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A Novel Application of the Ullmann Coupling Reaction for the Alkylsulfenylation of 2-Amino-Imidazo[1,2-*a*]pyridine

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Abstract

The Ullmann coupling reaction between the 2-trifluoroacetamido-3-iodo-6-benzoylimidazo[1,2-*a*]pyridine and dialkyldisulfides (Me, ^{i}Pr) mediated by copper bronze in pyridine, resulted in a novel and highly efficient method for the incorporation of alkylthiol groups at C-3 of this type of heterocyclic system.

Key words : Sulfenylation ; Ullman Coupling ; Imidazo[1,2-*a*]pyridines ; Rhinovirus

Enviroxime[1] (Figure 1), and related benzimidazoles[2] exhibited potent broad spectrum antiviral activity when tested against a range of both rhinoviruses and enteroviruses. However, when Enviroxime was evaluated in the clinic for the treatment of the common cold, it failed because of the poor oral bioavailability and emetic side effect. Efforts to identify a new generation of target structures with improved biological profiles, suggested the synthesis of the structurally related 2-amino imidazo[1,2-*a*]pyridine derivatives **1**.[3] To achieve this goal, we felt the need of having a method that allows the incorporation of alkyl sulfenyl groups at the C-3 of imidazopyridines.

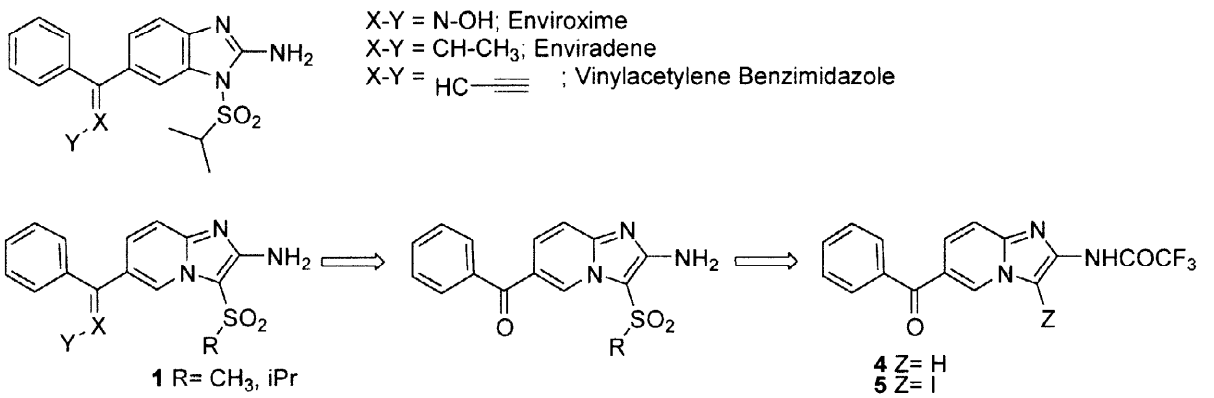

Figure 1

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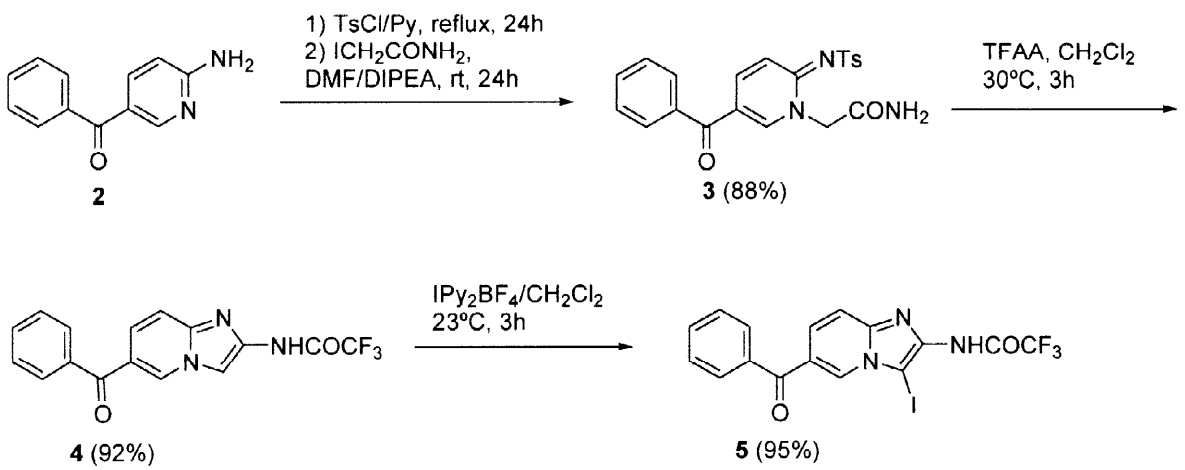
We have reported recently a convenient method for the arylsulfenylation of imidazopyridines[4] of type **4** mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA).[5] This reaction is chemoselective and quite effective for the direct substitution at C-3 by various thiophenols. However the method was limited to the preparation of imidazopyridine aryl sulfides. On the other hand, attempts to incorporate alkyl sulfides over iodo derivatives of type **5** using nucleophilic displacement with thiolates, SET reactions mediated by aromatic anion radicals, palladium catalyzed cross coupling reactions with $RSSnBu_3$[6] or halogen metal exchange furnished in all cases very low yields (<10%) along with decomposition products. Finally the intramolecular cyclization of 2-chloro *N*- pyridinium salts mediated by potassium cyanamide[7] were only effective in the preparation of non-substituted 2-amino imidazo[1,2-*a*]pyridines.

These difficulties prompted us to look for a convenient method that would provide the desired imidazopyridine alkyl sulfides in acceptable yields and being compatible with the presence of senzitive functions such as the ketone and the amino-imidazole.[8] Herein, we wish to report a new application of the Ullmann coupling reaction for the incorporation of alkyl sulfides at C-3 of imidazo[1,2-*a*]pyridine, that turned out to be synthetically useful for the access to new structurally related analogs of Enviroxime, potential inhibitors of human rhinovirus.

The synthesis of the iodoimidazopyridine **5** is outlined in Scheme 1. Reaction of **2**[9] with p-tolylsulfonyl chloride in pyridine and subsequent treatment with iodoacetamide in the presence of diisopropylethylamine in DMF, provided the corresponding carbamoylmethyl derivative **3** in 88% yield. Cyclization of **3** to the required imidazopyridine carbamate **4** was accomplished by treatment with trifluoroacetic anhydride in 92% yield.

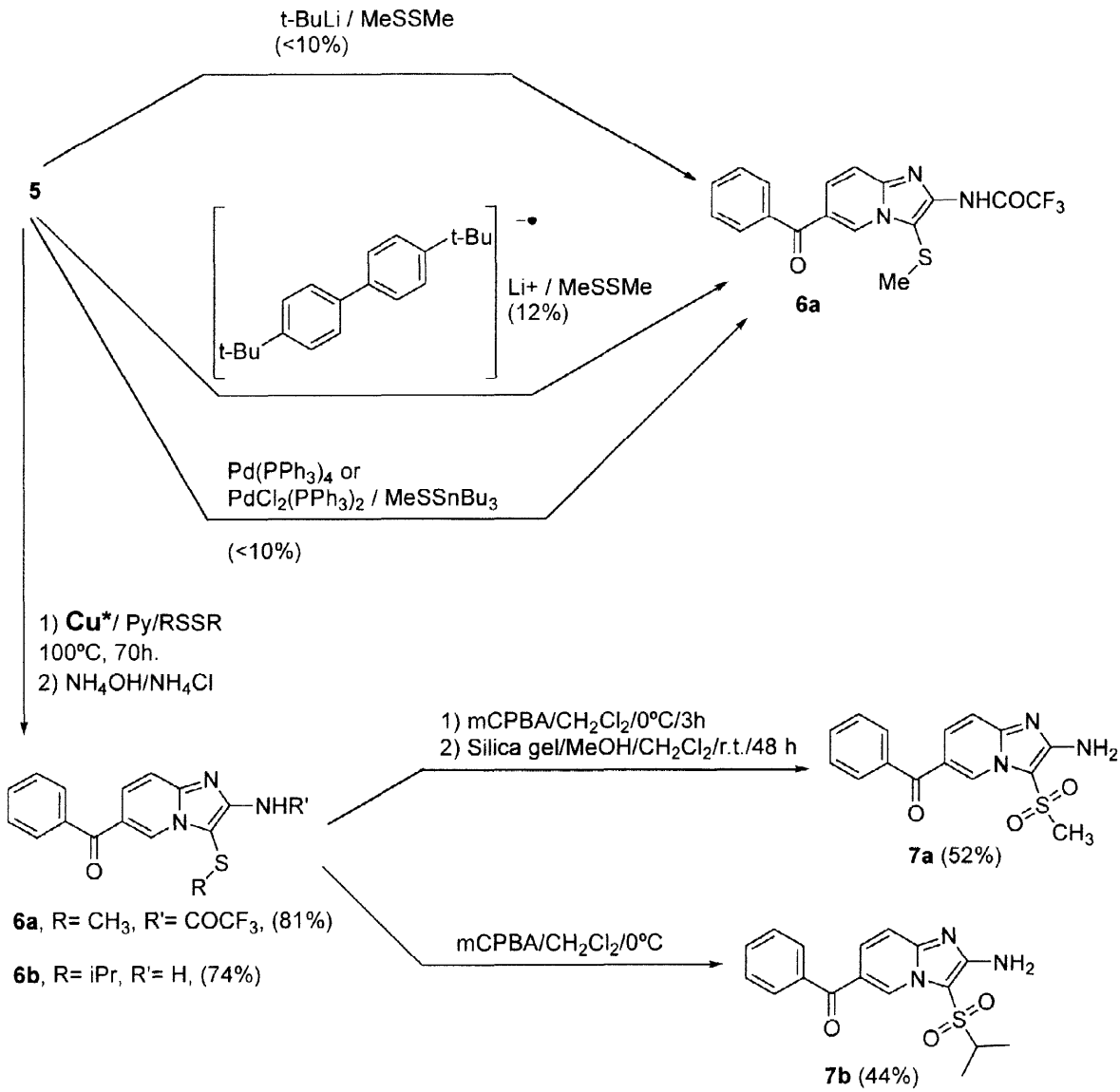


Scheme 1

The iodination at the position C-3 was performed successfully by treating imidazopyridine **4** with IPy_2BF_4, a highly regioselective iodinating reagent described

recently by Barluenga *et al.*[10] for aromatic rings, delivering **5** with almost quantitative yield. It should be noted that neither the left hand side aromatic moiety nor the pyrido moiety had competed during this iodination process.

As mentioned above, several sulfenylation methods were tried with the iodo derivative **5** (Sheme 2). This includes halogen-metal exchange reaction that resulted mainly in the addition of the organolithium to the carbonyl. Palladium catalysed cross coupling reactions using $Pd(PPh_3)_4$ and $RSSnBu_3$ was found to be very sluggish and afforded a low yield (<10%) of **6a**. Changing the stannanes ($RSSnMe_3$)[5] or the nature of the palladium catalyst did not improve the yield. Finally, a SET reaction mediated by di-tert-butylbiphenylide and MeSSMe delivered **6a** but with only 12% yield.



Scheme 2

After these unsuccessful attempts we elected to use the Ullmann coupling reaction.[11] We were pleased to discover that when compound **5** was mixed with dimethyl disulfide in the presence of copper bronze in pyridine and the resulting golden suspension in brown solution was heated at 100°C for 70h, the desired methylsulfide **6a** was isolated in 80% yield. It should be noted that neither the ketone function nor the imidazo moiety[8] were affected during the coupling process. The reaction appears clean by thin layer chromatography. However the removal of the traces of copper after the Ullmann reaction was not trivial. After trying different techniques we found that the work up with NH_4OH/NH_4Cl used in high dilution was the most effective.

Interestingly when compound **5** was subjected to the Ullmann reaction conditions with diisopropyl disulfide and the resulting crude was worked up under the same conditions, the desired isopropyl sulfide **6b** was isolated devoid of trifluoroacetyl moiety in 70% yield. This N-detrifluoroacetylation that takes place during the work up suggests that the nature of the group at C-3 must have a significant influence on the stability of the trifluoroacetamide group.

Methyl sulfide **6a** was first oxidized with mCBPA to the corresponding sulfone in 67% yield. As we have reported earlier[4] the N-detrifluoroacetylation of this type of compounds requires mild conditions. The use of strongly basic conditions such as NaOH or Hünig's base failed to yield the desired amine. Instead the reaction led to imidazo ring opening providing the aminopyridine as main product. However, when a cake of silica gel containing the crude product derived from the oxidation of compound **6a** in methanol/CH_2Cl_2 was subjected to a vigorous stirring, the corresponding amine **7a** was isolated in 78% yield.

On the other hand selective oxidation of the isopropyl sulfide **6b** to the desired sulfone **7b** was performed using excess of mCPBA at 0°C in a 44% isolated yield.

In summary we have demonstrated here the first application of Ullmann coupling reaction for the incorporation of alkyl sulfide groups in imidazopyridines which showed to be a very efficient approach in a situation where several methods failed to yield the desired target structures. Its compatibility with functions present in the molecule such as a ketone promises its application in various heterocyclic systems.

Experimental

All reagents were purchased from Aldrich and used without further purification unless stated otherwise. Column chromatography was carried out on silica gel (Merck 230-400 mesh). TLC analysis was conducted on silica gel plates Whatman. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer and (ν values in cm^{-1}).^1H and ^{13}C NMR spectra were recorded on 200 and 300 MHz with a Bruker instrument. Chemicals shifts (δ values) and coupling constants (J values) are given in ppm and Hz respectively. Mass spectra were recorded on VG-Autospec mass spectrometer. HRMS spectra, elemental

analyses, and some ^{1}H NMR spectra were provided by the Servicio Interdepartamental de Investigación (SIdI) at UAM (Madrid).

1-Carbamoylmethyl-1,2-dihydro-2-(4-toluenesulfonimido)-6-benzoylpyridine **(3).** *Step 1: 1,2-Dihydro-2-toluenesulfonimido-5-benzoylpyridine.* 1,2-Dihydro-2-Amino-5-benzoylpyridine (15.25 g 77 mmol) was dissolved in dry pyridine (60 mL). p-Toluenesulfonyl chloride (16.25 g, 85.56 mmol) was added and the solution was heated at 80-90 °C under argon overnight. Pyridine was removed under vacuum to give a solid. Water (1.5 L) was added and the mixture was stirred for 90 minutes. The white solid was collected, dried under vacuum, and crystallized from ethyl acetate (200 mL) to give the tosylated product (28,7 g; 91%) as a white solid: mp 207-209°C; IR (NaCl) 1656, 1630, 1596, 1521, 1423, 1381; ^{1}H-NMR (DMSO-d_6) δ 8.35 (s, 1H, H_6), 8.06 (d, 1H, J = 8.8, H_3), 7.84 and 7.52 (AA'BB' system, 4H, J = 7.5, tol,), 7.70 - 7.23 (m, 7H, Ar), 2.31 (s, 3H, Ar); ^{13}C-NMR (DMSO-d_6) d 192.7, 155.0, 148.0, 143.4, 140.4, 138.3, 136.9, 132.9, 129.7, 129.6, 128.8, 127.2, 125.4, 112.5, 21.2; MS (EI$^+$) m/z 352 M$^+$ (1), 287 (100), 115 (5), 105 (10), 77 (17), 65 (12); HRMS calcd. for $C_{19}H_{16}N_2O_3S$: 352.0882. Found: 352.0882.

Step 2: To a stirred suspension of 1,2-Dihydro-2-toluenesulfonimido-5-benzoylpyridine (11.65g, 32.10 mmol) in 100 ml of dry DMF was added DIPEA (6.34 ml, 34.2 mmol). After 15 min, the solution turned clear. Iodoacetamide (6.74g, 34.2 mmol) was added. The mixture was stirred for 24 h and then poured onto water (2000 ml) and stirred for an additional hour. Solid were collected and air-dried yielding 13.15g (97%) of a white solid: mp 210-212°C; IR (NaCl) 1679, 1633, 1530,1427, 1143; ^{1}H-NMR (DMSO-d_6) δ 8.54 (d, 1H, J = 2.0, H_6), 8.06 (dd, 1H, J = 9.5 and 2.0, H_4), 7.79-7.64 (m, 5H, Ar), 7.57 (AA'BB' system, 2H, J = 7.6, tol.), 7.47 (d, 1H, J = 9.5, H_3), 7.30 (AA'BB' system, 2H, J = 7.8, tol.), 4.91 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 191.0, 167.5, 156.1, 147.4, 142.0, 140.4, 136.6, 133.1, 129.6, (129.5, 2C), , 129.0, 126.1, 119.9, 115.9, 54.8, 21.1; MS (EI$^+$) m/z 409 M$^+$ (18), 345(24), 328(28), 287(11), 254(6), 209(36), 182(19), 155(9), 105(66), 91(100), 77(58); HRMS calcd. for $C_{21}H_{19}N_3O_4S$: 409.1096. Found: 409.1105.

2-Trifluoroacetamido-6-benzoylimidazo[1,2-a]pyridine **(4)**. To a suspension of **3** (7.150g, 17.46 mmol) in 85 ml of dry CH_2Cl_2 was added trifluoroacetic anhydride (62 ml). The mixture was stirred for 2.5 h at 30°C under argon atmosphere. The solvents were removed under vacuum and the foam was taken-up in EtOAc (600 ml), washed with $NaHCO_3$ (2 x 250 ml) and brine (1 x 250 ml). The organic layer was dried (Na_2SO_4) and solvents were removed under vacuum to afford 5.5 g (92%) of product as a white solid: mp 233-235°C; IR (NaCl) 1724, 1640, 1564, 1513, 1308, 1286; ^{1}H-NMR ($CDCl_3$) δ 10.80 (broad s, 1H, NH), 8.66 (s, 1H, H_5), 8.24 (s, 1H, H_3), 7.83-7.78 (m, 3H, Ar), 7.71-7.51 (m, 4H, Ar); ^{13}C-NMR (DMSO-d_6) δ 192.8, 141.8, 140.6, 137.0, 133.3, 133.1, 132.6, 129.5, 129.3, 128.6, 125.0, 122.5, 115.5, 104.3; MS (EI$^+$) m/z 333 M$^+$(100), 314(9), 264(49), 256(37), 236(7),

228(7), 209(8), 159(8), 146(6), 105(52), 77(53); HRMS calcd for $C_{16}H_{10}N_3O_2F_3$: 333.0725. Found: 333.0725.

2-Trifluoroacetamido-3-iodo-6-benzoylimidazo[1,2-a]pyridine **(5).** To suspension of imidazopyridine **4** (3g, 9 mmol) in 60 ml of dry CH_2Cl_2 was added IPy_2BF_4 (3.3g, 13.5mmol) portionwise. After the addition was complete HBF_4 (2.5 ml, 15.3 mmol, 54% in ether) was added dropwise. After 30 min a white suspension was formed. The suspension was stirred for 1 more hour then hydrolyzed with water and extracted with CH_2Cl_2. The organic layers were combined, washed with a solution of $Na_2S_2O_3$ and then with brine. The organic layer was dried (Na_2SO_4) and EtOAc was removed under vacuum to afford 3.93g (95% yield) of **5** as a yellow solid: mp 210-212°C; IR (NaCl) 1658, 1625, 1592, 1320, 1283; ^{1}H-NMR ($CDCl_3$) δ 9.08 (broad s, 1H, NH), 8.66 (t, 1H, J = 1.1, H_5), 7.86-7.79 (m, 3H, Ar), 7.72-7.52 (m, 4H, Ar); ^{13}C-NMR (DMSO-d_6) δ 192.5, 145.5, 143.1, 136.7, 133.0, 132.7, 131.6, 129.6, 128.7, 125.7, 123.7, 116.7, 115.5, 104.3; MS (EI^+) m/z 458 M^+(68), 390(31), 333(100), 264(48), 256(29), 237(8), 228(5), 209(7), 159(5), 146(6), 105(80), 77(80); HRMS calcd for $C_{16}H_9O_2N_3F_3I$: 458.9692. Found: 458.9695.

2-Trifluoroacetamido-3-methylthio-6-benzoylimidazo[1,2-a]pyridine **(6a).**
Iodoimidazopyridine **5** (1g, 2.17 mmol) was dissolved in 20 mL of pyridine under argon atmosphere. Copper bronze (3.25 mmol, 207 mg) was added. To the golden suspension in brown solution was added MeSSMe (150 µl, 1.6 mmol) *via* syringue. The reaction mixture was heated for 70 hours at 100°C. The evolution of the reaction was followed by NMR (in each case, a sample was taken, hydrolyzed and washed with ammonia/NH_4Cl 1:9 before checking by NMR). After the reaction was completed, the reaction mixture was diluted in ethyl acetate (1L). A solution of NH_4OH/NH_4Cl 1:9 (1L) was added and the mixture was strongly stirred for 30 min. The layers were separated and the organic layer was again treated with a solution of NH_4OH/NH_4Cl 1:9. The mixture was stirred for 30 min and kept without stirring for 5 to 10 min to allow better separation. The layers were separated and the organic layer was washed with saturated NaCl. The organic layers were evaporated under vacuum and the resulting brown solid (1g) was subjected to a rapid column chromatography (MeOH:CH_2Cl_2 3:97) to give 670 mg (81% yield) of **6a** as yellow solid. mp 195-198 °C; ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, SMe), 7.52-7.85 (m, 7H, H_7, H_8, ArH), 8.88 (d, 1H, J = 1.6, H_5), 10.25 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 17.5 (SMe), 109.3, 115.9 (q, J = 286.5), 116.6, 124.7, 127.0, 128.5, 128.7, 129.6, 133.3, 136.7, 143.6, 144.7, 155.3 (q, J = 38.0), 192.9; Anal. Calcd for $C_{17}H_{12}F_3N_3O_2S$: C, 53.82; H, 3.19; N, 11.08. Found: C, 53.68; H, 3.13; N, 11.12.

2-Amino-3-isopropylthio 6-benzoylimidazo[1,2-a]pyridine **(6b).** 6-Benzoyl-3-iodo-2-(trifluoroacetamido)imidazo[1,2-a]pyridine **5**, was subjected to the Ullmann reaction condition with diisopropyl disulfide in manner substantially analogous to the preparation of **6a**. After a column chromatography (silica gel, EtOAc:Hexane 1:1), compound **6b** was isolated in 74% yield as an oil: IR (NaCl) 1658, 1595, 1497, 1444, 1363, 1283; ^{1}H-NMR

($CDCl_3$) δ 8.75 (s, 1H, H_5), 7.79-7.47 (m, 7H, Ar), 4.62 (broad s, 2H, NH_2), 3.09 (hept., 1H, J = 6.4, C<u>H</u>-(CH_3)$_2$, 1.22 (d, 6H, J = 6.7, ($C\underline{H}_3$)$_2$-CH). ^{13}C-NMR ($CDCl_3$) δ 199.3, 157.1, 145.2, 137.3, 132.6, 129.5, 128.7, 128.4, 127.9, 126.0, 122.8, 113.6, 40.8, 23.4. MS (EI^+) m/z 311 M^+(28), 268 (100), 224 (27), 105 (41), 77 (29). HRMS calcd. for $C_{17}H_{17}N_3OS$: 311.1092. Found: 311.1096.

2-Amino-3-methylsulfonyl-6-benzoylimidazo[1,2-a]pyridine **(7a).** *Step 1: 2-Trifluoroacetamido-3-methylsulfonyl-6-benzoyl-imidazo[1,2-a]pyridine.* The sulfide **6a** (500 mg, 1.37 mmol) was mixed with mCPBA (80%, 563 mg, 2.62 mmol) in 20 ml of dry dichloromethane. The reaction mixture was stirred for 3h at 0°C and then hydrolyzed with 1 ml of saturated $NaHCO_3$. The mixture was filtered through celite and washed with EtOAc. The filtrate was evaporated under vacuum and the residue was purified by column chromatography to yield 385 mg (67%) of a white yellow solid: mp 138-141°C; ^{1}H-NMR ($CDCl_3$) δ 3.31 (s, 3H, SO_2Me), 7.52-8.03 (m, 8H, ArH, H_5, H_7, H_8), 8.54 (dd, 1H, J = 0.9 and 2.0, H_5); Anal. Calcd for $C_{17}H_{12}F_3N_3O_4S$: C, 49.64; H, 2.94; N, 10.21. Found: C, 49.53; H, 2.91; N, 10.30.

Step2: 2-Trifluoroacetamido-3-methylsulfonyl-6-benzoyl-imidazo[1,2-a]pyridine (100 mg, 0.240 mmol) was dissolved in 20 ml of a mixture of MeOH/CH_2Cl_2, and 5g of silica gel was added. The mixture was stirred at 23°C for 2 days. The residue was filtered and washed with CH_2Cl_2 and the solution was concentrated under vacuum to give **7a** as a white yellow solid in a 78% yield: mp 184-187°C; ^{1}H-NMR ($CDCl_3$) δ 3.06 (s, 3H, SO_2Me), 4.82 (bs, 2H, NH_2), 7.53-7.82 (m, 7H, ArH, H_7, H_8), 8.78 (d,1H, J = 1.6, H_5); Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 57.13; H, 4.16; N, 13.32. Found: C, 57.06; H, 4.19; N, 13.29.

2-Amino-3-isopropylsulfonylthio-6-benzoylimidazo[1,2-a]pyridine **(7b).** To a solution of **6b** (30 mg, 0.1 mmol) in dry CH_2Cl_2 (5 ml) cooled to 0°C was added dropwise mCPBA (50%, 73 mg, 0.22 mmol) dissolved in 15 ml of dry CH_2Cl_2. The reaction mixture was stirred for 90 min then washed with Na_2SO_3 (25 ml) and $NaHCO_3$ (2 x 25 ml). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by column chromatography (silica gel, AcOEt:Hexanes 1:2).to give 15 mg (44% yield) of **7b** as a white solid: mp 166-168; IR ($CHCl_3$) 3578, 3018, 2926, 1655, 1410, 1295; ^{1}H-NMR ($CDCl_3$) δ 9.01 (m, 1H), 7.88-7.40 (m, 7H), 6.32 (br s, 2H), 3.26 (hept, 1H, J = 6.8), 1.34 (d, 6H, J = 6.8). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.5, 157.8, 146.9, 136.7, 133.1, 130.1, 129.7, 129.3, 128.7, 127.3, 114.4, 96.3, 57.5, 14.4. MS (EI^+): 343 (M^+, 17), 284 (7), 262 (10), 237 (100), 224 (9), 160 (9), 105 (32), 77 (36).; HRMS calcd for $C_{17}H_{17}N_3O_3S$: 343.0991. Found: 343,0996.

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