Novel Chemoselective Annulation of Imidazole and 1,2,4-Thiadiazine Rings on Azoles Involving Acid Labile Methanesulfinyl Group

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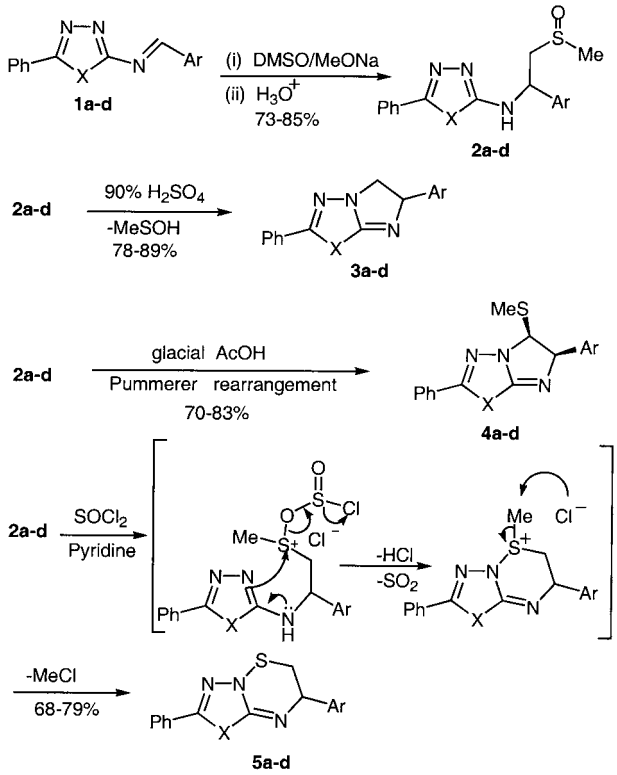
Abstract: Oxa(thia)diazole adducts **2a**–**d**, DMSO and azole Schiff bases **1a**–**d** are chemoselectively annulated with sulfuric acid, acetic acid, and thionyl chloride to yield imidazo[2,1-*b*]-1,3,4-oxa(thia)diazoles **3a**–**d**. Their 5-methylsulfenyl analogues **4a**–**d** and 1,3,4-oxa(thia)diazolo[3,2-*b*]-1,2,4-thiadiazines **5a**–**d**, respectively, **3**–**5** are formed via demethylsulfinylation, the Pummerer rearrangement, and deoxygenative demethylation, in a one-pot procedure.

Key words: chemoselective synthesis, Pummerer rearrangement, Schiff bases, imidazoles, 1,3,4-oxa(thia)diazoles, 1,2,4-thiadiazines

Recently, thieno-1,2,4-thiadiazines have evoked considerable attention as a new family of non-nucleoside HIV-1 reverse transcriptase inhibitors.[1,2] Likewise, benzo- and pyrido-1,2,4-thiadiazines have been reported to posses anti-hypertensive potential.[3] Azoles have a long history of applications in the pharmaceutical and agrochemical industries. Various imidazole derivatives, including those in which the ring system is annulated on biologically versatile heterocycles, are active in a wide spectrum of biological and therapeutic areas.[4–10] Thus, different combinations of biologically versatile azoles and 1,2,4-thiadiazine nuclei leading to a fused ring structure is an attractive scaffold to be utilized for exploiting chemical diversity and for generating a drug-like screening library.

Prompted by the above reports and in pursuing our work on sulfur- and phosphorus-based novel cyclization methods,[11–13] we have devised the present intramolecular chemoselective annulation of imidazole and 1,2,4-thiadiazine rings on azoles. The key element in our approach was the use of acid labile methanesulfinyl group, a moiety of β-keto sulfoxides whose transformations involving Bronsted catalysis are well documented.[14–18] The successful strategies for the annulation are depicted in Scheme 1.

Nucleophilic addition of the sulfur-stabilized carbanion of DMSO, generated in situ by the action of sodium methoxide with DMSO in methanol at room temperature, to C=N of azole Schiff bases **1** followed by quenching with dilute hydrochloric acid afforded **2** in 73–85% yield. Adducts **2** were annulated with 90% sulfuric acid at 0–5 °C with loss of the methanesulfinyl leaving group to furnish imidazo-1,3,4-oxa(thia)diazoles **3** in good yields (78–89%). The Pummerer rearrangement of **2** with glacial acetic acid yielded **4**, the methylsulfenyl analogues of **3**, in 70–83% yield. It is interesting to note that the Pummerer rearrangement products **4** were not obtained at all when 90% sulfuric acid was used.



1-5	X	Ar	1-5	X	Ar
a	O	Ph	**c**	S	Ph
b	O	4-ClC$_6$H$_4$	**d**	S	4-ClC$_6$H$_4$

Scheme 1

Adducts **2** underwent deoxygenative demethylation with thionyl chloride in pyridine to give 1,3,4-oxa(thia)diazolo-1,2,4-thiadiazines **5** in 68–79% yield. The Pummerer rearrangement leading to products **4** was highly diastereoselective. In this case the diastereomer ratios of crude products were checked by ^{1}H NMR, prior to purification, to ensure accurate and true diastereomeric ratios are reported.

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In summary, we have developed a general straightforward method for the library synthesis of various fused-ring azoles by chemoselective one-pot annualation of readily available acid labile adducts of DMSO and azole Schiff bases, which may find application in the search for therapeutic and agrochemical lead compounds of this class.

Mps were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as an internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in Coleman automatic carbon, hydrogen and nitrogen analyser. All chemicals used were reagent grade. The requisite Schiff bases were easily prepared following the known literature methods.[19,20]

2-[(1-Aryl)-(2-methylsulfinyl)ethyl]-5-phenyl-1,3,4-oxa(thia)diazoles 2; General Procedure

To a solution of NaOMe (2.16 g, 40 mmol) in MeOH (100 mL) was added DMSO (2.34 g, 30 mmol), and after stirring the reaction mixture at r.t. for 1 h, azole Schiff base **1** (30 mmol) was added. The resulting mixture was stirred for 1 h at r.t., followed by stirring at 50–60 °C for 30 min, it was quenched with H_2O (100 mL) and acidified with 5 M HCl (8.8 mL) to pH 7. The product thus precipitated was recrystallized from EtOH to obtain an analytical sample of **2** (Tables 1 and 2).

2,6-Diaryl-5,6-dihydroimidazo[2,1-*b*]-1,3,4-oxa(thia)diazoles 3; General Procedure

Methylsulfinyl derivative **2** (5 mmol) was dissolved in 90% H_2SO_4 (10 mL) under ice-cooling (maintaining the temperature of the reaction mixture at 0–5 °C) and allowed to stand in an ice-bath for 30 min. H_2O (50 mL) was added to the reaction mixture followed by basification with concd NH_4OH (density 0.91). The crude product thus obtained was purified by recrystallization from EtOH (Tables 1 and 2).

2,6-Diaryl-5,6-dihydro-5-methylsulfenylimidazo[2,1-*b*]-1,3.4-oxa(thia)diazoles 4; General Procedure

A solution of methylsulfinyl dervative **2** (5 mmol) in glacial HOAc (10 mL) was stirred at r.t. for 30 min and then heated under reflux for 1 h. The reaction mixture was cooled and filtered. The yellowish solid thus obtained was washed with H_2O to give the crude product, which was recrystallized from EtOH to afford a diastereomeric mixture (>97:3; in the crude products the ratio was >94:6 as determined by ^{1}H NMR spectroscopy). The products on second recrystallization from EtOH furnished an analytical sample of a single diastereomer **4** (Tables 1 and 2). On the basis of ^{1}H NMR spectra and literature precedent,[10,13,14] *cis*-stereochemistry was assigned to **4**, as the coupling constant ($J_{5,6}$ = 5.2–5.6 Hz) for **4** was lower than that for the minor (<3%) diastereomer (*trans*), $J_{5,6}$ = 10.5–10.8 Hz.

2,7-Diaryl-6,7-dihydro-1,3,4-oxa(thia)diazolo[3,2-*b*]-1,2,4-thiadiazines 5; General Procedure

A solution of methylsulfinyl dervative **2** (10 mmol) and SO_2Cl_2 (1 mL, 12.5 mmol) in pyridine (25 mL) was refluxed for 8 h. The pyridine was evaporated under reduced pressure at 40 °C, the residue obtained was washed with H_2O and recrystallized form EtOH to give a product which on second recrystallisation from EtOH furnished an analytical sample of **5** (Tables 1 and 2).

Table 1 Yields, and Melting Points of Compounds **2–5**

Product	Yield[a,b] (%)	Mp (°C)	Product	Yield[a,b] (%)	Mp (°C)
2a	76	165–166	**4a**	77	188–190
2b	85	201–203	**4b**	83	215–217
2c	73	170–172	**4c**	70	228–231
2d	81	220–223	**4d**	75	236–239
3a	84	173–174	**5a**	73	210–212
3b	89	161–162	**5b**	79	219–221
3c	78	185–187	**5c**	68	218–220
3d	82	196–198	**5d**	74	228–231

[a] Yield of isolated and purified product.
[b] All new compounds gave satisfactory microanalyses: C ± 0.32, H ± 0.21, N ± 0.23.

Table 2 IR, NMR and Mass Spectral Data for Compounds **2–5**

Product	IR (KBr) (cm^{-1})	^{1}H NMR (DMSO-d_6/TMS) δ, *J* (Hz)	^{13}C NMR (DMSO- d_6/TMS) δ	MS *m/z* (M^+)
2a[a]	3310, 3058, 2956, 1603, 1447, 1314, 1033, 739	2.61 (s, 3 H, Me), 3.70 (dd, 1 H, *J* = 5.1, 11.3, CH_2), 3.76 (dd, 1 H, *J* = 5.5, 11.3, CH_2), 4.93 (dd, 1 H, *J* = 5.1, 5.5, NCH), 7.35–7.63 (m, 10 H_{arom}), 8.63 (br s, 1 H, NH)	41.2 (Me), 58.1 (CH_2), 63.2 (NCH), 127.0, 127.6, 128.7, 129.4, 131.2, 132.6, 133.2, 133.9 (2 × Ph), 161.3 (Ph*C*), 164.1 (N C=N)	327
2b[a]	3314, 3061, 2960, 1605, 1445, 1316, 1035, 823, 736	2.65 (s, 3 H, Me), 3.72 (dd, 1 H, *J* = 5.3, 11.5, CH_2), 3.78 (dd, 1 H, *J* = 5.6, 11.5, CH_2), 4.96 (dd, 1 H, *J* = 5.3, 5.6, NCH), 7.15–7.77 (m, 9 H_{arom}), 8.68 (br s, 1 H, NH)	41.4 (Me), 58.4 (CH_2), 63.3 (NCH), 127.1, 128.6, 129.2, 130.7, 132.1, 133.2, 133.9, 134.6 (Ph, 4-ClC_6H_4), 161.4 (Ph-*C*), 164.3 (NC= N)	361
2c[a]	3303, 3046, 2953, 1596, 1448, 1310, 1030, 736	2.60 (s, 3 H, Me), 3.69 (dd, 1 H, *J* = 5.0, 11.1,CH_2), 3.74 (dd, 1 H, dd, *J* = 5.4, 11.1, CH_2), 4.90 (dd, 1 H, *J* = 5.0, 5.4, NCH), 7.32–7.61 (m, 10 H_{arom}), 8.60 (br s, 1 H, NH)	41.1 (Me), 58.0 (CH_2), 63.2 (NCH), 127.1, 127.8, 128.6, 129.5, 131.4, 132.3, 133.0, 133.7 (2 × Ph), 150.1 (Ph*C*), 159.6 (NC=N)	343

Table 2 IR, NMR and Mass Spectral Data for Compounds **2**–**5** (continued)

Product	IR (KBr) (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, *J* (Hz)	^{13}C NMR (DMSO- d_6/TMS) δ	MS *m*/*z* (M^+)
2d[a]	3308, 3052, 2955, 1600, 1452, 1313, 1032, 820, 731	2.63 (s, 3 H, Me), 3.71 (dd, 1H, *J* = 4.9, 11.2, CH_2), 3.77 (dd, 1 H, *J* = 5.2,11.2, CH_2), 4.93 (dd, 1 H, *J* = 4.9, 5.2, NCH), 7.13–7.74 (m, 9 H_{arom}), 8.64 (br s, 1 H, NH)	41.1 (Me), 58.2 (CH_2), 63.2 (NCH), 127.1, 128.7, 129.4, 130.7, 132.2, 133.0, 134.3 (Ph, 4-ClC_6H_4), 150.2 (Ph*C*), 159.8 (NC=N)	377
3a	3060, 2959, 1604, 1449, 1312, 741	4.13 (dd, 1 H, *J* = 5.3, 11.5, 5-H), 4.20 (dd, 1 H, *J* = 5.8, 11.5, 5-H), 5.21 (dd, 1 H, *J* = 5.3, 5.8, 6-H), 7.34–7.65 (m, 10 H_{arom})	59.4 (CH_2), 61.3 (NCH), 127.2, 127.9, 128.6, 129.5, 131.3, 132.4, 133.1, 133.7 (2 × Ph), 161.2 (Ph*C*), 163.9 (NC=N)	263
3b	3066, 2955, 1605, 1453, 1315, 826, 748	4.15 (dd, 1 H, *J* = 5.5, 11.8, 5-H), 4.23 (dd, 1 H, *J* = 5.9, 11.8, 5-H), 5.24 (dd, 1 H, *J* = 5.5, 5.9, 6-H), 7.34–7.74 (m, 9 H_{arom})	59.6 (CH_2), 61.7 (NCH), 127.2, 128.5, 129.4, 130.6, 132.3, 133.2, 133.7, 134.6 (Ph, 4-ClC_6H_4), 161.2 (Ph*C*), 164.0 (NC=N)	297
3c	3062, 2958, 1598, 1454, 1317, 739	4.11 (dd, 1 H, *J* = 5.2, 11.3, 5-H), 4.19 (dd, 1 H, *J* = 5.7, 11.3, 5-H), 5.20 (dd, 1 H, *J* = 5.2, 5.7, 6-H), 7.31–7.60 (m, 10 H_{arom})	59.2 (CH_2), 61.2 (NCH), 127.0, 127.7, 128.6, 129.3, 131.5, 132.2, 133.0, 133.8 (2 × Ph), 150.0 (Ph*C*), 159.4 (NC=N)	279
3d	3065, 2955, 1603, 1450, 1319, 820, 742	4.12 (dd, 1 H, *J* = 5.3, 11.7, 5-H), 4.18 (dd, 1 H, *J* = 5.8, 11.7, 5-H), 5.22 (dd, 1 H, *J* = 5.3, 5.8, 6-H), 7.32–7.71 (m, 9 H_{arom})	59.5 (CH_2), 63.4 (NCH), 127.1, 128.3, 129.5, 130.5, 132.1, 133.0, 133.6, 134.3 (Ph, 4-ClC_6H_4), 150.1 (Ph*C*), 159.6 (NC=N)	313
4a	3058, 2958, 1602, 1450, 1315, 738	2.19 (s, 3 H, Me), 4.80 (d, 1 H, *J* = 5.4, 5-H), 5.28 (d, 1 H, *J* = 5.4, 6-H), 7.30–7.64 (m, 10 H_{arom})	18.2 (Me), 62.0 (NCH), 63.3 (SCH), 127.0, 127.7, 128.6, 129.5, 131.1, 132.3, 133.0, 133.9 (2 × Ph), 161.3 (Ph*C*), 164.0 (C=N)	309
4b	3068, 2952, 1600, 1455, 1318, 822, 735	2.19 (s, 3 H, Me), 4.81 (d, 1 H, *J* = 5.6, 5-H), 5.30 (d, 1 H, *J* = 5.6, 6-H), 7.35–7.76 (m, 9 H_{arom})	18.3 (Me), 62.3 (NCH), 63.4 (SCH), 127.3, 128.5, 129.5, 130.7, 132.2, 133.0, 133.6, 134.4 (Ph, 4-ClC_6H_4), 161.3 (Ph*C*), 164.2 (NC=N)	343
4c	3060, 2959, 1597, 1450, 1315, 740	2.18 (s, 3 H, Me), 4.78 (d, 1 H, *J* = 5.2, 5-H), 5.26 (d, 1 H, *J* = 5.2, 6-H), 7.30–7.63 (m, 10 $H_{arom)}$	18.1 (Me), 62.0 (NCH), 63.2 (SCH), 127.1, 127.7, 128.6, 129.4, 131.3, 132.1, 133.2, 133.9 (2 × Ph), 150.1 (Ph*C*), 159.6 (NC=N)	325
4d	3065, 2962, 1603, 1448, 1323, 823, 738	2.19 (s, 3 H, Me), 4.79 (d, 1 H, *J* = 5.3, 5-H), 5.28 (d, 1 H, *J* = 5.3, 6-H), 7.33–7.74 (m, 9 H_{arom})	18.2 (Me), 62.2 (NCH), 63.3 (SCH), 127.2, 128.5, 129.3, 130.6, 132.2, 133.2, 133.9, 134.2 (Ph, 4-ClC_6H_4), 150.2 (Ph*C*), 159.8 (NC=N)	359
5a	3063, 2955, 1596, 1447, 1320, 740	2.60 (dd, 1 H, *J* = 4.9, 11.1, 6-H), 2.66 (dd, 1 H, *J* = 5.4, 11.1, 6-H), 5.19 (dd, 1 H, *J* = 4.9, 5.4, 7-H), 7.30–7.62 (m, 10 H_{arom})	30.2 (CH_2), 64.7 (NCH), 127.1, 127.6, 128.4, 129.7, 131.0, 132.1, 132.8, 133.7 (2 × Ph), 161.2, (Ph*C*), 164.1 (NC=N)	295
5b	3069, 2957, 1602, 1450, 1318, 825, 745	2.62 (dd, 1 H, *J* = 5.1, 11.3, 6-H), 2.69 (dd, 1 H, *J* = 5.7, 11.3, 6-H), 5.22 (dd, 1 H, *J* = 5.1, 5.7, 7-H), 7.31–7.66 (m, 9 H_{arom})	30.3 (CH_2), 64.8 (NCH), 127.4, 128.3, 129.4, 130.3, 132.0, 133.2, 133.8, 134.6 (Ph, 4-ClC_6H_4), 161.4 (Ph*C*), 164.3 (NC=N)	329
5c	3065, 2956, 1598, 1455, 1322, 742	2.57 (dd, 1 H, *J* = 4.8, 11.0, 6-H), 2.63 (dd, 1 H, *J* = 5.3, 11.0, 6-H), 5.17 (dd, 1 H, *J* = 4.8, 5.3, 7-H), 7.30–7.60 (m, 10 H_{arom})	30.1 (CH_2), 64.5 (NCH), 127.4, 128.3, 129.5, 130.6, 132.0, 132.9, 133.5 (2 × Ph), 150.0 (Ph*C*), 159.7 (NC=N)	311
5d	3067, 2962, 1601, 1458, 1320, 820, 743	2.60 (dd, 1 H, *J* = 5.0, 11.2, 6-H), 2.66 (dd, 1 H, *J* = 5.6, 11.2, 6-H), 5.17 (dd, 1 H, *J* = 5.0, 5.6, 7-H), 7.30–7.65 (m, 9 H_{arom})	30.2 (CH_2), 64.7 (NCH), 127.3, 128.4, 129.3, 130.1, 130.9, 132.5, 133.6, 134.4 (Ph, 4-ClC_6H_4), 150.1 (Ph*C*), 159.9 (NC=N)	345

[a] IR (KBr): 1030–1035 (S=O) cm^{-1}, this IR band was absent in case of compounds **3**–**5**.

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References

(1) Arranz, M. E.; Diaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; Clercq, E. D.; Vega, S. *Bioorg. Med.Chem.* **1999**, *7*, 2811.

(2) Arranz, M. E.; Diaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; Clercq, E. D.; Vega, S. *J. Med. Chem.* **1998**, *41*, 4109.

(3) Neilla, C. G.; Prestona, P. N.; Wightmana, R. H. *Tetrahedron* **1998**, *54*, 13645.

(4) Badger, A. M.; Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams, J. L.; Griswold, D. E. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 1453.

(5) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449.

(6) Makino, K.; Sakata, G.; Morimoto, K.; Ochiai, Y. *Heterocycles* **1985**, *23*, 2025.
(7) Collis, A. J.; Foster, M. L.; Halley, F.; Maslen, C.; McLay, I. M.; Page, K. M.; Redford, E. J.; Souness, J. E.; Wilsher, N. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 693.
(8) *Chem. Abstr.* **1977**, *86*, 189943.
(9) Slee, D. H.; Romano, S. J.; Yu, J.; Nguyen, T. N.; John, J. K.; Raheja, N. K.; Axe, F. U.; Jones, T. K.; Ripka, W. C. *J. Med. Chem.* **2001**, *44*, 2094.
(10) Callahan, J. F.; Burgess, J. L.; Fornwald, J. A.; Gaster, L. M.; Harling, J. D.; Harrington, F. P.; Heer, J.; Kwon, C.; Lehr, R.; Mathur, A.; Olson, B. A.; Weinstock, J.; Laping, N. J. *J. Med. Chem.* **2002**, *45*, 999.
(11) Yadav, L. D. S.; Kapoor, R. *Synthesis* **2002**, 1502.
(12) Yadav, L. D. S.; Sharma, S. *Synthesis* **1993**, 864.
(13) Yadav, L. D. S.; Vaish, A. *J. Chem. Res., Synop.* **1993**, 508.
(14) Russel, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1970**, *35*, 764.
(15) Moore, T. L. *J. Org. Chem.* **1967**, *32*, 2786.
(16) Russel, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5498.
(17) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(18) Rosowsky, A.; Chen, K. K. N. *J. Org. Chem.* **1973**, *38*, 2073.
(19) Singh, H.; Yadav, L. D. S.; Sharma, K. S.; Chaudhary, J. P. *Acta Chim. Hung.* **1984**, *115*, 377.
(20) Singh, H.; Yadav, L. D. S.; Sharma, K. S. *Indian J. Chem., Sect. B* **1982**, *21*, 480.