Synthesis of Novel 2,3-Dihydroimidazo[2,1-*b*][1,3]oxazoles Through Intramolecular Nucleophilic *ipso*-Substitution in 2-Alkylsulfonylimidazoles

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Received 18 July 2002

Abstract: Readily available 2-(benzylsulfanyl)imidazoles **6**, were studied as potential precursors toward the synthesis of novel diversely substituted 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles. Thus, the reaction between enolates derived from **6** and different electrophiles as well as the addition of Grignard reagents to the carbonyl group in **6** were explored. The formation of the fused imidazoxazoles **20** under mild conditions was successfully accomplished taking advantage of the key role played by the 2-alkylsulfonyl moiety in **19** as an efficient leaving group in intramolecular nucleophilic *ipso*-substitution reactions.

Key words: alkylsulfonyl groups, leaving groups, intramolecular nucleophilic *ipso*-substitution, imidazoles, 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles

Heteroaromatic nucleophilic addition-elimination reactions are common in many electron-deficient heterocycles.[1] However, analogous reactions with electron-rich heterocycles,[2–4] and more precisely, with electron-rich imidazoles and condensed imidazoles are very rare.[5–7] On the other hand, alkyl- or arylsulfinyl or -sulfonyl substituents as leaving groups in electron-deficient heteroaromatic systems have been reported to have reactivity equivalent to, or greater than, that of a chloro group, and many examples concerning the reactivity of electron deficient azines bearing alkylsulfinyl- and sulfonyl groups, with a wide variety of simple nucleophiles have been reported.[8,9] Analogous transformations using sulfinyl or sulfonyl substituents as efficient leaving groups on imidazoles are, however, rather uncommon, and previous to our own contribution in this field,[10] only strongly activated imidazoles bearing electron-withdrawing groups were reported to undergo *ipso*-substitution reactions with different nucleophiles under vigorous conditions.[11]

During the last few years, we have been engaged in a research program focused on the development of efficient methodologies that could be readily adapted for the combinatorial and/or parallel synthesis in solution or on solid supports of relevant core structures.[12–17] Imidazoles are important pharmacophores in different therapeutic areas, and many biologically active compounds incorporate this moiety into their structures. Particularly interesting are fused [1,2-*a*]imidazoles, which have been reported to have anti-ulcer, anti-depressant, anti-bacterial and T_xA_2 synthase inhibitory activities.[18–21] Successful synthetic approaches toward the synthesis of fused [1,2-*a*]imidazoles using intramolecular radical *ipso*-substitution reactions at the C-2 position have been recently disclosed,[22,23] and although many efforts have been directed to the synthesis of, for instance, imidazo[1,2-*a*]pyridines,[24] very little has been reported about imidazo[2,1-*b*][1,3]oxazoles.

In a recent report,[10] we did show for the first time that alkylsulfonyl substituents in electron-rich imidazoles are capable of behaving as efficient leaving groups in intramolecular nucleophilic *ipso*-substitution reactions. These findings were used to open an effective and convenient synthetic route toward a novel class of fused [2,1-*b*]imidazoles.

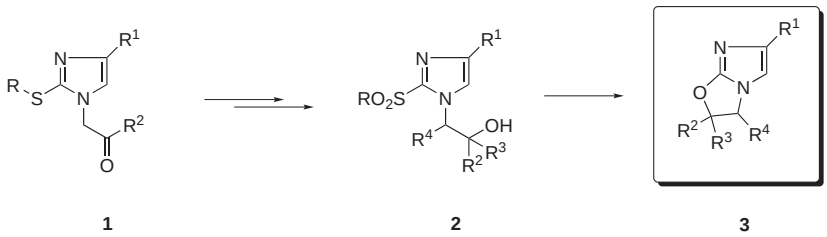
In continuation of our previous work in this field, an investigation was undertaken aimed to expand the scope of this methodology and its potential applications toward the synthesis of more elaborate heterocyclic scaffolds based on the imidazole nucleus. The results of this investigation are now disclosed herein.

Our objective in this study was to develop a synthetic protocol, which starting from N-alkylated 2-alkylthioimidazoles of type **1**, would effectively afford a variety of molecularly diverse dihydroimidazo[2,1-*b*][1,3]oxazoles of type **3** with different substitution patterns. The methodology would take advantage from the presence of the enolisable carbonyl group in **1**. Suitable synthetic manipulations (e.g. aldol condensations, alkylation followed by reduction of the carbonyl or additions of organometallics) followed by oxidation of the thioether moiety to the corresponding sulfone would allow the formation of compounds of type **2**. Finally, intramolecular nucleophilic *ipso*-substitution reaction through the alkoxy group in **2** would afford the required imidazoxazoles **3** (Figure 1).

Thus, when thiuronium salt **4** (easily available from thiourea and benzyl bromide in refluxing EtOH) was allowed to react in MeCN at room temperature with 2 equivalents of α-halo ketones **5a**–**c** in the presence of a suitable base such as diisopropylethylamine (DIPEA), the corresponding N-alkylated 2-(benzylsulfanyl)imidazoles **6a**–**c** were isolated in fair to good yields (50–78%) (Scheme 1, Tables 1 and 2).

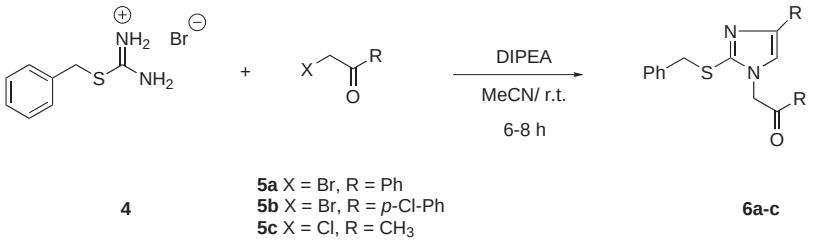
Synthesis 2002, No. 18, Print: 19 12 2002.
Art Id.1437-210X,E;2002,0,18,2691,2700,ftx,en;P03902SS.pdf.

ISSN 0039-7881



1 **2** **3**

Figure 1 Synthetic Scheme leading to **3**



4

5a X = Br, R = Ph
5b X = Br, R = *p*-Cl-Ph
5c X = Cl, R = CH_3

6a-c

Scheme 1

Table 1 2-(Benzylsulfanyl)imidazoles **6a–c** Prepared

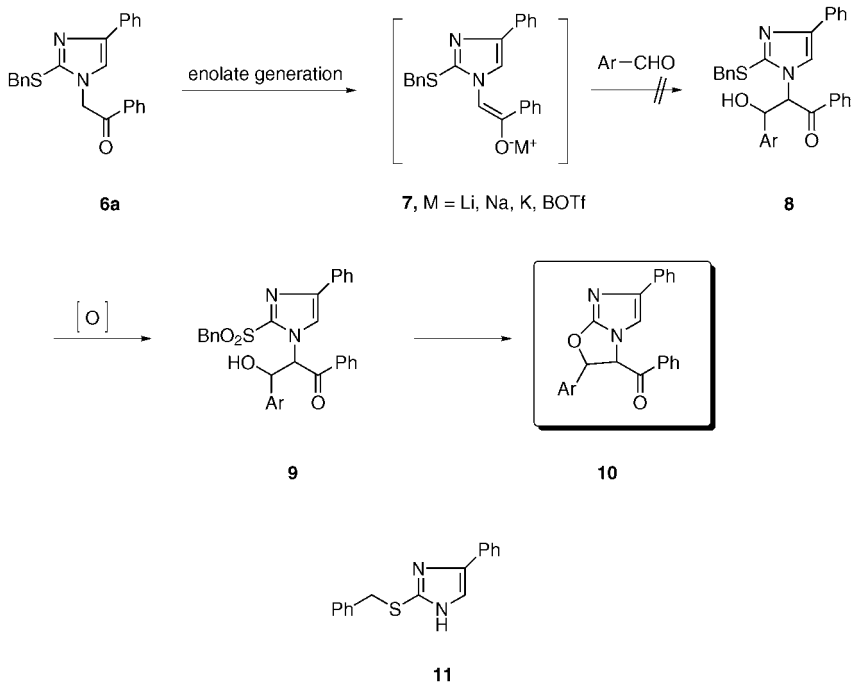
Product[a]	R	Yield (%)	mp (°C)
6a	Ph	78	142–143
6b	*p*-ClC_6H_4	60	176–177
6c	Me	50	207–208

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.28, N ±0.27, S ±0.29.

Consistent with our initial goal, we first attempted to generate the corresponding enolate derivatives from **6a** and its subsequent condensation with different aromatic aldehydes to afford key hydroxy derivatives **8**, which in turn would be the adequate precursors toward fused imidazoxazoles **10**. However, this type of manipulation proved to be rather unsuccessful under a set of different reaction conditions. Thus, the reaction between Li enolates (generated from BuLi, *t*-BuLi or LiHMDS), Na or K enolates (generated from NaHMDS or KHMDS, respectively) or boron enolates (generated from Bu_2BOTf and Et_3N or DIPEA), and aromatic aldehydes **7** in several combinations of temperatures (ranging from –100 °C to 0 °C) and solvents (THF, THF/HMPTA and CH_2Cl_2) did not yield the expected aldol products **8**, and only unreacted starting material **6a** and/or the formation of mixtures of decomposition products was observed. As decomposition product we could only detect the formation of **11** in varying amounts (Scheme 2).

Table 2 MS, IR and NMR Data of Imidazoles **6a–c**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
6a	386 ($[M + 2]^+$, 28), 385 ($[M + 1]^+$, 100), 384 ($[M]^{\cdot+}$, 12), 267 (21)	3055, 3051, 2926, 1696, 1598, 1491, 1450, 1422, 1346, 1228, 1074, 983, 913, 752, 691	4.19 (s, 2 H), 5.00 (s, 2 H), 7.20–7.90 (m, 16 H)	40.95, 52.0 (2 t, 2 CH_2), 118.5 (d, CH_{imid}), 124.9, 126.9, 127.4, 127.9, 128.5, 128.6, 128.8, 128.9 (8d, 14 CH_{arom}), 133.7 (s, C_{arom}), 134.15 (d, CH_{arom}), 137.97, 140.78, 142.76 (3 s, 4 C_{arom}) 191.4 (s, C=O)
6b	455 ($[M + 2]^+$, 75), 454 ($[M + 1]^+$, 39), 453 ($[M]^{\cdot+}$, 100), 457 (18), 456 (18), 452 (23)	3086, 3030, 2928, 1698, 1587, 1485, 1435, 1399, 1339, 1210, 1206, 1087, 990, 832, 766, 699, 668	4,26 (s, 2 H), 5,56 (s, 2 H), 7.25–8.05 (m, 14 H)	38.6, 52.7 (2 t, 2 CH_2), 120,1 (d, CH_{imid}), 125.8, 127.3, 128.4, 128.6, 128.8, 129.14, 129.95 (7 d, 13 CH_{arom}) 130.8, 132.75, 132.8, 137.5, 139.2, 139.5, 141.4 (7 s, 7 C_{arom}), 192.3 (s, C=O)
6c	262 ($[M + 2]^+$, 16), 261 ($[M + 1]^+$, 100), 260 ($[M]^{\cdot+}$, 12), 205 (14), 171 (12)	3084, 3026, 2921, 1719, 1562, 1493, 1429, 1360, 1171, 1003, 918, 805, 770, 707	2.0 (s, 3 H), 2.27 (s, 3 H), 4.11 (s, 2 H), 4.31 (s, 2 H), 6.6 (s, 1 H), 7.1–7.3 (m, 5 H)	13.8, 26.7 (2 q, 2 CH_3), 40.6, 55.0 (2 t, 2 CH_2), 118.7 (d, CH_{imid}), 127.4, 128.5, 128.6 (3 d, 5 CH_{arom}), 137.6, 139.1, 139.4 (3 s, 3 C_{arom}), 201.2 (s, C=O)

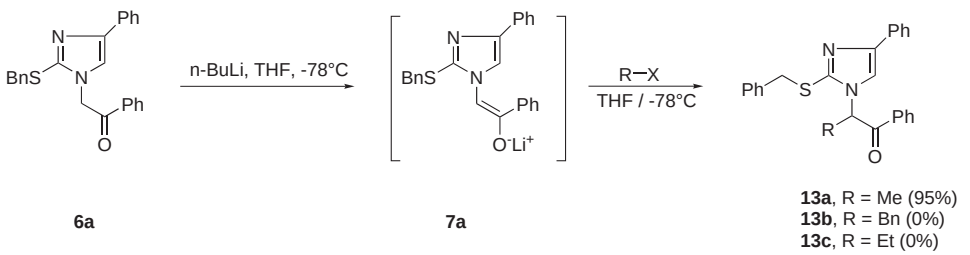


Scheme 2

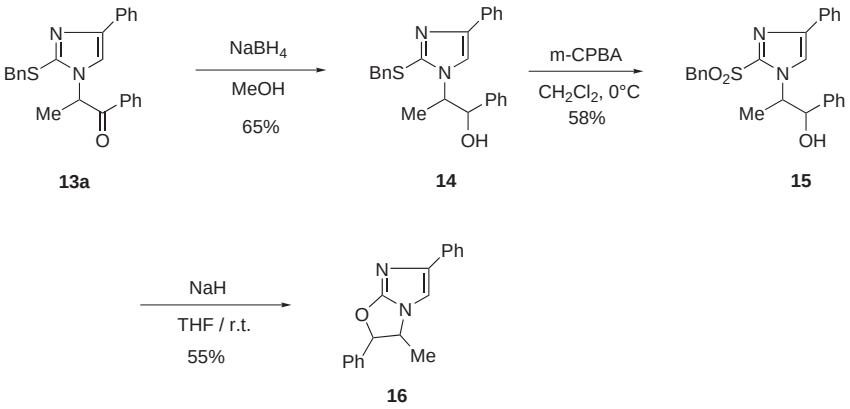
These discouraging results might be the consequence of a lack of reactivity of enolate derivatives **7** towards electrophiles (in this case aldehydes), and indeed this seemed to be the case, because when the lithium enolate derived from **6a** was allowed to react with the strong alkylating agent MeI in THF at –78 °C, the corresponding alkylated compound **13a** was obtained in excellent yield (95%). However, analogous reaction under identical conditions with benzyl bromide or with less reactive ethyl iodide proved to be totally unsuccessful, and again only starting material **6a** and decomposition product **11** could be recovered from the corresponding reactions mixtures (Scheme 3).

Although these results were not satisfactory, confirming therefore the lack of reactivity of enolates of type **7**, we could, however, obtain compound **13a** in 95% yield. In order, to check the feasibility of our initial plans for the synthesis of fused imidazoxazoles, we proceeded further by reducing the carbonyl group with 2.2 equivalents of $NaBH_4$ in MeOH. This reduction afforded the hydroxy derivative **14** in 65% isolated yield. Oxidation of **14** with 2.5 equivalents of *m*-CPBA, gave the sulfone derivative **15** in 58% yield. Subsequent treatment of **15** with NaH in THF at room temperature efficiently promoted the formation of targeted 2,3-dihydroimidazo[2,1-*b*][1,3]oxazole derivative **16** through the expected intramolecular nucleophilic *ipso*-substitution reaction (Scheme 4).

Finally, having established that the intramolecular nucleophilic displacement of the sulfone group in derivatives of type **2** (Figure 1) is an efficient approach toward the synthesis of 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles as exemplified by the synthesis of **16** (Scheme 4), we explored the addition of Grignard reagents to the carbonyl group in imidazole derivatives **6a**–**c** as well. Thus, when **6a**–**c** were prompted to react with organomagnesium derivatives **17a**,**b** in refluxing THF, the corresponding tertiary alcohol derivatives **18a**–**f** were obtained in moderate to good yields (35–70%). The analogous *ipso*-substitution reaction carried out at room temperature did not produce any result. Subsequent oxidation of the thioether moiety in **18a**–**d** with an excess of *m*-CPBA in CH_2Cl_2 gave the corresponding sulfones **19a**–**d** in good yields (50–60%). Treatment of **19a**–**c** with NaH in THF under mild conditions, afforded through an intramolecular *ipso*-substitution reaction with displacement of the benzylsulfone moiety, the required 2,2-disubstituted 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles **20a**–**c** in good yields (60–70%) (Scheme 5, Tables 3– 8).

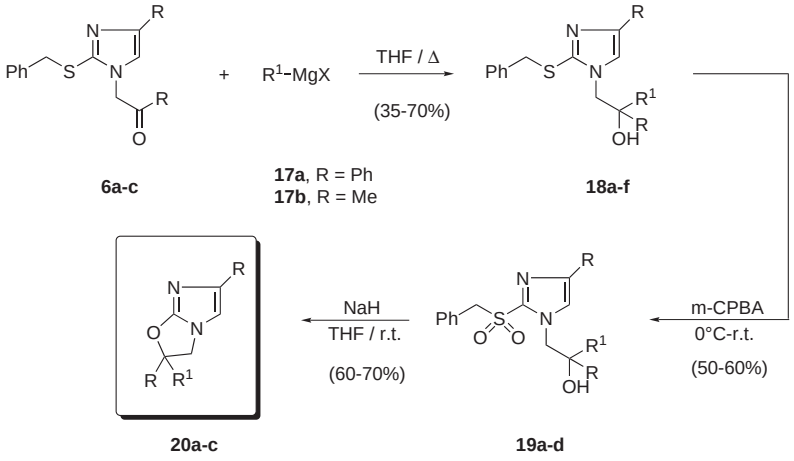


Scheme 3



13a **14** **15** **16**

Scheme 4



6a-c **17a**, R = Ph; **17b**, R = Me **18a-f** **19a-d** **20a-c**

Scheme 5

Table 3 Compounds **18a–f** Prepared by Grignard Additions and the Reduced Product **22**

Entry	Product[a]	R	R^1	Yield (%)	mp (°C)
1	**18a**	Ph	Ph	53	146–147
2	**18b**	Ph	Me	60	100–101
3	**18c**	*p*-ClC_6H_4	Ph	44	162–163
4	**18d**	*p*-ClC_6H_4	Me	70	150–151
5	**18e**	Me	Ph	40	pale yellow oil
6	**18f**	Me	Me	35	pale yellow oil
7	**22**	–	–	72	116–117

Table 4 MS, IR and NMR Data of Imidazoles **18a–f** and **22**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
18a	464 ([M + 2]$^+$, 33), 463 ([M + 1]$^+$, 100), 462 ([M]$^{\cdot+}$, 25), 280 (12), 247 (14), 190 (29), 189 (16), 183 (15), 154 (16), 136 (17)	3239, 3067, 2927, 2853, 1603, 1545, 1491, 1451, 1337, 1231, 1058, 758	2.68 (s, 1 H, OH), 4.13, 4.41 (s, CH_2), 6.90 (s, 1 H, CH_{imid}), 7.17–7.74 (m, 20 H)	40.6, 55.2 (2 t, 2 CH_2), 77.64 (s, C), 118.3 (d, CH_{imid}), 124.7, 126.2, 126.6, 127.3, 127.7, 128.3, 128.4, 128.5, 128.8 (9 d, 20 CH_{arom}), 133.9, 138.0, 141.5, 141.9, 143.6 (5 s, 6 C_{arom})
18b	402 ([M + 2]$^+$, 27), 401 ([M + 1]$^+$, 100), 400 ([M]$^{\cdot+}$, 31), 190 (22)	3371, 3153, 3059, 2983, 2929, 1487, 1384, 1197, 1114, 1070, 952, 754, 701	1.48 (s, 3 H), 2.23 (s, 1 H, OH), 3.8 (d, 1 H, *J* = 14.2), 3.99 (d, 1 H, *J* = 14.2), 4.20 (d, 1 H, *J* = 12.6), 4.27 (d, 1 H, *J* = 12.6), 7.05–7.45 (m, 14 H), 7.80–7.85 (m, 2 H)	26.7 (q, CH_3), 40.3, 56.8 (2 t, 2 CH_2), 74.5 (s, C), 118.3 (d, CH_{imid}), 127.7, 124.9, 126.7, 127.3, 127.6, 128.5, 128.6, 128.8 (8 d, 15 CH_{arom}), 133.9, 137.7, 141.8, 144.4 (4 s, 5 C_{arom})
18c	533 ([M + 2]$^+$, 69), 532 ([M + 1]$^+$, 32), 531 ([M]$^{\cdot+}$, 100), 307 (45), 282 (31), 281 (27), 179 (16), 178 (22), 166 (37), 165 (45)	3402, 3085, 1600, 1488, 1448, 1399, 1196, 1092, 1013, 951, 831, 766	3.48 (s, 1 H), 4.21 (s, 1 H), 4.63 (m, 2 H), 6.48 (s, 1 H), 7.42–7.81 (m, 18 H)	38.6, 54.6 (2 t, 2 CH_2), 76.2 (s, C), 119.3 (d, CH_{imid}), 125.6, 126.2, 127.1, 127.2, 127.7, 128.0, 128.2, 128.3, 128.5, 128.7 (10d, 18 CH_{arom}), 130.6, 131.7, 132.9, 137.8, 138.6, 142.1, 143.5, 144.4 (8 s, 8 C_{arom})
18d	471 ([M + 2]$^+$, 69), 470 ([M + 1]$^+$, 32), 469 ([M]$^{\cdot+}$, 100), 190 (35), 312 (15)	3316, 2929, 1663, 1599, 1551, 1490, 1448, 1397, 1193, 1050, 1011, 950, 833, 767, 699	1.46 (s, 3 H), 2.2 (s, 1 H, OH), 3.75 (d, 1 H, *J* = 14.2), 3.95 (d, 1 H, *J* = 14.4), 4.22 (d, 1 H, *J* = 13.6), 4.25 (d, 1 H, *J* = 13.6), 7.15–7.40 (m, 11 H), 7.7–7.75 (m, 2 H)	26.7 (q, CH_3), 40.2, 56.6 (2 t, 2 CH_2), 74.2 (s, C), 118.4 (d, CH_{imid}), 126.0, 126.5, 127.5, 128.5, 128.7, 128.8 (6 d, 13 CH_{arom}), 132.3, 133.6, 137.6, 140.8, 142.2, 142.8 (6 s, 7 C_{arom})
18e	278 ([M + 2]$^+$, 45), 277 ([M + 1]$^+$, 100), 276 ([M]$^{\cdot+}$, 37), 217 (25), 94 (17)	3249, 2971, 2931, 16565, 1411, 1291, 1191, 914, 767	1.10 (s, 6 H), 2.26 (s, 3 H), 3.2 (s, 1 H, OH), 3.57 (s, 2 H), 4.15 (s, 2 H), 6.83 (s, 1 H), 7.10-7.25 (m, 5 H)	13.7 (q, 2 CH_3), 27.0 (q, CH_3), 40.5, 56.0 (2 t, 2 CH_2), 70.7 (s, C), 119.1 (d, CH_{imid}), 127.3, 128.4, 128.7 (3 d, 5 CH_{arom}), 137.5, 138.4, 139.8 (3s, 3 C_{arom})
18f	340 ([M + 2]$^+$, 22), 339 ([M + 1]$^+$, 100), 338 ([M]$^{\cdot+}$, 18), 341 (7)	3157, 3028, 2976, 2931, 1493, 1450, 1410, 1291, 1146, 1070, 763	1.44 (s, 3 H), 2.1 (s, 1 H, OH), 2.24 (s, 3 H), 3.74 (d, 1 H, *J* = 14.4), 3.94 (d, 1 H, *J* = 14.4), 4.14 (d, 1 H, *J* = 1.2), 4.17 (d, 1 H, *J* = 1.6), 6.65 (s, 1 H), 7.18–7.4 (m, 14 H)	13.82, 26.76 (q, CH_3), 40.44, 56.53 (t, CH_2), 74.47 (s, C), 119.13 (d, CH_{imid}), 124.89, 125.07, 127.32, 128.38, 128.45, 128.8 (d, CH_{arom}), 137.59, 138.44, 140.17, 144.64 (q, C_{arom})
22	388 ([M + 2]$^+$, 6), 387 ([M + 1]$^+$, 24), 386 ([M]$^+$, 8), 293 (24), 279 (10), 266 (21), 265 (100), 264 (23), 247 (16), 145 (18), 121 (12), 105 (13), 93 (46), 92 (25), 91 (31), 79 (15), 63 (11), 55 (17)	3438, 3063, 1600, 1492, 1454, 1412, 1190, 1061, 751, 696	3.74 (dd, 1 H, *J* = 14.0, 8.8), 3.9 (dd, 1 H, *J* = 14.0, 3.3), 4.15 (s, 2 H), 4.8 (s, 1 H, OH), 4.96 (dd, 1 H, *J* = 8.8, 3.3), 7.1–7.65 (m, 16 H)	40.85 (t, CH_2), 54.5 (t, CH_2), 73.0 (d, CH), 118.6, 124.6, 125.8, 126.6, 127.3, 127.9, 128.4, 128.45, 128.5, 128.75 (10 d, 10 CH_{arom}), 133.45, 137.7, 140.2, 141.05,141.6 (5 s, 5 C_{arom})

Table 5 Imidazole Sulfone Derivatives **19a–d** and **23** Prepared

Entry	Product[a]	R	R^1	Yield (%)	mp (°C)
1	**19a**	Ph	Ph	60	172–173
2	**19b**	Ph	Me	52	127–128
3	**19c**	*p*-ClC_6H_4	Ph	58	198–199
4	**19d**	*p*-ClC_6H_4	Me	50	165–166
5	**23**	-	-	68	134–135

[a] Satisfactory microanalyses obtained: C ±0.21, H ±0.19, N ±0.27, S ±0.29.

Table 6 MS, IR and NMR Data of Sulfonyl Imidazoles **19a–d** and **23**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
19a	496 ([M + 2]$^+$, 31), 495 ([M + 1]$^+$, 100), ([M]$^+$, 30), 154 (57), 136 (56), 137 (34), 248 (30), 247 (28), 183 (21), 138 (20), 157 (18), 165 (17), 155 (15), 477 (15)	3563, 3500, 3059, 3033, 2972, 2910, 1542, 1450, 1388, 1300, 1228, 1195, 1151, 1110, 1057, 918, 863, 780, 759, 696, 636	3.45 (s, 1 H, OH), 4.55 (s, 2 H), 4.72 (s, 2 H), 6.23 (s, 1 H), 7.20–7.60 (m, 20 H)	56.4, 62.1 (2 t, 2 CH_2), 76.4 (s, C), 120.9 (d, CH_{imid}), 125.1, 126.2 (2 d, 2 CH_{arom}), 126.8, 127.6 (2 s, 2 C_{arom}), 127.8, 128.4, 128.5, 128.7, 129.2, 131.2 (6 d, 10 CH_{arom}), 132.41, 141.15, 141.18, 143.62 (4 s, 4 C_{arom})
19b	434 ([M + 2]$^+$, 28), 433 ([M + 1]$^+$, 100), 432 ([M]$^+$, 10), 247 (25), 248 (21), 279 (18), 136 (16), 145 (15)	3251, 3059, 2983, 2939, 1487, 1384, 1305, 1197, 1114, 1100, 1070, 952, 754, 701	1.48 (s, 3 H), 2.55 (s, 1 H, OH), 3.83 (d, 1 H, *J* = 14.4), 4.36 (d, 1 H, *J* = 14.2), 4.67 (d, 1 H, *J* = 13.6), 4.77 (d, 1 H, *J* = 13.6), 6.98 (s, 1 H), 7.18–7.8 (m, 15 H)	26.9 (q, CH_3), 57.4, 62.0 (2 t, 2 CH_2), 73.8 (s, C), 121.2 (d, CH_{imid}), 124.9, 125.2 (2 d, 2 CH_{arom}), 126.9 (s, C_{arom}), 127.6, 127.7, 128.4, 128.6, 128.7, 129.1, 131.2 (7 d, 7 CH_{arom}), 132.53 , 141.03, 141.57, 144.05 (4 s, 4 C_{arom})
19c	565 ([M + 2]$^+$, 69), 564 ([M + 1]$^+$, 32), 563 ([M]$^+$, 100), 165 (45), 307 (45), 166 (37), 167 (33), 282 (31), 289 (30), 281 (27), 217 (24), 178 (22), 191 (20), 164 (18), 179 (16), 391 (16), 168 (16), 283 (15), 163 (15)	3483, 3033, 2967, 1489, 1325, 1100, 1093,1013, 946, 831, 788, 699	4.78 (s, 2 H), 4.93 (d, 1 H, *J* = 14.4), 5.08 (d, 1 H, *J* = 13.8), 6.70 (s, 1 H), 7.35–8.05 (m, 18 H)	54.8, 61.3 (2 t, 2 CH_2), 76.5 (s, C), 121.8 (d, CH_{imid}), 126.2, 126.3 (2d, 2 CH_{arom}), 127.3 (s, C_{arom}), 127.4, 127.8, 128.1, 128.2, 128.3, 128.7, 130.5, 131.3, 131.9, 132.0, (10d, 16 CH_{arom}), 132.6, 138.6, 141.4, 142.9, 143.8 (5 s, 7 C_{arom})
19d	503 ([M + 2]$^+$, 69), 502 ([M + 1]$^+$, 45), 501 ([M]$^+$, 100), 331 (23), 155 (12)	3543, 2982, 1484, 1379, 1313, 1250, 1197, 1150, 1013, 834, 783, 699, 550	1.39 (s, 3 H), 3.47 (s, 1 H, OH), 4.14 (d, 1 H, *J* = 13.6), 4.5 (d, 1 H, *J* = 14), 4.9 (d, 1 H, *J* = 12.6), 5.04 (d, 1 H, *J* = 13.6), 7.35–7.95 (m, 14 H)	25.8 (q, CH_3), 56.6, 61.3 (2 t, 2 CH_2), 72.6 (s, C), 122.7 (d, CH_{imid}), 126.4, 127.0 (2 s, 2 C_{arom}), 127.4, 127.9, 128.0, 128.3, 128.6, 128.7, 129.2, 129.8, 130.5 (9 d, 13 CH_{arom}), 131.2, 131.5, 131.7, 131.9, 132.6, 133.3 (6 s, 7 C_{arom})
23	420 ([M + 2]$^+$, 28), 419 ([M + 1]$^+$, 100), 401 (10), 293 (11), 256 (45), 264 (10), 93 (16), 91 (16), 65 (22)	3448, 3149, 3070, 3050, 3030, 2924, 1596, 1496, 1455, 1412, 1376, 1329, 1256, 1236, 1152, 1113, 1089, 1061, 962, 906, 786, 762, 696	2.5 (s, 1 H, OH),3.73 (dd, 1 H, *J* = 14, 8.8), 4.2 (dd, 1 H, *J* = 14.0, 3), 4.55 (dd, 1 H, *J* = 8.8, 3), 4.67, 4.70 (2 d, 2 H, *J* = 14), 7.15–7.85 (m, 16 H)	54.85, 62.1 (2 t, 2 CH_2), 73.25 (d, CH), 121.75, 125.3, 126.6 (3 d, 3 CH_{arom}), 127.25 (s, C_{arom}), 127.8, 128.2, 128.6, 128.65, 128.7, 129.05, 131.2 (7 d, 13 CH_{arom}), 132.4, 138.8, 140.3, 141.74 (4 s, 4 C_{arom})

Table 7 Imidazo[2,1-*b*][1,3]oxazoles **20a–c** and **24** Prepared

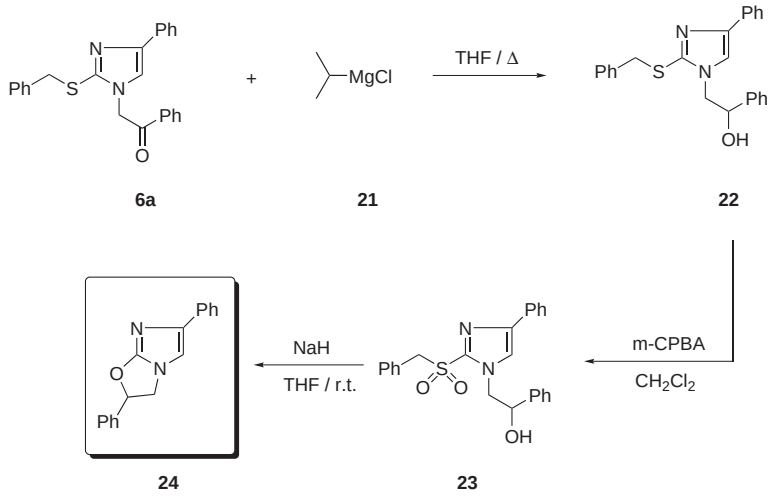
Entry	Product[a]	R	R^1	Yield (%)	mp (°C)
1	**20a**	Ph	Me	60	128–129
2	**20b**	p-ClC_6H_4	Ph	60	278–280
3	**20c**	*p*-ClC_6H_4	Me	70	177–178
4	**24**	–	–	78	192–193 (dec.)

[a] Satisfactory microanalyses obtained: C ±0.17, H ±0.23, N ±0.27.

Although this last synthetic sequence was in general rather satisfactory, the carbonyl group in **6a–c** showed to be not too reactive as deduced from the experimental conditions needed to drive the Grignard addition reactions to completion. Furthermore, this carbonyl group was found to be very sensitive toward steric effects. Indeed, when **6a** was allowed to react with sterically demanding *i*-PrMgCl (**21**) as the Grignard reagent, no addition product of the isopropyl group could be detected. Instead, the addition of hydride took place giving the reduced product **22** in 72% yield. Under analogous conditions as before, identical synthetic sequence produced 2,6-diphenyl-2,3-dihydroimidazo[2,1-*b*]oxazole (**24**) through intramolecular cyclisation of sulfone **23** (Scheme 6).

Table 8 MS, IR and NMR Data of Imidazo[2,1-*b*][1,3]oxazoles **20a–c** and **24**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
20a	277 ($[M + 1]^+$, 100), 276 ($[M]^{\cdot+}$, 32), 173 (10), 160 (11), 155 (13), 154 (51), 138 (17), 137 (33), 136 (58)	3133, 3063, 3028, 2973, 1579, 1497, 1380, 1267, 1185, 1063, 911, 766, 756, 701	1.98 (s, 3 H, CH_3), 4.43 (d, 1 H, *J* = 10.2), 4.54 (d, 1 H, *J* = 10), 7.25–7.75 (m, 11 H)	27.75 (q, CH_3), 56.0 (t, CH_2), 94.05 (s, C), 107.8 (d, CH_{imid}), 123.7, 124.25, 125.95, 128.05, 128.35, 128.6 (6 d, 10 CH_{arom}), 134.85, 140.65, 143.25, 158.25 (4 s, 4 C_{arom})
20b	409 ($[M + 2]^+$, 67), 408 ($[M + 1]^+$, 85), 407 ($[M]^{\cdot+}$, 100), 307 (61), 289 (35), 194 (20), 178 (39), 166 (51), 165 (55)	3150, 3059, 2926, 1572, 1500, 1374, 1178, 1093, 960, 818, 698	5.02 (s, 2 H), 7.45–7.80 (m, 14 H)	55.45 (t, CH_2), 96.21 (s, C), 108.8 (d, CH_{imid}), 125.4, 127.45, 128.35, 128.5, 128.65, 128.75 (6 d, 13 CH_{arom}), 130.31, 133.17, 133.52, 139.75, 140.80, 141.36, 157.91 (7 s, 7 C_{arom})
20c	346 ($[M + 2]^+$, 66), 345 ($[M + 1]^+$, 48), 344 ($[M]^{\cdot+}$, 100), 155 (23), 154 (93), 152 (45), 139 (19), 138 (32), 137 (52), 136 (80)	3100, 3055, 2988, 1566, 1455, 1377, 1200, 1110, 995, 850, 812, 705	1.97 (s, CH_3), 4.42 (d, 1 H, *J* = 10.4), 4.54 (d, 1 H, *J* = 10.4), 7.45–7.80 (m, 9 H)	27.5 (q, CH_3), 55.85 (t, CH_2), 93.80 (s, C), 108.55 (d, CH_{imid}), 125.30, 126.35, 128.35, 128.60 (4 d, 8 CH_{arom}), 130.17, 132.78, 133.70, 139.54, 142.11, 158.15 (6 s, 6 C_{arom})
24	263 ($[M + 1]^+$, 15), 262 ($[M]^{\cdot+}$, 65), 171 (28), 128 (12), 116 (23), 105 (81), 104 (100), 103 (23), 78 (16), 77 (18)	3029, 2882, 1604, 1585, 1571, 1494, 1480, 1381, 1286, 976, 930, 765, 709, 695	4.21 (dd, 1 H, *J* = 10, 8), 4.73 (dd, 1 H, *J* = 10, 8), 6.41 (t, 1 H, *J* = 8), 7.25–7.8 (m, 11 H)	50.25 (d, CH), 86.7 (t, CH_2), 107.9, 123.8, 126.05, 126.55, 128.5, 128.9, 129.2 (7 d, 11 CH_{arom}), 135.0, 137.9, 141.0, 159.1 (4 s, 4 C_{arom})



Scheme 6

The structural elucidation of the novel fused imidazoxazoles **16**, **20a–c** and **24**, was accomplished by the usual spectroscopic methods, and in addition, we were able to grow suitable crystals of adequate quality from **24** that were subjected to an X-ray crystal structure analysis, which unambiguously confirmed the structure (Figure 2).

In summary, we have shown that 2-(sulfanylalkyl)imidazoles of type **6**, are useful precursors for the preparation of novel 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles **20**. Grignard addition to the not so very reactive carbonyl group in **6a–c** smoothly afforded tertiary alcohols **18**. The success-

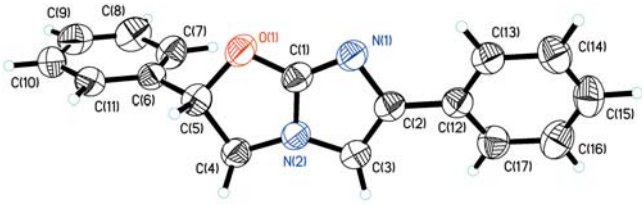


Figure 2 ORTEP plot[25] of the molecular structure of **24** with 50% probabilities ellipsoids

ful accomplishment of the fused imidazoxazoles **20** under mild conditions, took advantage of the key role played by the 2-alkylsulfonyl moiety in **19** as efficient leaving group in an intramolecular nucleophilic *ipso*-substitution reaction. On the other hand, the derived enolates from **6a–c** proved to be rather unreactive species, and for instance their reaction with electrophiles like aldehydes and alkylating reagents failed in almost all cases under a variety of reaction conditions. This limitation prevented the introduction of additional molecular diversity on the imidazoxazole moiety and therefore the scope of this chemistry. However additional experiments to circumvent these limitations as well as further developments that may have widespread synthetic utility are now in progress in our laboratory and the results will be reported in due course.

All commercially available chemicals were used as purchased, except THF that was dried over Na/benzophenone prior to use. All reactions were run under a positive pressure of dry N_2. Melting points (capillary tube) were measured with an electrothermal digital melting point apparatus IA 9100 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker DPX200 Avance instrument with TMS as the internal standard. MS spectra were recorded on a VG Quattro instrument in the positive ionisation FAB mode, using 3-NBA or 1-thioglycerol as the matrix or in a Thermo Quest 2000 series apparatus for the EI (70 eV) mode. Elemental analyses were performed on an apparatus from Thermo instruments, model EA1110-CHNS. Analytical TLC was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). Flash chromatography purifications were performed on silica gel 60 (230–400 mesh, Merck).

2-(Benzylsulfanyl)imidazoles 6a–c; General Procedure

To a mixture of thiuronium salt **4** (4.94 g, 20 mmol) and the appropriate α-halo ketone **5a–c** (40 mmol) in MeCN (100 mL) was added DIPEA (10.45 mL, 60 mmol) dropwise at r.t. The reaction mixture was stirred at r.t. for 6–8 h. The solution was evaporated to dryness, and the residue was partitioned between EtOAc (150 mL) and H_2O (100 mL). The organic phase was separated, washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated to give the crude product, which was purified by flash chromatography using *n*-hexane–EtOAc (4:1 to 1:1) as eluent to yield 2-(benzylsulfanyl)imidazoles **6a–c** (Tables 1 and 2).

2-(2-Benzylsulfanyl-4-phenylimidazol-1-yl)-1-phenylpropan-1-one (13a)

To a cooled (–78 °C) solution of **6a** (384 mg,1 mmol) in anhyd THF (3 mL) was added a 1 M solution of BuLi in hexanes (1.1 mL). The mixture was stirred under N_2 at –78 °C for 30 min; MeI (156 mg, 1.1 mmol, 1.1 equiv) was then added. The reaction mixture was stirred for 6 h allowing the temperature to rise to r.t. The solvent was evaporated under reduced pressure and the resulting residue was partitioned between CH_2Cl_2 (10 mL) and brine (10 mL). The layers were separated and the organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting residue was purified by flash chromatography using *n*-hexane–EtOAc (9:1) as eluent to afford **13a** as a yellowish oil; yield: 0.378 g (95%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 7.2 Hz, CH_3), 4.21 (d, 1 H, *J* = 12.4 Hz, PhCH_2S), 4.34 (d, 1 H, *J* = 12.8 Hz, PhCH_2S), 5.88 (q, 1 H, *J* = 7.2 Hz), 7.25–7.90 (m, 16 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.4 (q, CH_3), 40.3 (t, CH_2), 56.7 (d, CH), 115.4, 124.6, 126.8, 127.3, 128.4, 128.5, 128.6, 128.8, 128.9, (9 d, 15 CH_{arom}), 133.7 (s, C_{arom}), 133.9 (d, CH_{arom}), 134.1, 137.8, 139.7, 142.8 (4 s, 4 C_{arom}), 195.6 (s, C=O).

MS: *m*/*z* (%) = 400 ($[M + 2]^+$, 28), 399 ($[M + 1]^+$, 100), 398 ($[M]^+$, 23).

Anal. Calcd for $C_{25}H_{22}N_2OS$ (398.5): C, 75.35; H, 5.56; N, 7.03; S, 8.05. Found: C, 75.59; H, 5.23; N, 7.28; S, 8.34.

2-(2-Benzylsulfanyl-4-phenylimidazol-1-yl)-1-phenylpropan-1-ol (14)

To a stirred and cooled (0 °C) solution of 2-(benylsulfanyl)imidazole (**13a**; 396 mg, 1 mmol) in MeOH (5 mL) was added $NaBH_4$ (95 mg, 2.5 mmol) in small portions while stirring (evolution of gas). The stirring was continued for 1 h at 0 °C and at r.t. overnight. The solution was evaporated to dryness, and the crude residue was partitioned between EtOAc (15 mL) and aq sat. NH_4Cl solution (25 mL). The organic layer was separated, washed with H_2O (10 mL) dried ($MgSO_4$), and evaporated to give a residue which was purified by flash chromatography using hexane–EtOAc (9:1 to 4:1) as eluent, to afford pure **14** as a colourless oil; yield: 260 mg (65%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.48 (d, 3 H, *J* = 7 Hz, CH_3), 4.25 (d, 1 H, *J* = 11.6 Hz, PhCH_2S), 4.31 (d, 1 H, *J* = 11.6 Hz, PhCH_2S), 4.55 (m, 1 H), 4.85 (m, 1 H), 7.05–7.65 (m, 16 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7 (q, CH_3), 40.7 (t, CH_2), 55.8 (d, CH), 80.1 (d, *C*HOH), 118.6, 123.5, 127.8, 128.3, 129.1, 130.7, 130.9, 131.8, 131.9, (9 d, 15 CH_{arom}), 136.1 (s, C_{arom}), 138.9 (d, CH_{arom}), 139.1, 140.2, 141.7, 142.8 (4 s, 4 C_{arom}).

MS: *m*/*z* (%) = 402 ($[M + 2]^+$, 16), 401 ($[M + 1]^+$, 100), 400 ($[M]^+$, 12).

Anal. Calcd for $C_{25}H_{24}N_2OS$ (400.5): C, 74.97; H, 6.04; N, 6.99; S, 8.01. Found: C, 74.71; H, 6.26; N, 7.27; S, 7.79.

1-Phenyl-2-(4-phenyl-2-phenylmethanesulfonylimidazolyl)propan-1-ol (15)

To a cooled (0 °C) solution of **14** (237 mg, 0.6 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (3.99 g, 1.32 mmol, 2.2 equiv) in small portions. The reaction mixture was stirred overnight allowing the temperature to raise to r.t. The mixture was then diluted with EtOAc (25 mL) and washed with aq sat. $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL). The separated organic layer was dried ($MgSO_4$), filtered and evaporated to give a residue which was purified by flash chromatography using *n*-hexane–EtOAc (10:1) as eluent to afford pure **15** as a colourless oil; yield: 148.5 mg (58%).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.66 (d, 3 H, *J* = 7 Hz, CH_3), 4.78 (d, 1 H, *J* = 11.6 Hz, PhCH_2S), 4.81 (d, 1 H, *J* = 11.6 Hz, PhCH_2S), 4.85 (m, 1 H), 4.95 (m, 1 H), 7.15–7.75 (m, 16 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (q, CH_3), 49.7 (d, CH), 60.8 (t, CH_2), 79.6 (d, *C*HOH), 120.6, 124.5, 127.8, 129.3, 129.5, 129.8, 131.9, 132.8, 132.9, (9 d, 15 CH_{arom}), 136.5 (s, C_{arom}), 138.9 (d, CH_{arom}), 139.7, 140.5, 141.0, 142.7 (4 s, 4 C_{arom}).

MS: *m*/*z* (%) = 434 ($[M + 2]^+$, 19), 433 ($[M + 1]^+$, 100), 432 ($[M]^+$, 19)

Anal. Calcd for $C_{25}H_{24}N_2O_3S$ (432.5): C, 69.42; H, 5.59; N, 6.48; S, 7.41. Found: C, 69.59; H, 5.41; N, 6.25; S, 7.70.

3-Methyl-2,6-diphenyl-2,3-dihydroimidazo[2,1-*b*]oxazole (16)

To a solution of **15** (120 mg, 0.27 mmol) in anhyd THF (1 mL) was added NaH (60% dispersion in mineral oil, 11.5 mg, 0.30 mmol) in one portion at r.t. H_2 gas evolution began immediately. The mixture was stirred at r.t. under N_2 for 6 h. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic phase was separated, washed with brine (15 mL), dried ($MgSO_4$), filtered, and the filtrate was concentrated. The resulting residue was purified by

flash chromatography using *n*-hexane–EtOAc (5:1) as eluent to afford the pure imidazoxazole **16**; yield: 42.4 mg (55%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (d, 3 H, *J* = 6.8 Hz, CH_3), 4.78 (m, 1 H), 5.60 (d, 1 H, *J* = 9 Hz), 6.95 (s, 1 H), 7.20–7.35 (m, 8 H), 7.45–7.65 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.6 (q, CH_3), 56.2, 82.5 (2 d, 2 CH), 124.6, 125.8, 127.0, 128.3 128.8, 129.0, 129.6 (7 d, 11 CH_{arom}), 133.5, 136.7, 140.8, 142.7 (4 s, 4 C_{arom}).

MS: *m*/*z* (%) = 278 ([M + 2]$^+$, 8), 277 ([M + 1]$^+$, 100), 276 ([M]$^+$, 18).

Anal. Calcd for $C_{18}H_{16}N_2O$ (276.3): C, 78.24; H, 5.84; N, 10.14. Found: C, 78.36; H, 6.03; N, 9.87.

Addition of Grignard Reagents to 6a–c; Alcohol Derivatives 18a–f and 22; General Procedure

A solution of **6a**–**c** (2.6 mmol) in anhyd THF (8 mL) was added dropwise at r.t. to a solution of the corresponding Grignard reagents **17a**,**b** or **21** (1.1 mL, 3.3 mmol). The reaction mixture was refluxed for 24 h under a positive stream of N_2. The solvent was removed under reduced pressure and the resulting residue was partitioned between EtOAc (50 mL) and aq sat. NH_4Cl (40 mL). The organic phase was separated and washed with brine (15 mL). The separated organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography using *n*-hexane–EtOAc (10:1) as eluent to afford pure **18a**–**f** and **22** (Tables 3 and 4).

Oxidation of 18a–d to the Corresponding Sulfones 19a–d and 23; General Procedure

To a cooled (0 °C) solution of the corresponding imidazole alcohol derivative **18a**–**d** (0.6 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (3.99 g, 1.32 mmol, 2.2 equiv) in small portions. The reaction mixture was stirred overnight allowing the temperature to raise to r.t. The mixture was then diluted with EtOAc (50 mL) and washed with aq sat. $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL). The separated organic layer was dried ($MgSO_4$), filtered and evaporated to give a residue which was purified by flash chromatography using *n*-hexane–EtOAc (10:1) as eluent to afford pure **19a**–**d** and **23** (Tables 5 and 6).

Intramolecular *ipso*-Substitution Reaction; 2-Alkyl-2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles 20a–c and 24; General Procedure

To a solution of the appropriate alcohol sulfone **19a**–**c** (0.4 mmol) in anhyd THF (1.5 ml) was added NaH (60% dispersion in mineral oil, 17.6 mg, 0.44 mmol) in one portion at r.t. H_2 gas evolution began immediately. The mixture was stirred at r.t. under N_2 for 6 h. The residue was partitioned between EtOAc (50 mL) and H_2O (20 mL). The organic phase was separated, washed with brine (15 mL), dried ($MgSO_4$), filtered, and the filtrate was concentrated. The resulting residue was purified by flash chromatography using *n*-hexane–EtOAc (5:1) as eluent to afford the pure imidazoxazoles **20a**–**c** and **24** (Tables 7 and 8).

Crystal Data for Compound 24[26]

A suitable crystal of **24** (plate, colourless, dimensions 0.50 × 0.45 × 0.20 mm^3) was used for the structure determination. X-Ray data were collected using a Bruker SMART CCD area detector single-crystal diffractometer with graphite monochromatised Mo Kα radiation (λ = 0.71073 Å) by the ϕ-ω scan method at 298 (2) K. A total of 1271 frames of intensity data were collected for each compound. The first 50 frames were recollected at the end of data collection to monitor for decay. The crystal used for the diffraction study showed slight decomposition during data collection (0.1%). The integration process yielded a total of 8384 reflections, of which 3260 [*R*(int) = 0.0375] were independent. Absorption corrections were applied using SADABS[27] program (maximum and minimum transmission coefficients, 0.9834 and 0.9592). The structure was solved using the Bruker SHELXTL-PC[28] software by direct methods and refined by full-matrix least-squares methods on F^2. Hydrogen atoms were located on residual density maps and refined in the riding mode. The convergence was reached at a final *R*1 = 0.0437 [for $I > 2\sigma(I)$], *w*R2 = 0.1092 [for all data], 237 parameters, with allowance for the thermal anisotropy for all non-hydrogen atoms. The weighting scheme employed was $w = [\sigma^2(F_0^2 + (0.05224P)^2]]$ and $P = (|F_0|^2 + 2|F_c|^2)/3$ and the goodness of fit on F^2 was 0.912 for all observed reflections.

Acknowledgements

Generous financial support from Dirección General de Enseñanza Superior e Investigación Científica (DGESIC, Spain) through project PB98-0451, Universitat de Girona through project UdG98-452 and Roviall Química S.L. (Murcia) is gratefully acknowledged. Thanks are also due to Dr. Llüisa Matas (Servei d'Análisi, Universitat de Girona) for recording the NMR spectra and performing the microanalyses.

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