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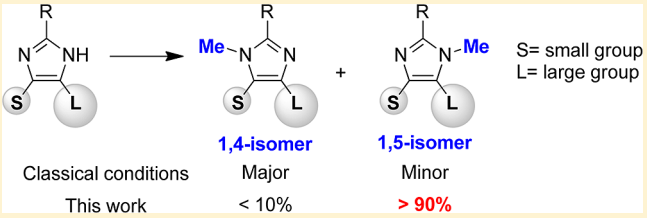
Development of a Regioselective N-Methylation of (Benz)imidazoles Providing the More Sterically Hindered Isomer

Emilie Van Den Berge and Raphaël Robiette*

Institute of Condensed Matter and Nanosciences, Université Catholique de Louvain, Place Louis Pasteur 1 bte L4.01.02, B-1348 Louvain-la-Neuve, Belgium

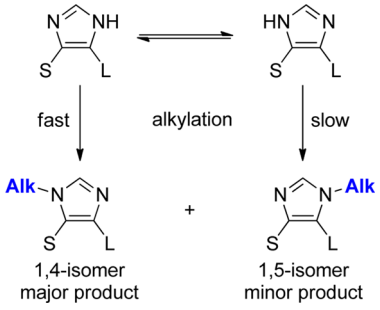
Supporting Information

ABSTRACT: An efficient and highly regioselective N-methylation of (NH)-(benz)imidazoles furnishing the sterically more hindered, less stable, and usually minor regioisomer has been developed. The methodology involves very mild reaction conditions and tolerates a wide range of functional groups.



Imidazoles are the central structure of numerous medicinally important compounds.[1] They are also versatile precursors in the preparation of synthetically useful compounds such as catalysts,[2] ligands,[3] or ionic solvents.[4] As a result, a number of strategies have been explored for the synthesis of this heterocyclic motif.[5] One common challenge in the synthesis of *N*-alkyl imidazoles is the control of the regioselectivity. Indeed, N-alkylation gives usually a mixture of isomers in which the major product is the sterically less hindered isomer, the 1,4-isomer (Scheme 1).[6,7] This observed poor regioselectivity is due to a rapid tautomeric equilibrium of (NH)-derivatives and the (slightly) faster alkylation of the less hindered nitrogen.

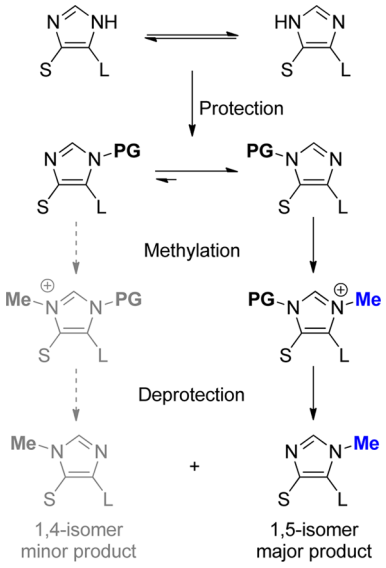
Scheme 1. Classical N-Alkylation Reaction of Imidazoles[a]



[a]S = small group; L = large group.

We recently reported the divergent synthesis of 1,2,4- and 1,2,5-trisubstituted imidazoles from a common N-protected intermediate.[7] In the course of this study, we showed that under our alkylation reaction conditions a rapid equilibrium between the two N-protected regioisomers was taking place, and a selective N-alkylation of the more stable 1,2,4-isomer ($K > 24$) was observed. We thus reasoned that this observation could be exploited to develop a general method for the N-methylation of (NH)-(benz)imidazoles providing selectively the sterically more hindered isomer. Indeed, replacing N−H by N-PG should allow displacing the tautomeric equilibrium toward the sterically less hindered isomer (Scheme 2). An alkylation/deprotection process (instead of classical deprotection/alkylation) should then lead selectively to the more hindered N-methylated derivatives.[8,9] Protection of the less hindered nitrogen should indeed prevent alkylation in this position and will therefore direct it on the other nitrogen, the most hindered one.[10]

Scheme 2. Designed Strategy for the Regioselective N-Methylation of the More Hindered Nitrogen of (NH)-(Benz)imidazoles



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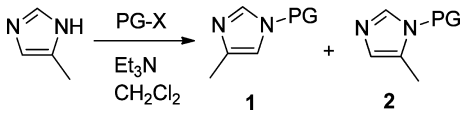
First, we have investigated each step of our designed strategy separately on a model compound, 4-methyl-1*H*-imidazole, in order to find the most appropriate protecting group (PG) and the best reaction conditions. We then have developed a one-pot procedure of our methodology before exploring its scope.

The ideal protecting group must allow high conversion in N-protected imidazole with a high regioselectivity. We thus investigated the reaction of our model compound with a series of protecting group, observing the evolution of the regioselectivity over time (Table 1).

Table 1. Investigation of the Protection Step[a]



	conversion (%)[b] (1/2)	
PG-X	after 1 h	after 15 h
TBSCl (**a**)	53 (55/45)	83 (60/40)
SEMCl (**b**)	81 (65/35)	91 (63/37)
BnBr (**c**)	40 (67/33)	45 (68/32)
$PhSO_2Cl$ (**d**)	97 (93/7)	100 (>98/2)
Me_2NSO_2Cl (**e**)	70 (71/29)	98 (85/15)
$(Boc_2)O$ (**f**)	88 (77/23)	100 (75/25)
$O(COCF_3)_2$ (**g**)	<5 (n.d.)	<5 (n.d.)

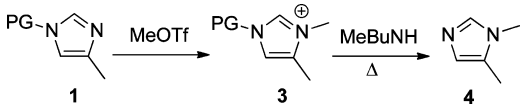
[a]Reaction conditions: 1.1 equiv of PG-X, 1.2 equiv of Et_3N, CH_2Cl_2, rt. [b]Conversion was determined by ^1H NMR using an internal standard.

Only two protecting groups led to both a high conversion and a good regioselectivity: *N*,*N*-dimethylsulfamoyl and phenylsulfone. It is interesting to note that it is the two cases in which an increase in regioselectivity was observed over time, suggesting the presence of an equilibrium between the two regioisomers under the reaction conditions. We selected these two protecting groups to carry on the next step.

The methylation was performed with methyltriflate[11] in dichloromethane-d_2 in order to study the reaction directly by ^1H NMR. Observed conversion in salt **3** was high for the two considered protecting groups (Table 2). No change in regioisomeric ratio was observed, salts **3d,e** being obtained in a similar regioisomeric distribution to starting **1d,e**.

The sequence alkylation-deprotection was then investigated. N-Protected 4-methyl-1*H*-imidazoles **1d,e** were reacted with methyltriflate at room temperature for one day and then in situ deprotected by addition of a nucleophile (*N*-butylmethylamine). Starting from **1e**, 1,5-dimethyl-1*H*-imidazole (**4**) was obtained in low yield, whereas in the case of phenylsulfonyl group (**1d**), the alkylation−deprotection process allowed obtaining **4** in excellent yield and regioselectivity. The phenylsulfonyl protecting group was thus considered for further developments of our methodology.

Table 2. Alkylation and Deprotection Steps[a]

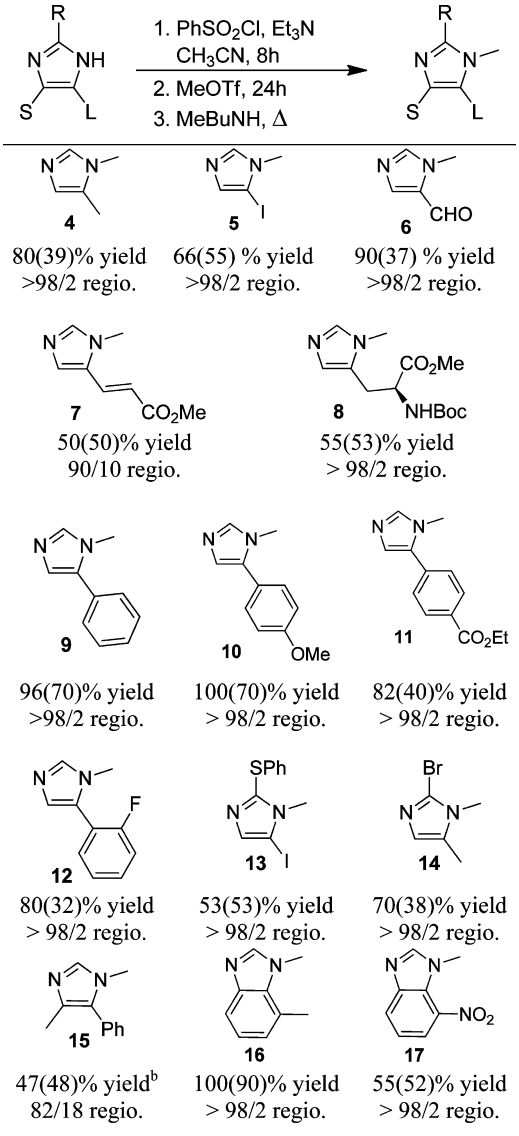


	3		4	
PG	conv	regio	conv[b]	regio
SO_2Ph (**d**)	>95%	>98/2	>95%	>98/2
SO_2NMe_2 (**e**)	>95%	83/17	40%	n.d.

[a]Conversion and regioselectivity were determined by ^1H NMR. Solvent for methylation is CD_2Cl_2 and for methylation-deprotection is CH_3CN. [b]Conversion over two steps (from **1**).

Relying on observations made during the optimization of each step, we searched for suitable reaction conditions allowing setting up a one-pot procedure of our methodology. In the event, we found that the three steps could be performed sequentially by dissolution of 4-methyl-1*H*-imidazole in acetonitrile and successive addition of triethylamine, phenylsulfonyl chloride, methyltriflate, and then *N*-methylbutylamine[12] (Table 3). This procedure allows obtaining 1,5-dimethyl-1*H*-imidazole (**4**) in good yield (80%) with an excellent regioselectivity (>98/2) in one synthetic step.

Table 3. Regioselective N-Methylation of (NH)-(Benz)imidazoles[a]



[a]Regioselectivity and yield were determined by ^1H NMR on the crude mixture (using an internal standard). Isolated yields are reported in parentheses. See Supporting Information for determination of regiochemistry. [b]Heating during the methylation step.

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With the optimized one-pot reaction conditions in hand, the substrate scope of the regioselective N-methylation was explored. As shown in Table 3, a variety of 5-substituted *N*-methyl-1*H*-imidazoles could be obtained in moderate to quantitative yield with excellent regioselectivities.[13] No 1,4-isomer could be detected by ^{1}H NMR in the crude mixture (except in the case of **7** where 10% of the undesired isomer was observed). Interestingly, the mild reaction conditions of our methodology tolerate a wide range of functional groups: esters, Boc groups, aldehydes, and α,β-unsaturated carbonyls.[14]

2,4(5)-Disubstituted imidazoles can also be N-methylated with good regioselectivity (>98/2). Even 4,5-disubstituted derivatives such as 4-methyl-5-phenyl-1*H*-imidazole led to corresponding *N*-methylimidazole compound (**15**) with a high regioselectivity (82/18) showing a good discrimination between phenyl and methyl substituents.[15]

Our methodology can also be applied to 4-substituted (NH)-benzimidazole derivatives with the more hindered isomer, the 7-substituted *N*-methyl-1*H*-benzimidazole, being obtained with a total regiocontrol.

In conclusion, we have developed a highly regioselective N-methylation of (NH)-(benz)imidazoles. The interest of our methodology does not only reside in the excellent observed regioselectivity but also in the nature of the regioisomer formed: the sterically more hindered, less stable, and usually minor regioisomer. Finally, our methodology involves very mild reaction conditions and tolerates a wide range of functional groups which should make it very practical in the context of total synthesis.

EXPERIMENTAL SECTION

NMR spectra were recorded at 300 or 500 MHz for ^{1}H NMR, and at 75 or 125 MHz for ^{13}C NMR. Chemical shifts (δ) are given in parts per million downfield from TMS. For ^{1}H−^{15}N HMBC experiments, CH_3NO_2 was used as internal standard (381.70 ppm). Mass spectra (MS) were recorded on an Orbitrap instrument; masses are given in Daltons. Regiochemistry was determined by ^{1}H−^{15}N HMBC for compounds **4**, **15**, and **16** (see the Supporting Information for full details). For compounds **5**−**14** and **17**, data were compared to the literature (see below for references). Flash chromatography was performed on silica gel (230−400 mesh). For compounds **4**−**6**, the purification was done on a C18 solid phase extraction.

(NH)-(Benz)imidazoles used in the regioselective methylation were either commercially available or prepared according to a reported procedure: (*E*)-methyl 3-(1*H*-imidazol-5-yl)acrylate,[16] (*S*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-imidazol-4-yl)propanoate,[17] 4,5-methyl-phenylimidazole, 4-(*p*-substituted-aryl)imidazoles,[18] 5-(2-fluorophenyl)-1*H*-imidazole,[19] and benzimidazoles.[20]

General Procedure for Protection of 4-Methyl-1*H*-imidazole. 4-Methyl-1*H*-imidazole (1.83 mmol, 1 equiv, 150 mg) was dissolved in DCM (4.5 mL) under argon atmosphere. Successively, Et_3N (2.20 mmol, 1.2 equiv, 0.31 mL) and PG-Cl (2.01 mmol, 1.1 equiv) were added dropwise. The mixture was stirred overnight. DCM/MeOH (30 mL) were added and washed twice with an aqueous solution of 10% of K_2CO_3 (15 mL). The combined aqueous phases were extracted twice with DCM/MeOH (15 mL). The organic phases were collected and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure.

*Characterization of 4-Methyl-1-(phenylsulfonyl)-1H-imidazole (**1d**).* Purification by flash chromatography DCM/MeOH 98/2. Yield: 102 mg, 75%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97−7.92 (m, 3H), 7.71−7.55 (m, 3H), 7.00 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 138.3, 136.3, 134.8, 129.9 (2C), 127.3 (2C), 113.5, 13.7; IR (cm^{-1}) ν 3107, 1448, 1375, 1174, 1091, 1080, 997, 729, 685; mp 70−71 °C; ESI-MS *m*/*z* M + 1 223; HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2S$ 223.0541, found 223.0551.

*Characterization of N,N-4-Trimethyl-1H-imidazole-1-sulfonamide (**1e**).*[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.95 (s, 1H), 2.85 (s, 6H), 2.25 (s, 3H).

General Procedure for N-Methylation. (Benz)imidazole (1 equiv, 100 mg) was dissolved in acetonitrile under argon atmosphere. Et_3N (1.2 equiv) and $PhSO_2Cl$ (1.1 equiv) were successively added dropwise, and the mixture was stirred for 8 h. Methyltriflate (1.5 equiv) was then added. After 24 h, *N*,*N*-butylmethylamine (2.1 equiv) was added, and the solution was heated at 80 °C overnight. DCM (10 mL) was added, and the solution was washed twice with $NaOH_{aq}$ 1 M (10 mL). The aqueous phases were extracted with DCM (10 mL). The organic phases were dried ($MgSO_4$) and concentrated under reduced pressure.

*Characterization of 1,5-Dimethyl-1H-imidazole (**4**).*[22] Purification by semipreparative HPLC CH_3CN/H_2O 10/90. Isolated yield: 44.6 mg, 49%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.77 (s, 1H), 3.54 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 127.8, 126.1, 31.3, 9.1.

*Characterization of 5-Iodo-1-methyl-1H-imidazole (**5**).*[23] Purification by semipreparative HPLC CH_3CN/H_2O 10/90. Isolated yield: 55.2 mg, 55%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.16 (s, 1H), 3.64 (s, 3H).

*Characterization of 1-Methyl-1H-imidazole-5-carbaldehyde (**6**).*[24] Purification by semipreparative HPLC CH_3CN/H_2O 10/90. Isolated yield: 41.2 mg, 37%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.61 (s, 1H), 3.95 (s, 3H).

*Characterization of (E)-Methyl 3-(1-methyl-1H-imidazol-5-yl)-acrylate (**7**).*[25] Purification by flash chromatography DCM/MeOH 92/8 + 3% Et_3N. Isolated yield: 116 mg, 51%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.47 (m, 3H), 6.27 (d, 2H, J = 16.2 Hz), 3.80 (s, 3H), 3.73 (s, 3H).

*Characterization of (S)-Methyl 2-(tert-butoxycarbonylamino)-3-(1-methyl-1H-imidazol-5-yl)propanoate (**8**).*[26] Purification by flash chromatography DCM/MeOH 92:08 + 3% Et_3N. Isolated yield: 56 mg, 53%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.77 (s, 1H), 5.15 (m, 1H), 4.52 (m, 1H), 3.72 (s, 3H), 3.55 (s, 3H), 3.07−3.08 (m, 2H), 1.40 (s, 9H).

*Characterization of 1-Methyl-5-phenyl-1H-imidazole (**9**).*[27] Purification by flash chromatography DCM/MeOH 97/3 + 3% Et_3N. Isolated yield: 77 mg, 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.61 (s, 1H), 7.45−7.38 (m, 5H), 7.12 (s, 1H), 3.69 (s, 3H).

*Characterization of 5-(4-Methoxyphenyl)-1-methyl-1H-imidazole (**10**).*[27] Purification by flash chromatography CH_2Cl_2 + 3% Et_3N. Isolated yield: 75 mg, 70%; Et_3N ^{1}H NMR (300 MHz, $CDCl_3$) δ7.54 (s, 1H), 7.31 (d, 2H, J = 8.73 Hz), 7.04 (s, 1H), 6.97 (d, 2H, J = 8.73 Hz), 3.85 (s, 3H), 3.64 (s, 3H).

*Characterization of 4-(1-Methyl-1H-imidazol-5-yl)phenyl propionate (**11**).* Purification by flash chromatography DCM + 3% Et_3N. Isolated yield: 42 mg, 40%, yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 2H, J = 8.4 Hz), 7.62 (s, 1H,), 7.47 (d, 2H, J = 8.4 Hz), 7.20 (S, 1H), 4.40 (q, 2H, J = 7.1 Hz), 3.72 (s, 3H), 1.41 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 Hz, $CDCl_3$) δ 166.2, 140.0, 134.2, 132.6, 130.0, 129.6, 129.2, 127.8, 61.2, 32.9, 14.4; IR (cm^{-1}) ν 1709, 1610, 1489, 1275, 1180, 1103, 1013, 922, 825, 773, 706; ESI-MS *m*/*z* M + 1 231; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2$ 231.1134, found 231.1126.

*Characterization of 5-(2-Fluorophenyl)-1-methyl-1H-imidazole (**12**).* Purification by flash chromatography DCM + 3% Et_3N. Isolated yield: 34 mg, 32%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.43−7.13 (m, 4H), 7.10 (s, 1H), 3.59 (s, 3H); ^{19}F NMR (282 MHz, CDF_3) δ −113.1; ^{13}C NMR (75 Hz, $CDCl_3$) δ 160.0 (J = 246.4 Hz), 139.2, 131.9, 130.5 (J = 8.1 Hz), 129.5, 127.7, 124.5, 117.7 (J = 15.4 Hz), 116.0 (J = 21.9 Hz), 32.2; IR (cm^{-1}) ν 1556, 1477, 1229, 1203, 1111, 916, 760; APCI-MS *m*/*z* M + 1 177; HRMS (APCI) calcd for $C_{10}H_9N_2F$ 176.07443, found 176.07414.

*Characterization of 5-Iodo-1-methyl-2-(phenylthio)-1H-imidazole (**13**).*[7a] Purification by flash chromatography DCM/MeOH 95/5 + 3% Et_3N. Isolated yield: 55 mg, 53%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.19 (m, 6H), 3.64 (s, 3H).

*Characterization of 2-Bromo-1,5-dimethyl-1H-imidazole (**14**).*[28] Purification by flash chromatography DCM + 3% Et_3N. Isolated yield:

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42 mg, 38%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H), 3.47 (s, 3H), 2.20 (s, 3H); APCI-MS m/z M + 1 175 (^{79}Br), 177 (^{81}Br).

*Characterization of 1,4-Dimethyl-5-phenyl-1H-imidazole (**15**).*[29] Purification by flash chromatography DCM/MeOH 93/7 + 3% Et_3N. Isolated yield: 26 mg, 47%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.28 (m, 6H), 3.55 (s, 3H), 2.23 (s, 3H).

*Characterization of 1,7-Dimethyl-1H-benzo[d]imidazole (**16**).*[30] Purification by flash chromatography DCM/MeOH 98/2. Isolated yield: 89 mg, 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.63 (d, 1H, J = 8.1 Hz), 7.15 (t, 1H, J = 7.7 Hz), 7.03 (d, 1H, J = 7.2 Hz), 4.08 (s, 3H), 2.74 (s, 3H).

*Characterization of 1-Methyl-7-nitro-1H-benzo[d]imidazole (**17**).*[31] Purification by flash chromatography DCM/MeOH 95/5. Isolated yield: 57 mg, 52%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.16−8.07 (m, 2H), 7.41 (t, 1H, J = 8.1 Hz), 4.11 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C, and ^{1}H−^{15}N HMBC NMR spectra and details on determination of regiochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: raphael.robiette@uclouvain.be.

Notes

The authors declare no competing financial interest.

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(8) This provided that the reactivity of the two isomers of the protected imidazole toward N-methylation is similar. The observed high regioselectivity in our previous study (see ref 7) suggests that it will be the case.

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(10) For steric and electronic (availability of the lone pair) reasons, only the nonsubstituted nitrogen reacts with alkylating reagents. See, for instance: (a) Lee, H. K.; Bang, M.; Pak, C. S. *Tetrahedron Lett.* **2005**, *46*, 7139−7142. (b) Beaudouin, S.; Kinsey, K. E.; Burns, J. F. *J. Org. Chem.* **2003**, *68*, 115−119. (c) Horvath, A. *Synthesis* **1995**, 1183−1189.

(11) We have also attempted to alkylate **1d** with other alkylating reagents such as ethyl bromoacetate, ethyltriflate, or benzyl bromide, but no alkylation product could be observed.

(12) In some cases, a simple workup with $NaOH_{aq}$ was found to be sufficient for deprotecting N(1).

(13) The significant difference between isolated and NMR yields for some compounds is due to chromatographic tailing during the purification (probably because of a protonation/deprotonation process) and the subsequent difficulty of separating the imidazole compound from the side product ($Me_2NSO_2N(Me)Bu$).

(14) The absence of variation in regioselectivity with electronic properties of substituents suggest that electronic effects have no significant role in determining regioselectivity, this latter being governed by steric factors.

(15) The regioselectivity could be increased without heating during the methylation step, but the yield was then lower (reactant found).

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