HETEROCYCLES, Vol. 53, No. 3, 2000, pp. 729 - 732, Received, 11th November , 1999

EFFICIENT ROUTE TO 1-DIMETHYLSULFAMOYL-4-IODO-IMIDAZOLE, ISOMERISATION OF 1-DIMETHYLSULFAMOYL-5-IODOIMIDAZOLE TO 1-DIMETHYLSULFAMOYL-4-IODO-IMIDAZOLE

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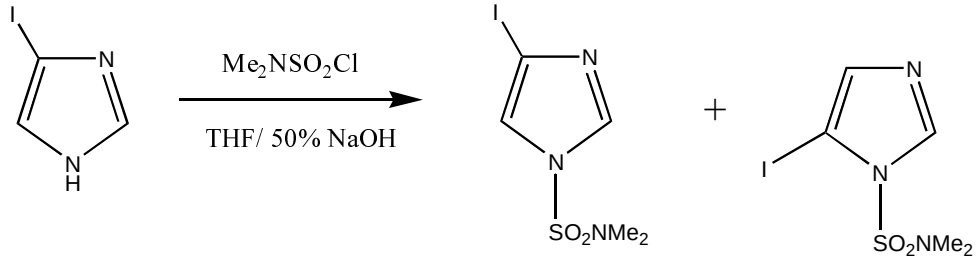
Abstract- An efficient method has been developed for regioselective protection of of 4-iodoimidazole using *N,N*-dimethylsulfamoyl chloride and 50% aqueous NaOH in THF leading to *N,N*-dimethylsulfamoyl-4-iodoimidazole(**1**) in 97% yield and >98% purity. The rearrangement of by-product 5-iodosulfonamide (**2**) to the desired product (**1**) is a key feature of this procedure.

During the course of our investigations toward an efficient synthesis of an α_{1A} adrenoceptor agonist, we required large amounts of *N*-protected 4- or 5-iodoimidazole.[1] Throughout the literature, the most popular procedure for protection of substituted imidazoles has been that of Chadwick and Ngochindo,[2] by which the desired protected imidazoles are produced in 95% reported yield. Specifically, the *N*-protection of 4(5)-iodoimidazole with trityl-, *N,N*-dimethylsulfamoyl- and trimethylsilylethoxymethyl-groups has been reported,[3] however little experimental detail was provided.

In our hands, the *N*-protection of 4(5)-iodoimidazole with *N,N*-dimethylsulfamoyl chloride and triethylamine in various solvents[2] afforded mixtures of *N*-protected 4- and 5- iodoimidazoles.[4] Typically, the ratio of 4-iodosulfonamide (**1**) to the 5-isomer (**2**) was in the range of 6:1 to 1:1. Pure *N,N*-dimethylsulfamoyl-4-iodoimidazole can be separated from the oily 5-iodo regioisomer in 60-70% yield by crystallization from the crude reaction mixture. We discovered that pure *N,N*-dimethylsulfamoyl-5-iodoimidazole (**2**) converted to the 4-iodo regioisomer over a period of time. This rearrangement takes place at ambient temperature over the course of 3-4 days, as well as in solution albeit at a significantly slower rate, eventually leading to >99% conversion to the single regioisomer. The 4-iodo compound does not revert to the 5-iodo isomer under any circumstances. Thus, our goal was to identify optimal conditions for an efficient protection/isomerisation procedure to provide the title compound in high yield and regioisomeric purity.



1 **2**

Extensive screening of various bases, solvents and reaction temperatures quickly revealed optimal conditions for the protection.

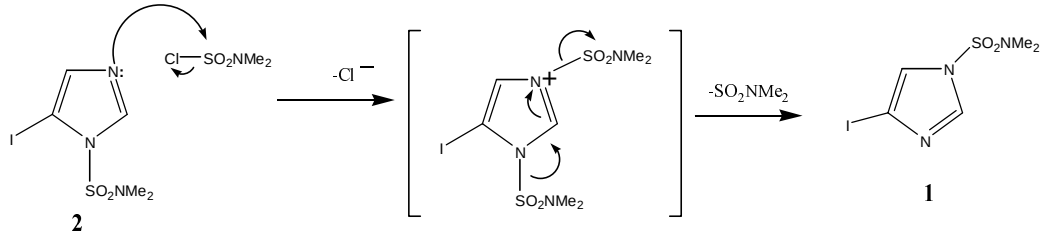
entry	Solvent	Base	4-Iodo, **1**	5-Iodo, **2**	SM
1	Toluene	K_2CO_3	20 %	20 %	60 %
2	Toluene	NEt_3, 60°C	65 %	35 %	
3	Toluene	50 % NaOH	69 %		31 %
4	NMP	K_2CO_3	41 %	10 %	49 %
5	DMF	K_2CO_3	23 %		77 %
6	MeCN	Na_2CO_3	5 %		95 %
7	MeCN	iPr_2NEt	49 %	11 %	40 %
8	MeCN	NEt_3, 50°C	82 %	18 %	
9	THF	50 % NaOH	90 %	10 %	None
10	THF	NaOH (powdered)	91 %	9 %	None
11	THF/Water (6:1)	50% NaOH	86 %	14 %	None
12	THF/ Water (3:1)	50 % NaOH	83 %	17 %	None
13	THF/ Water (1:1)	50 % NaOH	80 %	20 %	None

NMP = 1-Methyl-2-pyrrolidinone

While the reaction did go to completion in MeCN/NEt_3 (entry 8), crystallization yielded only about 60% of the desired 4-iodoimidazolide(**1)**. Treatment of 4(5)-iodoimidazole (entry 9) with 50 % aqueous NaOH in THF at room temperature afforded a quantitative yield of **1** and **2**, in a ratio of 9:1. The selectivity of the reaction is dependent on the THF/water ratio (entries 11-13), since increasing the amount of water in the reaction, the 4:5-iodo selectivity decreases. While the reaction proceeds quickly with solid powdered NaOH (entry 10), we chose to use 50 % (w/w) aqueous NaOH, for ease of use and also it solubilises some of the NaCl formed during the reaction.

In order to allow for a truly efficient synthetic process, an isomerisation protocol was required to drive the crude reaction mixture toward higher yields of **1**. It was initially observed that the isomer ratio changed during drying of the crude reaction mixture in a vacuum oven at elevated temperatures (90°-110°C). It was also found that the rate of isomerisation was dependent on the residual amount of the reagent *N,N*-dimethylsulfamoyl chloride; 3-5 mol% being optimal. A systematic study was carried out to find a solvent system to effect such a transformation. It was found that the isomerisation took place readily in non-polar solvents relative to polar solvents (isopropyl acetate, THF) due to solubility difference between the desired **1** and undesired isomer (**2**). Solubility of 4-iodosulfonamide (**1**) is >80 mg/mL in THF and isopropyl acetate whereas in heptane the solubility is 0.85 mg/mL.

Scheme I

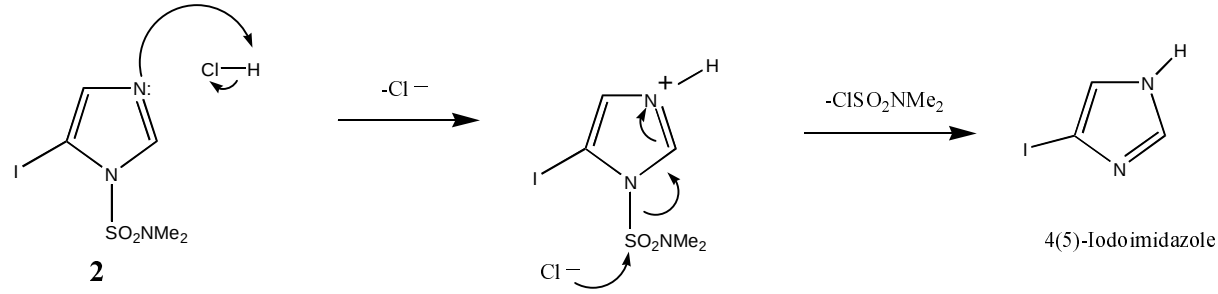


Thus heating the crude 4-/ 5-iodosulfonamide mixture in heptane to 70°C , in the presence of 5 mol % of *N,N*-dimethylsulfamoyl chloride resulted in >99 % conversion to the 4-iodosulfonamide. A mechanism is suggested for this transformation above. It is believed that the lone pair of electrons from **2** reacts with

N,N-dimethylsulfamoyl chloride and thus leading to an intermediate which loses a sulfonamide group (from position 1) to satisfy the electron deficient nitrogen atom at position 3. Heptane is a convenient vehicle for this transformation since only 5-iodosulfonamide (**2**) is soluble (solubility of 5-iodosulfonamide is >80 mg/mL). When the amount of 5-iodosulfonamide is less than 1%, the isomerisation is stopped and the product is filtered. Excess *N,N*-dimethylsulfamoyl chloride and unreacted 5-iodosulfonamide remain in filtrate.

Although such an isomerisation of *N*-protected iodoimidazole is not reported in the literature, base catalysed rearrangement of 1-(*N,N*-dimethylsulfamoyl)-5-imidazolecarboxaldehyde to the 4-regioisomer[5] has been reported. However treatment of our crude reaction mixture under basic conditions afforded no isomerisation. Under acidic conditions (5 mol% HCl in heptane) the isomerisation was comparatively slower and much more of 4(5)-iodoimidazole (upto 6 %) was generated as the by product. This could be attributed to the protonation of the sulfonamide (**2**) as suggested in the mechanism below.

Scheme II



2

In conclusion, we have demonstrated an efficient process for the preparation of 1-dimethylsulfamoyl-4-iodoimidazole (**1**) which utilises the rearrangement of unwanted 1-dimethylsulfamoyl-5-iodoimidazole (**2**). This procedure has been utilised to prepare multi-kilogram quantities of the title compound.

PROCEDURE : To a mechanically stirred solution of 4(5)-iodoimidazole (2.7 Kg, 13.92 mol) and *N,N*-dimethylsulfamoyl chloride (2.1 Kg, 14.61 mol) in THF (27 L) at 0-5^{o} C was added 50 % aq. sodium hydroxide (1.1 L, 20.9 mol) over a period of 40 min so that the internal temperature does not rise above 8^{o}C. It was then allowed to warm up to rt overnight and the amount of unreacted 4(5)-iodoimidazole is less than 1% area by HPLC (typical 0.5 %). The product is then extracted with isopropyl acetate (27 L) and water (13.5 L). The layers were separated and the organics washed with 2% NaCl solution (15 L). It was then concentrated and solvent exchanged into isopropyl acetate (27 L) to remove THF and water. Isopropyl acetate was then removed by distillation and solvent exchanged with heptane (40 L). At this time it is a suspension of solid 4-iodosulfonamide (**1**) and the supernatant contains mostly the 5-iodosulfonamide (7.33 mg/ mL). The heptane solution is concentrated to 12 L (3X the volume of the expected product, 3-8 % isopropyl acetate is tolerated) and then the solution is heated to 70^{o}C. After heating for 4 h at 70$_{o}$C , the amount of 5-iodosulfonamide (**2**) is 3.25 mg/mL (less than 1 % of total yield) and that of the 4(5)-iodoimidazole is 0.7 % area. The product is filtered after cooling to ambient temperature. The wetcake is rinsed with heptane (3 X 7 L). The ratio of **1** to **2** at the wetcake is stage is >200:1. It was dried in a vacuum oven at 45^{o}C for 10 h and ^{1}H NMR spectrum shows no solvent is present. Yield = 4.075 Kg (97.3 %).

HPLC Conditions : Zorbax SB-C8, 4.6 mm X 25 mm column, mobile phase is 60 % water with 0.1 % phosphoric acid, 40 % acetonitrile to 20 % water with 0.1 % phosphoric acid, 80 % acetonitrile for 10 min; flow rate 1.5 mL/min, UV detection at 230 nm. Retention time for **1** is 4.6 min, retention time for **2** is 4.2 min (response factor = 2.2 X with respect to **1**), retention time for 4(5)-iodoimidazole is 1.5 min, retention time for *N,N*-dimethylsulfamoyl chloride is 4.9 min. Major impurity in the product is 4(5)-iodoimidazole which is 0.73 % by area (0.36 % by wt% assay). Spectral Data for **1** : ^{1}H ($CDCl_3$) δ 7.78 (d, *J* =1.04 Hz, 1H), δ 7.34 (d, *J* = 1.47 Hz, 1H), δ 2.89 (s, 6H); MS : 302 (M+1) ; Anal. Calcd for

$C_5H_8N_3O_2IS$: C, 19.94; H, 2.68; N, 13.96; I, 42.15; S,10.65. Found: C, 19.85; H, 2.61; N, 13.87; I, 42.10; S, 10.59. Spectral Data for **2** : ^1H ($CDCl_3$) δ 8.09 (d, *J* = 1.11 Hz, 1H), δ 7.18 (d, *J* = 0.74 Hz, 1H), δ 3.01 (s, 6H); MS : 302 (M+1); Anal. Calcd for $C_5H_8N_3O_2IS$: C, 19.94; H, 2.68; N, 13.96; I, 42.15; S 10.65. Found: C, 19.90; H,2.63; N, 13.82; I, 42.08; S, 10.60.

REFERENCES

1. J. H. M. Lange, H. C. Wals, A. van den Hoogenband, A. van de Kuilen, and J. A. J. den Hartog, *Tetrahedron*, 1995, **51**, 13447, J. G. Phillips, L. Fadnis, and D. R. Williams, *Tetrahedron Lett*. 1997, **38**, 7835, S. Achab, *Tetrahedron Lett*., 1996, **37**, 5503, R. M. Turner, S. V. Ley, and S. D. Lindell, *Synlett*, 1993, 748.

2. D. J. Chadwick and R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 1984, 481, R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1645.

3. S. V. Ley , *J. Org. Chem.,* 1991, **56**, 5739.

4. Trityl group could be used instead of the *N,N*-dimethylsulfamoyl group since the reported procedure yields the desired 4-regioisomer but our synthetic sequence had a hydrogenation step wherein the trityl group will be unstable. For the preparation of trityl derivative, see K. L. Kirk, *J. Heterocycl. Chem.,* 1985, **22**, 57.

5. J. - W. Kim, S. M. Abdelaal, L. Bauer, and N. E. Heimer, *J. Heterocycl. Chem.,* 1995, **32**, 611.