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REACTIONS WITH *N*-CHLOROSUCCINIMIDE OF VARIOUS 5-METHYLIMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES WITH AN ELECTRON-WITHDRAWING GROUP SUBSTITUTED AT THE 3-POSITION

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Abstracts-Chlorination reactions using *N*-chlorosuccinimide (NCS) was investigated for various 5-methylimidazo[1,2-*a*]pyridine derivatives with an electron-withdrawing group substituted at the 3-position. These reactions showed different results, and by examining these, we proposed a reaction mechanism *via* the appropriate 3-halogenoimidazo[1,2-*a*]pyridium compounds as the reaction intermediates.

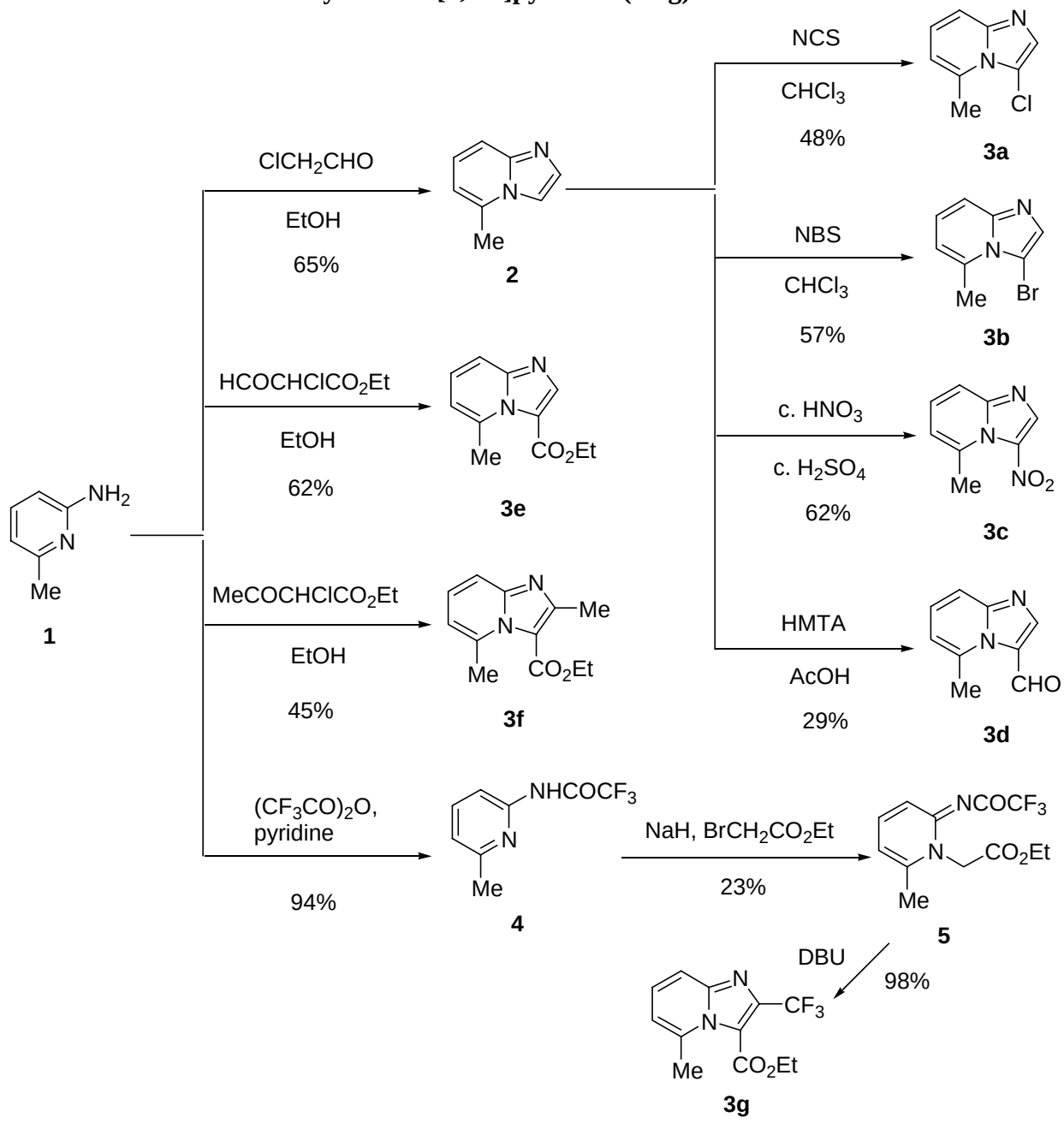
INTRODUCTION

Imidazo[1,2-*a*]pyridine moieties have attracted much recent interest because of their broad range of pharmacological activities,[1] and products incorporating imidazo[1,2-*a*]pyridine are already on the market, e.g. zolimidine,[2a] an anti-ulcer drug, and zolpidem,[2b] which is used as a hypnotic drug. Electrophilic reagents react preferentially at the 3-position of imidazo[1,2-*a*]pyridine, such as halogenation, nitration,[3,4] acylation,[3] and the Mannich reaction.[3a,4] By contrast, there were few reports of any electrophilic reactions for substrates blocked at this position.[5] The only reports are by Hand and Paudler for the case of halogenation, where they have reported that the treatment of 3-methylimidazo[1,2-*a*]pyridine[5b] or 3-bromo-7-methylimidazo[1,2-*a*]pyridine[5a] with *N*-bromosuccinimide (NBS) in chloroform gave rise to compounds by apparent nucleophilic substitution at the 2-position. However, we have found that ethyl 5-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**3e**) reacted with *N*-chlorosuccinimide (NCS) in ethyl acetate or tetrahydrofuran to give regioselectively ethyl 5-(chloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate (**6e**) in 83% and 76% yields respectively, while the reaction of **3e** with NCS in acetic acid gave ethyl 5-methyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridine-3-carboxylate (**8e**) in 83% yield.[6] These results are similar to those for the reaction of 2-methylimidazo[1,2-*a*]pyridine[4] with NBS in chloroform, which gave 3-halogeno-halomethylimidazo[1,2-*a*]pyridines *via* 1-halogenoimidazo[1,2-*a*]pyridiums (**11**) as the reaction intermediates. Thus, the chlorination of 3-substituted imidazo[1,2-*a*]pyridines show different products depending on whether the imidazo[1,2-*a*]pyridines have a methyl group or not. In this paper, we will discuss our investigation of the reactions of NCS with various 3-substituted 5- methylimidazo[1,2-*a*]pyridine derivatives substituted with an electron-withdrawing group. Moreover, the reactions of 2,3-disubstituted 5-methylimidazo[1,2-*a*]pyridines with NCS were also studied, because the unsubstituted

compound (**3e**) at the 2-position reacted with NCS in acetic acid to give the 2-oxo-imidazo[1,2-*a*]pyridine (**8e**).

RESULTS AND DISCUSSION

Synthesis of 3-substituted 5-methylimidazo[1,2-*a*]pyridines(3a-g)



Scheme 1

Imidazo[1,2-*a*]pyridines (**3a**-**g**) were synthesized as shown in Scheme 1. Condensation of 2-amino-6-methylpyridine (**1**) with 2-chloroacetaldehyde, ethyl 2-chloro-3-oxopropanoate, or ethyl 2-chloroacetoacetate according to the procedure of Tchitchibain[7] gave the products (**2**, **3e**, and **3f**)in 65%, 62%, and 45% yields, respectively. Subsequently, treatment of **2** with the appropriate respective electrophilic reagents gave **3a**-**d**. The reaction of **2** with NCS or NBS gave **3a** and **3b** in 48% and 57% yields,

respectively. Compound (**2**) was readily nitrated with concentrated nitric acid in the presence of concentrated sulfuric acid to give **3c** in 62% yield. The Vilsmeier-Haack reaction[1a] of **2** afforded **3d** in less than 2% yield (analyzed by HPLC) under the reported conditions. However, the reaction of **2** with hexamethylenetetramine in acetic acid at 90°C gave **3d** in 29% yield. Our results are of interest in the context of the previously reported literature, while Hand and Paudler have reported that the condensation of **2** with acetaldehyde does not proceed by the *peri*-effect.[8] Compound (**3g**) was synthesized by the reaction of 2,2,2-trifluoro-*N*-(6-methyl-2-pyridinyl)acetamide (**4**) with ethyl 2-bromoacetate, followed by treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU).

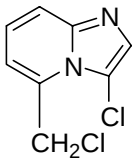
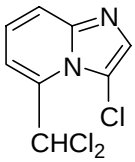
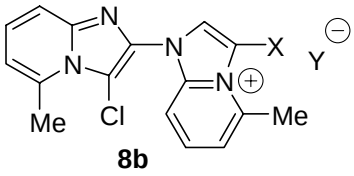
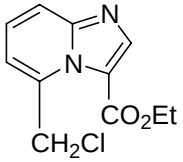
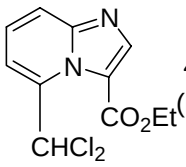
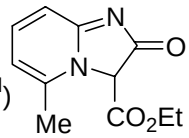
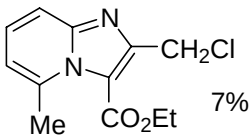
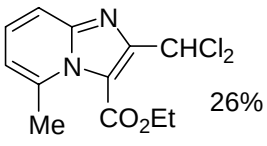
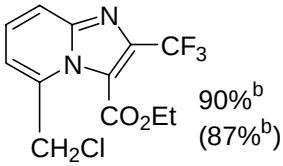
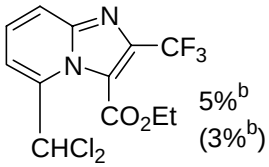
Reactions of 3 with NCS

The reactions of **3** with NCS (1.2 eq.) in tetrahydrofuran was carried out at room temperature (Table 1). The chlorination of **3a** showed similar reactivity in **3e** to yield the chloromethyl derivatives (**6a** and **7a**), which lost their methyl protons to become the methylene or methyne proton (s), as analyzed by their ^{1}H-NMR spectra. On the other hand, the treatment of **3b** with NCS provided unexpected results, because it give a mixture (**8b-1** and **8b-2**) that could not be separated. The FAB-MS (Na) spectrum of the mixture of **8b-1** and **8b-2** showed peaks at m/z 398 and 354. The ^{1}H-NMR spectra of a mixture of **8b-1** and **8b-2** revealed a pair of two methyl protons, with each singlet proton corresponding to the H-2 (8.99 and 8.96 ppm). From these results and the related reports,[5] these structures of **8b-1** and **8b-2** were confirmed to be mixed compounds in which the imidazo[1,2-*a*]pyridine (**3a**) is replaced by the chloride at the 3-position of **3b**, bonds the N-1 of the parent (**3b**) or itself (**3a**) at the 2-position, respectively. These compounds would not occur if the reaction of **3b** with NCS proceeded *via* 1-chloroimidazo[1,2-*a*]pyridium (**11a**)[5] as the intermediate. Therefore, from these results, a possible reaction mechanism might be that 3-halogenoimidazo[1,2-*a*]pyridium (**12a**) as an intermediate reacted with **3b**, or that compound (**3a**) was replaced by the chloride to yield the appropriate mixtures, as shown in Scheme 2. In our previous report,[6] the mechanism of formation of **6e** and **8e** from **3e** was thought from the AM1 calculations of **3e** to be that the carbon at the 3-position attacked NCS (or AcOCl) to give the 3-chloroimidazo[1,2-*a*]pyridium (**12b**). The successive 1,4-chlorine shift produced the chloromethyl derivative (**6e**), while acetic acid (quenching water) nucleophilically substituted the intermediate (**12b**) at the 2-position to lead to **3e** in the case where acetic acid was the solvent. The reaction mechanism for **3b** is similar to that for **3e**. The treatment of **3c** with NCS produced the *ipso*-replacement reaction to obtain **3a** and **6a** in 6% and 41% yields respectively, and to recover **3c** in 36% yield. This result showed that the chlorination of the methyl group in **3a** took place preferentially when compared with the *ipso*-replacement reaction in **3c**, by considering the relative quantities of **3c**, **3a**, **6a** and NCS. Similarly, replacement at the 3-position occurred by the treatment of **3d** with NCS (30% yield recovery).

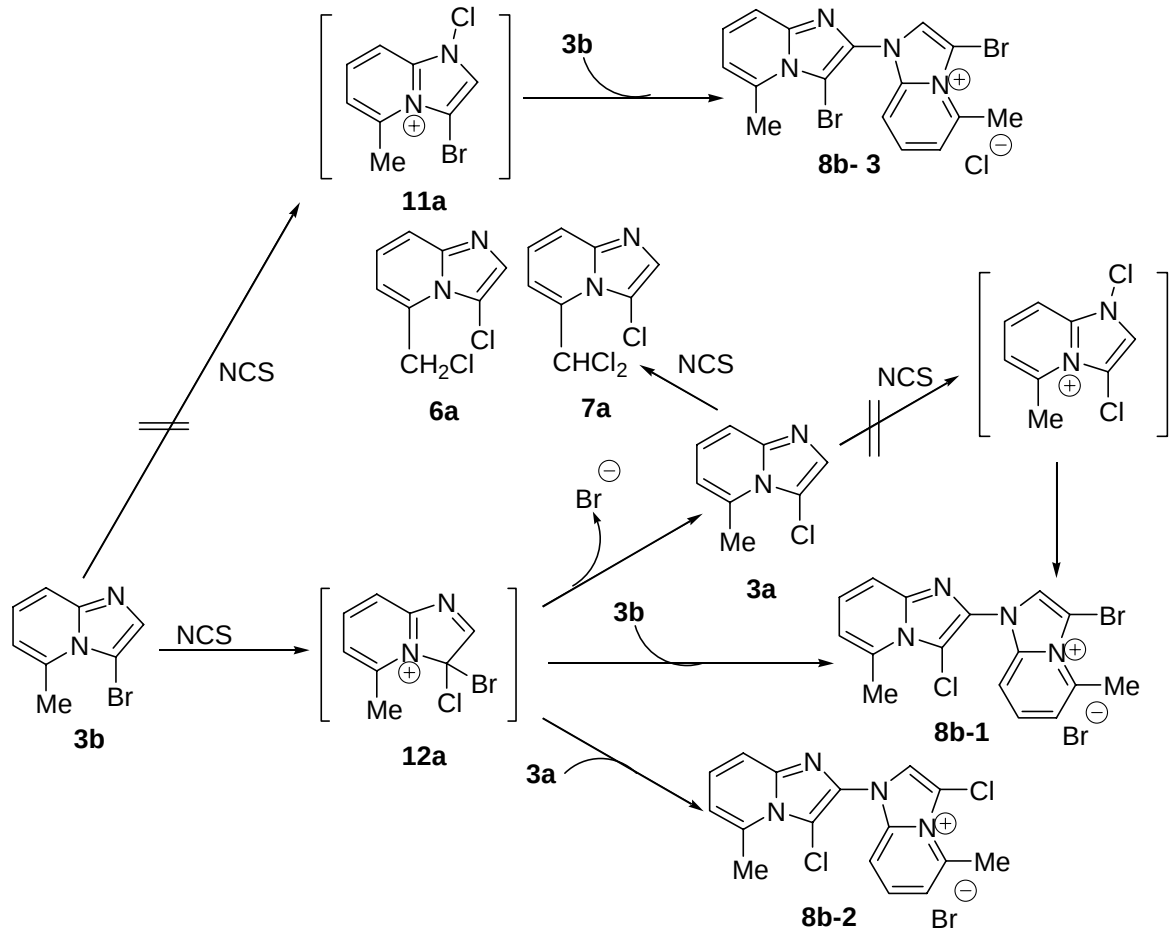
The treatment of **3f** with NCS gave the chloromethyl derivatives (**9f** and **10f**), substituted at the 2-methyl group. The structures of **9f** and **10f** were confirmed by long-range proton-carbon decoupling experiments, and ^{1}H-NMR spectral data indicated the loss of methyl protons at the 2-position rather than the 5-position. The reaction of **3g** with NCS at 50°C yielded **6g** and **7g**, in which the chlorination occurred at the 5-methyl group, while the reaction at room temperature did not go to completion due to the effect of an electron-withdrawing group (trifluoromethyl group) at the 2-position.

Furthermore, the reactions of 5-methylimidazo[1,2-*a*]pyridines (**3a**, **3c** and **3g**) with NCS in acetic acid as a solvent showed similar results to those obtained when tetrahydrofuran was used as the solvent.

Table 1. Reaction of **3** with NCS (1.2 eq.) in THF

Entry	Substrate	Conditions	Products
1	**3a**	rt, 2 h	 **6a** 32% (35%[b])  **7a** 14% (11%[b])
2[a]	**3b**	rt, 1 h	 **8b** 18% **8b-1** ; X = Br **8b-2** ; X = Cl Y = Br or Cl or mixture
3	**3c**	rt, overnight	**3a** ; 6% (12%[b]), **6a** ; 41% (29%[b]), **3c** ; 36% (40%[b])
4	**3d**	rt, overnight	**6a** ; 7%[b], **3d** ; 30%[b]
5[6]	**3e**	rt, 4 h	 **6e** 76%[b] (1%[b])  **7e** 4%[b] (ND[b,d])  **8e** 6%[b] (83%[b])
6	**3f**	rt, 2 h	 **9f** 7%  **10 f** 26% **3f•HCl** ; 21%
7	**3g**	50°C, 2 h	 **6g** 90%[b] (87%[b])  **7g** 5%[b] (3%[b])

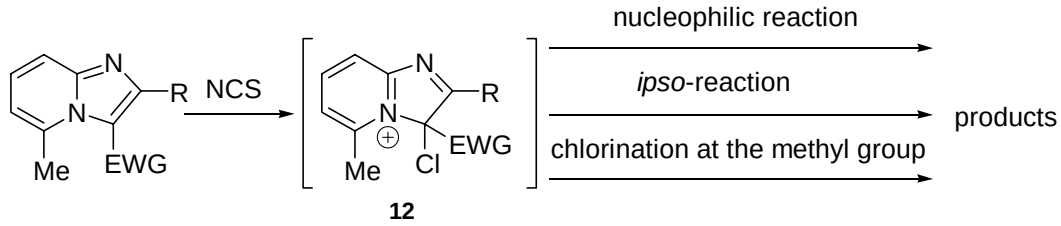
a. Yield as chloride anion, and the ratio of the mixture was analyzed by ^{1}H-NMR in DMSO-d_6 (**8b-1** : **8b-2** = 20 : 13).
b. Analyzed by HPLC.
c. The yields in parentheses using acetic acid as a solvent.
d. ND = Not detected.



Scheme 2

CONCLUSION

The reactions of various 5-methylimidazo[1,2-*a*]pyridine derivatives substituted by an electron-withdrawing group at the 3-position with NCS provided a variety of products. Treatment of the imidazo[1,2-*a*]pyridines with a formyl, nitro, or bromide group at the 3-position using NCS produced the *ipso*-reaction products. The reactions with NCS of the imidazo[1,2-*a*]pyridines with an ester or chlorine group effected chlorination at the methyl group. From these results, we proposed that these reactions gave their various products *via* 3-halogenoimidazo[1,2-*a*]pyridium (**12**), as shown in Scheme 3. NCS might electrophilically react with the imidazo[1,2-*a*]pyridines at the 3-position to lead to the subsequent reactions, such as the *ipso*-replacement reaction, the nucleophilic reaction of the other imidazo[1,2-*a*]pyridines(or water or AcOH) or chlorination at the methyl group.



Scheme 3

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro-melting apparatus, and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. Column chromatography was performed with a Wakogel C-200 (75-150μm) system. HPLC was performed on a YMC-Pack ODS-A302 column (6i.d. x 150 mm) with 0.05M KH_2PO_4 aqueous solution-MeCN (55:45) at 25℃. Detection was effected with a Shimadzu SPD-10A spectrophotometric detector at 254 nm. Elemental analyses and MS spectra were carried out by Takeda Analytical Research Laboratories, Ltd.

5-Methylimidazo[1,2-*a*]pyridine (**2**)

40% 2-Chloroacetaldehyde solution (588.5 g, 2.2 mol) was added to a mixture of 2-amino-6-methylpyridine (108.1 g, 1.0 mol) and EtOH (1 L). The whole was stirred under reflux for 2 h. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was diluted with water, neutralized with 30% NaOH solution and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with n-hexane-AcOEt (4 : 1, v/v) to give **2** (77.1 g, 65 %) as a light brown oil. EI-MS : 132 (M^+). ^{1}H-NMR ($CDCl_3$) : δ 2.57 (s, 3H), 6.63 (d, J=6.8, 1H), 7.13 (dd, J=6.8, 9.1, 1H), 7.47 (s, 1H), 7.55 (d, J=9.1, 1H), 7.79 (s, 1H). IR (Neat, cm^{-1}) : 1639, 1540, 1509, 1299, 1149, 781, 700.

3-Chloro-5-methylimidazo[1,2-*a*]pyridine (**3a**)

NCS (5.2 g, 37.8 mmol) was added to a mixture of **2** (5.0 g, 37.8 mmol) and $CHCl_3$ (50 mL). After the whole was stirred at RT for 2 h, the reaction mixture was extracted with 1 N-HCl solution. The aqueous layer was neutralized with 1 N-NaOH solution and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with n-hexane, collected by filtration to give **3a** (3.1 g, 48 %) as a colorless solid. mp 82-84°C (AcOEt / n-hexane). *Anal*. Calcd for $C_8H_7N_2Cl$: C, 57.67 ; H, 4.23 ; N, 16.81 ; Cl, 21.28. Found : C, 57.54 ; H, 4.22 ; N, 16.63 ; Cl, 21.08. ^{1}H –NMR ($CDCl_3$) : δ 2.97 (s, 3H), 6.50 (d, J=6.8, 1H), 7.01 (dd, J=6.8, 9.1, 1H), 7.45 (d, J=9.1, 1H), 7.48 (s, 1H). IR (Nujol, cm^{-1}) :2923, 2854, 1286, 1238, 1149, 1081, 840.

3-Bromo-5-methylimidazo[1,2-*a*]pyridine (**3b**)

NBS (18.0 g, 100 mmol) was added to a mixture of **2** (12.0 g, 90.8 mmol) and $CHCl_3$ (120 mL). After the whole was stirred at rt for 2 h, the reaction mixture was extracted with 1 N-HCl solution. The aqueous layer was neutralized with 1 N-NaOH solution and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with n-hexane, collected by filtration to give **3b** (11.0 g, 57 %) as a colorless solid. mp 81-83°C (AcOEt / n-hexane). *Anal*. Calcd for $C_8H_7N_2Br$: C, 45.53 ; H, 3.34 ; N, 13.27 ; Br, 37.86. Found : C, 45.50 ; H, 3.32 ; N, 13.22 ; Br, 37.53. ^{1}H-NMR ($CDCl_3$) : δ 3.04 (s, 3H), 6.50 (d, J=6.8, 1H), 7.05 (dd, J=6.8, 9.1, 1H), 7.48 (d, J=9.1, 1H), 7.53 (s, 1H). IR (Nujol, cm^{-1}) :2923, 2854, 1459, 1376, 1228, 1147, 838.

5-Methyl-3-nitroimidazo[1,2-*a*]pyridine (**3c**)

Concentrated nitric acid (61 %, 32 mL) was slowly added to a mixture of **2** (24.0 g, 181.6 mmol) and conc. sulfuric acid (40 mL) at 0°C. The whole was stirred at rt for 5 h. The reaction mixture was added to water, adjusted to pH 2.0 with 30% NaOH solution. The resulting precipitate was collected by filtration and washed successively with water to give **3c** (19.7 g, 62 %) as a light yellow solid. mp 116-117°C (EtOH). *Anal*. Calcd for $C_8H_7N_3O_2 \cdot 0.1H_2O$: C, 53.69 ; H, 4.06 ; N, 23.48. Found : C, 53.70 ; H, 3.94 ; N, 23.79. ^{1}H-NMR ($CDCl_3$) : δ 2.68 (s, 3H), 7.31 (d, J=6.9, 1H), 7.73-78.4 (m, 2H), 8.73 (s, 1H). IR (Nujol, cm^{-1}) : 2923, 2854, 1633, 1434, 1276, 889.

3-Formyl-5-methylimidazo[1,2-*a*]pyridine (**3d**)

Hexamethylenetetramine (56.1 g, 400 mmol) was added to a mixture of **2** (24.0 g, 181.6 mmol) in AcOH (240 mL). The whole was stirred at 90°C for 3 h. After cooling, the reaction mixture was poured into water and extracted with AcOEt. The AcOEt extract was neutralized with 30% NaOH solution, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with diisopropyl ether, collected by filtration to give **3d** (8.4 g, 29 %) as a colorless solid. mp 131-132°C (AcOEt / n-hexane). *Anal*. Calcd for $C_9H_8N_2O$: C, 67.49 ; H, 5.03 ; N, 17.49. Found : C, 67.45 ; H, 5.06 ; N, 17.45. ^{1}H –NMR ($CDCl_3$) : δ 2.97 (s, 3H), 6.90 (d, J=7.0, 1H), 7.46 (dd, J=6.8, 9.1, 1H), 7.65 (d, J=9.1, 1H), 8.40 (s, 1H), 9.90 (s, 1H). IR (Nujol, cm^{-1}) : 2921, 2854, 1635, 1440, 1157, 890.

Ethyl 2,5-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (**3f**)

Ethyl 2-chloroacetoacetate (54.0 g, 329 mmol) was added to a mixture of 2-amino-6-methylpyridine (17.8 g, 164 mmol) and EtOH (89 mL), and the whole was refluxed for 2 h. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was added to AcOEt, extracted with 1 N-HCl solution. The aqueous layer was neutralized with 30% NaOH solution and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with n-hexane-AcOEt (4 : 1, v/v) to give **3f** (16.0 g, 45 %) as a light brown oil. EI-MS : 218 (M^+). ^{1}H-NMR ($CDCl_3$) : δ 1.44 (t, J=7.1, 3H), 2.65 (s, 6H), 4.42 (q, J=7.1, 2H), 6.74 (d, J=7.0, 1H), 7.31 (dd, J=7.0, 8.8, 1H), 7.50 (d, J=8.8, 1H). IR (Nujol, cm^{-1}) : 2829, 1702, 1542, 1509, 1407, 572.

2,2,2-Trifluoro-*N*-(6-methyl-2-pyridinyl)acetamide (**4**)

Trifluoroacetic anhydride (48.0 g, 220 mmol) was dropped into a mixture of 2-amino-6-methylpyridine (21.6 g, 200 mmol), pyridine (31.6 g, 400 mmol) and THF (200 mL) at 0°C. The whole was stirred at rt overnight. The reaction mixture was concentrated *in vacuo*. The residue was added to water, extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **4** (41.6 g, 94 %) as a colorless oil. EI-MS : 204 (M^+). ^{1}H-NMR ($CDCl_3$) : δ 2.94 (s, 3H), 7.03 (d, J=7.6, 1H), 7.68 (dd, J=7.6, 8.3, 1H), 7.96 (d, J=8.3, 1H), 8.05 (br s, 1H). IR (Neat, cm^{-1}) : 2933, 2859, 1737, 1606, 1577, 1294, 1168, 1157, 792.

Ethyl {2-[(trifluoroacetyl)imino]pyridin-1-(2*H*)-yl}acetate (**5**)

60% Sodium hydride (6.8 g, 170 mmol) was added to a suspension of **4** (34.7 g, 170 mmol) in DMF (170 mL) in an ice-bath. After this the solution was stirred at the same temperature for 30 min, ethyl 2-

bromoacetate (28.4 g, 170 mmol) was added and then the whole was stirred at rt for 4 h. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with diisopropyl ether, collected by filtration to give **5** (11.3 g, 23 %) as a colorless solid. mp 119-120°C (AcOEt / n-hexane). *Anal*. Calcd for $C_{12}H_{13}N_2O_3F_3$: C, 49.66 ; H, 4.51 ; N, 9.65 ; F, 19.64. Found : C, 49.34 ; H, 4.48 ; N, 9.58 ; F, 19.62. ^{1}H-NMR ($CDCl_3$) : δ 1.30 (t, J=7.2, 3H), 2.55 (s, 3H), 4.25 (q, J=7.2, 2H), 5.12 (s, 2H), 6.75 (d, J=7.2, 1H), 7.70 (dd, J=7.2, 8.9, 1H), 8.40 (d, J=8.9, 1H). IR (Nujol, cm^{-1}) :2919, 2854, 1739, 1619, 1558, 1168, 1124, 792.

Ethyl 2-trifluoromethyl-5-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**3g**)

DBU (0.1 mL, 0.7 mmol) was added to a mixture of **5** (1.0 g, 3.5 mmol) and THF (10 mL). The whole was stirred at 50°C for 16 h. After cooling, AcOH (0.1mL) was added to the reaction mixture and concentrated *in vacuo*. The residue was poured into water and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with diisopropyl ether, collected by filtration to give **3g** (0.92 g, 98 %) as a colorless solid. mp 44-45°C (AcOEt / n-hexane). *Anal*. Calcd for $C_{12}H_{11}N_2O_2F_3$: C, 52.95 ; H, 4.07 ; N, 10.29 ; F, 20.94. Found : C, 52.84 ; H, 4.00 ; N, 10.30 ; F, 20.98. ^{1}H-NMR ($CDCl_3$) : δ 1.44 (t, J=7.1, 3H), 2.65 (s, 3H), 4.47 (q, J=7.1, 2H), 6.85 (d, J=7.0, 1H), 7.40 (dd, J=7.0, 9.0, 1H), 7.68 (d, J=9.0, 1H). IR (Nujol, cm^{-1}) : 2848, 1725, 1519, 1461, 1176, 1145.

Reaction of **3a** and NCS

NCS (0.96 g, 7.2 mmol) was added to a mixture of **3a** (1.0 g, 6.0 mmol) and THF (12 mL). The whole was stirred at rt for 2 h. The reaction mixture was poured into AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with n-hexane-AcOEt (1 : 1, v/v) to give **6a** (385 mg, 32 %) and **7a** (200 mg, 14 %) as a colorless solid. **6a** : mp 98-99°C (AcOEt / n-hexane). *Anal*. Calcd for $C_8H_6N_2Cl_2$: C, 47.79 ; H, 3.01 ; N, 13.93. Found : C, 47.59 ; H, 3.14 ; N, 13.85. ^{1}H-NMR ($CDCl_3$) : δ 5.21 (s, 2H), 6.88 (d, J=6.9, 1H), 7.15 (dd, J=6.9, 9.1, 1H), 7.62 (d, J=9.1, 1H), 7.59 (s, 1H). IR (Nujol, cm^{-1}) : 2944, 2881, 1509, 1290, 846. **7a** : mp 74-75°C (AcOEt / n-hexane). *Anal*. Calcd for $C_8H_5N_2Cl_3$•$0.1H_2O$: C, 40.49 ; H, 2.17 ; N, 11.81 ; Cl, 44.89. Found : C, 40.97 ; H, 2.24 ; N, 11.85 ; Cl, 44.76. ^{1}H-NMR ($CDCl_3$) : δ 7.27 (dd, J=7.4, 9.0, 1H), 7.61 (s, 1H), 7.64-7.69 (m, 2H), 8.08 (s, 1H). IR (Nujol, cm^{-1}) : 2967, 2850, 1290, 1205, 1149, 848.

Reaction of **3b** and NCS

NCS (1.52 g, 9.5 mmol) was added to a mixture of **3b** (2.0 g, 11.4 mmol) and THF(24 mL). The whole was stirred at rt for 1 h. The resulting crystals were collected by filtration, washed with AcOEt, and recrystallized from MeOH to give a mixture (0.69 g, 18 % as chloride salt) of **8b-1** and **8b-2** as a colorless solid. FAB-MS : 398 $(M+Na)^+$, 354 $(M+Na)^+$. ^{1}H-NMR (DMSO-d_6) : δ; **8b-1** : **8b-2**=20 : 13; **8b-1**; 3.03 (s, 3H), 3.25 (s, 3H), 7.03 (d, J=7.0, 1H), 7.47 (dd, J=7.0, 9.0, 1H), 7.57-7.59 (m, 2H), 7.65 (d, J=9.0, 1H), 8.03-8.15(m, 1H), 8.99 (s, 1H); **8b-2**; 3.03 (s, 3H), 3.19 (s, 3H), 7.03 (d, J=7.0, 1H), 7.47 (dd, J=7.0, 9.0, 1H), 7.57-7.59 (m, 2H), 7.65 (d, J=9.0, 1H), 8.03-8.15(m, 1H), 8.96 (s, 1H).

Reaction of **3c** and NCS

NCS (0.50 g, 3.8 mmol) was added to a mixture of **3c** (0.50 g, 3.1 mmol) and THF (7 mL). The whole was stirred at rt overnight. The reaction mixture was poured into AcOEt and extracted with 1 N-HCl solution. The aqueous layer was neutralized with 30% NaOH solution and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with n-hexane-AcOEt (2 : 1, v/v) to give **3c** (0.18 g, 36 %) as a colorless solid and the mixed oil of **3a** and **6a** (0.29 g, 6 % (**3a**) and 41% (**6a**) analyzed by ^{1}H-NMR).

Reaction of **3d** and NCS

NCS (0.45 g, 3.4 mmol) was added to a mixture of **3d** (0.50 g, 2.8 mmol) and THF (6 mL). The whole was stirred at rt overnight. Yields (**6a**; 7 %, **3d**; 30 %) were determined by HPLC.

Reaction of **3f** and NCS

NCS (0.73 g, 5.5 mmol) was added to a mixture of **3f** (1.0 g, 4.6 mmol) and THF (12 mL). The whole was stirred at rt for 2 h. The resulting crystals were collected by filtration, washed with AcOEt to give **3f•HCl** (0.21 g, 21 %) as a colorless solid. The filtrate was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with n-hexane-AcOEt (4 : 1, v/v) to give **9f** (80 mg, 7%) and **10f** (0.3 g, 26 %) as colorless solids. **9f** : mp 67-68°C (AcOEt / n-hexane). *Anal*. Calcd for $C_{12}H_{13}N_2O_2Cl$•1/4H_2O : C, 56.03 ; H, 5.29 ; N, 10.89. Found : C, 56.07 ; H, 5.07 ; N, 10.89. ^{1}H-NMR($CDCl_3$) : δ 1.47 (t, J=7.1, 3H), 2.66 (s, 3H), 4.76 (q, J=7.1, 2H), 4.96 (s, 2H), 6.79 (d, J=7.0, 1H), 7.35 (dd, J=7.2, 8.8, 1H), 7.58 (d, J=8.8, 1H). IR (Nujol, cm^{-1}) : 2913, 2856, 1712, 1509, 1207, 1097. **10f** : mp 68-69°C (AcOEt / n-hexane). *Anal*. Calcd for $C_{12}H_{12}N_2O_2Cl_2$: C, 50.19 ; H, 4.21 ; N, 9.76. Found : C, 49.99 ; H, 4.16 ; N, 9.53. ^{1}H-NMR ($CDCl_3$) : δ 1.49 (t, J=7.1, 3H), 2.66 (s, 3H), 4.49 (q, J=7.1, 2H), 6.84 (d, J=7.0, 1H), 7.40 (s, 1H), 7.41 (dd, J=7.0, 8.9, 1H), 7.69 (d, J=8.9, 1H). IR (Nujol, cm^{-1}) : 2921, 2852, 1710, 1508, 1159, 796.

Ethyl 5-chloromethyl-2-trifluoromethylimidazo[1,2-*a*]pyridine-3-carboxylate (**6g**)

NCS (0.59 g, 4.4 mmol) was added to a mixture of **3g** (1.0 g, 3.7 mmol) and THF (12 mL). The whole was stirred under reflux for 2 h. The reaction mixture was poured into AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with n-hexane-AcOEt (4 : 1, v/v) to give **6g** (0.56 g, 50 %) as a colorless solid. mp 114-116°C (AcOEt / n-hexane). *Anal*. Calcd for $C_{12}H_{10}N_2O_2ClF_3$: C, 47.00 ; H, 3.29 ; N, 9.13 ; Cl, 11.56 ; F, 18.59. Found : C, 46.91 ; H, 3.15 ; N, 9.11 ; Cl, 11.55 ; F, 18.42. ^{1}H-NMR ($CDCl_3$) : δ 1.47 (t, J=7.2, 3H), 4.50 (q, J=7.2, 2H), 5.18 (s, 2H), 7.13 (d, J=7.0, 1H), 7.47 (dd, J=7.0, 9.0, 1H), 7.86 (d, J=9.0, 1H). IR (Nujol, cm^{-1}) : 2923, 2854, 1722, 1539, 1211, 802.

Ethyl 5-dichloromethyl-2-trifluoromethylimidazo[1,2-*a*]pyridine-3-carboxylate (**7g**)

NCS (0.54 g, 4.1 mmol) was added to a mixture of **3g** (0.5 g, 1.8 mmol) and THF (6 mL). The whole was stirred under reflux for 2 h. The reaction mixture was poured into AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on SiO_2 with

n-hexane-AcOEt (4 : 1, v/v) to give **7g** (0.32 g, 51 %) as a colorless solid. mp 122-123°C (AcOEt / n-hexane). *Anal*. Calcd for $C_{12}H_9N_2O_2Cl_2F_3 \cdot 0.5H_2O$: C, 41.17 ; H, 2.88 ; N, 8.00 ; Cl, 20.25 ; F, 16.28. Found : C, 40.97 ; H, 2.53 ; N, 8.11 ; Cl, 20.285 ; F, 16.37. ^{1}H-NMR ($CDCl_3$) : δ 1.46 (t, J=7.2, 3H), 4.52 (q, J=7.2, 2H), 7.62 (dd, J=7.8, 8.6, 1H), 7.86 (s, 1H), 7.91-7.95 (m, 2H) . IR (Nujol, cm^{-1}) : 2921, 2854, 1712, 1513, 1201, 808.

Reaction of **3g** and NCS

NCS (0.29 g, 2.2 mmol) was added to a mixture of **3g** (0.50 g, 1.8 mmol) and THF (6 mL). The whole was stirred at 50°C for 2 h. Yields (**6g**; 90 %, **7g**; 5 %) were determined by HPLC.

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