Synthesis of 1-(Dimethylsulfamoyl)-2- and 5-Imidazolecarboxaldehydes. Rearrangement of 1-(Dimethylsulfamoyl)-5-imidazolecarboxaldehyde to the 4-Carboxaldehyde [1]

Jang-Woo Kim, Salma M. Abdelaal and Ludwig Bauer*

Department of Medicinal Chemistry, m/c 781,
College of Pharmacy, University of Illinois at Chicago
833 S. Wood Street, Chicago IL 60612-7231

Norman E. Heimer

Department of Chemistry, US Air Force Academy,
USAFA CO 80840-1134

Received September 27, 1994

Lithiation of 1-(dimethylsulfamoyl)imidazole by *n*-butyllithium, followed by substitution with dimethylformamide provided 1-(dimethylsulfamoyl)-2-imidazolecarboxaldehyde in 19% yield. When 1-(dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)imidazole was lithiated by *sec*-butyllithium, followed by methyl formate, there was obtained 1-(dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-5-imidazolecarboxaldehyde (57%). Removal of the silyl group by acetic acid yielded 1-(dimethylsulfamoyl)-5-imidazolecarboxaldehyde (**11**, 96%) as a gum. Isomerization of **11** took place slowly at room temperature (10 days), or faster in tetrahydrofuran solution containing triethylamine (2 hours) to form crystalline 1-(dimethylsulfamoyl)-4-imidazolecarboxaldehyde (**12**) in 68% yield. Proton and carbon-13 nmr spectra were analyzed to determine the structure of the isomers. However, only X-ray crystallography established the structure of 1-(dimethylsulfamoyl)-4-imidazolecarboxaldehyde, unequivocally. A mechanism for the isomerization of **11** to **12** is proposed.

J. Heterocyclic Chem., **32**, 611 (1995).

Introduction.

As part of a program to synthesize a variety of *N*-substituted imidazolecarboxaldehydes, we explored the use of lithiation-substitution of 1-substituted imidazoles [2] toward this goal. The *N*-substituent on the starting imidazole can be a more or less permanent group (*e.g.* methyl, phenyl) or one which can be hydrolyzed or reduced off at later stages of a synthesis. Some of the popular protective groups on *N*-1 of imidazole, which are able to withstand lithiation, are triphenylmethyl (CPh_3), alkoxymethyl (CH_2OR), bis(alkoxy)methyl [$CH(OR)_2$], (dialkylamino)methyl (CH_2NR_2), dimethylsulfamoyl (SO_2NMe_2), and [2-(trimethylsilyl)ethoxy]methyl ($CH_2OCH_2CH_2SiMe_3$) [2]. Apparently, acyl (COR) groups should be avoided. It had been reported that *N*-acyl groups are cleaved within minutes of exposure to butyllithium or lithium diisopropylamide [4]. Also, ring lithiation of *N*-sulfonylimidazoles is reported to be very slow. For example, lithiation of 1-methylimidazole proceeds rapidly at -78° while 1-(benzenesulfonyl)imidazole required a higher temperature (-20°) [4].

For our current project, the dimethylsulfamoyl (SO_2NMe_2) group was chosen as the protective group. Imidazole (**1**) reacts readily with dimethylsulfamoyl chloride to form crystalline 1-(dimethylsulfamoyl)imidazole (**2**) [3,4,11]. Within 0.5 hour, *n*-butyllithium (1.1 equivalents) lithiates **2** at -78° to generate **3**, with a minimum of *C*-5 lithiation. The extent of metallation can be monitored by withdrawing samples from the reaction mixture at periodic intervals, quenching with deuterium oxide and examining the ^1H nuclear magnetic resonance (nmr) signals by integration. The signal for H-2 disappears quickly while the relative intensities of H-4 and the *N*-methyl signals remain constant. However, there tends to be also some diminution of the H-5 signal. 2,5-Dilithiation of **2** [6,8] with excess *n*-butyllithium is based on the isolation of 1-(dimethylsulfamoyl)-5-methyl- and 2,5-dimethylimidazole upon the addition of excess methyl iodide (or methyl sulfate) [4]. Similarly, reaction of trimethylsilyl chloride with such a dilithiated intermediate yielded 1-(dimethylsulfamoyl)-2,5-bis(trimethylsilyl)imidazole (85%) [8].

1-(Dimethylsulfamoyl)-2-imidazolecarboxaldehyde (**4**).

Although lithiation of **2** proceeded quickly and quantitatively to the lithio derivative **3**, subsequent reaction with *N*,*N*-dimethylformamide (DMF, 18 hours at room temperature) produced 1-(dimethylsulfamoyl)-2-imidazolecarboxaldehyde (**4**) in relatively poor yield (19%). It is claimed that this substitution failed at 0° [9]. Attempts to hydrolyze the sulfamoyl group of **4** by aqueous base were unsuccessful in the sense that neither starting material, nor 2-imidazolecarboxaldehyde (**5**) could be isolated. Successful hydrolyses of sulfamoyl groups of differently substituted imidazoles proceeded quite well [5,11]. It appears that the problem stems from the destruction of **5** by base. This premise was tested independently when an authentic sample of **5** became available. Aqueous alkaline solutions of **5** turned dark brown rapidly and no starting

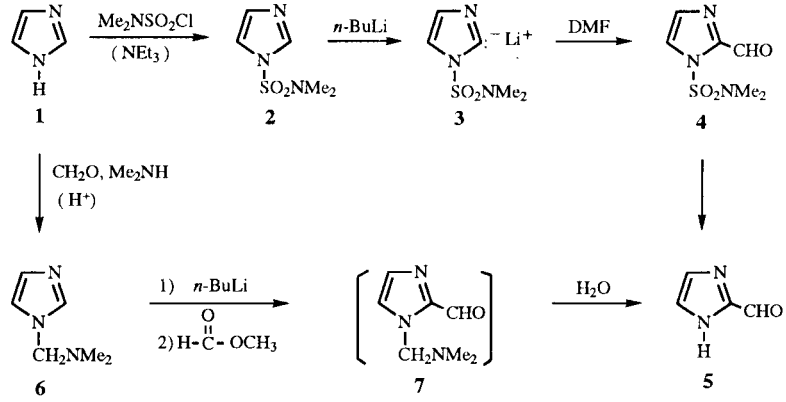
aldehyde could be retrieved, once the *p*H is re-adjusted.

2-Imidazolecarboxaldehyde (**5**).

During this investigation, a facile alternate synthesis of **5** was discovered. Lithiation and substitution of aminals of imidazole is well documented [7]. The reaction of **1** with formaldehyde and diethylamine generated **6**, quantitatively. Lithiation of **6** was complete within 1 hour at -70° [7] and subsequent reaction with methyl formate lead to **7**. Attempts to isolate **7** failed, presumably due to the (almost instant) hydrolysis of the aminal to provide **5** (68%). Attempted acylations of **5** with dimethylsulfamoyl chloride to form **4**, under a number of different conditions (in the presence of either an aqueous or organic base) failed. In most instances, intractable mixtures were obtained, as judged by chromatographic and spectroscopic methods.

sized by this approach. The majority of reactions commence with imidazoles bearing a "permanent" group on the ring nitrogen, *e.g.* methyl, while our interest focused primarily starting with *N*-1 protected imidazoles. Syntheses of a number of specific 1-(dimethylsulfamoyl) 5-substituted-imidazoles have been described, starting from **2** [6]. A useful intermediate to our target compound **11**, is 1-(dimethylsulfamoyl)-2-*(tert*-butyldimethylsilyl)-imidazole (**8**), which is readily prepared by lithiation of **2**, followed by reaction with *tert*-butyldimethylsilyl chloride (TBDMSiCl) [6].

Lithiation of **8** by *sec*-butyllithium generates **9**, *in situ* [5]. To introduce the aldehyde group in **9**, we switched from using DMF (as the "standard") to methyl formate, as suggested by Ngochindo [13]. There was isolated **10** which was purified by column chromatography on silica gel and provided pure product (^{1}H and ^{13}C nmr spectra).



1-Dimethylsulfamoyl-5-imidazolecarboxaldehyde (**11**).

We turned our attention to the synthesis of this aldehyde. Lithiation of **2** forms **3** in which *C*-2 can be now be protected effectively by a trialkylsilyl group. Initially, the trimethylsilyl group was used [4,8] but for compelling reasons the use of bulkier trialkylsilyl groups [5,11], such as triethylsilyl ($SiEt_3$) [5] or *tert*-butyldimethylsilyl (SiTBDM) is recommended [6]. Since *n*-butyllithium is known to displace a trialkylsilyl group to generate the *C*-2 imidazolyl carbanion [12], a bulkier trialkylsilyl group might suppress this annoying side reaction. This aspect becomes more critical when such displacements compete with the lithiation of *C*-5 of 1-(dimethylsulfamoyl)-2-(trialkylsilyl)imidazole. Furthermore, to minimize carbanion attack on a 2-trialkylsilyl group, it is recommended that the more hindered *sec*-butyllithium is used for *C*-5 lithiation. Removal of any 2-trialkylsilyl protective group in such 2,5-disubstituted imidazoles proceeds smoothly using either acetic acid or fluoride ion.

Many 1,5-disubstituted imidazoles have been synthe-

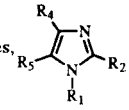
which was however too unstable to survive satisfactory microanalysis. Besides **10**, there is also isolated some **11**. Complete removal of the silyl protective group was achieved (quantitatively) when **10** was treated with acetic acid. The ^{1}H and ^{13}C nmr spectral data agreed with structure **11** (Tables 1 and 2).

Isomerization of **11** to form **12**.

At room temperature, after 7-10 days, or after 2 hours in tetrahydrofuran solution (containing some triethylamine), gummy **11** "crystallized". Microanalysis of the new solid agreed with molecular formula, $C_6H_9N_3O_3S$. However, dramatic changes took place in the ^{1}H and ^{13}C nmr spectra as the gum crystallized. The four proton and the five carbon signals of **11** were replaced in their entirety by new sets of signals. The ^{1}H nmr signals (deuteriochloroform) of **11** at 9.97 (CHO), 8.12, 7.88 (imidazole protons) and 2.98 ppm (NCH_3) were replaced by signals at 9.91, 7.98, 7.92 and 2.94 ppm. Similarly, the five ^{13}C nmr signals (deuteriochloroform) of **11** at 178.1 (CHO), 143.6, 141.6, 131.4 (imidazole carbons) and 38.29 ppm (NCH_3) disappeared and five

new signals at 185.6, 142.3, 137.4, 121.9 and 38.16 ppm arose. It appeared that an isomerization had occurred. While the aldehyde and *N*-methyl resonances are readily identified in the respective ^1H and ^{13}C nmr spectra, the substitution pattern of the imidazole ring is not evident from the nmr signals only. One thing was clear that the new solid could not

Table 1

^1H Chemical Shifts of Selected Imidazoles,  [a]

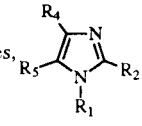
Compound	Solvent [b]	R_1	R_2	R_4	R_5	H-2	H-4	H-5	NMe	CHO	Others	Ref [c]
1	C	H	H	H	H	7.74	7.19	7.19	–	–	12.58 (NH)	OW
1	D	H	H	H	H	7.67	7.03	7.03	–	–	[d]	OW
–	C	Me	H	H	H	7.32	6.94	6.79	3.58	–	–	OW
–	C	Me	H	H	H	7.41	7.03	6.87	3.87	–	–	[17]
–	C	Me	D	H	H	–	7.04	6.87	3.68	–	–	OW
–	C	Me	D	H	D	–	7.03	–	3.68	–	–	OW
–	D	Me	H	H	H	7.55	7.09	6.88	3.62	–	–	OW
[f]	C	H	H	Me	H	7.54	6.76	6.76	–	–	2.40 (Me), [d]	[5]
		H	H	H	Me							
–	C	Me	Me	H	H	–	6.84	6.76 [h]	3.52	–	2.32 (Me)	OW
5	C	H	CHO	H	H	–	7.41	7.41	–	9.63	[d]	OW
5	C	H	CHO	H	H	–	7.43	7.43	–	9.67	[d]	[18]
5	D	H	CHO	H	H	–	7.41	7.41	–	9.63	[d]	OW
13 [f]	D	H	H	CHO	H	8.26	8.56	8.56	–	9.80	8.5-7.5 (NH)	OW
		H	H	H	CHO							
–	C	Me	CHO	H	H	–	7.27	7.18 [h]	4.03	9.80	–	OW
–	C	Me	CHO	H	H	–	7.33	7.22	4.02	9.93	–	[19]
–	C	Me	H	H	CHO	7.79	7.65	–	3.95	9.77	–	[20]
–	C	Me	H	H	CHO	7.79	7.64	–	3.96	9.77	–	[23]
–	C	Me	$SiMe_3$	H	H	–	6.88	6.88	3.67	–	0.31($SiMe_3$)	[21]
–	C	Me	H	$SiMe_3$	H	7.60	–	7.03	[e]	–	[e]	[8]
–	C	Me	H	H	$SiMe_3$	7.58	7.17	–	[e]	–	[e]	[8]
–	C	Me	H	H	$Si(Me)_2t$-Bu	7.50	7.14	–	3.68	–	0.88($SiCMe_3$), 0.26($SiMe_2$)	[12]
–	C	Me	H	$SiMe_3$	$SiMe_3$	7.65	–	–	[e]	–	[e]	[8]
–	C	Me	$SiMe_3$	H	$SiMe_3$	–	7.17	–	–	–	[e]	[8]
2	C	SO_2NMe_2	H	H	H	7.92	7.27	7.16	2.86	–	–	OW
2	C	SO_2NMe_2	H	H	H	7.91	7.26	7.15	2.83	–	–	[4]
2	D	SO_2NMe_2	H	H	H	8.19	7.65	7.18	2.82	–	–	OW
–	C	SO_2NMe_2	D	H	H	–	7.27	7.16	2.86	–	–	OW
–	C	SO_2NMe_2	D	H	D	–	7.27	–	2.86	–	–	OW
–	C	SO_2NMe_2	Me	H	H	–	7.20	6.89	2.86	–	2.56 (Me)	[4]
–	C	SO_2NMe_2	H	H	Me	7.81	6.95	–	2.80	–	2.23 (Me)	[4]
–	C	SO_2NMe_2	H	H	Me	7.89	6.84	–	2.90	–	2.40 (Me)	[6]
–	C	SO_2NMe_2	Me	H	Me	–	6.89	–	2.84	–	2.53 (C-2 Me), 2.11 (C-5 Me)	[4]
–	C	SO_2NMe_2	H	$SiMe_3$	H	8.05	–	7.32	[e]	–	[e]	[8]
–	C	SO_2NMe_2	H	H	$SiMe_3$	7.99	7.11	–	2.85	–	0.34 ($SiMe_2$)	[5]
–	C	SO_2NMe_2	H	H	$SiMe_3$	8.60	7.20	–	[e]	–	[e]	[8]
8	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	H	–	7.23	7.32	2.85	–	0.96 ($SiCMe_3$), 0.40 ($SiMe_2$)	OW
8	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	H	–	7.28	7.37	2.90	–	1.0 ($SiCMe_3$), 0.43 ($SiMe_2$)	[6]
8	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	D	–	7.25	–	2.87	–	0.98 ($SiCMe_3$), 0.42 ($SiMe_2$)	[6]
16	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	Me	–	6.93	–	2.87	–	1.00 ($SiCMe_3$), 0.40 ($SiMe_2$)	[6]
10	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	CHO	–	7.94	–	2.89	10.03	1.02 ($SiCMe_3$), 0.44 ($SiMe_2$)	OW
17 [g]	C	SO_2NMe_2	$SiEt_3$	H	CHO	–	7.96	–	2.94	9.98	1.00 ($SiEt_3$)	[11]
–	C	Me	CHO	H	$SiMe_3$	–	7.30	–	4.05	9.86	0.38 ($SiMe_3$)	[12]
4	C	SO_2NMe_2	CHO	H	H	–	7.59	7.31	3.01	9.95	–	OW
11	C	SO_2NMe_2	H	H	CHO	8.13	7.89	–	2.98	9.97	–	OW
11	D	SO_2NMe_2	H	H	CHO	8.49	8.03	–	2.94	9.93	–	OW
12	C	SO_2NMe_2	H	CHO	H	7.96	–	7.89	2.93	9.95	–	OW

Table 1

Compound	Solvent [b]	R_1	R_2	R_4	R_5	H-2	H-4	H-5	NMe	CHO	Others	Ref [c]
12	D	SO_2NMe_2	H	CHO	H	8.55	–	8.41	2.90	9.84	–	OW
6	C	CH_2NEt_2	H	H	H	7.51	7.04	6.96	–	–	4.82 (N-CH_2-N) 2.55 [$N(CH_2)_2$], 1.10 (Me)	OW
–	C	CH_2Me_2	H	H	H	7.49	7.03	6.96	2.25	–	4.64 (N-CH_2-N)	[7]

[a] In ppm (δ), downfield from tetramethylsilane. [b] In deuteriochloroform, C, or deuteriodimethyl sulfoxide, D. [c] OW is our work. [d] NH signal is not observed. [e] No other signals are reported. [f] Represents a tautomeric 4(5)-1-imidazole system, hence signals for 4 and 5 are interchangeable. [g] It is suggested that this is the correct structure instead of the reported one, **16** [Ref 11]. [h] Assignments confiremd through nOe experiments. enhancement of either N-methyl or H-5 signals, if one or the other is irradiated.

Table 2

^{13}C Chemical Shifts of Selected Imidazoles,  [a]

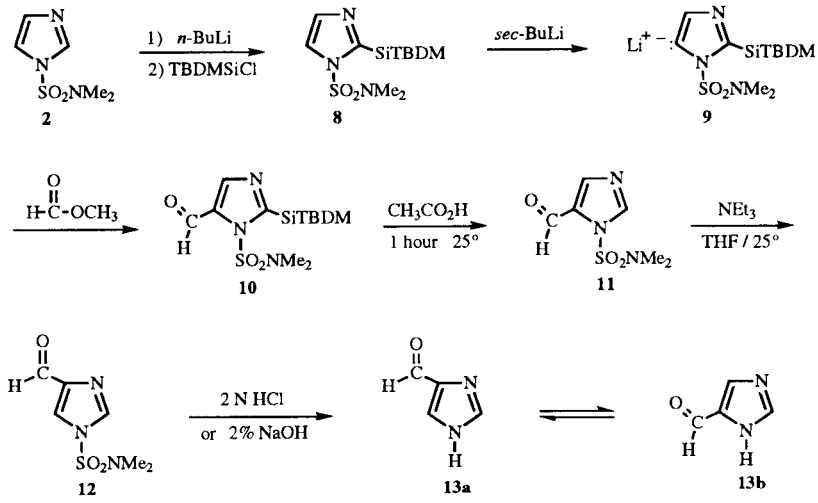
Compound	Solvent [b]	R_1	R_2	R_4	R_5	C-2	C-4	C-5	NCH_3	CHO	Others	Ref [c]
13 [f]	D	H	H	CHO	H	138.5	128.9 [d]	135.6 [d]	–	182.4	–	OW
		H	H	H	CHO				–	182.4	–	
–	C	Me	H	H	H	137.6	129.3	119.7	32.9	–	–	[15]
–	C	Me	Me	H	H	144.1	126.1	120.0	32.0	–	12.11 (Me)	OW
–	C	Me	CHO	H	H	143.3	131.0	127.1	34.51	181.6	–	OW
–	C	COMe	H	H	H	136.2	130.5	115.9	–	–	22.3 (Me)	[15]
–	C	SO_2CF_3	H	H	H	139.0	133.3 [e]	119.6 [e]	–	–	119.8 (CF_3)	[15]
2	C	SO_2NMe_2	H	H	H	136.6	117.5	130.3	37.91	–	–	OW
2	C	SO_2NMe_2	H	H	H	136.6	117.7	130.4	38.14	–	–	[4]
2	D	SO_2NMe_2	H	H	H	136.9	118.4	129.9	37.70	–	–	OW
8	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	H	136.2	130.7	120.1	38.27	–	27.01 ($SiCMe_3$), 18.09 ($SiCMe_3$), -3.94 ($SiMe_2$)	OW
10	C	SO_2NMe_2	$Si(Me)_2t$-Bu	H	CHO	141.1	130.7	120.1	38.08	179.0	27.07 ($SiCMe_3$) 18.48 ($SiCMe_3$), -3.75 ($SiMe_2$)	OW
4	C	SO_2NMe_2	CHO	H	H	143.4	130.2	125.8	38.50	179.1	–	OW
11	C	SO_2NMe_2	H	H	CHO	143.6	141.6	131.4	38.28	178.1	–	OW
12	C	SO_2NMe_2	H	CHO	H	137.5	142.3	122.0	38.24	185.8	–	OW
12	D	SO_2NMe_2	H	CHO	H	138.5	141.6	126.3	37.79	185.1	–	OW
6	C	CH_2NEt_2	H	H	H	136.7	128.3	118.8	–	–	63.1 (N-CH_2-N) 44.4 [$N(CH_2)_2$], 12.0 (Me)	OW
–	C	CH_2NMe_2	H	H	H	136.7	127.8	118.9	40.8	–	68.1 (N-CH_2-N)	[7]

[a] In ppm (δ), downfield from tetramethylsilane. [b] In deuteriochloroform, C, or deuteriodimethyl sulfoxide, D. [c] OW is our work. [d] In the tautomeric 4(5)-1-(*H*)-imidazole system, signals for 4 and 5 are interchangeable. [e] Based on our unequivocal assignments of δ C-4 and C-5 of sulfonamide **2** (deuteration, ^{1}H-^{13}C HETCOR spectrum), it could be that these ^{13}C-assignments should be in reverse.

be 1-(dimethylsulfamoyl)-2-imidazolecarboxaldehyde (**4**) since this isomer had been synthesized in our laboratory and its ^{1}H and ^{13}C nmr parameters differed considerably from those of the gum, or new solid (Tables 1 and 2).

Structure proof of **12**.

It was anticipated that the structure proofs of **11** and **12** could be achieved by an analysis of their ^{1}H and ^{13}C nmr spectra. Of course, data from suitable reference imidazoles would have to be available. Analysis of chemical shift data from many imidazoles (Tables 1 and 2) was not convincing enough to assign structures to the new aldehydes, with any degree of certainty. In general, ^{1}H chemical shifts of imidazoles, in general, follow this order: H-2 is the most deshielded proton, H-4 less so, and H-5 is most shielded. From the limited ^{13}C nmr data available, it



appears that C-2 resonances tended to be furthest downfield, but chemical shifts of C-4 and C-5 do not necessarily parallel those of H-4 and H-5 [15-17, 22]. The range of ^1H and ^{13}C chemical shifts of imidazoles fall into a relatively small range and are greatly affected by electronic, anisotropic and solvent effects. Without clear-cut definitions of chemical shift differences brought on by various substituents, structure determination of **11** and **12** from nmr data alone, was tenuous.

We checked a number of chemical shift assignments by means of ^1H-^{13}C HETCOR 2D, as well as by nuclear Overhauser enhancement (nOe) experiments. For example, we found that the ^{13}C chemical shift assignments of the starting material **2** was contrary to that anticipated from literature values quoted for *N*-acylimidazoles (Table 2). In **2**, ^1H signals at 7.92, 7.27 and 7.16 ppm were assigned to H-2, H-4, and H-5, respectively. A HETCOR experiment revealed that the 7.92 ppm proton signal correlated well with the carbon signal for C-2, at 136.6 ppm. However, the proton signals at 7.27 and 7.16 ppm (H-4, and H-5) correlated with the carbon signals at 117.5 and 130.3 ppm. Therefore, these carbon signals are attributed to C-4 and C-5, respectively (Tables 1 and 2).

The nOe experiments were definitive when the aldehyde proton was irradiated, the neighboring ring proton signal showed enhancement, (2.33% for **11**) and (2.43% for **12**). However, no nOe effects were observed between H-5 and the *N*-methyl of the sulfamoyl group in **12** [24]. Assuming that **11** is the expected 5-substituted aldehyde, the product of the well-established synthetic sequence, irradiation of the aldehyde proton caused nOe enhancement of the 7.89 ppm signal, thereby confirming the chemical shift for H-4. From the ^{13}C nmr spectrum, one would expect the carbon signal for C-5 of **11**, being quaternary, to be of considerably lower intensity (lower height) and be further upfield from those of C-2, C-4. Indeed, the signal at 131.4 ppm was obtained only after considerably longer period of signal acquisitions and was then only about 20% of the height of the resonances at 143.6 and 141.6 ppm. HETCOR 2D nmr experiments confirmed that the 131.4 ppm carbon signal did not correlate with any ^1H signal, confirming the fact that this carbon lacked a proton (being quaternary). However, the carbon signals at 143.6 and 141.6 ppm correlated with the proton signals at 8.13 and 7.89 ppm, respectively. Since the 7.89 ppm signal was that of H-4, the 141.6 ppm signal is assigned to C-4, and the one at 143.6 ppm to C-2.

By means of similar experiments on **12**, the intensity of the furthest downfield signal, at 142.3 ppm, was only about 15% of that of the other two signals and is therefore assigned to C-4. The nOe experiments indicated that irradiation of the proton of the aldehyde at C-5 enhanced the neighboring 7.89 ppm signal. Therefore, the signal at 7.89 is from H-5. The two stronger signals at 137.4 (C-2) and 121.9 ppm (C-5) correlated with the proton nmr signals at 7.96 and 7.89 ppm, respectively.

However, only single crystal X-ray structure determination proved unequivocally that the structure of the new aldehyde was **12**, apparently formed in an unusual and unexpected rearrangement. During the isomerization of **11** to **12** at room temperature, there was isolated a small quantity of the known 4(5)-imidazolecarboxaldehyde (**13**). This aldehyde is a logical product of hydrolysis of either **11** or **12**. Because **13** was only slightly soluble in deuteriochloroform, its nmr spectra were recorded in deuteriodimethyl sulfoxide (Table 1 and 2). Crude samples of **11** or **12** initially contained but a few percent of **13** (^1H nmr).

Mechanism of Isomerization of **11** to **12**.

Isomers **11** and **12** are in effect *N*-acylimidazoles and thus the isomerization appears as a "migration" of the dimethylsulfamoyl group from *N*-1 to *N*-3. One can also

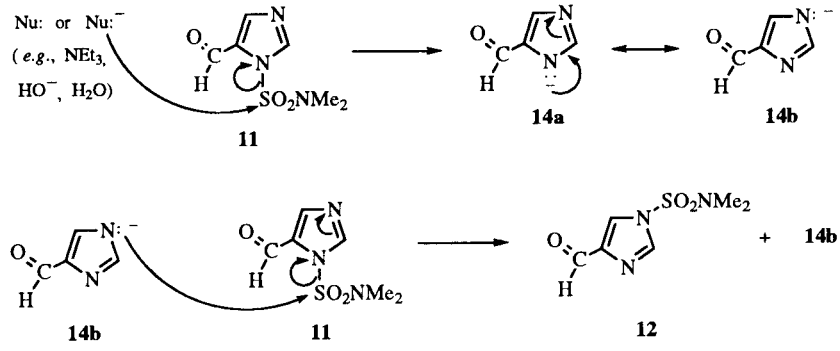


Table 3

Crystal Data and Structure Refinement for 1-(Dimethylsulfamoyl)-4-imidazolecarboxaldehyde

Empirical formula	$C_6H_9N_3O_3S$
Formula weight	203.22
Temperature	294(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 6.4940(10) Å
	α = 90 °
	b = 25.447(5) Å
	β = 97.91(3) °
	c = 11.104(2) Å
	γ = 90 °
Volume	1817.5(6) Å^3
Z	8
Density	Calculated: 1.485 Mg/m^3
Found: 1.48 Mg/m^3	
Absorption coefficient	0.336 mm^{-1}
F(000)	848
Crystal size	0.4 x 0.4 x 0.6 mm
Theta range for data collection	1.60 to 22.56 °
Index ranges	0<=h<=7, 0<=k<=27,
-11<=l<=11	
Reflections collected	2611
Independent reflections	2377 [R(int) = 0.0146]
Refinement method	Full-matrix least-squares on F^2
SHELXL-93	
Data / restraints / parameters	2374 / 4 / 251
Goodness-of-fit on F^2	0.960
Final R indices [I>2σ(I)]	R1 = 0.0358, wR2 = 0.1049
R indices (all data)	R1 = 0.0432, wR2 = 0.1182
Extinction coefficient	0.0070(10)
Largest diff. peak and hole	0.182 and -0.236 e.A^{-3}

Weighted R-factors wR and all goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The observed criterion of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R factor obs etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on all data will be even larger.

surmise that **12** is the thermodynamically more stable isomer since the equilibrium is favored in this direction. It is perhaps somewhat anomalous that **11** isomerizes so easily to **12**, when a number of 1-dimethylsulfamoyl-5-substituted-imidazoles, prepared by similar synthetic sequences, seem to be perfectly stable [6]. The relative ease by which **11** isomerizes to **12** can be attributed to the highly nucleophilic resonance-stabilized 4(5)-formylimidazole anion **14** being a good leaving group. In this anion, the negative charge is delocalized over both ring nitrogens, as well as the oxygen of the aldehyde. Such resonance interactions involving the aldehyde as a *C*-5 substituent are absent when other groups are attached at *C*-5 [6]. It is suggested that the isomerization is triggered by initial nucleophilic attack of triethylamine (or some other nucleophilic entity in the medium) on the *N*-1 sulfamoyl group of **11**, to release anion **14**. Now, the more exposed anionic site of

Table 4

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (A^2 x 10^3) for 1-(Dimethylsulfamoyl)-4-imidazolecarboxaldehyde.

Atom	x/a	y/b	z/c	U(eq) [a]
S(1)	2803(1)	1166(1)	1627(1)	44(1)
O(1)	1803(4)	1212(1)	418(2)	60(1)
O(2)	1913(4)	1373(1)	2623(2)	59(1)
O(7)	544(6)	-1117(2)	3644(4)	92(1)
O(7')	3697(13)	-716(4)	4633(7)	57(3)
N(1)	2909(4)	505(1)	1888(2)	41(1)
N(3)	3081(4)	-356(1)	1539(2)	59(1)
N(10)	5122(4)	1373(1)	1698(2)	49(1)
C(2)	2871(5)	105(1)	1030(3)	57(1)
C(4)	3283(4)	-260(1)	2777(3)	45(1)
C(5)	3173(4)	265(1)	3003(2)	42(1)
C(6)	3510(5)	-668(2)	3734(5)	69(1)
C(11)	6399(6)	1400(1)	2890(3)	68(1)
C(12)	6255(6)	1274(1)	661(3)	67(1)
S(1A)	8314(1)	-2121(1)	2971(1)	45(1)
O(1A)	7773(4)	-2377(1)	4015(2)	65(1)
O(2A)	7024(3)	-2143(1)	1837(2)	62(1)
O(7A)	8067(3)	99(1)	1929(2)	58(1)
N(1A)	8373(3)	-1472(1)	3365(2)	40(1)
N(3A)	8665(4)	-760(1)	4530(2)	51(1)
N(10A)	10610(4)	-2286(1)	2792(2)	48(1)
C(2A)	8620(5)	-1271(1)	4527(2)	49(1)
C(4A)	8437(4)	-615(1)	3311(2)	40(1)
C(5A)	8258(4)	-1049(1)	2586(2)	39(1)
C(6A)	8367(5)	-61(1)	2960(3)	49(1)
C(11A)	12164(6)	-2342(1)	3878(3)	65(1)
C(12A)	11422(6)	-2114(2)	1688(3)	71(1)

[a] U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 5

Bond Lengths [Å] and Angles [deg] for 1-(Dimethylsulfamoyl)-4-imidazolecarboxaldehyde

S(1)-O(1)	1.414(2)	S(1A)-O(2A)	1.414(2)
S(1)-O(2)	1.418(2)	S(1A)-O(1A)	1.416(2)
S(1)-N(10)	1.587(3)	S(1A)-N(10A)	1.587(3)
S(1)-N(1)	1.707(2)	S(1A)-N(1A)	1.708(2)
O(7)-C(6)	1.149(5)	O(7A)-C(6A)	1.205(3)
O(7')-C(6)	0.996(7)		
N(1)-C(5)	1.369(3)	N(1A)-C(5A)	1.377(3)
N(1)-C(2)	1.390(4)	N(1A)-C(2A)	1.377(3)
N(3)-C(2)	1.301(4)	N(3A)-C(2A)	1.300(4)
N(3)-C(4)	1.384(4)	N(3A)-C(4A)	1.392(3)
N(10)-C(11)	1.463(4)	N(10A)-C(12A)	1.467(4)
N(10)-C(12)	1.471(4)	N(10A)-C(11A)	1.469(4)
C(4)-C(5)	1.364(4)	C(4A)-C(5A)	1.363(4)
C(4)-C(6)	1.477(5)	C(4A)-C(6A)	1.460(4)
O(1)-S(1)-O(2)	121.73(14)	O(2A)-S(1A)-O(1A)	121.8(2)
O(1)-S(1)-N(10)	109.14(14)	O(2A)-S(1A)-N(10A)	109.29(14)
O(2)-S(1)-N(10)	108.86(14)	O(1A)-S(1A)-N(10A)	108.92(14)
O(1)-S(1)-N(1)	104.27(13)	O(2A)-S(1A)-N(1A)	104.78(13)
O(2)-S(1)-N(1)	104.23(12)	O(1A)-S(1A)-N(1A)	103.57(13)
N(10)-S(1)-N(1)	107.67(12)	N(10A)-S(1A)-N(1A)	107.40(12)
C(5)-N(1)-C(2)	106.4(2)	C(5A)-N(1A)-C(2A)	106.7(2)
C(5)-N(1)-S(1)	126.1(2)	C(5A)-N(1A)-S(1A)	126.7(2)
C(2)-N(1)-S(1)	127.4(2)	C(2A)-N(1A)-S(1A)	126.5(2)
C(2)-N(3)-C(4)	105.3(2)	C(2A)-N(3A)-C(4A)	105.3(2)
C(11)-N(10)-C(12)	115.7(3)	C(12A)-N(10A)-C(11A)	115.5(3)
C(11)-N(10)-S(1)	118.4(2)	C(12A)-N(10A)-S(1A)	118.5(2)
C(12)-N(10)-S(1)	118.5(2)	C(11A)-N(10A)-S(1A)	118.3(2)
N(3)-C(2)-N(1)	111.7(3)	N(3A)-C(2A)-N(1A)	112.0(2)
C(5)-C(4)-N(3)	110.7(3)	C(5A)-C(4A)-N(3A)	110.4(3)
C(5)-C(4)-C(6)	123.9(3)	C(5A)-C(4A)-C(6A)	128.9(3)
N(3)-C(4)-C(6)	125.3(3)	N(3A)-C(4A)-C(6A)	120.7(3)
C(4)-C(5)-N(1)	105.8(2)	C(4A)-C(5A)-N(1A)	105.7(2)
O(7)-C(6)-C(4)	129.6(5)	O(7A)-C(6A)-C(4A)	125.1(3)
O(7')-C(6)-C(4)	142.5(7)		
O(7')-C(6)-O(7)	87.9(6)		

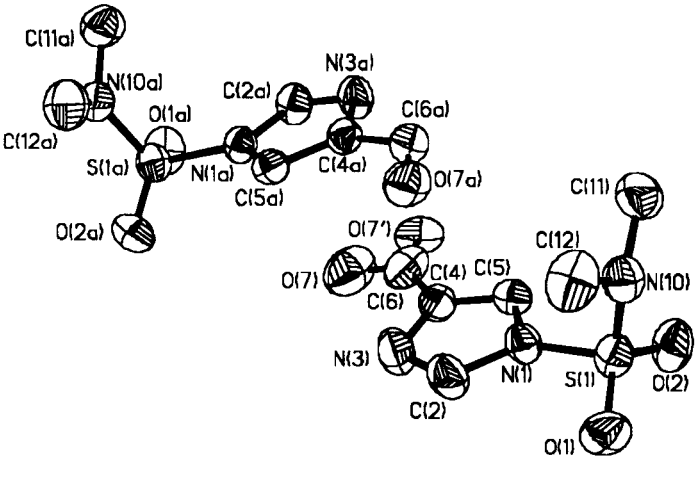


Figure 1. ORTEP Diagram of the two molecules in the asymmetric unit. Hydrogen atoms are omitted for clarity.

resonance-stabilized anion, namely *N*-3 of **14b** attacks the sulfamoyl group of another molecule, **11**. During this process, the sterically less hindered sulfamoyl derivative **12** is formed with concomitant release of **14**, thus maintaining a chain reaction.

Table 6

Anisotropic Displacement Parameters ($A^2 \times 10^3$) for 1-(Dimethylsulfamoyl)-4-imidazolecarboxaldehyde

Atom	U11	U22	U33	U23	U13	U12
S(1)	52(1)	43(1)	36(1)	2(1)	11(1)	7(1)
O(1)	67(2)	72(2)	40(1)	9(1)	2(1)	10(1)
O(2)	75(2)	57(1)	50(1)	-1(1)	24(1)	16(1)
O(7)	73(2)	72(3)	130(4)	20(2)	11(2)	0(2)
O(7')	71(6)	71(7)	27(4)	32(5)	-1(4)	-1(5)
N(1)	49(1)	42(1)	34(1)	-3(1)	8(1)	-1(1)
N(3)	72(2)	45(2)	59(2)	-11(1)	8(1)	-2(1)
N(10)	58(2)	42(1)	47(2)	3(1)	11(1)	-1(1)
C(2)	70(2)	60(2)	40(2)	-12(2)	9(2)	0(2)
C(4)	41(2)	41(2)	54(2)	0(1)	7(1)	-3(1)
C(5)	41(2)	49(2)	37(2)	0(1)	7(1)	-2(1)
C(6)	43(2)	44(2)	119(4)	16(2)	9(2)	-5(2)
C(11)	74(2)	50(2)	73(2)	3(2)	-9(2)	-7(2)
C(12)	68(2)	63(2)	77(2)	10(2)	33(2)	2(2)
S(1A)	51(1)	39(1)	47(1)	-1(1)	12(1)	-4(1)
O(1A)	82(2)	51(1)	69(2)	12(1)	33(1)	-7(1)
O(2A)	62(2)	61(2)	60(2)	-14(1)	-6(1)	-8(1)
O(7A)	63(1)	54(1)	58(1)	10(1)	5(1)	2(1)
N(1A)	47(1)	41(1)	33(1)	0(1)	10(1)	5(1)
N(3A)	68(2)	50(2)	37(1)	-6(1)	10(1)	6(1)
N(10A)	53(2)	44(1)	47(1)	0(1)	10(1)	5(1)
C(2A)	64(2)	51(2)	32(2)	2(1)	13(1)	8(2)
C(4A)	40(2)	42(2)	37(2)	-2(1)	7(1)	4(1)
C(5A)	40(2)	46(2)	33(2)	1(1)	6(1)	2(1)
C(6A)	46(2)	47(2)	53(2)	-5(2)	6(2)	2(1)
C(11A)	64(2)	58(2)	72(2)	6(2)	0(2)	6(2)
C(12A)	71(2)	92(3)	56(2)	-7(2)	24(2)	4(2)

[a] The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$.

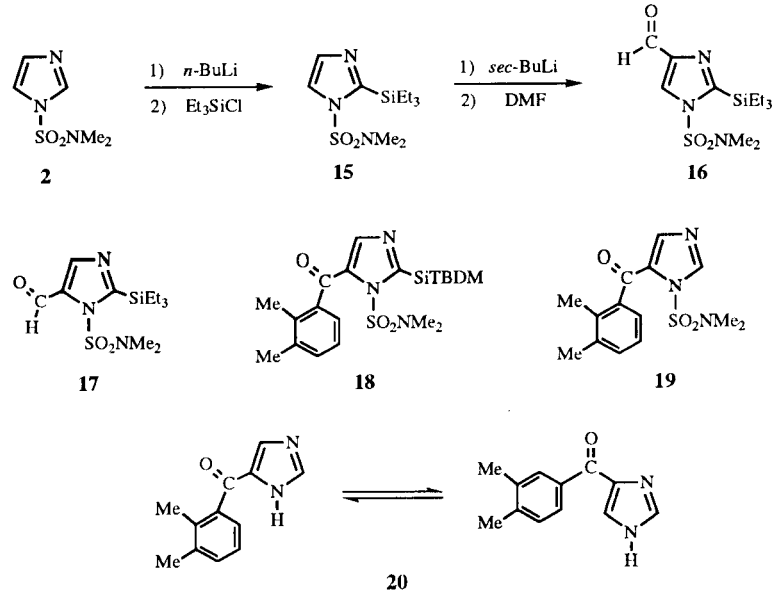
Related Experiments.

After completion of this work, we became aware of some related research [11]. Lithiation of **2**, followed by the addition of triethylsilyl chloride yielded **15**. Treatment of **15** with *sec*-butyllithium, followed by DMF purportedly provided **16** [11]. Based on our experience relayed above, but using the TBDM silyl protective group, we suggest that the actual structure of **16** is **17.** Naturally, complete hydrolysis of **16** or, for that matter **17** would provide only **13** [11].

In a series of somewhat related reactions, Kudzma *et al.* reacted **8** with *n*-butyllithium, followed by 2,3-dimethylbenzoyl chloride and obtained 1-(dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-5-(2,3-dimethylbenzoyl)-imidazole (**18**) in 99% yield [14]. These authors hydrolyzed the silyl and sulfamoyl groups simultaneously to obtain 4(5)-(2,3-dimethylbenzoyl)imidazole **20**, directly. Since these workers did not desilylate selectively, one would never know if the 5-ketone **19** was an intermediate to **20**, or, perhaps more interestingly, if **19** would

have rearranged to the 4-isomer, prior to the hydrolysis of the sulfamoyl group.

It is also of interest to note that an interesting acyl migration has just been reported when 3-amino-1- and -2-(chloroacetyl)pyrazoles rearranged to 3-(chloroacetamido)pyrazole [15].



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer (at 300 and 75.4 MHz, respectively). Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane (TMS). Pertinent nmr data are assembled in Tables 1 and 2. All research chemicals, as well as anhydrous solvents, tetrahydrofuran (THF), dimethylformamide (DMF) and hexane, were purchased from Aldrich Chemical Co., Milwaukee, WI, unless specified otherwise, and were used as supplied. Dichloromethane was dried by storing over 4Å molecular sieves for 2 days and DMF was stored over 4Å molecular sieves once the container had been opened. Nitrogen gas was purchased from AGA, Maunee, OH, and dried by passing through a calcium chloride tube. Evaporation, or distillation of solvents, *in vacuo*, implies that solvents were removed by means of a rotary evaporator at the water pump (20-30 torr) at about 40°, unless specified otherwise. Thin layer chromatograms (tlc) were run on Aldrich silica gel coated polyester plates containing a 254 nm fluorescent indicator. Column chromatography was performed on Aldrich grade 60 silica gel (70-230 mesh), unless noted otherwise. Whenever (tlc) indicated sufficient separation between spots, flash chromatography on silica gel was used for the separation.

1-(Dimethylsulfamoyl)imidazole (**2**).

For the preparation of this compound [5,6], the work-up procedure was modified. This enabled us to obtain a better yield of a purer compound. To a mixture of imidazole (**1**, 9.54 g, 0.14 mole), dry dichloromethane (200 ml) and dimethylsulfamoyl chloride (13.0 ml, 0.12 mole) *was added* triethylamine (18.0 ml, 0.13 mole). The mixture was stirred at room temperature for 16 hours, during which time a solid separated. The mixture was transferred to a separatory funnel and washed with water (2 x 200 ml) and the organic layer was separated. The solvent was removed, *in vacuo*, and the product was distilled as a colorless oil (20.1 g, 82%), bp 112°/0.3 torr, lit [4] bp, 110°/0.4 torr, [11] 89-90°/0.2 torr; mp 43-45°, lit mp [3], 45-48°, [4] 42-44°, [11] 41-42°.

In a recent paper, more or less the same method was used to prepare **2** (91%), except that the solid (presumably, triethylammonium chloride) was filtered before further processing to obtain the final product [11].

1-(Dimethylsulfamyl)-2-imidazolecarboxaldehyde (**4**).

To a stirred solution of **2** (5.0 g, 0.029 mole) in anhydrous tetrahydrofuran (170 ml), at -78° (under nitrogen) was added, dropwise, *n*-butyllithium (13.0 ml of 2.5*M* in hexanes, 0.032 mole), and lithiation was allowed to proceed at -70° for 25 minutes. Anhydrous DMF (3.0 g, 0.04 mole) was added at once and the reaction mixture was permitted to warm to room temperature and then stirred for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (100 ml). The volume of organic solvents was reduced, *in vacuo,* to one forth of original volume and the mixture was extracted with ethyl acetate (3 x 100 ml). The organic extract was dried (magnesium sulfate). Evaporation of the solvent, *in vacuo*, furnished a red oil which crystallized from methylene chloride (1.10 g, 19%), mp 92°.

Anal. Calcd. for $C_6H_9N_3SO_3$: C, 35.46; H, 4.46; N, 20.68. Found: C, 35.45; H, 4.49; N, 20.48.

1-(*N,N*-Diethylaminomethyl)imidazole (**5**).

The method of Katritzky *et al.* (1988) [7] was used in this preparation. Imidazole (**1**, 10.0 g, 0.15 mole) and diethylamine (11.0 g, 0.15 mole) were dissolved in water (25 ml). Concentrated hydrochloric acid was added until the *p*H of solution was about 5. Aqueous formaldehyde solution (13.8 g, 37% w/w solution, 0.17

mole) was added and the mixture was stirred at room temperature for 48 hours. The solution was made strongly basic with 20% aqueous potassium hydroxide solution and solid potassium carbonate (2.0 g) was added to salt out the organic material which was extracted with methylene chloride (3 x 100 ml). The extracts were combined, dried (magnesium sulfate) and evaporated, *in vacuo*, to yield **5** as a colorless oil (23.0 g, 100%).

Anal. Calcd. for $C_8H_{15}N_3 \cdot H_2O$: C, 56.11; H, 10.00; N, 24.54. Found: C, 55.86; H, 9.78; N, 24.18.

2-Imidazolecarboxaldehyde (**5**).

To a solution of **5** (5.0 g, 0.033 mole) in anhydrous tetrahydrofuran (50 ml) at -40°, under nitrogen, was added, dropwise, *n*-butyllithium (15.7 ml, 2.5 *M* in hexane solution, 0.039 mole) over a period of 15 minutes. The mixture was stirred for 1 hour at -40°, under nitrogen. Anhydrous methyl formate (3.0 g, 0.05 mole) was added at once and the cooling bath removed. The reaction was stirred at room temperature for 18 hours. The reaction mixture was poured into 2*N* hydrochloric acid (70 ml) and the organic layer was separated. The acidic aqueous layer was made strongly basic with saturated aqueous sodium bicarbonate and was extracted with ethyl acetate (3 x 100 ml). The organic extracts were combined, dried (magnesium sulfate), and evaporated, *in vacuo*, to provide an off-white solid, which was crystallized from hot water to furnish **5** (2.1 g, 68%), mp 205-207° dec, lit [25] 204°, [18] 206-207°.

1-(Dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)imidazole (**8**).

This synthesis was carried out by a known procedure [5,6], which involved lithiation of **2** with *n*-butyllithium (2.5 *M* solution in hexane), followed by TBDMSiCl. After column chromatography on silica gel, and elution by ethyl acetate-hexane (1:1) **8** was isolated in 84% yield, mp 57-58°, lit [6] mp 63-66°.

1-(Dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)-5-imidazolecarboxaldehyde (**10**).

To a solution of 1-(dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)imidazole (**8**, 1.85 g, 6.4 mmoles) in anhydrous tetrahydrofuran (60 ml) at -78°, under nitrogen) was added *sec*-butyllithium (10.0 ml, 1.3 *M* suspension, 0.013 mole), dropwise, at -78°. After 1 hour, a small portion of the reaction mixture was treated with deuterium oxide to ascertain that lithiation had taken place completely, as was evident from the ^1H nmr spectrum. To the stirred reaction mixture for 1 hour at -78° (nitrogen), was added methyl formate (1.19 ml, 19.2 mmoles) was added and then was permitted to reach room temperature, slowly. After stirring the reaction mixture (15 hours), it was quenched with water (2 ml). Solvents were evaporated, *in vacuo*, and residue was dissolved in dichloromethane (300 ml) and washed with water (2 x 50 ml). After removal of dichloromethane, *in vacuo*, the residue was subjected to flash column chromatography (silica gel, 70-230 mesh, 30.0 g). Elution with ethyl acetate-hexane (1:1) yielded a pale yellow oil (1.16 g, 57%). This compound was not stable enough for elemental analysis, starting to decompose within a few days, apparently, in part due to desilylation (nmr).

Desilylation of **10**, Formation of **11**.

To a solution of the compound (**10**, 0.214 g, 0.674 mmole) in tetrahydrofuran (5 ml) was added a solution of 70% aqueous acetic acid (5 ml). After stirring at room temperature for 1 hour, solvents were removed, *in vacuo*, and the residue was neutralized with aqueous saturated sodium hydroxide solution. The solution was extracted with dichloromethane (180 ml) and washed with water (20 ml). The dichloromethane layer was dried (magnesium sulfate) and was evaporated, *in vacuo*. The product **11** (0.132 g, 96%) was a colorless gum.

Rearrangement of **11** to **12**.

After standing at room temperature for 1 week, compound **11** (3.4 g, 16.73 mmoles) rearranged mainly to compound **12**, with a small amount of adhering 4(5)-imidazolecarboxaldehyde (**13**). The mixture was diluted with some ethyl acetate and filtered. The insoluble solid proved to be **13**, mp 158-159°, lit [11] mp 169°.

Evaporation of ethyl acetate provided **12**, which was recrystallized from a small amount of ethyl acetate to give 2.3 g (68%), mp 103-104°. A faster method consisted of permitting a solution of **11** (49 mg) in THF (2 ml) containing triethylamine (0.3 ml) to stand at room temperature for 2 hours. Evaporation of the solvent, *in vacuo*, at low temperatures yielded **12** (32 mg).

Anal. Calcd. for $C_6H_9N_3O_3S$: C, 35.46; H, 4.46; N, 20.68; S, 15.78. Found: C, 35.52; H, 4.42; N, 20.43; S, 15.89.

Crystal Structure Analysis.

A clear colorless crystal of dimensions 0.4 x 0.4 x 0.6 mm was trimmed from a larger crystal and mounted on a glass capillary for X-ray measurements. Crystal data were determined at room temperature, 21°, on a Siemens P4 diffractometer using a graphite monochromator and MoKα radiation, λ = 0.71073Å. The cell parameters were determined from least squares treatment of the centered angles for 50 reflections in the range of $15° < 2\theta < 30°$. The intensity data were measured over the 2θ range from 3-45° and 3 reflections checked every 50 reflections measured showed no significant change in intensity with time. Of the 2611 reflections collected, 2377 were independent and used for solution and refinement. As a consequence of the unit cell dimensions and the density, there must be 8 molecules in the unit cell. Since the space group was determined to be $P2_1/n$ for which Z is 4, the asymmetric unit must be composed of two molecules. The structure was solved by direct methods using SHELXTL PLUS (PC Version) and refined on F^2 for all reflections except for 3 with negative F^2 using SHELXL-93 [26]. In the refinement, the C-O bond lengths in the disordered formyl group were restrained to be the same within a standard deviation of 0.03Å. In the final stages of the refinement, the hydrogen atoms were placed in calculated positions and allowed to ride on the atom to which they were attached. The hydrogen atoms of the methyl groups were treated as two equally populated sets rotated 60° relative to each other after difference Fourier peaks were found at those positions. The crystal data and details of the refinement are given in Table 3.

The structure for the asymmetric unit is shown in Figure 1, the atomic coordinates are given in Table 4, selected bond lengths and angles are given in Table 5, and anisotropic displacement parameters are given in Table 6. The relative positions of the sulfamoyl and the formyl groups, 1 and 3, are certain showing that the sulfamoyl group must have migrated from one nitrogen to the other in the rearrangement. The primary difference between the two molecules in the asymmetric unit is disorder of the formyl group in the molecule whose atoms are labeled S(1)-C(12). The disordered oxygen atom positions, O(7) and O(7'), each show half occupancy and are related to each other by rotation of 180° about the C(4)-C(6) bond.

Acknowledgements.

Support of this work by the National Institute of Child Health

Development through Research Contract NO1-HD-3-3178 is gratefully acknowledged. We thank Dr. H. K. Kim for many helpful suggestions. Doctor K. Zaw's help in performing some of the nmr experiments is greatly appreciated.

REFERENCES AND NOTES

[1] Presented at the 208th American Chemical Society National Meeting, August 21, 1994, Washington DC, ORG Abstract, No. 22 and taken in part from the PhD Dissertation of S. M. Abdelaal, University of Illinois at Chicago, June, 1994.

[2] B. Iddon, *Heterocycles*, **23**, 417 (1985).

[3] J. F. King, and T. M.-L. Lee, *Can. J. Chem.*, **59**, 356 (1981).

[4] D. J. Chadwick and R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 481 (1984).

[5] A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, **42**, 2351 (1986).

[6] R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 1645 (1990).

[7] A. R. Katrizky, G. W. Newcastle and W.-Q. Fan, *J. Org. Chem.*, **53**, 5685 (1988).

[8] F. Effenberger, M. Roos, R. Ahmad and A. Krebs, *Chem. Ber.*, **124**, 1639 (1991).

[9] T. S. Manoharan and R. S. Brown, *J. Org. Chem.*, **53**, 1107 (1988).

[10] R. C. Vollinga, J. P. de Koning, F. P. Jansen, R. Leurs, W. M. P. B. Menge, and H. Timmerman, *J. Med. Chem.*, **37**, 332, (1994).

[11] J. Winter and J. Rétey, *Synthesis*, 245 (1994).

[12] G. Shapiro and M. Marzi, *Tetrahedron Letters*, **34**, 3401 (1993).

[13] R. I. Ngochindo, *J. Chem. Res. (S)*, 58 (1990).

[14] L. V. Kudza and S. P. Turnbull Jr., *Synthesis*, 1021 (1991).

[15] M. Begtrup, J. Elguero, R. Faure, P. Camps, C. Estopá, D. Ilavský, A. Fruchier, C. Marzin and J. de Mendoza, *Magn. Reson. Chem.*, **26**, 134 (1988).

[16] D. Clarke, R. W. Mares, H. McNab and F. G. Riddell, *Magn. Reson. Chem.*, **32**, 256 (1994).

[17] S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, Y. Nagashima and T. Yoshikawa, *Chem. Pharm. Bull. Japan*, **42**, 821, (1994).

[18] L. A. M. Bastiaansen, P. M. Van Lier and E. F. Godefroi, *Org. Synth.*, **60**, 72 (1980).

[19] D. A. Goff, G. A. Koolpe, A. B. Kelson, H. M. Vu, D. L. Taylor, C. D. Bedford, H. A. Mussalam, I. Koplovitz and R. N. Harris III, *J. Med. Chem.*, **34**, 1363, (1991).

[20] R. Kirchlechner, M. Casutt, U. Heywang and M. W. Schwarz, *Synthesis*, 247 (1994).

[21] F. H. Pinkerton and S. F. Thames, *J. Heterocyclic Chem.*, **9**, 67 (1972).

[22] F. Benedini, F. Ferrario and A. Sala, *Magn. Reson. Chem.*, **30**, 1137 (1992).

[23] J. M. Dener, L.-H. Zhang and H. Rapoport, *J. Org. Chem.*, **58**, 1159 (1993).

[24] R. P. Subrayan, E. L. Thurber and P. G. Rasmussen, *Tetrahedron*, **50**, 2641 (1994) have used nOe effectively to distinguish between 1-methyl-2-amino-4- and 5-imidazolecarbonitrile. Irradiation of the *N*-methyl signal showed considerable differences in the nOe's with H-5 and H-4, respectively.

[25] H. Schubert and H.-D. Rudorf, *Angew. Chem., Int. Ed. Engl.*, **5**, 674 (1966).

[26] SHELXL-93, Sheldrick G. M., 1994, SHELXL93, Program for Crystal Structure Refinement, University of Göttingen, Germany.