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Divergent and Regioselective Synthesis of 1,2,4- and 1,2,5-Trisubstituted Imidazoles

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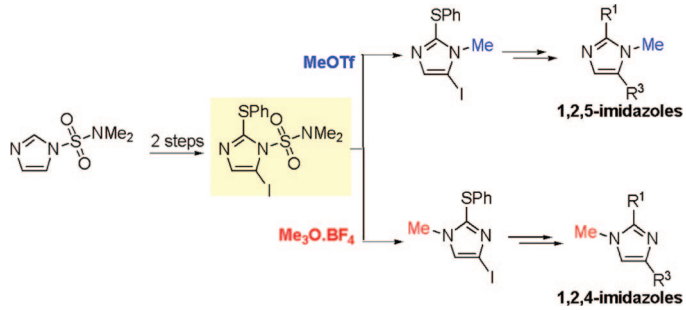

A divergent and regioselective synthesis of 1,2,4- and 1,2,5-trisubstituted imidazoles from a readily available (two steps) common intermediate has been developed. This methodology is based on the regiocontrolled N-alkylation of 1-(*N*,*N*-dimethylsulfamoyl)-5-iodo-2-phenylthio-1*H*-imidazole (**10**). When this intermediate is engaged in reaction with methyl triflate, selective formation of the corresponding 1,2,5-trisubsituted 1*H*-imidazole is observed. NMR studies have revealed that this regioselectivity can be accounted for by in situ rapid isomerization of **10** into its 1,2,4-isomer (**13**) followed by regiospecific N-alkylation of the latter. Conversely, when key intermediate **10** is slowly added to Meerwein's salt, isomerization can be constrained and regiospecific N-alkylation of **10** leads to 1,2,4-trisubstituted 1*H*-imidazole with a high selectivity. The general character of this methodology has been illustrated by showing that iodine in position 4 or 5 could be easily substituted by an aryl group by Suzuki coupling, whereas the phenylthio group at position 2 could, after oxidation into sulfone, be displaced by nucleophilic substitution.

Introduction

Substituted imidazoles are key substructures present in many compounds possessing interesting pharmacological properties.[1,2] As a result, a number of strategies have been explored for the preparation of these motifs. One such route consists of the introduction of substituents prior to imidazole ring formation. Suitable precursors may, however, be difficult, or impossible, to synthesize. Many substituents are also sensitive and do not tolerate the reaction conditions for the cyclization. A more general strategy is to introduce substituents to the preformed ring. However, the limitation of such an approach is often a lack of regioselectivity.

We are interested in developing a short and divergent synthesis of 1,2,4- and 1,2,5-trisubstituted imidazoles. So, our goal is to find a key intermediate which would be readily available (in a few steps), storable, and could lead *selectively* to *both* families of compounds, with a large range of substituents.

The main challenge faced by the regioselective substitution of imidazoles is the differentiation of positions 4 and 5.[1] An elegant way to solve this issue is the introduction of a protecting

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(1) For some reviews on imidazole synthesis, see: (a) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press, Inc.: San Diego, CA, 1997. (b) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon Press: Oxford, 2008; Vol. 4, pp 143−364. (c) Kamijo, S.; Yamamoto, Y. *Chem. Asian J.* **2007**, *2*, 568–578. (d) Du, H.; He, Y.; Rasapalli, S.; Lovely, C. J. *Synlett* **2006**, *7*, 965–992. (e) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624. (f) Begtrup, M. *Bull. Soc. Chim. Belg.* **1988**, *97*, 573–597.

(2) For reviews on biological activities of imidazoles, see: (a) Bolani, M.; Gonzalez, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409–424. (b) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464–496.

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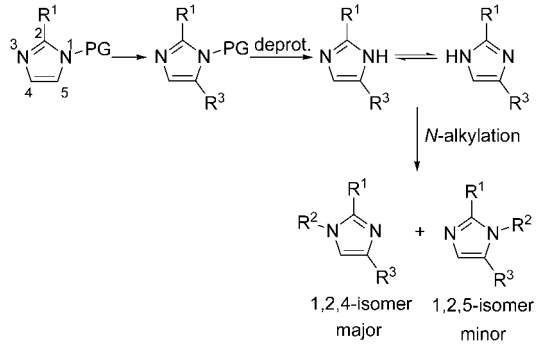
SCHEME 1. Common Strategy for the Synthesis of Substituted Imidazoles



group on the nitrogen atom (position 1) which will direct the substitution at position 5 (or 4). However, when this assistant group has served its purpose and one needs to change it for another, the deprotection/substitution process leads to mixtures of 1,4- and 1,5-isomers (Scheme 1). Indeed, the 5-substituted 1*H*-imidazole obtained after N-deprotection undergoes a rapid tautomeric equilibrium, and alkylation leads to mixtures in which the 1,4-isomer is usually the major product (due to steric factors).[3,4]

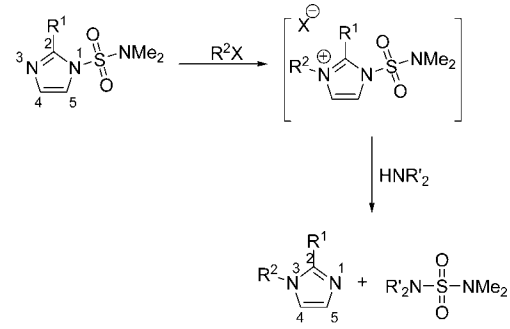
We reasoned that one way to overcome this problem would be to find a protecting group which could direct both the C(5)-substitution and the subsequent N-alkylation. To serve these purposes, we envisaged the use of the *N*,*N*-dimethylsulfamoyl group.

When positioned on an aromatic ring, the *N*,*N*-dimethylsulfamoyl group is known to direct lithiation in the ortho position.[5] If position 2 of the 1*H*-imidazole is already substituted, the presence of this sulfamoyl group on N(1) of the imidazole enables thus highly selective deprotonation and substitution in position 5 (see Scheme 1; PG = SO_2NMe_2).[1a,6]

Moreover, *N*-sulfamoylimidazoles are known to react with alkylating reagents exclusively via their nonsubstituted nitrogen atom (position 3).[7] Alkylation on N(1) is indeed blocked by the *N*,*N*-dimethylsulfamoyl group. Formation of a salt by N(3)-alkylation increases the lability of the dimethylsulfamoyl group which is then easily removed upon addition of a nucleophile (Scheme 2).[7] The outcome of this procedure is thus the N-alkylation of the imidazole ring selectively at the previously nonsubstituted nitrogen atom (numbered 3 in Scheme 2).[8]

The use of the *N*,*N*-dimethylsulfamoyl group then should allow regioselective lithiation/substitution of 2-substituted 1*H*-imidazoles at position 5 (**1** → **2**; Scheme 3). Subsequent selective alkylation of the nonsubstituted nitrogen atom (**2** → **3**) and deprotection should then lead to 1,2,4-trisubstituted imidazoles (**4**).

SCHEME 2. Alkylation/Deprotection of *N*-Sulfamoylimidazoles



Finally, it has been shown that 5-substituted *N*-sulfamoyl-1*H*-imidazoles (**2**) isomerize under equilibrating conditions to give the corresponding, more stable, 4-substituted *N*-sulfamoylimidazoles (**5**).[9] Application of the alkylation/deprotection procedure (vide supra) to this isomer should allow now obtaining 1,2,5-trisubstituted imidazoles (**7**) (Scheme 3).

Therefore, if R^1 and R^3 are functional groups which can be easily transformed into a wide variety of substituents, 2,5-substituted 1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazoles **2** could constitute a general, selective, and divergent route to 1,2,4- and 1,2,5-substituted imidazoles.

We selected phenylsulfonyl (R^1) and iodine (R^3) as transformable functional groups so that our designed key intermediate is **12** (Scheme 4). Indeed, the phenylsulfonyl group at position 2 should be easily displaced by nucleophilic substitution,[10] and the iodine atom at position 4 or 5 will enable metal-catalyzed coupling.[11]

Results and Discussion

Synthesis of the Key Intermediate. The synthesis of the intermediate (**12**) leading to 1,2,4- and 1,2,5-trisubstituted imidazoles was envisaged in three steps.

It has been shown that 1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazole (**8**) can be monolithiated selectively in position 2.[6] Thus, selective deprotonation of 1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazole (**8**) followed by addition of phenyl disulfide gives 2-substituted *N*-sulfamoyl-1*H*-imidazole **9** in excellent yield (Scheme 4).[6a] Subsequent oxidation of the sulfide leads to the corresponding 2-phenylsulfonyl-substituted 1*H*-imidazole **11**.[12] This latter showed, however, to be poorly stable, leading to

(3) For some recent examples, see: (a) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Dias, H. V. R. *J. Org. Chem.* **2007**, *72*, 3741–3749. (b) He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529–5532.

(4) For a personal example, see Supporting Information.

(5) (a) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662–3670. (b) Watanabe, H.; Schwarz, R. A.; Hauser, C. R.; Lewis, J.; Slocum, D. W. *Can. J. Chem.* **1969**, *47*, 1543–1546.

(6) (a) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929–931. (b) Winter, J.; Rétey, J. *Synthesis* **1994**, 245–246. (c) Kudzma, L. V.; Turnbull, S. P. *Synthesis* **1991**, 1021–1022. (d) Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645–1648. (e) Katritzky, A. R.; Slawinski, J. J.; Brunner, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1139–1145. (f) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351–2358.

(7) (a) Lee, H. K.; Bang, M.; Pak, C. S. *Tetrahedron Lett.* **2005**, *46*, 7139–7142. (b) Beaudoin, S.; Kinsey, K. E.; Burns, J. F. *J. Org. Chem.* **2003**, *68*, 115–119.

(8) For punctual examples of 1,5-substituted imidazole synthesis using a similar strategy with other protecting groups, see: (a) Chandana, P.; Nayyar, A.; Jain, R. *Synth. Commun.* **2003**, *33*, 2925–2933. (b) Panosyan, F. B.; Still, I. W. J. *Can. J. Chem.* **2001**, *79*, 1110–1114. (c) Chivikas, C. J.; Hodges, J. C. *J. Org. Chem.* **1987**, *52*, 3591–3594.

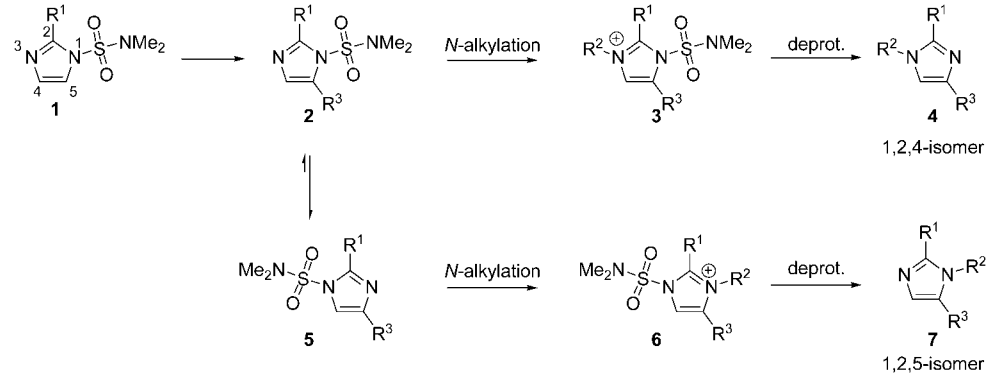
(9) Bhagavatula, L.; Premchandran, R. H.; Plata, D. J.; King, S. A.; Morton, H. E. *Heterocycles* **2000**, *53*, 729–732.

(10) (a) Jones, T. K.; Mani, N. US 2005250948, **2005**; *Chem. Abstr.* **2005**, *143*, 460319. (b) Bogenstaetter, M.; Carruthers, N. I.; Lovenberg, T. W.; Ly, K. S.; Jablonowski, J. A. WO 2002079168, **2002**; *Chem. Abstr.* **2002**, *137*, 279192.

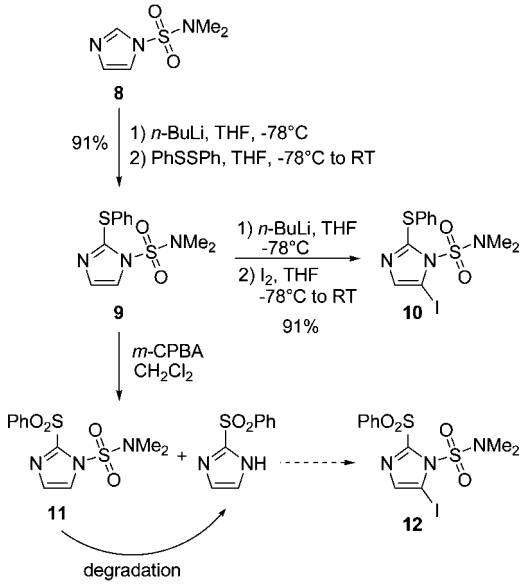
(11) For some examples of metal-catalyzed coupling involving 4- or 5-iodoimidazoles, see: ref 1c. (a) Yang, X.; Knochel, P. *Chem. Commun.* **2006**, 2170–2172. (b) Langhammer, I.; Erker, T. *Heterocycles* **2005**, *65*, 1975–1984. (c) Yoshida, T.; Nishiyachi, M.; Nakashima, N.; Murase, M.; Kotani, E. *Chem. Pharm. Bull.* **2003**, *51*, 209–214. (d) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319–1322. (e) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901. (f) Carver, D. S.; Lindell, S. D.; Saville-Stones, E. A. *Tetrahedron* **1997**, *53*, 14481–14496. (g) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1995**, *60*, 2378–2383.

(12) (a) Moreno, P.; Heras, M.; Maestro, M.; Villagordo, J. M. *Synthesis* **2002**, *18*, 2691–2700. (b) Schickaneder, H.; Engler, H.; Szelenyi, I. *J. Med. Chem.* **1987**, *30*, 547–551.

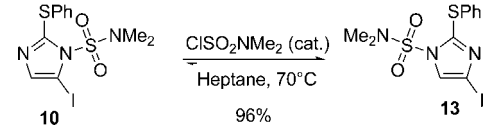
SCHEME 3. Designed Strategy to 1,2,4- and 1,2,5-Trisubstituted Imidazoles



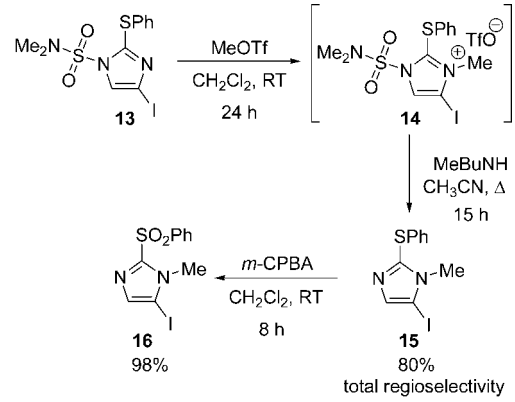
SCHEME 4. Synthesis of the Key Intermediate



SCHEME 5. Isomerization of 10



SCHEME 6. Alkylation/Deprotection of 13



N-deprotected 2-phenylsulfonylimidazole upon workup conditions. This observation can be attributed to the electron-withdrawing character of the phenylsulfonyl substituent which increases the lability of the sulfamoyl group.

In order to keep a high stability of our key intermediate, we decided therefore to redesign our strategy and leave the group at position 2 as a sulfide. The oxidation could indeed be performed later in the synthesis (right before the nucleophilic substitution), giving a new key intermediate **10**. This new intermediate is obtained in excellent yield by regioselective deprotonation of **9** in position 5[1a,6] and iodination. Intermediate **10** is a nice solid obtained in crystalline form which can be stored in the refrigerator for months[13] and of which structure could be confirmed by X-ray analysis (see Supporting Information).[14]

Having our key intermediate in hand (two steps, 83% overall yield), we investigated its potential as a platform for the selective synthesis of 1,2,4- and 1,2,5-trisubstituted imidazoles.

Isomerization of 10 into 13. According to our strategy, the access to 1,2,5-trisubstituted 1*H*-imidazoles from our key intermediate **10** necessitates the isomerization of the latter into its 1,2,4-regioisomer **13** (Scheme 5). As previously described on similar substrates, this can be done at 70 °C in the presence of a catalytic amount of *N*,*N*-dimethylsulfamoyl chloride.[9] Upon these conditions, the more stable 1,2,4-isomer **13** was obtained in excellent yield (96%). Isomerization could be observed by the low field shift of *H*C(imidazole) signal from 7.03 to 7.49 ppm in ^{1}H NMR (see Experimental Section for the full characterization data).

We have thus shown that both 1,2,4- and 1,2,5-isomers of our key intermediates, respectively, **13** and **10**, are readily available in high yields. We investigated then their respective regioselective N-alkylation.

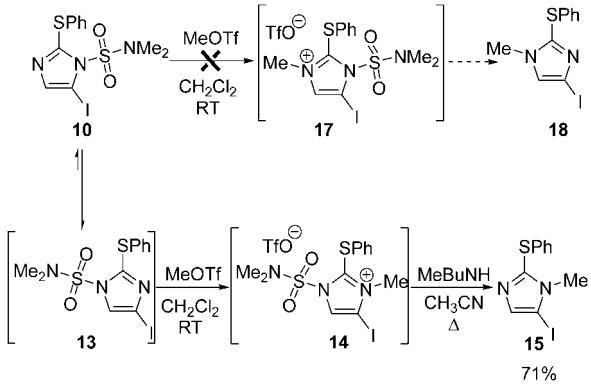
Alkylation/Deprotection of 13: Synthesis of 1,2,5-Trisubstituted Imidazoles. Previous studies have shown that *N*-sulfamoyl-1*H*-imidazoles react with alkylating reagent exclusively via N(3), alkylation on N(1) being blocked by the N-protecting group.[7] Accordingly, addition of methyltriflate to **13** gives selectively the salt **14** (Scheme 6). Slow formation of this salt could be detected in ^{1}H NMR when carrying out the reaction in CD_2Cl_2: H(4) is low field shifted in **14** (7.71 ppm), as compared to **13** (7.50 ppm), and a new C*H*$_3$ signal appears at 3.83 ppm.

Alkylation of **13** increases the lability of the dimethylsulfamoyl group which can then be removed upon addition of methylbutylamine to yield 1,2,5-trisubstituted imidazole **15** in

(13) Neither isomerization nor degradation was observed after 4 months at −18 °C.

(14) For both structures determined by X-ray diffraction analysis in this paper, **10** and **18**, two independent molecules are observed in the asymmetric parts of the unit cell; they differ only by a slight different orientation of the phenyl group. The bond lengths indicate clearly a greater conjugation in the imidazole ring of **10** as compared to **18**.

SCHEME 7. Alkylation/Deprotection of 10



good overall yield (80%) and total regioselectivity (no 1,2,4-isomer could be detected in the crude mixture).[15]

Oxidation of **15** by *m*-CPBA gives quantitatively sulfone **16**, which is now on hand for further functionalization in positions 2 and 5.

Alkylation/Deprotection of 10: Synthesis of 1,2,4-Trisubstituted Imidazoles. According to our strategy, 1,2,4-trisubstitued imidazole derivatives could be accessible by regioselective alkylation/deprotection of **10** (see Scheme 3). Key imidazole (**10**) was reacted with methyl triflate followed by addition of methylbutylamine under the same reaction conditions as for **13** but to our surprise this led to **15** (71% isolated yield), with only traces of **18** (4%) observed in the crude mixture (Scheme 7).[15]

In order to investigate formation of **15**, we performed the reaction in CD_2Cl_2 and followed it by ^1H NMR. No signal which could be attributed to salt **17** was detected. Instead, formation of salt **14** was observed. This suggests a rapid isomerization (faster than alkylation) of **10** into **13** under the reaction conditions, subsequent alkylation/deprotection of **13** yielding 1,2,5-isomer **15** as observed above (see Scheme 6).

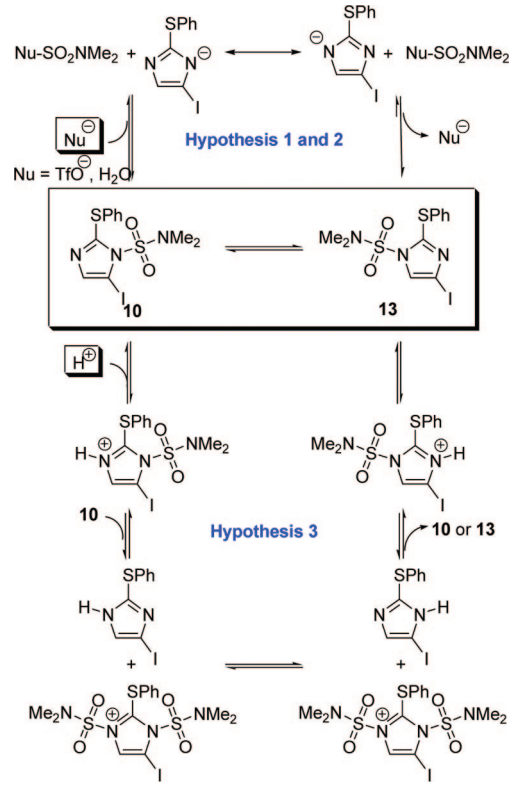
In fact, it is interesting to note that access to **15** does not actually necessitate a prior isolation of **13** but that **15** can be directly obtained in good yield (71%) by addition of methyl triflate to **10**, the isomerization step taking place in situ.

However, to access 1,2,4-imidazoles from **10**, one needs to be capable of preventing this in situ rapid isomerization. We tried therefore to identify the causes of this isomerization. First, we demonstrated the importance of alkylating reagent in isomerization by showing that imidazole **10** was stable in CH_2Cl_2 for 5 days. We thus reasoned that the origin of the isomerization could lie in the low nucleophilicity of triflate counterion (Scheme 8; hypothesis 1). Accordingly, we performed the reaction with alkylating reagents producing non-nucleophilic counterions (Table 1, entries 2−4). As anticipated, the use of dimethyl sulfate and Meerwein's salt enabled formation of the desired isomer **18**. The latter is, however, the minor product with the selectivity still being in favor of imidazole **15**. The nucleophilicity of the counterion cannot thereby account for all the observed isomerization of **10**.

We thought then that three other reasons could explain the isomerization (Schemes 8 and 9). First, it is likely that traces of water are present in the medium and act as nucleophile (Scheme 8; hypothesis 2). Second, isomerization may be catalyzed by traces of acid (Scheme 8; hypothesis 3). Finally,

(15) As a comparison, methylation of corresponding N-deprotected imidazole leads to a 57/43 mixture of 1,2,4- and 1,2,5-isomers (see Supporting Information).

SCHEME 8. Potential Causes of the In Situ Isomerization of 10



it is possible that isomerization is mediated by the salt **17** (and **14**) (Scheme 9; hypothesis 4).

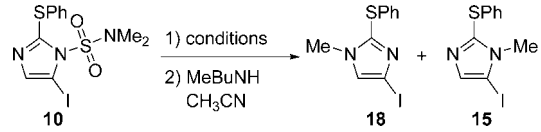
In order to test hypothesis 2 and 3, we carried out the reaction in the presence of, respectively, molecular sieves and a non-nucleophilic base, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)[16] (Table 1, entries 5 and 6). Molecular sieves provided exclusive formation of isomer **15**, whereas the presence of 10% of DTBMP in the medium did not lead to any significant change in regioselectivity. Isomerization is thereby not due to traces of water or acid.[17]

Hypothesis 4 was then investigated. In this scenario, at the initial stage of the reaction (<5% conversion), the salt **17** is formed. Then, this very small amount of **17** in the medium catalyzes the rapid isomerization of **10** into **13** which eventually leads to isomer **15** (Scheme 9).[18] In order to prevent this pathway, one needs thereby to avoid, or strongly reduce, the coexistence of **10** and **17**. Accordingly, imidazole **10** was slowly added to a solution of Meerwein's salt in dichloromethane over 15 h (Table 1, entry 9). We were pleased to find that this procedure leads quantitatively to alkylated imidazole **18** with a good regioselectivity (**18/15** = 83/17), the two regioisomers being easily separable by standard flash chromatography.[15,19]

The structure of **18** has been unambiguously confirmed by X-ray diffraction analysis (see Supporting Information).[14] The two regioisomers, **15** and **18**, have very similar analytical properties, but we found that they could be clearly differentiated

(16) Deutsch, E.; Cheung, N. K. V. *J. Org. Chem.* **1973**, *38*, 1123–1126.
(17) Test experiment showed that DTBMB does not isomerize **10** after stirring in CH_2Cl_2 for 3 days in the presence of 0.3 equiv of the base. Conversely, formation of **13** is observed when stirring **10** in the presence of molecular sieve.
(18) Once formed, the salt **14** may as well catalyze isomerization of **10**.
(19) It has been noted that purity of reactants and solvent is crucial for reproducibility of this experiment (see Supporting Information).

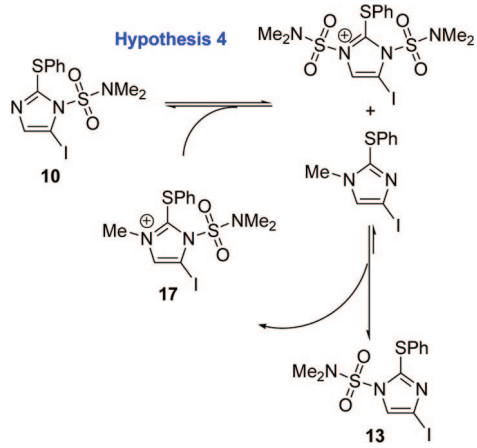
TABLE 1. Alkylation of 10



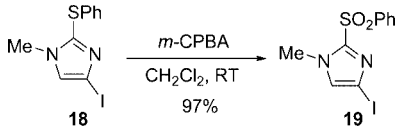
entry	conditions	yield (%)	18/15[a]
1	MeOTf (2 equiv), CH_2Cl_2, RT, 24 h	73	0/100
2	Me_2SO_4 (2.6 equiv), CH_2Cl_2, RT, 5 days	91	13/87
3	$Me_3S{\cdot}BF_4$ (2.6 equiv), CH_3CN, 80 °C, 2 days	0	
4	$Me_3O{\cdot}BF_4$ (1.2 equiv), CH_2Cl_2, RT, 15 h	74	43/57
5	$Me_3O{\cdot}BF_4$ (3 equiv), CH_2Cl_2, RT, 3 days, ms 4 Å	100	0/100
6	$Me_3O{\cdot}BF_4$ (2 equiv), CH_2Cl_2, RT, 3 days, DTBMP (0.1 equiv)	96	50/50
7	$Me_3O{\cdot}BF_4$ (5 equiv), CH_2Cl_2, RT, 4 days	91	67/33
8	Me_2SO_4 (2.6 equiv), toluene, RT, 5 days	100	26/74
9	slow addition (15 h) to $Me_3O{\cdot}BF_4$ (5 equiv), CH_2Cl_2, RT, 4 days	100	83/17
10	slow addition (15 h) to MeOTf (4 equiv), CH_2Cl_2, RT, 3 days	100	6/94

[a] Determined by ^{1}H NMR and/or GC analysis.

SCHEME 9. Isomerization of 10 Catalyzed by 17



SCHEME 10. Oxidation of 18



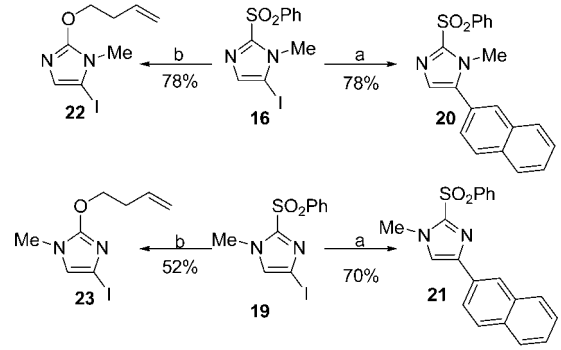
by ^{1}H NMR when using benzene-d^6 as solvent; chemical shift of CH_3 is 2.85 and 2.54 ppm, and chemical shift of *H*C(imidazole) is 7.31 and 6.21 ppm, for **15** and **18**, respectively (see Supporting Information for a full comparison).

Our experiments confirm that isomerization of **10** into **13** can be catalyzed both by triflate anion (hypothesis 1) and by the salt **17** (hypothesis 4). In order to investigate the relative importance of these factors, we performed the slow addition of **10** to an excess of methyl triflate (Table 1, entry 10). The observed 4/96 selectivity in that case suggests that triflate anion is the main factor accounting for isomerization of **10** into **13** when using MeOTf as alkylating reagent.

Oxidation of **18** by *m*-CPBA gives sulfone **19** in excellent yield (Scheme 10). Overall thus, **19** could be obtained in four steps from commercially available products. This intermediate is now ready to undergo further functionalization at C2 and C4 positions.

Functionalization of 16 and 19. In order to demonstrate the synthetic potential of compounds **16** and **19**, the possibility of substitution at positions 5 and 4, respectively, was first explored. It has been reported that the presence of iodine atom in these positions makes possible functionalization by metal-catalyzed coupling reactions.[11] Accordingly, as illustrated, we performed the palladium-catalyzed coupling of **16** and **19** with 2-naphthaleneboronic acid (Scheme 11). In both cases, the corresponding substituted imidazoles were obtained in good yield.

SCHEME 11. Functionalization of 16 and 19[a]



[a] Reagents and conditions: (a) naphthalen-2-ylboronic acid, $Pd(PPh_3)_4$ (cat.), Cs_2CO_3, DMF, 80 °C; (b) 3-butene-1-oxide, THF, microwave, 80 °C.

As planned, sulfone group at position 2 can also be substituted. Indeed, addition of sodium butenolate to **16** and **19** followed by microwave heating gives the corresponding 2-alkoxy imidazoles in moderate to good yield (Scheme 11).[20]

The interest of **16** has also been demonstrated by Blass et al.[21] In their study, these authors describe the synthesis of some potentially positive inotropes by successive Suzuki coupling and amination of **16**.

Conclusion

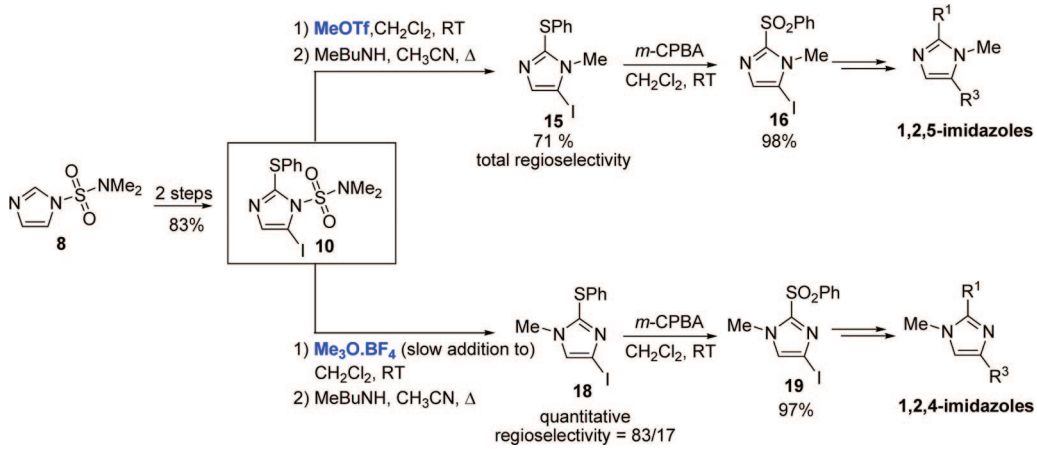
We have developed a divergent and regioselective synthesis of 1,2,4- and 1,2,5-trisubstituted imidazoles from a stable and readily available (two steps) common intermediate, **10** (Scheme 12).

Our strategy is based on regiocontrolled N-alkylation of *N*-sulfamoyl-1*H*-imidazole **10**. When this intermediate is engaged in reaction with methyl triflate selective formation of 1,2,5-trisubstituted 1*H*-imidazole **15** is observed. NMR studies

(20) The reaction was also tried under classical thermal conditions (heating bath), but it was found to be much slower and leading to more side products.

(21) Blass, B. E.; Huang, C. T.; Kawamoto, R. M.; Li, M.; Liu, S.; Portlock, D. E.; Rennels, W. M.; Simmons, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1543–1545.

SCHEME 12. Divergent and Regioselective Synthesis of 1,2,4- and 1,2,5-Trisubstituted Imidazoles



have shown that this regioselectivity can be accounted for by in situ rapid isomerization of **10** into **13** followed by regiospecific N-alkylation of this latter. Experiments have also revealed that observed isomerization is catalyzed both by the triflate anion and the salt **17**.

This identification of factors controlling isomerization enabled us then to control it. Indeed, when key intermediate **10** is slowly added to an excess of Meerwein's salt, isomerization can be constrained and regiospecific N-alkylation of **10** leads to 1,2,4-isomer **18** with a high selectivity.

We have thus demonstrated that **10** can lead regioselectively to either 1,2,4- or 1,2,5-trisubstituted 1*H*-imidazoles according to alkylating reagent and reaction conditions.

Furthermore, in order to make this strategy general, the key intermediate **10** was designed so as to allow, after N-alkylation, further selective functionalizations. Indeed, we have shown that iodine in position 4 or 5 could be easily substituted by an aryl group by Suzuki coupling, whereas a phenylthio group at position 2 can, after oxidation into sulfone, be displaced by nucleophilic substitution.

Thus, we have shown that *N*-sulfamoyl-1*H*-imidazole **10** constitutes a platform enabling the access to 1,2,4- and 1,2,5-trisubstituted imidazoles in a regioselective manner. The application of this methodology to the synthesis of biologically active compounds will be reported shortly.

Experimental Section

Synthesis of 1-(*N*,*N*-Dimethylsulfamoyl)-5-iodo-2-phenylthio-1*H*-imidazole (10). A 1.6 M solution of *n*-butyllithium in hexane (1.45 mL, 2.29 mmol, 1.3 equiv) was added dropwise to a solution of 1-(*N*,*N*-dimethylsulfamoyl)-2-phenylthio-1*H*-imidazole (**9**, 0.5 g, 1.77 mmol, 1 equiv) in dry THF (13 mL), at −78 °C under Ar. The reaction mixture was stirred for 3.25 h at −78 °C, and a solution of iodine (0.58 g, 2.29 mmol, 1.3 equiv) in THF (3 mL) was added slowly. The reaction mixture was then allowed to warm to room temperature and stirred overnight. Ethyl acetate (60 mL), a saturated solution of ammonium chloride (20 mL), and sodium bisulfite (75 mg) were added. The phases were separated, and the organic phase was washed twice with a saturated aqueous solution of ammonium chloride. The combined aqueous phases were extracted twice with ethyl acetate. The organic phases were collected and washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product crystallized spontaneously and was rinsed with a minimum of cyclohexane/ethyl acetate 70/30 to yield 514 mg of colorless crystals. Mother liquors were concentrated. A second crop of product crystallized to yield 45 mg of product. The oily residue was purified by flash chromatography over silica with cyclohexane/ethyl acetate 70/30 as eluent to yield 52 mg of white solid. This solid could be recrystallized in diisopropyl ether. Overall yield: 84%; mp 98 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.54−7.57 (m, 2H), 7.40−7.42 (m, 3H), 7.03 (s, 1H), 3.10 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 148.1, 140.9, 135.1, 131.7, 130.0, 129.9, 67.2, 39.2; IR (cm^{-1}) ν 1477, 1419, 1218, 1180, 1145, 972, 825, 783, 725; MS (APCI) *m*/*z* 410, 303, 302, 301, 225, 219; HRMS calcd for $C_{11}H_{12}IN_3O_2S_2Na$ 431.9313, found 431.9317.

Synthesis of 1-(*N*,*N*-Dimethylsulfamoyl)-4-iodo-2-phenylthio-1*H*-imidazole (13). Dimethylsulfamoyl chloride (26 μL, 0.24 mmol, 0.05 equiv) was added to a solution of 1-(*N*,*N*-dimethylsulfamoyl)-2-phenylthio-5-iodo-1*H*-imidazole (**10**, 2 g, 4.89 mmol, 1 equiv) in dry heptane (30 mL), in the dark under Ar atmosphere. The suspension was heated at 70 °C for 2.5 h and then filtered. The white crystals were washed with heptane and dried under reduced pressure. Yield: 96%; mp 116−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.42−7.48 (m, 2H), 7.31−7.39 (m, 3H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 143.5, 133.5, 131.5, 130.1, 129.6, 128.2, 83.3, 38.9; IR (cm^{-1}) ν 1388, 1276, 1176, 1149, 1049, 968, 725, 686; MS (APCI) *m*/*z* 410, 303, 302, 301, 283, 219; HRMS calcd for $C_{11}H_{12}IN_3O_2S_2Na$ 431.9313, found 431.9317.

Synthesis of 5-Iodo-1-methyl-2-phenylthio-1*H*-imidazole (15) from *N*,*N*-Dimethyl-5-iodo-2-phenylthio-1*H*-imidazole-1-sulfonamide (10). Methyltrifluoromethanesulfonate (633 μL, 5.59 mmol, 1.3 equiv) was added dropwise to a solution of 1-(*N*,*N*-dimethylsulfamoyl)-2-phenylthio-5-iodo-1*H*-imidazole (**10**, 1.76 g, 4.3 mmol, 1 equiv) in dichloromethane (8 mL), at 0 °C under Ar. The mixture was then allowed to warm to room temperature and stirred overnight in the dark. The solvent was evaporated under reduced pressure. The crude solid was dissolved in acetonitrile (15 mL), and butylmethylamine (1.07 mL, 9.03 mmol, 2.1 equiv) was added at room temperature. The solution was stirred for 15 h. The suspension was then filtered and washed with acetonitrile to yield 971 mg of white crystals of 1-methyl-2-phenylthio-5-iodo-1*H*-imidazole. Yield: 71%; mp 178−179 °C; R_f = 0.40 (dichloromethane/acetone 99/1), 0.53 (cyclohexane/ethyl acetate 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.09−7.14 (m, 2H), 6.76−6.89 (m, 3H), 3.63 (s, 3H); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.26 (s, 1H), 7.09−7.14 (m, 2H), 6.76−6.89 (m, 3H), 3.69 (s, 3H); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.28 (s, 1H), 7.09−7.14 (m, 2H), 6.76−6.89 (m, 3H), 3.66 (s, 3H); ^{1}H NMR (300 MHz, C_6D_6) δ 7.31 (s, 1H), 7.09−7.14 (m, 2H), 6.76−6.89 (m, 3H), 2.85 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 140.1, 138.3, 135.7, 130.3, 128.7, 127.6, 75.9, 35.5; IR (cm^{-1}) ν 1434, 1396, 1373, 1249, 929, 779, 732, 686; GC (140 °C for 5 min and then → 290 at 10 °C/min) 19.6 min; MS (APCI) *m*/*z* 317, 239, 190, 189, 157, 112.

Synthesis of 4-Iodo-1-methyl-2-phenylthio-1*H*-imidazole (18). To a solution of trimethyloxonium tetrafluoroborate[22] (54 mg, 0.3664 mmol, 5 equiv) in 1.5 mL of extra dry dichloromethane was slowly added a solution of 1-(*N*,*N*-dimethylsulfamoyl)-2-phenylthio-5-iodo-1*H*-imidazole **10** (30 mg, 0.0733 mmole) in 1 mL of extra dry dichloromethane. The addition was performed over a period of 15 h by means of a syringe pump. The resulting mixture was then stirred for 4 days at room temperature. Butylmethylamine (87.5 μL, 0.7327 mmol, 10 equiv) was added at once, and the solution was stirred for 15 h. Dichloromethane (20 mL) was added, and the solution was washed three times with water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was obtained as a mixture of regioisomers **18/15** in a 83/17 ratio. The two regioisomers can be separated by flash chromatography over silica with dichloromethane/acetone 99/1 as eluent, which gave pure **18**: mp 63−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2H), 7.22−7.15 (m, 3H), 7.16 (s, 1H), 3.62 (s, 3H); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.52 (s, 1H), 7.36−7.30 (m, 2H), 7.28−7.17 (m, 3H), 3.71 (s, 3H); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35−7.19 (m, 5H), 7.22 (s, 1H), 3.64 (s, 3H); ^{1}H NMR (300 MHz, C_6D_6) δ 7.11−7.08 (m, 2H), 6.86−6.78 (m, 3H), 6.21 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 134.2, 129.7, 129.5, 128.4, 127.1, 82.0, 34.1; GC (140 °C for 5 min and then → 290 at 10 °C/min) 18.6 min; HRMS calcd for $C_{10}H_{10}IN_2S$ 316.9609, found 316.9599.

Synthesis of 4-Iodo-1-methyl-2-phenylsulfonyl-1*H*-imidazole (19). *m*-CPBA 70% (307 mg, 1.25 mmol, 2.2 equiv) was added to a solution of 1-methyl-2-phenylthio-4-iodo-1*H*-imidazole (**18**, 179 mg, 0.57 mmol, 1 equiv) in 10 mL of dichloromethane, in a flask surrounded by aluminum foil to protect the solution from light. After 8 h at room temperature, sodium bisulfite (131 mg, 1.25 mmol, 2.2 equiv), water (4 mL), and a saturated sodium bicarbonate solution (6 mL) were successively added. Phases were separated, and the organic phase was washed with saturated sodium bicarbonate. The aqueous phases were extracted three times with dichloromethane. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 191 mg of pure product as a white solid. Yield: 97%; mp 91−92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 2H, J = 9.4 Hz), 7.5−7.7 (m, 3H), 7.04 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 139.6, 134.4, 131.4, 129.6, 128.3, 82.5, 35.6; MS (APCI) *m*/*z* 349; HRMS calcd for $C_{10}H_9IN_2O_2SNa$ 370.9327, found 370.9317.

Synthesis of 1-Methyl-5-(naphthalene-3-yl)-2-phenylsulfonyl-1*H*-imidazole (20). $Pd(PPh_3)_4$ (5 mg, 0.04 mmol, 0.03 equiv), 1-methyl-5-iodo-2-phenylsulfonylimidazole (**16**, 50 mg, 0.14 mmol, 1 equiv), naphthalen-2-ylboronic acid (27 mg, 0.16 mmol, 1.1 equiv), and Cs_2CO_3 (70 mg, 0.22 mmol, 1.5 equiv) were dissolved in dry DMF (6 mL). A flow of Ar was passed through the solution for 20 min. The solution was transferred into a sealed tube and heated under microwave for 4 h at 80 °C. The reaction mixture was poured into water, and ethyl acetate was added. The solution was filtered on Celite. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography over silica with ethyl acetate/cyclohexane 30/70 as eluent affords the desired product. Yield: 70%; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.10−7.95 (m, 6H), 7.80−7.57 (m, 6H), 7.28 (s, 1H), 4.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 140.1, 138.5, 134.4, 133.5, 133.4, 129.7, 129.4, 129.1, 128.7, 128.5, 128.2, 127.6, 127.4, 126.7, 125.6, 77.6, 33.7; MS-APCI: *m*/*z* = 350; HRMS calcd for $C_{20}H_{16}N_2O_2NaS$ 371.0830, found 371.0832.

Synthesis of 1-Methyl-4-(naphthalene-3-yl)-2-phenylsulfonyl-1*H*-imidazole (21). $Pd(PPh_3)_4$ (5 mg, 0.04 mmol, 0.03 equiv), 1-methyl-4-iodo-2-phenylsulfonylimidazole (**18**, 50 mg, 0.14 mmol, 1 equiv), naphthalen-2-yl-boronic acid (27 mg, 0.16 mmol, 1.1 equiv), and Cs_2CO_3 (70 mg, 0.22 mmol, 1.5 equiv) were dissolved in dry DMF (6 mL). A flow of Ar was passed through the solution for 20 min. The solution was transferred into a sealed tube and heated under microwave for 4 h at 80 °C. The reaction mixture was poured into water, and ethyl acetate was added. The solution was filtered on Celite. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography over silica with ethyl acetate/cyclohexane 30/70 as eluent affords the desired product. Yield: 47%; mp 168−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.14−8.10 (m, 2H), 7.88−7.79 (m, 4H), 7.68−7.55 (m, 3H), 7.35 (s, 1H), 4.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 140.2, 133.9, 133.5, 133.0, 129.7, 129.4, 128.3, 128.2, 128.1, 127.7, 126.3, 125.9, 123.9, 123.5, 121.9, 77.2, 35.6; HRMS calcd for $C_{20}H_{16}N_2O_2NaS$ 371.0830, found 371.0824.

Synthesis of 2-(But-3-enyloxy)-5-iodo-1-methyl-1*H*-imidazole (22). 3-Buten-1-ol (900 μL, 750 mg, 10.40 mmol, 5 equiv) was added to a solution of sodium hydride (383 mg of a 60% suspension in mineral oil, 9.58 mmol, 4.6 equiv) in dry THF (7 mL), under argon. The solution was stirred until no more gas evolution was observed and then added to a solution of 1-methyl-5-iodo-2-phenylsulfonylimidazole (**16**, 725 mg, 2.08 mmol, 1 equiv) in dry THF (35 mL). The reaction mixture was transferred into a sealed tube and heated under microwave for 6.5 h at 80 °C. Ethyl acetate (50 mL) and 10% sodium hydroxide solution (30 mL) were successively added. The organic phase was further washed twice with a 10% solution of sodium hydroxide (30 mL). Combined aqueous phases were extracted with ethyl acetate (20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography over silica with dichloromethane/methanol 99/1 as eluent affords a colorless oil (R_f = 0.3). Yield: 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.84 (tdd, 1H, J = 6.7, 10.2, 17.0 Hz), 5.06−5.19 (m, 2H), 4.37 (t, 3H, J = 6.6 Hz), 3.32 (s, 3H), 2.52 (tq, 2H, J = 1.3, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 153.7, 134.0, 130.3, 117.4, 68.8, 63.6, 33.5, 31.2; IR (cm^{-1}) ν 3115, 2982, 2947, 1639, 1539, 1496, 1473, 1407, 1369, 1254; MS-APCI *m*/*z* = 279, 225; HRMS calcd for $C_8H_{11}N_2ONaI$ 300.9814, found 300.9811.

Synthesis of 2-(But-3-enyloxy)-4-iodo-1-methyl-1*H*-imidazole (23). 3-Buten-1-ol (185 μL, 156 mg, 2.15 mmol, 5 equiv) was added to a solution of sodium hydride (47.5 mg of a 60% suspension in mineral oil, 1.98 mmol, 4.6 equiv) in dry THF (2 mL), under argon. The solution was stirred until no more gas evolution was observed and then added to a solution of 1-methyl-4-iodo-2-phenylsulfonylimidazole (**19**, 150 mg, 0.43 mmol, 1 equiv) in dry THF (7 mL). The reaction mixture was transferred into a sealed tubes and heated under microwave for 6.5 h at 80 °C. Ethyl acetate (30 mL) and 10% sodium hydroxide solution (10 mL) were successively added. The organic phase was further washed twice with a 10% solution of sodium hydroxide (10 mL). Combined aqueous phases were extracted with ethyl acetate (10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography over silica with dichloromethane/methanol 99/1 as eluent affords 62 mg of a colorless oil (R_f = 0.3). Yield: 52%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1H), 5.81 (m, 1H), 5.10−5.18 (m, 2H), 4.39 (t, 3H, J = 6.6 Hz), 3.36 (s, 3H), 2.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 134.2, 122.0, 117.6, 74.3, 69.4, 33.7, 30.8; MS-APCI *m*/*z* = 279, 225; HRMS calcd for $C_8H_{11}N_2ONaI$ 300.9814, found 300.9816.

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(22) $Me_3O^+BF_4^-$ was purchased from Acros and purified prior to use (following the procedure described by: Curphey, T. J. *Org. Synth.* **1971**, *51*, 142–147.

R.R. is a Chargé de recherches F.R.S.-FNRS and J.M.-B. is a senior research associate of the F.R.S.-FNRS.

Supporting Information Available: Detailed experimental procedures and characterization data for all compounds. Copies of ^{1}H and ^{13}C NMR spectra of new compounds. Crystal structure data (CIF) for **10** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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