HETEROCYCLES, Vol. 65, No. 11, 2005, pp. 2721 - 2728
Received, 28th July, 2005, Accepted, 15th September, 2005, Published online, 16th September, 2005

# SYNTHESIS OF 1,2-DISUBSTITUTED IMIDAZOLES *VIA* CROSS-COUPLING AND SUBSTITUTION REACTIONS

Ingo Langhammer and Thomas Erker*

Department of Medicinal/ Pharmaceutical Chemistry, University of Vienna, Althanstraße 14, A-1090 Wien, Austria
thomas.erker@univie.ac.at

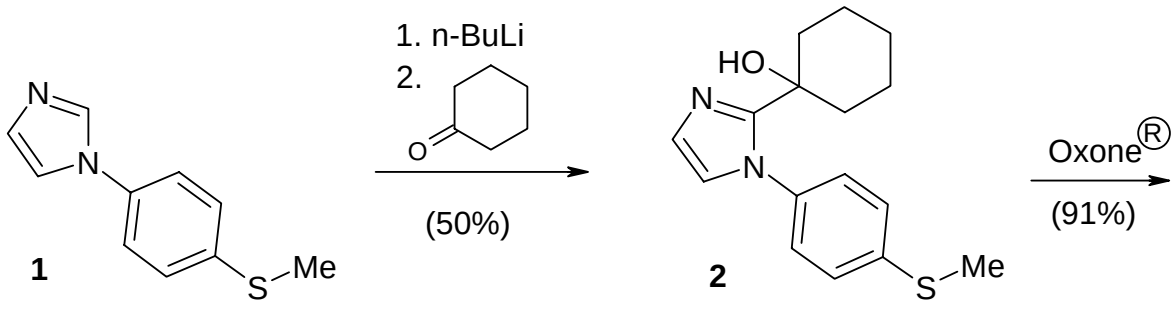
**Abstract** - Lithiation of imidazole compound (**1**) in position 2 and subsequent quenching with electrophiles provided a route to 1,2-diaryl-, 1-aryl-2-cycloalkyl- and 1-aryl-2-heterocyclyl-substituted imidazoles.

## Introduction

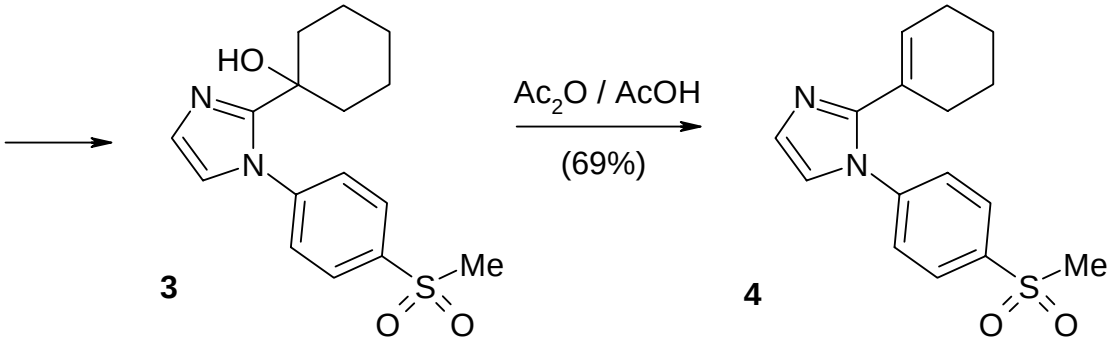
Diarylimidazoles have been described as pharmacologically active compounds in several publications over the last twenty years. Certain 1,2-diarylimidazoles for example showed COX-2-inhibiting activity.[1,2] All of these 1,2-diarylimidazoles were prepared by condensating amidines with α-halogen ketones. This paper describes an alternative approach to 1,2-disubstituted imidazoles, starting from imidazole compound (**1**) and utilising cross-coupling reactions and substitution reactions to form C-C-bonds and C-N-bonds.

## Results

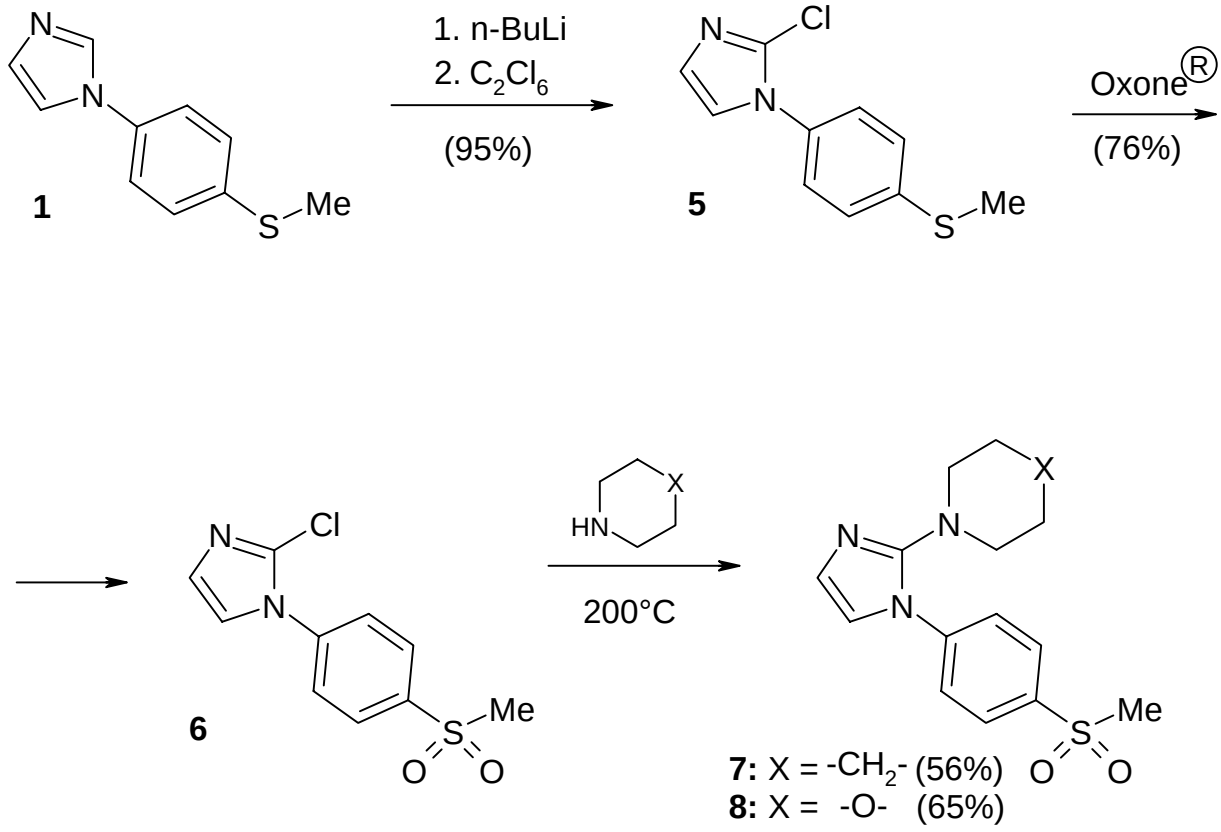
Starting from 1-(4-methylsulfanylphenyl)-1*H*-imidazole (**1**)[3] we prepared compound (**2**) *via* lithiation of substance (**1**), followed by quenching with cyclohexanone. Refering to experiments presented in literature[4-6] we assumed a selective lithiation of the imidazole ring of compound (**1**) onto position 2. The real structural evidence for the substitution in position 2 was confirmed by $^{1}H$ and $^{13}C$ NMR data.



As a methylsulfone moiety is desireable for COX-enzyme affinity, substance (**2**) was oxidized to **3** with Oxone®. Dehydration of **3** with $Ac_2O$ / AcOH yielded **4**.

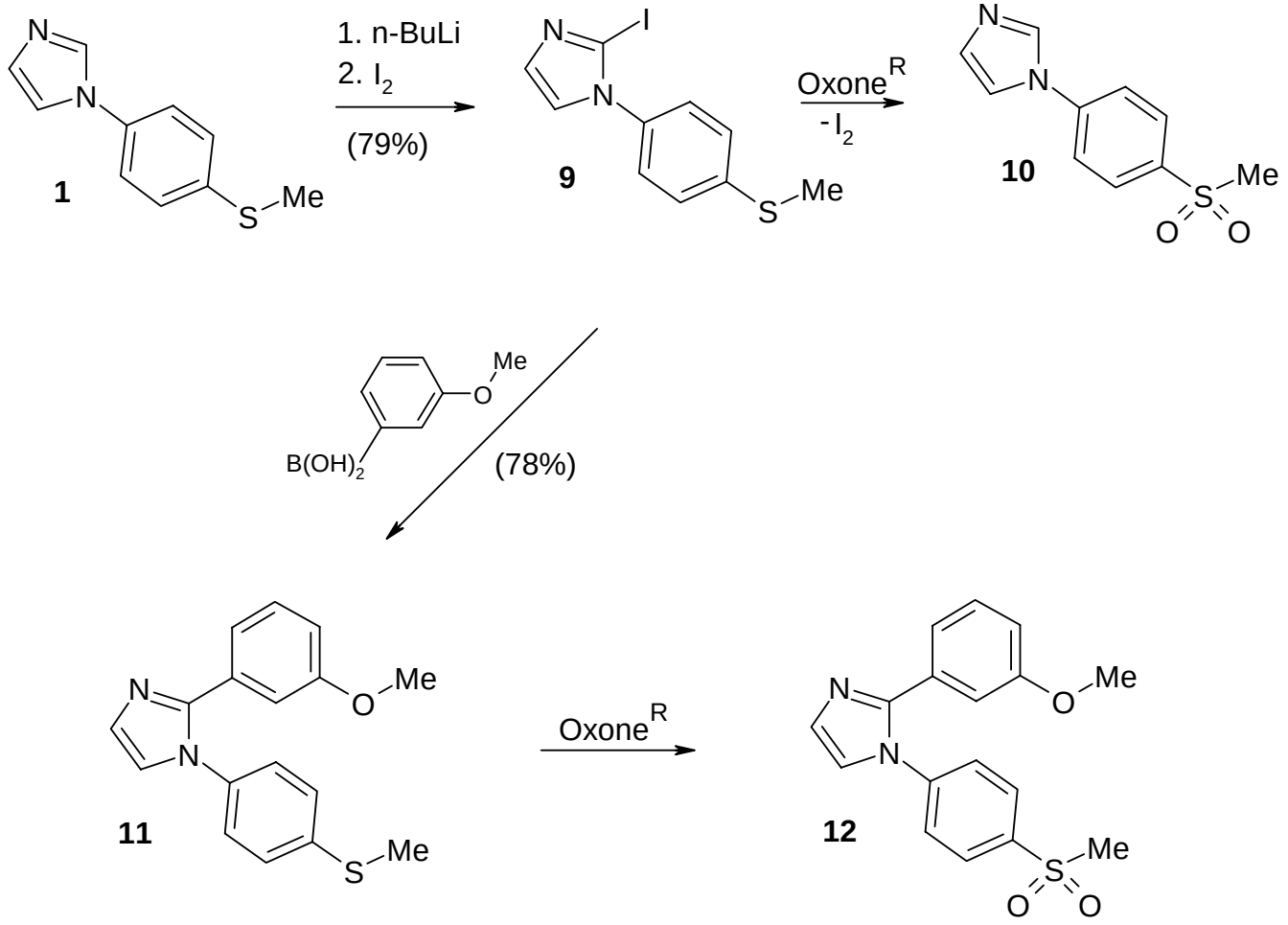



Lithiation of **1** and subsequent quenching with hexachloroethane gave product (**5**). Sulfide (**5**) was oxidized with Oxone® to yield **6**. The 2-chloro-substituted **6** proved to be a good substrate for nucleophilic substitutions. Heating **6** with piperidine or morpholine in an autoclave gave products (**7**) or (**8**) respectively.




Whilst compounds (**2**) and (**5**) could be easily oxidized with Oxone®, 2-iodo-substituted **9** turned out to be not stable enough for oxidation. Frequent deiodination of **9** to **10** forced us to put back the oxidation step

until formation of a C-C-bond in position 2 had been accomplished. Thus we reacted compound (**9**) with 3-methoxyphenylboronic acid under Suzuki conditions which gave **11** in good yield. Oxidation of **11** with Oxone® finally yielded **12**.




Very recently, direct coupling reactions of 1-aryl-1*H*-imidazoles with aryl halides has been reported by Bellina *et al.*.[7] This work has demonstrated, that a variety of 1,5-diaryl-1*H*-imidazoles can be selectively synthesized in moderate yields by direct palladium catalyzed C-arylation of 1-aryl-1*H*-imidazoles with aryl iodides or bromides. The electrophilic attack of the arylpalladium halide species occur onto position C-5 of the heteroaromatic ring.

## EXPERIMENTAL

$^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DPx200 spectrometer, using TMS as an internal standard. MS spectra were recorded on a Shimadzu QP 5000. Column chromatography was performed on Merck silica gel 60, 0.063 - 0.200 mm. Melting points were determined with a Kofler melting point apparatus and are uncorrected. Microanalyses were determined by Johannes Theiner at the Institute of Physical Chemistry of the University of Vienna.

**1-[1-(4-Methylsulfanylphenyl)-1*H*-2-imidazolyl]-1-cyclohexanol (2)**

To 0.381 g (0.002 mol) of **1** in 30 mL of anhydrous THF at -78°C under argon 1.4 mL (0.0022 mol) of 1.6 M *n*-BuLi in hexane was slowly added. After 15 min 0.25 mL (0.0024 mol) of cyclohexanone was added. The reaction mixture was stirred 30 min at -78°C and then allowed to warm to rt. Then the reaction mixture was washed with 70 mL of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted twice with 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude product was recrystallized from ethanol to yield 0.288 g (50%) of **2**; mp 122 - 143°C; MS: m/z (rel. int.) 288 ($M^+$, 53), 245 (100), 217 (57), 137 (43), 69 (35); $^1$H-NMR ($CDCl_3$): δ = 7.36 - 7.17 (m, 4H, Ar*H*), 7.03 - 6.93 (m, 1H, Ar*H*), 6.90 - 6.80 (m, 1H, Ar*H*), 2.74 (br s, 1H, -O*H*), 2.53 (s, 3H, -C*H*$_3$), 1.96 - 1.02 (m, 10H, -C$_5$*H*$_{10}$-); $^{13}$C-NMR ($CDCl_3$): δ = 152.7 (Ar*C*), 139.7 (Ar*C*), 136.1 (Ar*C*), 127.9 (Ar*C*H), 126.0 (Ar*C*H), 123.9 (Ar*C*H), 71.7 (carbinol C), 37.3 (-*C*H$_2$-), 25.2 (-*C*H$_2$-), 21.8 (-*C*H$_2$-), 15.4 (-*C*H$_3$); one Ar*C*H signal was not detectable; Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.51; H, 7.05; N 9.49.

**1-[1-(4-Methylsulfonylphenyl)-1*H*-2-imidazolyl]-1-cyclohexanol (3)**

A solution of Oxone® (1.230 g, 0.002 mol) in 10 mL of water was added to a solution of **2** (0.288 g, 0.001 mol) in 15 mL of methanol. The reaction is slightly exothermic, and the temperature of the reaction was prevented from rising by a surrounding water bath. After being stirred at rt for 1 h, the mixture was treated with dilute ammonium hydroxide (10%, 13 mL). The contents were stirred for 1 h and then the methanol was evaporated. The aqueous phase was extracted four times with 20 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude product was recrystallized from ethanol to yield 0.292 g (91 %) of **3**; mp 148 - 163°C; MS: m/z (rel. int.) 320 ($M^+$, 23), 277 (100), 249 (66), 223 (39), 95 (50); $^1$H-NMR ($CDCl_3$): δ = 8.07 - 7.96 (m, 2H, Ar*H*), 7.74 - 7.62 (m, 2H, Ar*H*), 7.02 (s, 1H, Ar*H*), 6.91 (s, 1H, Ar*H*), 2.71 (br s, 1H, -O*H*), 3.13 (s, 3H, -C*H*$_3$), 2.03 - 1.11 (m, 10H, -C$_5$*H*$_{10}$-); $^{13}$C-NMR (DMSO-d$_6$): δ = 152.4 (Ar*C*), 144.1 (Ar*C*), 140.1 (Ar*C*), 128.4 (Ar*C*H), 127.4 (Ar*C*H), 126.3 (Ar*C*H), 123.7 (Ar*C*H), 70.6 (carbinol C), 43.3 (-*C*H$_3$), 37.3 (-*C*H$_2$-), 25.2 (-*C*H$_2$-), 21.8 (-*C*H$_2$-); Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.93; H, 6.51; N 8.54.

**2-(1-Cyclohexenyl)-1-(4-methylsulfonylphenyl)-1*H*-imidazole (4)**

A solution of **3** (0.320 g, 0.001 mol) in a mixture of $Ac_2O$ (7.5 mL, 0.079 mol) and AcOH (15 mL) was refluxed for 4 h at 130°C. After cooling to rt the volatiles were evaporated under reduced pressure. The crude product was recrystallized from ethanol to yield 0.209 g (69%) of **4**; mp 140 - 142°C; MS: m/z (rel.

int.) 302 ($M^+$, 81), 301 (100), 287 (11), 273 (39), 133 (27); $^1$H-NMR ($CDCl_3$): δ = 8.14 - 7.94 (m, 2H, Ar*H*), 7.64 - 7.44 (m, 2H, Ar*H*), 7.20 - 7.10 (m, 1H, Ar*H*), 7.09 - 6.97 (m, 1H, Ar*H*), 5.83 - 5.70 (m, 1H, -C=C*H*-), 3.13 (s, 3H, -C*H*$_3$), 2.38 - 2.18 (m, 2H, -C*H*$_2$-), 2.12 - 1.93 (m, 2H, -C*H*$_2$-),1.76 - 1.48 (m, 4H, -C*H*$_2$-); $^{13}$C-NMR ($CDCl_3$): δ = 148.7 (Ar*C*), 143.4 (Ar*C*), 139.5 (Ar*C*), 132.7 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 127.8 (Ar*C*) 125.8 (Ar*C*H / -C=*C*H-), 121.1 (Ar*C*H / -C=*C*H-), 44.4 (-*C*H$_3$), 27.3 (-*C*H$_2$-), 25.4 (-*C*H$_2$-), 22.3 (-*C*H$_2$-) 21.5 (-*C*H$_2$-); Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.78; H, 6.30; N, 9.14.

**2-Chloro-1-(4-methylsulfanylphenyl)-1*H*-imidazole (5)**

To 0.951 g (0.005 mol) of **1** in 100 mL of anhydrous THF at -78°C under argon 3.3 mL (0.0052 mol) of 1.6 M *n*-BuLi in hexane was slowly added. After 15 min 3.551 g (0.015 mol) of hexachloroethane dissolved in 15 mL of anhydrous THF were added. The reaction mixture was stirred 30 min at -78°C and then allowed to warm to rt. Then the reaction mixture was washed with 70 mL of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted twice with 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was subjected to column chromatography with ethyl acetate/*n*-hexane/TEA (60 + 35 + 5). The product was recrystallized from ethanol to yield 1.067 g (95 %) of **5**; mp 80 - 83°C; MS: m/z (rel. int.) 224 / 226 ($M^+$, 100 / 27), 209 (51), 162 (48), 108 (28), 75 (59); $^1$H-NMR ($CDCl_3$): δ = 7.40 - 7.22 (m, 4H, Ar*H*), 7.12 - 7.03 (m, 2H, Ar*H*), 2.53 (s, 3H, -C*H*$_3$); $^{13}$C-NMR ($CDCl_3$): δ = 140.1 (Ar*C*), 133.0 (Ar*C*), 131.8 (Ar*C*), 128.6 (Ar*C*H), 126.6 (Ar*C*H), 125.9 (Ar*C*H), 122.4 (Ar*C*H), 15.4 (-*C*H$_3$); Anal. Calcd for $C_{10}H_9N_2ClS$: C, 53.45; H, 4.04; N, 12.47. Found: C, 53.64; H, 4.24; N, 12.38.

**2-Chloro-1-(4-methylsulfonylphenyl)-1*H*-imidazole (6)**

A solution of Oxone® (1.230 g, 0.002 mol) in 10 mL of water was added to a solution of **5** (0.225 g, 0.001 mol) in 15 mL of methanol. The reaction is slightly exothermic, and the temperature of the reaction was prevented from rising by a surrounding water bath. After being stirred at rt for 1 h, the mixture was treated with dilute ammonium hydroxide (10%, 13 mL). The contents were stirred for 1 h and then the methanol was evaporated. The aqueous phase was extracted four times with 20 mL of ethyl acetate. The combined organic layers were evaporated. The residue was subjected to column chromatography with ethyl acetate/ TEA (95 + 5). The product was recrystallized from ethanol to yield 0.195 g (76%) of **6**; mp 125 - 133°C; MS: m/z (rel. int.) 256 / 258 ($M^+$, 100 / 36), 241 (9), 177 (38), 150 (25), 116 (57); $^1$H-NMR ($CDCl_3$): δ = 8.18 - 8.01 (m, 2H, Ar*H*), 7.70 - 7.54 (m, 2H, Ar*H*), 7.21 - 7.04 (m, 2H, Ar*H*), 3.14 (s, 3H, -C*H*$_3$); $^{13}$C-NMR ($CDCl_3$): δ = 140.6 (Ar*C*), 140.5 (Ar*C*), 131.4 (Ar*C*), 129.4 (Ar*C*H), 128.9 (Ar*C*H), 126.3 (Ar*C*H), 122.1

(Ar*C*H), 44.4 (-*C*$H_3$); Anal. Calcd for $C_{10}H_9N_2O_2ClS$: C, 46.79; H, 3.53; N, 10.91. Found: C, 46.79; H, 3.53; N 10.91.

**1-[1-(4-Methylsulfonylphenyl)-1*H*-2-imidazolyl]piperidine (7)**

A solution of **6** (0.257 g, 0.001 mol) in piperidine (15 mL) was put in an autoclave and heated at 200°C for 36 h. After cooling to rt the piperidine was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic phase was evaporated under reduced pressure and the residue was subjected to column chromatography with ethyl acetate / methanol / TEA (90 + 5 + 5). The crude product was recrystallized from ethanol to yield 0.171 g (56 %) of **7**; mp 164 - 167° C; MS: m/z (rel. int.) 305 ($M^+$, 82), 276 (100), 249 (29), 122 (87), 96 (97); $^1$H-NMR ($CDCl_3$): δ = 8.12 - 7.97 (m, 2H, Ar*H*), 7.89 - 7.77 (m, 2H, Ar*H*), 6.98 - 6.83 (m, 2H, Ar*H*), 3.12 (s, 3H, -C*H*$_3$), 3.07 - 2.91 (m, 4H, -C*H*$_2$-), 1.55 (br s, 6H, -C*H*$_2$-); $^{13}$C-NMR ($CDCl_3$): δ = 152.4 (Ar*C*), 142.9 (Ar*C*), 138.3 (Ar*C*), 128.8 (Ar*C*H), 126.4 (Ar*C*H), 123.4 (Ar*C*H), 117.2 (Ar*C*H), 51.2 (-*C*$H_2$-), 44.4 (-*C*$H_3$), 25.3 (-*C*$H_2$-), 23.8 (-*C*$H_2$-); Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76. Found: C, 59.01; H, 6.51; N, 13.67.

**4-[1-(4-Methylsulfonylphenyl)-1*H*-2-imidazolyl]morpholine (8)**

A solution of **6** (0.257 g, 0.001 mol) in morpholine (15 mL) was put in an autoclave and heated at 200°C for 36 h. After cooling to rt the piperidine was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic phase was evaporated under reduced pressure and the residue was subjected to column chromatography with ethyl acetate / methanol / TEA (90 + 5 + 5). The crude product was recrystallized from ethanol to yield 0.200 g (65 %) of **8**; mp 184 - 191°C; MS: m/z (rel. int.) 307 ($M^+$, 25), 250 (100), 170 (29), 138 (48), 108 (37); $^1$H-NMR ($CDCl_3$): δ = 8.11 - 8.01 (m, 2H, Ar*H*), 7.88 - 7.76 (m, 2H, Ar*H*), 6.99 - 6.87 (m, 2H, Ar*H*), 3.79 - 3.65 (m, 4H, -C*H*$_2$-), 3.12 (s, 3H, -C*H*$_3$), 3.09 - 2.99 (m, 4H, -C*H*$_2$-); $^{13}$C-NMR ($CDCl_3$): δ = 151.0 (Ar*C*), 142.4 (Ar*C*), 138.8 (Ar*C*), 129.0 (Ar*C*H), 126.6 (Ar*C*H), 123.8 (Ar*C*H), 117.9 (Ar*C*H), 66.3 (-*C*$H_2$-), 50.2 (-*C*$H_2$-), 44.4 (-*C*$H_3$); Anal. Calcd for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.57; N, 13.67. Found: C, 54.66; H, 5.66; N, 13.53.

**2-Iodo-1-(4-methylsulfanylphenyl)-1*H*-imidazole (9)**

To 0.381 g (0.002 mol) of **1** in 30 mL of anhydrous THF at -78°C under argon 1.4 mL (0.0022 mol) of 1.6 M *n*-BuLi in hexane was slowly added. After 15 min 0.508 g (0.002 mol) $I_2$ dissolved in 15 mL of dry THF was added. The reaction mixture was stirred 30 min at -78°C and then allowed to warm to rt. Then the reaction mixture was washed with 20 mL of a saturated aqueous solution of ammonium chloride. The

aqueous phase was extracted twice with 50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was subjected to column chromatography with ethyl acetate/ TEA (95 + 5). The product was recrystallized from ethanol to yield 0.500 g (79 %) of **9**; mp 122 - 143°C; mp 83 - 85°C; MS: m/z (rel. int.) 316 ($M^+$, 100), 301 (3), 189 (4), 174 (15), 142 (78); $^1$H-NMR ($CDCl_3$): δ = 7.40 - 7.12 (m, 6H, Ar*H*), 2.54 (s, 3H, -C*H*$_3$); $^{13}$C-NMR ($CDCl_3$): δ = 140.4 (Ar*C*), 135.0 (Ar*C*), 132.8 (Ar*C*H), 127.0 (Ar*C*H), 126.4 (Ar*C*H), 124.7 (Ar*C*H), 90.5 (Ar*C*), 15.4 (-*C*H$_3$); Anal. Calcd for $C_{10}H_9N_2IS$: C, 37.99; H, 2.87; N, 8.86. Found: C, 38.21; H, 3.13; N, 8.78.

**2-(3-Methoxyphenyl)-1-(4-methylsulfanylphenyl)-1*H*-imidazole (11)**

A mixture of **9** (0.316 g, 0.001 mol), 3-methoxyphenylboronic acid (0.182 g, 0.0012 mol), tetrakis(triphenylphosphine)palladium(0) (0.116 g, 0.0001 mol), toluene (18 mL), methanol (3.6 mL) and 2M potassium carbonate (1 mL) was refluxed for 16 h under argon atmosphere. The reaction mixture was cooled to rt and washed with 10 mL of a saturated aqueous solution of ammonium chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was subjected to column chromatography with ethyl acetate/TEA (95 + 5). The product was recrystallized from ethanol to give 0.231 g (78%) of **11**; mp 103 - 110°C; MS: m/z (rel. int.) 296 ($M^+$, 100), 280 (21), 222 (14), 147 (43), 77 (23); $^1$H-NMR ($CDCl_3$): δ = 7.32 - 7.08 (m, 8H, Ar*H*), 6.93 - 6.79 (m, 2H, Ar*H*), 3.71 (s, 3H, -OC*H*$_3$), 2.50 (s, 3H, -SC*H*$_3$); $^{13}$C-NMR ($CDCl_3$): δ = 159.2 (Ar*C*), 146.4 (Ar*C*), 139.1 (Ar*C*), 135.4 (Ar*C*), 131.4 (Ar*C*), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 126.7 (Ar*C*H), 126.1 (Ar*C*H), 122.9 (Ar*C*H), 120.9 (Ar*C*H), 114.9 (Ar*C*H), 113.2 (Ar*C*H), 55.1 (-O*C*H$_3$), 15.5 (-S*C*H$_3$); Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.65; H, 5.69; N 9.25.

**2-(3-Methoxyphenyl)-1-(4-methylsulfonylphenyl)-1*H*-imidazole (12)**

A solution of Oxone® (1.230 g, 0.002 mol) in 10 mL of water was added to a solution of **11** (0.296 g, 0.001 mol) in 15 mL of methanol. The reaction is slightly exothermic, and the temperature of the reaction was prevented from rising by a surrounding water bath. After being stirred at rt for 1 h, the mixture was treated with dilute ammonium hydroxide (10%, 13 mL). The contents were stirred for 1 h and then the methanol was evaporated. The aqueous phase was extracted four times with 20 mL of ethyl acetate. The combined organic layers were evaporated. The residue was subjected to column chromatography with ethyl acetate / methanol / TEA (90 + 5 + 5). The product was recrystallized from ethanol (70%) to yield 0.151 g (46%) of **12**; mp 146 - 150°C; MS: m/z (rel. int.) 328 ($M^+$, 100), 312 (6), 248 (42), 89 (16), 63 (14); $^1$H-NMR ($CDCl_3$): δ = 8.05 - 7.92 (m, 2H, Ar*H*), 7.48 - 7.37 (m, 2H, Ar*H*), 7.34 - 6.73 (m, 6H, Ar*H*), 3.75 (s, 3H,

-OC*H*$_3$), 3.10 (s, 3H, -SC*H*$_3$); $^{13}$C-NMR ($CDCl_3$): δ = 159.5 (Ar*C*), 146.7 (Ar*C*), 142.9 (Ar*C*), 139.7 (Ar*C*), 130.8 (Ar*C*), 129.8 (Ar*C*H), 129.4 (Ar*C*H), 128.8 (Ar*C*H), 126.3 (Ar*C*H), 122.3 (Ar*C*H), 121.1 (Ar*C*H), 115.1 (Ar*C*H), 113.8 (Ar*C*H), 55.2 (-O*C*$H_3$), 44.4 (-$SO_2$*C*$H_3$); Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.05; H, 4.74; N, 8.49.

## REFERENCES


1. I. K. Khanna, R. M. Weier, Y. Yu, X. Xu, F. J. Koszyk, P. W. Collins, C. M. Koboldt, A. W. Veenhuizen, W. E. Perkins, J. J. Casler, J. L. Masferrer, Y. Y. Zhang, S. A. Gregory, K. Seibert, and P. C. Isakson, *J. Med. Chem.*,1997, **40**, 1634.
2. I. K. Khanna, Y. Yu, R. M. Huff, R. M. Weier, X. Xu, F. J. Koszyk, P. W. Collins, J. N. Cogburn, P. C. Isakson, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, K. Seibert, A. W. Veenhuizen, J. Yuan, D. Yang, and Y. Y. Zhang, *J. Med. Chem.*, 2000, **43**, 3168.
3. P. Hölscher, H. Rehwinkel, G. Burton, G. Philipps, and J. Parkinson, *Patent Publication DE 19541146A1*, 1997.
4. D. Pettersen, P. Diner, M. Amedjkouh, and P. Ahlberg, *Tetrahedron: Asymmetry*, 2004, **15**, 1607.
5. M. Amedjkouh, D. Pettersen, S. O. Nilsson Lill, O. Davidsson, and P. Ahlberg, *Chem. Eur. J.*, 2001, **7**, 4368.
6. M. Amedjkouh, *Tetrahedron: Asymmetry*, 1999, **15**, 573.
7. F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi, and S. Viel, *J. Org. Chem.*, 2005, **70**, 3997.