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SYNTHESIS OF NOVEL IMIDAZO[1,5–a]PYRIDINE DERIVATES

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An new, efficient synthesis of imidazo[1,5-a]pyridine derivatives starting from (3-chloro-5-(trifluoromethyl)pyridine-2-yl)methanamine(**1**) has been developed. A protocol to a 100 g scale synthesis of the amine (**1**) is given. Good yields are obtained. The structures of two products were confirmed by single crystal X-ray methods

INTRODUCTION

The imidazo[1,5-a]pyridines are an important class of fused heterocyclic compounds because of their biological and photophysical properties. They are found *e.g.* in the antibiotic cribrostatin–6 (figure 1) isolated from blue marine sponge[1] and have found utility in many different areas of research including potential applications in organic light–emitting diodes (OLED)[2] or in organic thin–layer field effect transistors (FET)[3] and as precursors of *N*-heterocyclic carbenes.[4] Pharmaceutical applications such as cardiotonic agents,[5] aromatase inhibitors in estrogen–dependent diseases.[6] Thromboxane A_2 synthesis inhibitors[7] and HIV – protease inhibitors[8] have also been reported in the literature.

Therefore a convenient synthesis of this fused ring system is still of interest. A variety of methods have been employed in the synthesis of the imidazo[1,5-a] pyridines and their derivatives. Most routes are based either on traditional Vilsmeier–type cyclizations of *N*-2-pyridylmethyl amides[9-11] or cyclizations of *N*-2-pyridylmethyl thioamides with various reagents such as dicyclohexylcarbodiimide,[12] Lawesson's reagents and mercury(II) acetate,[13] or more recently using iodine/pyridine[14]. Multistep preparations of imidazo[1,5-a]pyridines have also been reported, such as sequential van Leusen/intramolecular Heck reactions,[15] benzotriazole–mediated reactions[16] and ammonium acetate–mediated condensation of pyridyl ketones with aldehydes.[17]

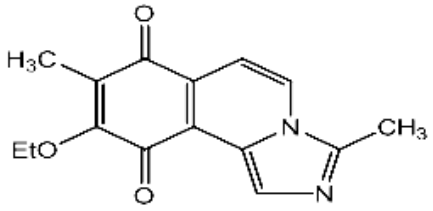

Fig. 1 – Structure of cribrostatin-6.

Recent reports include (i) an oxidative condensation–cyclization of aldehydes and aryl-2 pyridylmethylamines in the presence of elemental sulfur as an oxidant, affording a variety of 1,3-diarylated imidazo[1,5-a]pyridines;[18] (ii) a one pot synthesis of imidazo[1,5-a]pyridines starting from a carboxylic acid and 2-methylaminopyridines, using a propane phosphoric acid anhydride (T3P) in ethyl or n-butyl acetate at reflux, allowing the

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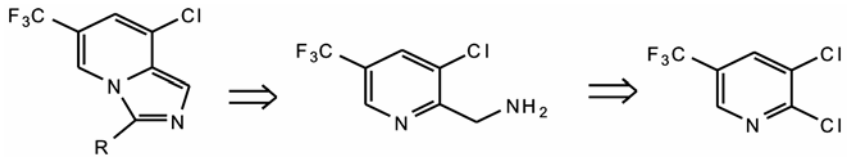
introduction of various substituents at the 1- and 3-positions;[19] (iii) a convenient synthesis of 3-substituted-imidazo[1,5-a]pyridines in two steps from commercially available picolinic esters under microwave irradiation conditions;[20] and (iv) the preparation of imidazo[1,5-a]pyridines from the reaction of 1,1-dibromo-1-alkenes with 2-aminomethylpyridines.[21]

RESULTS AND DISCUSSION

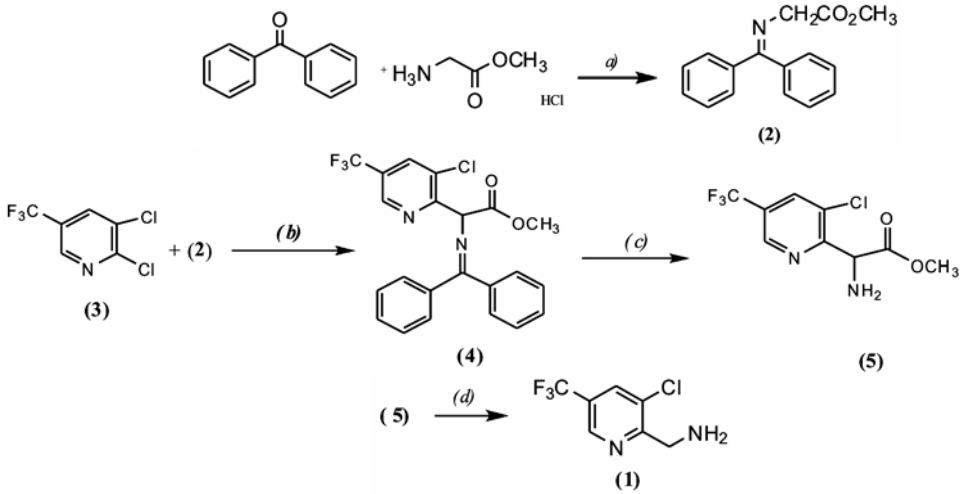
Here we report a new method to obtain imidazo[1,5-a]pyridines starting from 2,3-dichloro-5-(trifluoromethyl)pyridine (**3**) (Scheme 1). 2-Aminomethyl-3-chloro-5-trifluoromethyl-pyridine (**1**) is a key intermediate and in reaction with triphosgene [bis(trichloromethyl)carbonate] or thiophosgene (thiocarbonyl chloride) gave direct access to 3-substituted imidazo[1,5-a]pyridine derivatives. During the last decade, triphosgene has become a versatile synthetic auxiliary for the synthesis of some important classes of organic compounds.[22-24] In our case we use triphosgene and thiophosgene for cyclization to imidazo[1,5-a]pyridine derivatives.



Scheme1 – Retrosynthetic analysis of imidazo[1,5-a]pyridines derivatives.

*Synthesis of (3-chloro-5-(trifluoromethyl)pyridine-2-yl)methanamine (**1**)*

The expensive[25] (3-chloro-5-(trifluoromethyl)pyridine-2-yl)methanamine (**1**) was synthesized starting from pyridine (**3**) in a three-step reaction[26]. In a preliminary step, glycine methyl ester hydrochloride is reacted with benzophenone at reflux in toluene in the presence of *p*-toluensulfonic acid and *N,N*-diisopropyl *N*-ethylamine to provide methyl-2-(diphenylmethyleneamino) acetate (**2**). The first step involved the reaction of the acetate (**2**) with 2,3-dichloro-5-(trifluoromethyl)pyridine (**3**) in the presence of potassium carbonate, in proprionitrile / toluene under reflux, to provide methyl-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-(diphenylmethyleneamino)acetate (**4**) . The NH_2 protecting benzophenone is cleaved under mild acid conditions in the next step, giving methyl-2-amino-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)acetate (**5**). The third step involved the conversion of methyl ester (**5**) into 2-aminomethyl-3-chloro-5-trifluoromethyl-pyridine (**1**) by heating under reflux in dilute hydrochloric acid. The total yield over 3 steps is 50 % (Scheme2).



a) *p*-toluenesulfonic acid, *N, N*-DIEA, $C_6H_5CH_3$, reflux. b) K_2CO_3, tetrabutylammonium bromide, $C_6H_5CH_3/C_3H_5N$, reflux. c) aq. HCl, H_2O, room temperature. d) Reflux for several hours.

Scheme 2 – Synthesis of (3-chloro-5-(trifluoromethyl)pyridine-2-yl)methanamine.

*Synthesis of 8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-thiol (**6**)*

With the (3-chloro-5-(trifluoromethyl)pyridine-2-yl)methanamine (**1**) "in hand", the synthesis of imidazo[1,5-a]pyridines was achievable in a one-pot reaction.

Various reaction conditions were tested for the conversion of this amine (**1**) into thiol (**6**) . For this purpose, the influence of solvents, reaction temperature, reaction time and the number of the equivalents of thiophosgene were studied. Results are summarized in Table 1.

When we used THF or acetone as solvents (see entry 8 and 9) instead of dichloromethane (entry 7) almost half of the starting material (**1**) hydrochloride is precipitated and was recovered unreacted at the end of the reaction by filtration. A reaction time of 4 hours seemed to be more favorable than 3 hours (entry 1 and 2), but the yields were moderate in both cases. Also the temperature affects the reaction; when we carried out the reactions at – 15^0 C the yield was lower than at 0^0C using the same equivalents of thiophosgene (entry 5 and 6). The reactions proceeded rapidly in dichloromethane, under mild basic conditions, cooled down to 0^0 C in the first step, followed by warming up to room temperature. The best conversion rate was obtained for the product (**6**) by performing the reaction with 1.08 eq of thiophosgene using dichloromethane as solvent and sodium hydrogen carbonate as a base (entry 10). In all cases, the formation of the products was monitored by disappearance of the starting amine (**1**) by TLC analysis. The optimized conditions are given in Scheme 3.

*Synthesis of 8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridin-3-ol (**7**)*

Various reaction conditions were tested for the conversion of amine (**1**) into compound (**7**) (Table 2).

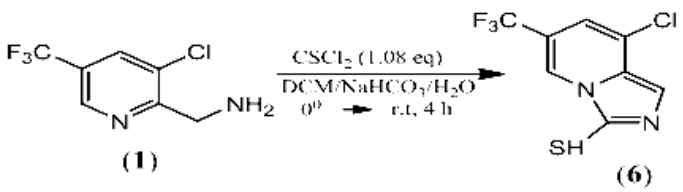
The reaction time seemed not to affect the conversion, the obtained yields were moderate (entry 1 and 2). The temperature seemed to have an influence, because when we carried out the reaction at -15^0 C, using the same equivalents of triphosgene and keeping the reaction time constant, the yield was lower (entry 3 and 4). In the case of entry 5, 6 and 7 we also changed the protocol[27]. In those cases the solvents had no influence but the yields were lower. The best conversion rate was obtained for (**7**) by performing the reaction with 0.7 eq of triphosgene using dichloromethane as solvent and sodium hydrogen carbonate as a base (entry 8 and 9). The optimized conditions are given in Scheme 4.

Table 1

Optimization of reaction conditions in the synthesis of the compound (**6**)

entry	Time (h)	Temperature [a] (^{0}C)	Solvent	Thiophosgene (eq)	Yield [b] (%)
1	4	0	DCM	1.8	65
2	3	0	DCM	1.8	57
3	3	0	DCM	1.6	55
4	3	0	DCM	0.9	50
5	4	0	DCM	1.2	70
6	4	-15	DCM	1.2	55
7	3	-15	DCM	1.1	60
8	3	-15	Acetone	1.1	30
9	3	-15	THF	1.1	35
10 [c]	4	0	DCM	1.08	80

a) Given temperatures are the temperatures during the addition of thiophosgene. After addition the reaction was allowed to warm at room temperature in all cases. b) Given yields are after work up and purification. c) Reaction was made on 100 times larger scale then the others.



(**1**) (**6**)

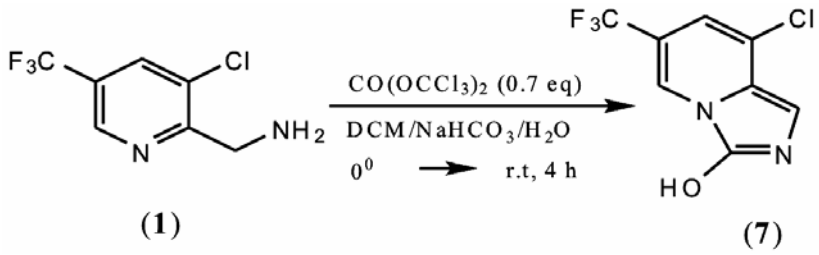
Scheme 3 – Synthesis of 8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-thiol.

Table 2

Optimization of reaction conditions in the synthesis of compound (**7**).

entry	Time (h)	Temperature [a] (^{0}C)	Solvent	Triphosgene (eq)	Yield [b] (%)
1	3	0	DCM	0.7	50
2	4	0	DCM	0.7	55
3	4	0	DCM	0.3	55
4	4	-15	DCM	0.3	40
5	4	0	chlorobenzene	1.25	45
6	4	0	benzene	1.25	40
7	4	0	toluene	1.25	40
8	4	0	DCM	0.6	60
9[c]	4	0	DCM	0.7	72

a) Given temperatures are the temperatures during the addition of triphosgene and during the addition of amine (**1**) (entry 5,6 and 7). After addition the reaction was allowed to warm to room temperature in all cases. b) Given yields are after work up and purification. c) Reaction was performed on 100 times larger scale then the others.



Scheme 4 – Synthesis of 8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridin-3-ol.

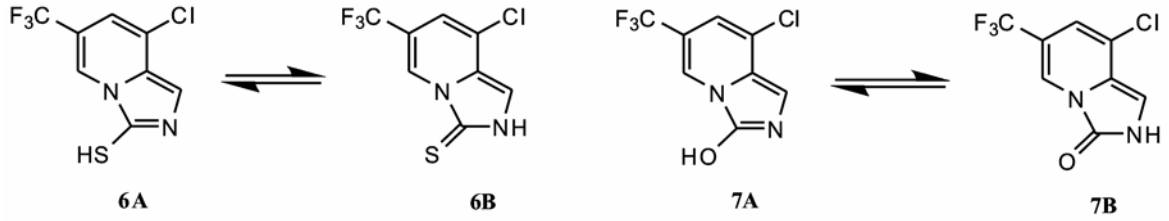


Fig. 2 – The tautomeric forms of compounds **6** and **7**.

The imidazo[1.5-a]pyridine compounds (**6**) and (**7**) could exist in two tautomeric forms **6A/6B** and **7A/7B** (Fig. 2), these involve the structure of a 2-thiol/2-hydroxy-imidazole (**A**) or alternatively the structure of a thione/ketone (**B**).

The ^{1}H NMR experiment of **6** shows one broad signal at 13.1 ppm which is characteristic of an aromatic C-SH proton and therefore is consistent with the **6A** form. In the case of compound (**7**) the ^{1}NMR experiment shows a broad signal at 12.06 ppm which is characteristic of an acid OH proton and thus consistent with the **7A** form. Single crystal X-ray structures were established for both compounds (**6**) and (**7**) (Figure 3). The results in the solid state demonstrate the formation of the thione/ketone forms **6B** (8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3(2H)-thione) and **7B** (8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridin-3(2H)-one).

Compound **6B** crystallizes in the triclinic space group *P*-1 with four molecules in the unit cell (two independent molecules). One of the CF3 groups is disordered. Similarly to compound **7B**, the bond length C1-S 1.684(2) Å is comparable to the double bond C-S 1.672 Å reported in literature for thioamides. The molecules associate via two independent N–H···S hydrogen bonds to form inversion-symmetric dimers.

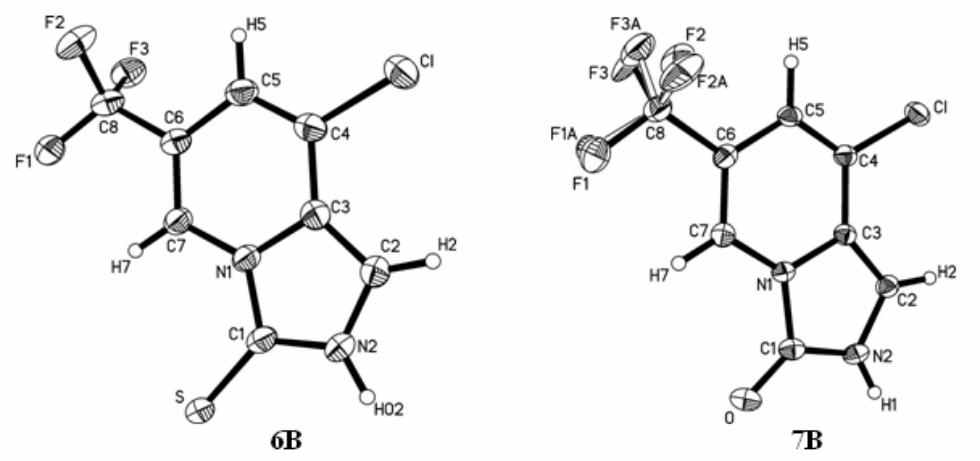


Fig. 3 – Molecular structures of (8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3(2H)-thione) (**6B**) and of (8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridin-3(2H)-one) (**7B**). Atoms are drawn as 50% thermal ellipsoids for **6B** and as 30% thermal ellipsoids for **7B**. The CF_3 group of **7B** is disordered. Selected bond lengths [Å]: for **6B**: C1-N1 1.383(2), C1-N2 1.347(3), C1-S 1.684(2), C2-N2 1.375(3), C4-Cl 1.721(2); for **7B**: C1-N1 1.395(3), C1-N2 1.353(4), C1-O 1.235(3), C2-N2 1.390(4), C4-Cl 1.729(3).

Compound **7B** crystallizes in the orthorhombic space group *Pbca* with 24 molecules in the unit cell (three independent molecules). Two molecules involve CF_3 groups disordered over two positions. The characteristic bond length for a C-OH bond is ca. 1.45 Å and for a double bond C=O ca. 1.222 Å in the lactam moiety. In our case the bond length is 1.235(3) which clearly shows the double bond character of the C1=O bond. The molecules associate via three independent N–H···O hydrogen bonds, each between different molecules in the asymmetric unit.

EXPERIMENTAL

All manipulations were carried out under N_2 atmosphere. All reagents were of commercial quality. Solvents were dried and purified by standard methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$–d_6 at room temperature, operating at 200 MHz and 50 MHz respectively on a Bruker DPX200 spectrometer. The products were dissolved in $CDCl_3$ and the chemical shifts were recorded as δ values in parts per million (ppm) relative to tetramethylsilane used as internal standard. In the description of the NMR spectra, the designation "br" used alone indicates a broad peak of undetermined multiplicity. Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254 (0.25 mm thickness) and visualized using a UV lamp.

Preparation of methyl 2-(diphenylmethyleneamino)acetate (**2**). Benzophenone (1640 g, 2eq), glycine methyl ester hydrochloride (565 g, 1eq), paratoluenesulfonic acid (428 g , 0.05eq) and toluene (2.4 L) were loaded into a flask equipped with a distillation section and a Dean and Stark separator. The reaction mixture was heated to reflux, whereupon when *N, N*-diisopropyl *N*-ethylamine (824 mL) was added dropwise over 2 hours. During the reaction, water was formed and distilled off as the water/toluene azeotrope. Reaction was continued 3 hours after the end of the amine addition. When the reaction was complete, the reaction mixture was cooled down to 25^0 C and then washed with water (2×1 L), and the phases were separated. The toluene solution containing the acetate (**2**) was used for the next step without any further purification. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.66 (dd, $^3J_{H,H}$ =8.3, $^4J_{H,H}$ = 1,5 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.41-7.29 (m, 3H), 7.17 (m, 2H), 4.22 (s, 2H, CH_2), 3.74 (s, 3H, CO_2CH_3).

Preparation of methyl-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-(diphenylmethyleneamino)-acetate (**4**). Potassium carbonate (600 g, 3eq), toluene (1 L), tetrabutylammonium bromide (23 g, 0.05eq), propionitrile (1.26 L) and the imine (**2**) were heated at reflux and pyridine (**3**) (310 g, 1eq) was added dropwise over 2 hours, maintaining reflux and separating the condensate in the Dean and Stark separator. Reflux was continued overnight (20 hours) after the pyridine addition. When reaction was complete (monitored by NMR analyses) the propionitrile was distilled off at atmospheric pressure. Then the reaction mixture was cooled down to 25^{0}C and washed with water (2 × 1 L). The toluene solution containing the acetate (**4**) was used without any further purification in the next step. **^{1}H NMR** (200 MHz, $CDCl_3$) 8.7 (s, 1H, CH), 7.84 (s, 1H, CH), 7.66 (dd, $^3J_{H,H}$ =8.3, $^4J_{H,H}$ = 1,5 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.41-7.29 (m, 3H), 7.17 (m, 2H), 5.1 (s, 1H, CH), 3.74 (s, 3H, CO_2CH_3).

Preparation of methyl 2-amino-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)acetate (**5**). To the solution of (**4**) in toluene, 300 mL of aqueous 10 % hydrochloric acid were added at room temperature. The reaction was stirred for several hours. After completion of the reaction (monitored by TLC analyses) the two liquid phases were separated and the aqueous phase containing the acetate hydrochloride salt (**5**) was used in the following decarboxylation step.**^{1}H NMR** (200MHz, $CDCl_3$) δ 8.7 (s, 1H, CH), 7.84 (s, 1H, CH), 4.7 (s, 1H, CH), 3.18 (s, 3H, CH_3), 1.55 (br s, 2H, NH_2).

*Preparation of 2-aminomethyl-3-chloro-5-trifluoromethyl-pyridine (**1**).* The previous aqueous solution of acetate hydrochloride salt (**5**) was heated under reflux for 5 hours. After the reaction was complete (as monitored by TLC analyses) the reaction mixture was cooled down to 25^0 C and

washed with toluene (3×300 mL). Then the pH of the aqueous solution was adjusted to 14 and extracted with dichloromethane (4×300 mL), dried over anhydrous sodium sulfate, filtered and evaporated in vacuum. The residue was then purified by distillation (b.p.= 67-70^0 C) under a reduced pressure of 0.5 mbar to give a blue liquid at room temperature and blue crystals at 0^{0}C. Blue schist liquid (50 %): **^{1}H NMR** (200MHz, $CDCl_3$), δ 8.75 (s, 1H, CH), 7.88 (s, 1H, CH), 4.17 (s, 2H, CH_2), 1.78 (br s, 2H. NH_2). **MS** (m/z) 212 [M^+(^{37}Cl), 12], 211 [28], 210 [M^+(^{35}Cl), 36], 209 [100], 208 [12], 194 [10].

Synthesis of 8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridine-3-thiol (**6**)**.** To a stirred suspension of sodium hydrogen carbonate (8.2 g, 2.6 eq) in 30 mL of water, kept at 0^{0}C, was added a solution of thiophosgene (4.7 g, 1.08 eq) in 30 mL of dichloromethane. To this vigorously stirred reaction mixture a solution of the amine (**1**) (8 g, 1 eq) in 60 mL of dichloromethane was added dropwise over 40 min. The reaction mixture was then allowed to warm up slowly to room temperature. After stirring for 4 hours at room temperature the aqueous layer was separated and extracted several times with dichloromethane (3×100 mL). The combined organic layers were washed with water (2×100 mL) and saturated sodium chloride solution (2 × 100 mL), dried over anhydrous sodium sulfate , filtered and evaporated in vacuum. The residue was crystallized from dichloromethane as a yellow-greenish solid. *Yellow-greenish crystals* (80%) **^{1}H NMR** (200MHz, $CDCl_3$), δ 13.10 (br s, SH) , 8.4 (s, 1H), 7.68 (s, 1H), 7.24 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ 139,63 (s. C_q), 125,40 (s, C_q), 123,78 (q, $^2J(CF_3)$ = 264.24 Hz, C_q) , 122,81(q, ^1J (CF_3) = 270,5 Hz, C_q), 121,00 (q, $^3J(CF_3)$ = 6.5 Hz, CH), 120.19 (s, C_q), 115.06 (q, $^3J(CF_3)$ = 2.4 Hz, CH), 99.56 (s, CH). **MS** (m/z) 255 [4], 254 [M^+(^{37}Cl), 36], 253 [12], 252 [M^+(^{35}Cl), 100], 251 [8], 233 [10], 220 [80], 194 [30].

Synthesis of 8-chloro-6-(trifluoromethyl)imidazo[1,5-a]pyridin-3-ol (**7**). To a stirred suspension of sodium hydrogen carbonate (6.7 g, 2.6 eq) in 25 mL of water kept at 0^{0}C was added a solution of triphosgene (6.4 g, 0.7 eq) in 30 mL of dichloromethane. To this vigorously stirred reaction mixture a solution of the amine (**1**) (6.5 g, 1 eq) in 60 mL of dichloromethane was added drop-wise within 40 min. The reaction mixture was then allowed to warm up slowly at room temperature. After stirring for 3 hours to room temperature the aqueous layer was separated and extracted several times with dichloromethane (3× 100 mL). The combined organic layers were washed with water (3×100 mL) and saturated sodium chloride solution (2×100 mL), dried over anhydrous sodium sulfate , filtered and evaporated in vacuum. The residue was crystallized from dichloromethane to give yellow crystals. *Yellow crystals* (72 %) ; **^{1}H NMR** (200 MHz, $CDCl_3$), δ 12.06 (br s, OH) , 7.89 (s, 1H,), 6.68 (s, 1H,), 6.56 (s, 1H,). **^{13}C NMR** $CDCl_3$ δ (149,63 (s. C_q), 125,40 (s, C_q), 123,78 (q, $^2J(CF_3)$ = 264.24 Hz, C_q) , 122,81(q, ^1J (CF_3) = 270,5 Hz, C_q), 121,00 (q, $^3J(CF_3)$ = 6.5 Hz, CH), 120.19 (s, C_q), 115.06 (q, $^3J(CF_3)$ = 2.4 Hz, CH), 99.56 (s, CH). **MS** (m/z) 239 [3], 238 [M^+ (^{37}Cl), 20], 237 [8], 236 [M^+ (^{35}Cl), 70], 235 [6], 217 [7], 208 [16], 183 [30], 181 [100].

X-ray Crystal Structure Determinations: Data were recorded on an Oxford Diffraction Nova area detector at low temperature using mirror-focussed Cu-*K*α radiation (λ = 1.54184 Å). Absorption corrections were performed on the basis of multi-scans. The structures were refined anisotropically using the program SHELXL-97[28]. Hydrogen atoms of NH groups were refined freely; other H atoms were included using rigid methyl groups or a riding model. Two CF_3 groups of **7B** and one of **6B** were disordered over two positions.

Crystal data for **6B**: $C_8H_4ClF_3N_2S$, M_r = 252.64, triclinic, space group p-1, a = 4.4758(4), b = 13.0350(12), c = 16.5242(16) Å; α = 83.604(8), β = 84.813(8), γ = 80.963(8)°; V = 943.55(15) Å^3; Z = 4; T = 100(2) K; μ = 5.838 (mm^{-1}). Of 12256 reflections measured, 3881 were independent (R_{int} = 0.0443). Final $R1(I > 4\sigma(I))$, = 0.0389, $wR2$ = 0.1107 (all data).

Crystal data for **7B**: $C_8H_4ClF_3N_2O$; M_r = 236.58; orthorhombic; space group *Pbca*; a = 25.0918(16), b = 6.7973(4), c = 31.9279(18) Å; V = 5445.5(6) Å^3; Z = 24; T = 100(2) K; μ = 4.013 (mm^{-1}). Of 88124 reflections measured, 5665 were independent (R_{int} = 0.130). Final $R1$ ($I > 4\sigma(I)$), = 0.0437, $wR2$ = 0.1087 (all data).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication no. CCDC-773166 (**6B**) and CCDC-773167 (**7B**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

CONCLUSION

A facile synthesis of imidazo[1.5-a]pyridines is described. This method employs the use of triphosgene and thiophosgene, and is clearly different from known syntheses of this class of compounds. The compounds (**6**) and (**7**) could be synthesized in good yields. The amine (**1**) is synthesized on a 100 g scale in 50 % yield over 3 steps. Therefore, the method should be complementary to the existing syntheses of imidazo[1.5-a]pyridines and will find applications in synthetic organic chemistry and medicinal chemistry.

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