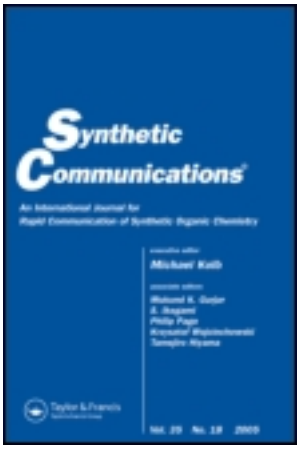

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Synthesis of N-(Dimethylsulfamoyl)aldimines, a New Type of Aldimine Derivative

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SYNTHESIS OF *N*-(DIMETHYLSULFAMOYL)ALDIMINES, A NEW TYPE OF ALDIMINE DERIVATIVE

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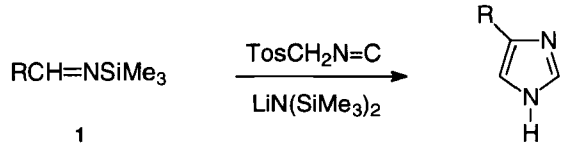
Abstract : *N*-(Dimethylsulfamoyl)aldimines (**3**), a new type of shelf-stable aldimine derivatives, are readily prepared from aldehydes and *N*-(dimethylsulfamoyl)amide (**2**) in refluxing toluene.

This paper describes the synthesis of a series of *N*-(dimethylsulfamoyl)aldimines (**3**) from aldehydes and *N*-(dimethylsulfamoyl)amide (**2**). These novel aldimine derivatives are precursors in a synthesis of 4(5)-monosubstituted imidazoles. Histamine [*i.e.* 4(5)-(2-aminoethyl)-1*H*-imidazole] and several other agonists of the H_1, H_2, and H_3 receptors are essentially 4(5)-monosubstituted imidazoles.[1]

We are presently engaged in the development of a new synthesis of 4(5)-monosubstituted 1*H*-imidazoles.[2] Clearly, there is a need for efficient syntheses of such compounds, as follows from recent reports of various research groups.[3-8] One of the newer methods, due to Shih,[6] involves a base-induced cycloaddition of tosylmethyl isocyanide (TosMIC)[4] to *in situ* prepared *N*-(trimethylsilyl)aldimines (**1**), in which the trimethylsilyl group serves as temporary protection of the precursor-imine (Eq 1).

* To whom correspondence should be addressed.



1 (Eq 1)

(R = Me, Bu, Ph ; 23 -55 %)

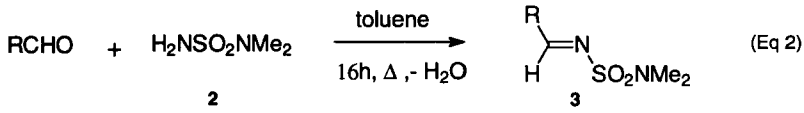
We have found that an approach similar to Eq 1, using dimethylsulfamoyl instead of trimethylsilyl protected aldimines, forms a good alternative for the synthesis of 4(5)-monosubstituted imidazoles.[10] The dimethylsulfamoyl group was introduced in 1984 by Chadwick and Ngochindo *et al.* as the very best *N*-H protector in 2- and 4-monoalkylation and 2,5-dialkylation studies of lithiated imidazoles.[11] Their experiences have recently be substantiated by Kudzma *et al.*[3] and Vollinga *et al.*[7] in an attractive synthesis of *inter alia* 4(5)-(ω-aminoalkyl)-1*H*-imidazoles from *N*-(dimethylsulfamoyl)imidazole. When the substitution reactions at the imidazole ring are completed, the dimethylsulfamoyl protection is readily removed with aqueous acid or base.[3,7,11]

Much to our surprise *N*-(dimethylsulfamoyl)imines (**3**) have not been described earlier. It turns out that the desired sulfamoylaldimines **3** are readily prepared by reaction of equimolar quantities of *N*-(dimethylsulfamoyl)amide[12] (**2**) and an aldehyde in refluxing toluene, under azeotropic removal of water. The aldimines **3** so obtained (Table 1, Eq 2) are shelf-stable solids, with the exception of **3i**. Even compound **3i**, being an oil, has been stored for more than 18 months at -20 °C without appreciable deterioration.

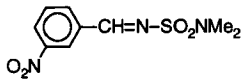
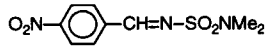
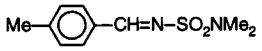
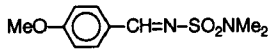
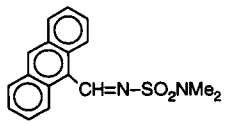
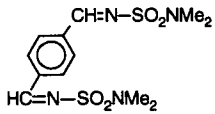
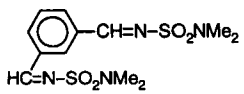
The formation of imino compounds with the use of *N*-(dimethylsulfamoyl)amide (**2**) appears to be more facile than the corresponding reaction with ordinary sulfonamides, probably as a result of enhanced nucleophilicity of **2**. In reactions of aldehydes with arenesulfonamides, Lewis acids (notably $TiCl_4$) are normally employed as catalysts/dehydration agents.[13] The difference in reactivity is demonstrated in the reaction of *p*-methoxybenzaldehyde. Under the same conditions where 40 % of **3e** is obtained in reaction with **2** (Table 1, entry 5), no reaction takes place between *p*-methoxybenzaldehyde and *p*-toluenesulfonamide. Even when the reaction time in the latter case was extended to 65 h, still no reaction was observed. This remarkable difference in results was found to be less pronounced in reaction of the more electrophilic benzaldehyde and *p*-nitrobenzaldehyde.

According to ^1H and ^{13}C NMR, the aldimines **3** of Table 2 are formed as single stereoisomers to which the *E* configuration is assigned on the basis of NOSY experiments carried out with **3b** and **3f**.

TABLE 1. *N*-(Dimethylsulfamoyl)aldimines (**3**) Prepared According to :



(Eq 2)

Entry	Product **3**		Yields[a] (%)	Mp (°C)
1	PhCH=N–SO_2NMe_2	(**3a**)	55	85-86
2		(**3b**)	66	115-116
3		(**3c**)	70	178-179
4		(**3d**)	51	98-99
5		(**3e**)	40	99-100
6		(**3f**)	68	164-165
7		(**3g**)	57[b]	212-213
8		(**3h**)	65[b]	208-209
9	Me_2N-N=CH-CH=N–SO_2NMe_2	(**3i**)	62	oil
10		(**3j**)	67[c]	87-88

[a] Isolated yield, after one crystallisation. [b] Two equivalents of amine **2** are used, instead of one.
[c] Reaction time 6 h instead of 16 h.

The yield of entry 1 (55%) was not improved when the reaction time was prolonged from 16 to 32 h. Unsuccessful experiments were carried out, under the conditions of Tabel 1, with aqueous glyoxal, ethyl glyoxalate (50% in toluene), and 2,4-hexadienal. The corresponding reaction of 2-pyridinecarboxaldehyde only gave impure aldimine that could not be obtained in pure form.

In addition to their application in the synthesis of 4(5)-monosubstituted imidazoles[10], the new *N*-(dimethylsulfamoyl)aldimines (**3**) may well become attractive substrates in (cyclo)addition reactions of the type where ordinary sulfonylimines have been utilized so far.[13]

Experimental Section

N-(Dimethylsulfamoyl)amide (**2**) was readily prepared on 0.15 mol-scale from commercial dimethylsulfamoyl chloride (Aldrich) and 30 % aqueous ammonia.[12] The precursor of **3i** was prepared from glyoxal and 1,1-dimethylhydrazine according to the literature procedure.[14] The other aldehydes are commercial products that have been used as received. Al_2O_3 (aluminiumoxide 90, activity I, neutral, Merck) was used for filtration purposes. Melting points were measured on a Reichert melting point apparatus, equipped with a Reichert microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini spectrometer (200 MHz).^{1}H NMR chemical shifts are determined relative to the solvent and converted to the TMS scale using δ ($CHCl_3$) = 7.26. ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer (75.43 MHz). ^{13}C NMR chemical shifts are determined relative to the solvent and converted to the TMS scale using δ ($CDCl_3$) = 76.91. Mass spectra were recorded on a AEI-MS-902 mass spectrometer (DI system; e.v. 70 eV; acc.v. 8 kV; multiplier 2.1 kV; I.S. temp. 120 °C; D.I. temp. 110-120 °C). Elemental microanalyses were carried out in the Analytical Department of this laboratory.

Synthesis of *N*-(dimethylsulfamoyl)aldimines (3)

General procedure. A solution of *N*-(dimethylsulfamoyl)amide (**2**) (10-11 mmole) and an aldehyde (10 mmole) in toluene (100 mL) was refluxed for 16 h in a Dean-Stark apparatus. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2. After filtration through a short colomn of Al_2O_3 (CH_2Cl_2), the eluent was concen-

trated. Products **3a-3f** and **3j** were crystallized from isopropanol. Products **3g** and **3h** were obtained in analytically pure form by cooling the reaction mixture to room temperature and collecting the precipated solid. Product **3i** was obtained in analytically pure form by distillative removal of impurities.

***N*-(Dimethylsulfamoyl)benzaldimine (3a):**

White solid, 55 %, mp 85-86 °C ; ^{1}H NMR ($CDCl_3$, 200 mHz) δ : 2.88 (s, 6H), 7.51-7.96 (m, 5H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.13 (q), 129.03 (d), 130.75 (d), 134.43 (s), 170.53 (d); MS (relative intensity): m/z 28 (52.89), 44 (100.00), 51 (25.44), 77 (49.29), 104 (38.03), 106 (51.51), 108 (94.57), 212 (M^+, 54.42); HRMS calcd. $C_9H_{12}N_2O_2S$: 212.062, found 212.061; Anal. calcd. for $C_9H_{12}N_2O_2S$: C, 50.93; N, 13.20; H, 5.70; S, 15.10, found C, 50.86; N, 13.04; H, 5.72; S, 15.19.

***N*-(Dimethylsulfamoyl)-*m*-nitrobenzaldimine (3b):**

Pale yellow solid, 66 %, mp 115-116 °C ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.92 (s, 6H), 7.72-7.76 (t, J = 8.06 Hz, 1H), 8.23-8.26 (d, J = 7.69 Hz, 1H), 8.44-8.45 (d, J = 8.05 Hz, 1H) 8.80 (s, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.30 (q), 124.89 (d), 128.35 (d), 130.41 (d), 134.10 (s), 136.11 (d) 167.80 (d); MS (relative intensity): m/z 28 (30.10), 42 (13.18), 43 (15.51), 44 (27.64), 76 (11.89), 108 (100.00), 151 (12.14), 257 (M^+,21.30); HRMS calcd. $C_9H_{11}N_3O_4S$ 257.047, found 257.047; Anal. calcd. for $C_9H_{11}N_3O_4S$: C, 42.02; N, 16.33 ; H, 4.31; S, 12.46, found C, 41.49; N, 15.86; H, 4.32; S, 12.32.

***N*-(Dimethylsulfamoyl)-*p*-nitrobenzaldimine (3c):**

Yellow solid, 70 %, 178-179 °C;^{1} H NMR ($CDCl_3$, 200 MHz) δ : 2.93 (s, 6H), 8.11-8.15 (d, J = 9.03 Hz, 2H), 8.35-8.39 (d, J = 8.79 Hz, 2H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.29 (q), 124.24 (d), 131.41 (d), 137.61 (s), 151.03 (s), 167.70 (d); MS (relative intensity): m/z 28 (18.10), 43 (10.11), 44 (19.35), 76 (13.23), 108 (100), 151 (9.29); HRMS calcd. $C_9H_{11}N_3O_4S$ 257.047, found 257.047; Anal. calcd. for $C_9H_{11}N_3O_4S$: C, 42.02; N, 16.31; H, 4.31; S, 12.46, found C, 42.15; N, 16.08; H, 4.56; S, 12.24.

***N*-(Dimethylsulfamoyl)-*p*-tolualdimine (3d):**

White solid, 51 %, mp 98-99 °C ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.45 (s, 3H), 2.85 (s, 6H), 7.30-7.33 (d, J = 8.06 Hz, 2H,), 7.81-7.84 (d, J = 8.06 Hz, 2H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 21.99 (q), 38.14 (q), 129.88 (s), 129.94 (d), 130.99 (d), 145.91 (s), 170.50 (d); MS (relative intensity): m/z ; 28 (50.85), 39 (13.18, 42 (20.06), 44 (100), 65

(21.58), 91 (44.51), 108 (52.23), 118 (60.49), 119 (45.04), 226 (M^+, 46.42); HRMS calcd. $C_{10}H_{14}N_2O_2S$ 226.078, found 226.078; Anal. calcd.for $C_{10}H_{14}N_2O_2S$: C, 53.08; N, 12.38; H, 6.24; S, 14.17, found C, 52.81; N, 12.30;H, 6.22; S, 14.20.

***N*-(Dimethylsulfamoyl)-*p*-methoxybenzaldimine (3e):**

White solid, 40 %, mp 99-100 °C;^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.86 (s, 6H), 3.90 (s, 3H), 6.97-7.02 (d, J = 9.03 Hz, 2H), 7.88- 7.92 (d, J = 8.78 Hz, 2H), 8.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.29 (q), 55.55 (q), 114.54 (d), 125.14 (s), 133.07 (d), 164.79 (s), 169.58 (d); MS (relative intensity): m/z 28 (12.88), 42 (23.38), 44 (60.79), 64 (18.52), 77 (34.46), 92 (32.93), 107 (23.90), 108 (27.44), 134 (100), 135 (86.07), 242 (M^+, 39.53); HRMS calcd. $C_{10}H_{14}N_2O_3S$ 242.073, found 242.073; Anal. calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57; N, 11.57; H, 5.83; S, 13.21, found C, 49.37; N, 11.44; H, 5.91; S, 13.29.

***N*-(Dimethylsulfamoyl)-9-anthraldimine (3f):**

Orange solid, 68 %, mp 164-165 °C ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.98 (s, 6H), 7.55-7.61 (m, 2H), 7.67-7.73 (m 2H), 8.07-8.11 (d, J = 8.79 Hz, 2H), 8.72 (s, 1H), 8.92-8.96 (d, J = 8.42 Hz, 2H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.48 (q), 124.19 (d), 125.86 (d), 129.31 (d), 129.62 (d), 131.12 (s), 132.71 (s), 135.77 (d), 168.83 (d) ; MS (relative intensity): m/z 28 (78.35), 32 (16.62), 176 (21.28), 177 (24.64), 180 (31.85), 182 (10.06), 203 (68.59), 204 (100), 312 (M^+, 14.58); HRMS calcd. $C_{17}H_{16}N_2O_2S$ 312.093, found 312.093; Anal. calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; N, 8.97; H, 5.16; S, 10.26, found C, 65.11; N, 8.83; H, 5.17; S, 10.31.

***N,N'*-Bis-(dimethylsulfamoyl)terephthaldimine (3g):**

Pale yellow solid, 57 %, 212 -213 °C ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.93 (s, 6H), 8.09 (s, 4H), 8.96 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.21 (q), 130.98 (d), 137.20 (s), 168.64 (d); MS (relative intensity): m/z 28 (100), 32 (23.12), 44 (23.79), 108 (41.73), 180 (6.71), 346 (M^+, 4.39); HRMS calcd. $C_{12}H_{18}N_4O_4S_2$ 346.077, found 346.077; Anal. calcd. for $C_{12}H_{18}N_4O_4S_2$: C, 41.61; N, 16.17; H, 5.24; S, 18.51, found C, 41.25; N, 15.77; H, 5.30; S, 18.11.

***N,N'*-Bis-(dimethylsulfamoyl)isophthaldimine (3h):**

3h: Off-white solid, 65 %, mp 208-209 °C ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.93 (s, 6H), 7.67-7.76 (t, J =7.9 Hz, 1H), 8.17-8.21 (d, J = 7.9 Hz, 2H), 8.53 (s, 1H), 8.99 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.52 (q), 130.29 (d), 132.54 (d), 133.81 (s), 135.98 (d),

169.02 (d); MS (relative intensity): m/z; 28 (15.6), 42(19.3), 44 (86.5), 76 (11.5), 108 (100), 212 (24.8), 239 (53.1), 346 (M^+, 0.1); HRMS was not observed ; Anal. calcd. for $C_{12}H_{18}N_4O_4S_2$: C, 41.61; N, 16.17; H, 5.24; S, 18.51, found C, 41.25; N, 15.77; H, 5.30; S, 18.11.

_N_-(Dimethylamino)-_N'_-(dimethylsulfamoyl)-1,4-diaza-1,3-butadiene (3i):

Red-brown oil, 62 % ; ^1H NMR ($CDCl_3$, 200 MHz) δ : 2.76 (s, 6H), 3.20 (s, 6H), 6.82-6.83 (d, J = 8.30, 1H), 8.44-8.48 (d, J = 8.52 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.34 (q), 124.55 (d), 169.75 (d); MS (relative intensity): m/z 28 (31.59), 42 (55.08), 43 (27.54), 44 (100), 45 (45.25), 58 (17.17), 71 (23.08), 83 (13.91), 98 (64.89), 108 (22.42), 205 (17.45), 206 (M^+, 1.48); HRMS calcd. $C_6H_{14}N_4O_2S$ 206.84, found 206.84; Anal. calcd. for $C_6H_{14}N_4O_2S$: C,34.94; N, 27.16; H, 6.84; S, 15.54, found C, 34.93; N, 27.07; H, 6.76; S, 15.38.

_N_-(Dimethylsulfamoyl)cinnamaldimine (3j):

Pale yellow solid, 67 %, mp 87-88 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ : 2.82 (s, 6H), 6.93-7.02 (dd, J = 9.52 Hz, 1H), 7.41-7.57 (m, 6H), 8.60-8.63 (d, J = 9.52 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ : 38.11 (q), 124.40 (d), 128.30 (d), 129.00 (d), 131.25 (d), 134.08 (s), 152.65 (d), 171.38 (d); MS (relative intensity): 28 (37.05), 32 (8.22), 44 (11.42) 77 (11.44), 103 (14.51), 108 (13.44), 130 (100), 238 (M^+, 7.39); m/z; HRMS calcd. $C_{11}H_{14}N_2O_2S$ 238.078, found 238.078; Anal. calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; N, 11.76; H, 5.93; S, 13.43, found C, 55.23; N, 11.53; H,5.90; S,13.40.

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