, 3H), 1.33 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 140.7, 134.7, 128.4, 84.9, 83.9, 68.9, 30.3, 24.8, 24.6, 23.2. HRMS (EI) *m/z* calcd: 312.14118, found: 312.14189. Anal. Calcd for $C_{14}H_{22}N_2O_3BCl$: C, 53.79; H, 7.09; N, 8.96. Found: C, 53.95; H, 7.23; N, 9.14.

4.5. 1-(Tetrahydropyran-2-yl)-5-(4,4′,5,5′-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-imidazole (**6**)

Compound **5** (18.5 g, 59.2 mmol) and 10% palladium on carbon (3.2 g) in methanol (400 mL) at 0 °C were stirred under hydrogen at 1 atm for 1 h followed by another 1 h at room temperature. The mixture was filtrate through Celite and the solvent was removed. Extractive work up of the residue with CH_2Cl_2 and saturated aqueous solution of $NaHCO_3$ give, after drying over $MgSO_4$ and concentrating, **6** (13.51 g, 82%) as a white solid. Mp 132 °C. IR (KBr): 3435, 3165, 2966, 2862, 1642, 1156, 759. ^1H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.56 (s, 1H), 5.63 (dd, J=1.7, 10.2 Hz, 1H), 4.12–4.09 (m, 1H), 3.72–3.66 (m, 1H), 2.08–1.60 (m, 6H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 141.7, 138.3, 84.4, 83.7, 68.4, 32.4, 25.0, 24.9, 24.7, 23.1 (a quaternary carbon's signal was not observed). HRMS (EI) *m/z* calcd: 278.18016, found: 278.17998. Anal. Calcd for $C_{14}H_{23}N_2O_3B$: C, 60.45; H, 8.33; N, 10.07. Found: C, 60.69; H, 8.52; N, 10.25.

4.6. Typical procedure for the cross-coupling reaction

To a mixture of 1-(THP)-5-(4,4′,5,5′-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-imidazole **6** (1.0 g, 3.6 mmol, 1.1 equiv) and halocompound (3.3 mmol, 1 equiv) in dry DMF (40 mL) under argon were added CsF (1.24 g, 8.2 mmol, 2.5 equiv), CuI (62 mg, 0.33 mmol, 0.1 equiv) and $Pd(PPh_3)_4$ (189 mg ,0.16 mmol, 0.05 equiv). The reaction mixture was heated at 90 °C and the consumption of halocompound was followed by

TLC. The resulting mixture was poured into 50 mL of water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give **7a–k** as a brown residue. Purification was possible by column chromatography using dichloromethane/MeOH as eluent.

4.6.1. 5-(4-Methoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-imidazole (*7c*)

White solid. Following typical cross-coupling procedure using 4-iodoanisole (66%) as halocompound. Mp 106 °C. ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H), 7.38 (d, J=7.8 Hz, 2H), 7.02 (s, 1H), 6.98 (d, J=7.8 Hz, 2H), 5.00 (d, J=9.8 Hz, 1H), 4.14–4.12 (m, 1H), 3.86 (s, 3H), 3.58 (t, J=10.8 Hz, 1H), 2.07–1.91 (m, 3H), 1.72–1.56 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 159.5, 130.4, 127.3, 122.1, 114.1, 82.3, 68.2, 55.3, 31.4, 24.8, 23.3 (two quaternary carbon's signals were not observed). HRMS (EI) *m/z* calcd: 258.13681, found: 258.13693.

4.6.2. 3-[1-(Tetrahydro-2H-pyran-2-yl)-1H-imidazol-5-yl]-pyridine (*7i*)

White solid. Following typical cross-coupling procedure using 3-bromopyridine (36%) as halocompound. Mp 79 °C. ^{1}H NMR ($CDCl_3$): δ 8.72 (d, J=2.2 Hz, 1H), 8.64 (dd, J=4.9, 1.7 Hz, 1H), 7.88 (s, 1H), 7.81 (dt, J=8.0, 2.0 Hz, 1H), 7.39 (dd, J=7.8, 4.9 Hz, 1H), 7.15 (s, 1H), 4.99 (dd, J=10.8, 2.2 Hz, 1H), 4.15–4.11 (m, 1H), 3.62–3.48 (m, 1H), 2.09–1.95 (m, 3H), 1.72–1.57 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 149.6, 149.3, 136.3, 136.2, 129.8, 129.0, 126.1, 123.5, 82.6, 68.2, 31.2, 24.7, 23.3. HRMS (EI) *m/z* calcd: 229.1215, found: 229.1214.

4.7. Typical procedure for deprotection

To a solution of crude **7** in EtOH (5 mL) was added ethanol/HCl solution (10 mL) and the reaction mixture was refluxed for 45 min (dioxane/HCl for **7f** and **7h**). After neutralization with saturated aqueous $NaHCO_3$, the resulting solution was extracted with EtOAc and the organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by column chromatography (dichloromethane/MeOH) to afford the expected 4(5)aryl-1*H*-imidazoles **8a–k**.

4.7.1. 4(5)-Phenyl-1H-imidazole (*8a*)

White solid (35%). Following typical procedure using bromobenzene as halocompound. Mp 130 °C (lit.[20] 131–132 °C). ^{1}H NMR ($CDCl_3$): δ 7.73–7.69 (m, 3H), 7.40–7.35 (m, 3H), 7.27–7.24 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 139.3, 135.6, 132.9, 128.8, 127.0, 124.9, 116.4.

4.7.2. 4(5)-p-Tolyl-1H-imidazole (*8b*)

White solid (20%). Following typical procedure using 4-bromotoluene as halocompound. Mp 128 °C (lit.[20] 112–114 °C). ^{1}H NMR ($CDCl_3$): δ 8.48 (br s, 1H), 7.64 (s, 1H), 7.59 (d, J=8.0 Hz, 2H), 7.28 (s, 1H), 7.16 (d, J=8.2 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 138.1, 136.7, 135.5, 129.9, 129.4, 124.8, 115.7, 21.1.

4.7.3. 4(5)-(4-Methoxyphenyl)-1H-imidazole (*8c*)

White solid (58%). Following typical procedure using 4-iodoanisole as halocompound. Mp 128 °C (lit.[21] 137–138 °C). ^{1}H NMR ($CDCl_3$): δ 7.66–7.63 (m, 3H), 7.25 (s, 1H), 6.90 (d, J=6.6 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 158.8, 138.4, 135.4, 128.8, 126.2, 125.8, 114.6, 55.3.

4.7.4. 4(5)-(3-Methoxyphenyl)-1H-imidazole (*8d*)

White solid (37%). Following typical procedure using 3-iodoanisole as halocompound. Mp 104 °C. ^{1}H NMR ($CDCl_3$): δ 10.83 (br s, 1H), 7.59 (s, 1H), 7.25 (s, 1H), 7.20–7.13 (m, 3H), 6.68 (d, J=8.0 Hz, 1H), 3.61 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 126.6, 105.0, 102.5, 101.0, 96.5, 84.1, 82.9, 79.5, 77.0, 21.8.

4.7.5. 4(5)-(2-Chlorophenyl)-1H-imidazole (*8e*)

White solid (48%). Following typical procedure using 1-chloro-2-iodobenzene as halocompound. Mp 93 °C. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, J=7.6 Hz, 1H), 7.70 (s, 13H), 7.65 (s, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 135.1, 131.7, 131.2, 130.6, 129.9, 128.1, 127.2, 119.5 (a quaternary carbon's signal was not observed).

4.7.6. 2-(1H-Imidazol-4(5)-yl)benzonitrile (*8f*)

White solid (37%). Following typical procedure using 2-bromobenzonitrile as halocompound. Mp 162 °C. ^{1}H NMR ($CDCl_3$): δ 12.4 (br s, 1H), 8.06 (d, J=8.1 Hz, 1H), 7.83–7.78 (m, 3H), 7.69 (t, J=7.5 Hz, 1H), 7.38 (t, J=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 137.5, 136.3, 133.9, 133.2, 127.3, 126.6, 119.6, 115.5, 106.6 (a quaternary carbon's signal was not observed). HRMS (EI) *m/z* calcd: 169.06399, found: 169.06412.

4.7.7. Ethyl 2-(1H-imidazol-4(5)-yl)benzoate (*8g*)

White solid. Following typical procedure using ethyl 2-iodobenzoate (57%) or ethyl 2-bromobenzoate (33%) as halocompound. Mp 97 °C. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J=7.8 Hz, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.63 (s, 1H), 7.49 (dt, J=7.6, 1.3 Hz, 1H), 7.33 (dt, J=7.6, 1.2 Hz, 1H), 7.26 (s, 1H), 4.30 (q, J=7.1 Hz, 2H), 1.28 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 170.0, 132.0, 130.5, 129.9, 129.6, 127.2, 62.0, 14.4 (two quaternary carbon's signals were not observed). HRMS (EI) *m/z* calcd: 216.0899, found: 216.0893. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.82; H, 5.80; N, 13.15. See Ref. 22 for crystallographic data.

4.7.8. 2-(1H-Imidazol-4(5)-yl)benzaldehyde (*8h*)

White solid (39%). Following typical procedure using 2-bromobenzaldehyde as halocompound. Mp 200 °C. ^{1}H NMR (DMSO): δ 10.51 (s, 1H), 7.83 (s, 1H), 7.77–7.72 (m, 2H), 7.67 (s, 1H), 7.62 (t, J=7.3 Hz, 1H), 7.39 (t, J=7.3 Hz, 1H). ^{13}C NMR (DMSO): δ 193.7, 137.9, 137.6, 136.6, 133.4, 133.1, 128.7, 127.0, 126.6, 116.3. HRMS (EI) *m/z* calcd: 172.06365, found: 172.06381. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.98; H, 4.82; N, 16.41.

*4.7.9. 3-(1H-Imidazol-4(5)-yl)pyridine (**8i**)*

White solid (21%). Following typical procedure using 3-bromopyridine as halocompound. Mp 108 °C. ^{1}H NMR ($CDCl_3$): δ 9.00 (s, 1H), 8.48 (s, 1H), 7.49–7.47 (m, 1H), 7.37–7.30 (m, 2H), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 147.1, 145.8, 136.4, 132.5, 130.0, 123.8, 114.9 (a quaternary carbon's signal was not observed). HRMS (EI) *m/z* calcd: 145.06399, found: 145.06332.

*4.7.10. 4(5)-(Thiophen-3-yl)-1H-imidazole (**8j**)*

White solid (26%). Following typical procedure using 3-bromothiophene as halocompound. Mp 121 °C. ^{1}H NMR ($CDCl_3$): δ 9.10 (br s, 1H), 7.65 (s, 1H), 7.49–7.47 (m, 1H), 7.37–7.30 (m, 2H), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 135.3, 134.7, 134.3, 126.1, 125.5, 118.9, 115.6. HRMS (EI) *m/z* calcd: 150.0252, found: 150.0252.

*4.7.11. 2-(1H-Imidazol-4(5)-yl)thiazole (**8k**)*

Yellow solid (34%). Following typical procedure using 2-bromothiazole as halocompound. Mp 136 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, J=2.7 Hz, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.27 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 163.3, 142.8, 135.7, 136.1, 117.9, 115.6. HRMS (EI) *m/z* calcd 151.0204, found: 151.0204. Anal. Calcd for $C_6H_5N_3S$: C, 47.66; H, 3.33; N, 27.79. Found: C, 47.87; H, 3.48; 27.99.

Acknowledgements

This work was supported by the 'Conseil Régional de Basse-Normandie' and BoroChem S.A.S. We thank Dr. Rémi Legay for high resolution mass spectrometry analysis.

References and notes

1. For a recent review about imidazoles, see: Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571.
2. Ellis, G. P.; Epstein, C.; Fitzmaurice, C.; Golberg, L.; Lord, G. H. *J. Pharm. Pharmacol.* **1964**, *16*, 400.
3. Li, Y.-K.; Hsu, H.-S.; Chang, L.-F.; Chen, G. *J. Biochem.* **1998**, *123*, 416.
4. Elliott, R. L.; Oliver, R. M.; LaFlamme, J. A.; Gillaspy, M. L.; Hammond, M.; Hank, R. F.; Maurer, T. S.; Baker, D. L.; DaSilva-Jardine, P. A.; Stevenson, R. W.; Mack, C. M.; Cassella, J. V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3593.
5. (a) Heerding, D. A.; Chan, G.; DeWolf, W. E.; Fosberry, A. P.; Janson, C. A.; Jaworski, D. D.; McManus, E.; Miller, W. H.; Moore, T. D.; Payne, D. J.; Qiu, X.; Rittenhouse, S. F.; Slater-Radosti, C.; Smith, W.; Takata, D. T.; Vaidya, K. S.; Yuan, C. C. K.; Huffman, W. F. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2061; (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543; (c) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979.
6. Han, Q.; Chang, C. H.; Li, R.; Ru, Y.; Jadhav, P. K.; Lam, P. Y. S. *J. Med. Chem.* **1998**, *41*, 2019.
7. Gérard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665.
8. Primas, N.; Bouillon, A.; Lancelot, J.-C.; Sopkova-de Oliveira Santos, J.; Lohier, J.-F.; Rault, S. *Lett. Org. Chem.* **2008**, *5*, 8.
9. Manfredini, S.; Baraldi, P. G.; Bazzanini, R.; Guarneri, M.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1994**, 583.
10. Meltzer, P. C.; Wang, P.; Blundell, P.; Madras, B. K. *J. Med. Chem.* **2003**, *46*, 1538.
11. Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351.
12. (a) Eriksen, B. L.; Vedso, P.; Begtrup, M. *J. Org. Chem.* **2001**, *66*, 8344; (b) Eriksen, B. L.; Vedso, P.; Morel, S.; Begtrup, M. *J. Org. Chem.* **1998**, *63*, 12.
13. (a) Wang, L.; Wang, G. T.; Wang, X.; Tong, Y.; Sullivan, G.; Park, D.; Leonard, L. M., et al. *J. Med. Chem.* **2004**, *47*, 612; (b) Lee, Y.; Martasek, P.; Roman, L. J.; Masters, B. S. S.; Silverman, R. B. *Bioorg. Med. Chem.* **1999**, *7*, 1941; (c) Harusawa, S.; Moriyama, H.; Murai, Y.; Imazu, T.; Ohishi, H.; Yoneda, R.; Kurihara, T.; Hata, H.; Sakamoto, Y. *Chem. Pharm. Bull.* **1997**, *45*, 53.
14. Coudret, C. *Synth. Commun.* **1996**, *26*, 3543.
15. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.
16. Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813.
17. For a general review, see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
18. (a) Cailly, T.; Fabis, F.; Legay, R.; Oulyadi, H.; Rault, S. *Tetrahedron* **2007**, *63*, 71; (b) Hansen, H. M.; Lysen, M.; Begtrup, M.; Kristensen, J. L. *Tetrahedron* **2005**, *61*, 9955; (c) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
19. (a) Röder, J. C.; Meyer, F.; Kaifer, E. *J. Organomet. Chem.* **2002**, *641*, 113; (b) Röder, J. C.; Meyer, F.; Kaifer, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2304.
20. Have, R. T.; Huisman, M.; Meetsma, A.; van Leusen, A. M. *Tetrahedron* **1997**, *53*, 11355.
21. Yamazaki, C. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1846.
22. Crystallographic data for the structural analysis of **8g** have been deposited with the Cambridge Crystallographic Data Centre, publication number: CCDC 675462.