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SHORT COMMUNICATIONS

Chemoselective iodination of 6-substituted imidazo[1,2-*a*]pyridine

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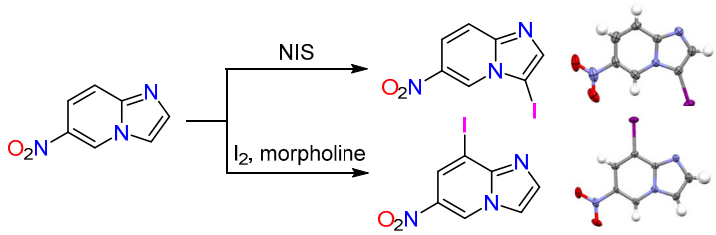


3- and 8-Iodoimidazo[1,2-*a*]pyridines were synthesized from imidazo[1,2-*a*]pyridine under different substitution conditions. The molecular electrostatic potential calculations were performed to investigate the chemoselectivity of the substitution reaction. The molecular structures of the target compounds were characterized by single crystal X-ray diffraction analysis.

Keywords: imidazo[1,2-*a*]pyridine, heteroaryl iodides, synthesis, X-ray diffraction.

Imidazo[1,2-*a*]pyridine (IP), a fundamental class of heterocycles, is attractive for both synthetic and medicinal chemists owing to its wide use as the core structure in many different drugs.[1,2] To date, IP-based drugs have been developed and used as antiviral, fungicidal, antibacterial, anti-inflammatory agents and for the treatment of neurodegenerative disorders, including zolpidem (**1**),[3] minodronic acid (**2**) (for anxiety and heart failure),[4] olprinone (**3**),[5] alpidem (**4**),[6] zolimidine (**5**) (for peptic ulcers),[7] and GSK812397 (**6**) (for HIV infection)[8] (Fig. 1). IP derivatives have also been studied for application in the field of materials sciences.[9] In addition, Castera-Ducros and coworkers reported that an IP scaffold acts as a novel and promising selective antileishmanial pharmacophore, targeting the human parasite *Leishmania donovani*.[10]

Thus, the development of synthetic strategies for the functionalization of IP from readily available starting materials is important. Substitution at different positions of imidazo[1,2-*a*]pyridines gives compounds with diverse pharmacological properties.[11] In particular, heteroaryl iodides are frequently used as synthons in organic synthesis and are useful in producing a series of IP derivatives possessing biological activities through further substitution.

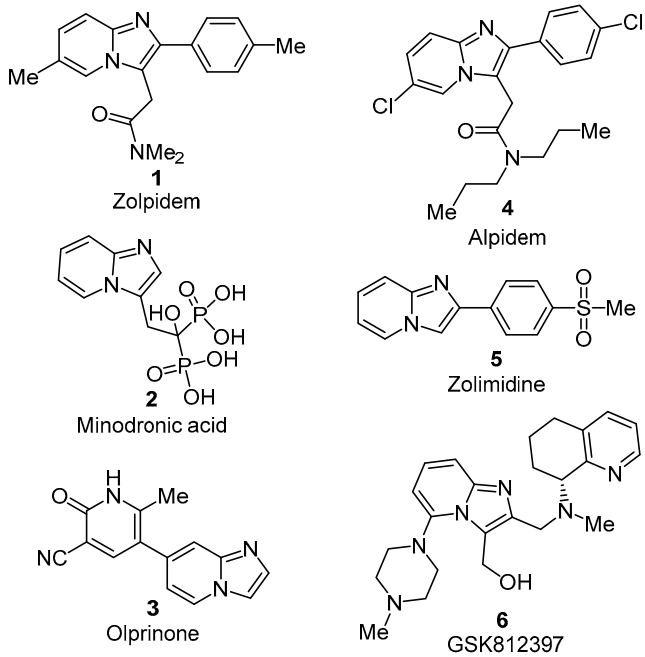
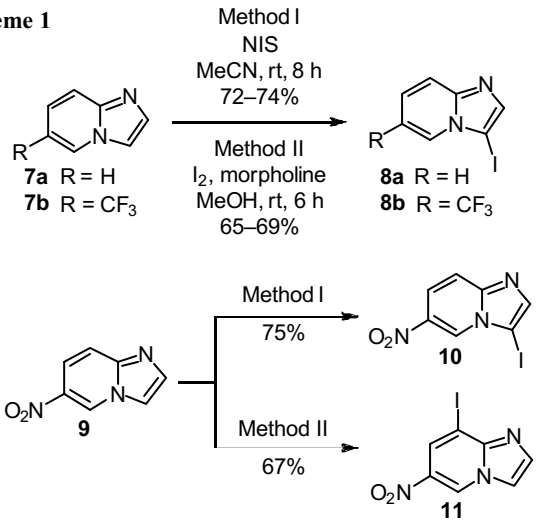


Figure 1. Structures of representative drugs containing imidazo[1,2-*a*]pyridine fragment.

Scheme 1



The substitution of imidazo[1,2-*a*]pyridines with an iodine takes place at the C-3 atom.[12] *N*-Iodosuccinimide (NIS) and I_2–morpholine were chosen as iodination reagents. Imidazo[1,2-*a*]pyridine (**7a**) and 6-(trifluoromethyl)imidazo-[1,2-*a*]pyridine (**7b**) were used as starting materials, and compounds **8a**,**b** with the substitution at the C-3 atom were obtained at room temperature both under action of NIS and I_2–morpholine (Scheme 1). Next, we performed the substitution of 6-nitroimidazo[1,2-*a*]pyridine (**9**) at C-3 and C-8 atoms under different reaction conditions. Both reactions proceeded smoothly and provided compounds **10** and **11**, respectively. The reaction of compound **9** with NIS in acetonitrile at room temperature afforded 3-iodo-6-nitro-imidazo[1,2-*a*]pyridine (**10**) in 75% yield. The chemo-selectivity of the reaction was controlled by HPLC, the content of the desired product **10** in the crude mixture reached 99.92%. Interestingly, that in the presence of the other iodination reagent (I_2, morpholine) the reaction did not yield the expected 3-iodo-6-nitroimidazo[1,2-*a*]-pyridine (**10**). After spectroscopic characterization, the chemical structure of this compound was assigned as 8-iodo-6-nitroimidazo[1,2-*a*]pyridine (**11**). The reaction proceeds with 67% yield, and the chemoselectivity was 99.95%. The molecular structures of all synthesized compounds were determined based on ^{1}H and ^{13}C NMR, MS, and IR spectroscopic methods. The crystal structures were confirmed through single crystal X-ray diffraction analysis (Fig. 2).

For the further understanding of the chemoselectivity of an iodine insertion reaction of 6-nitroimidazo[1,2-*a*]-pyridine (**9**), the molecular electrostatic potential of compound **9** was investigated in comparison to imidazo[1,2-*a*]-pyridine (**7a**) using the B3LYP approximation[13] and Gaussian 6-311G(d,p)[14] computational calculation methods.

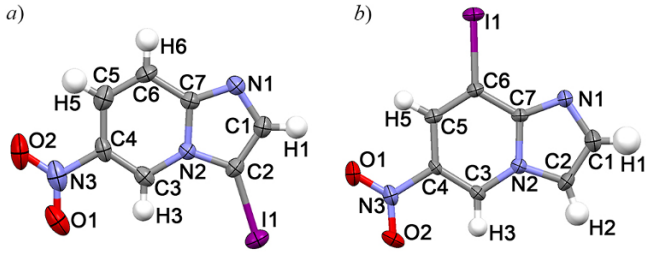


Figure 2. Molecular structures of compounds *a*) **10** and *b*) **11** with atoms represented by thermal vibration ellipsoids of 50% probability.

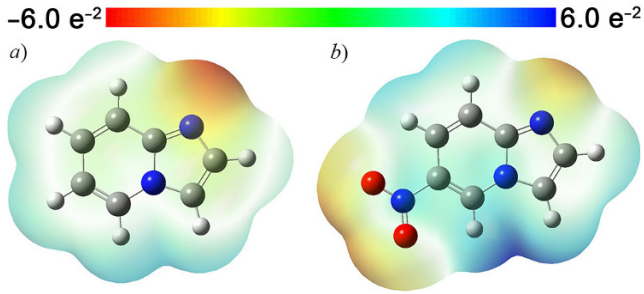


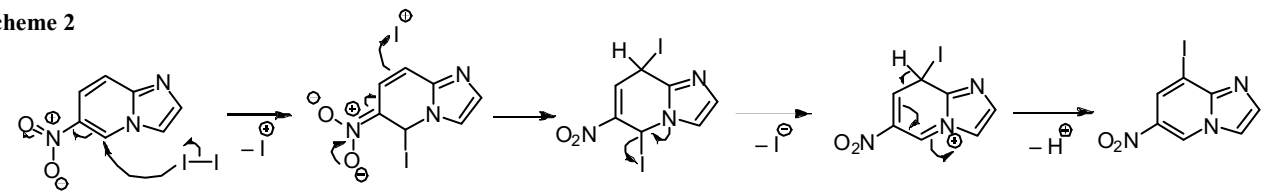
Figure 3. Molecular electrostatic potential map of *a*) imidazo-[1,2-*a*]pyridine (**7a**) and *b*) 6-nitroimidazo[1,2-*a*]pyridine (**9**).

The Figure 3 shows a molecular electrostatic potential (MEP) map, in which the different electrostatic potentials at the surface are represented with different colors, and the potential increases in the following order – red < orange < < yellow < green < blue. Clearly, the electron cloud density at the C-8 atom of imidazo[1,2-*a*]pyridine (**7a**) is higher than that of the C-5 atom in 6-nitroimidazo[1,2-*a*]pyridine (**9**). A plausible reaction mechanism for the synthesis of compound **11** by method II was put forward based on the calculated MEP results (Scheme 2).

The electron cloud density at the C-5 atom decreased when the H-6 hydrogen atom of IP was replaced with a nitro group (Fig. 3), owing to the inductive effect of the nitro group. In this case, I^- obtained in the presence of I_2–morpholine attacked the C-5 atom affording compound **11**. Probably, in the case of NIS, iodinated compound **10** was formed because the reaction proceeds *via* the free radical mechanism. Furthermore, the process described in Scheme 2 would not occur when 6-(trifluoromethyl)-imidazo[1,2-*a*]pyridine is used as the reactant because the trifluoromethyl group cannot tolerate the pair of electrons between C-5 and C-6 atoms, resulting in 3-iodo-6-(tri-fluoromethyl)imidazo[1,2-*a*]pyridine.

In summary, we have synthesized and studied different imidazo[1,2-*a*]pyridine-based iodine-substituted products using the positioning effects of the orienting groups under different reaction conditions. The molecular electrostatic

Scheme 2



potential and reaction mechanism were investigated. Structures of the synthesized compounds were proved with ^{1}H and ^{13}C NMR, MS, and IR spectroscopic methods. The crystal structures were confirmed through single crystal X-ray diffraction analysis.

Experimental

IR spectra of the sample were recorded on a FT-IR-8400S spectrometer in the 4000–400 cm^{-1} region in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AM-400 spectrometer (400 and 100 MHz, respectively) with TMS as internal standard. Mass spectra were taken in ESI mode on an Agilent 1100 LC/MSD trap system VL. HPLC performed on a Shimadzu LC-15C system, using Zorbax SB-C18 column (250 mm × 4.6 mm, 5 μm), the mobile phase acetonitrile–water, 45:55, the flow rate 0.8 ml/min. Reaction completion was monitored by TLC. Column chromatography was carried out using 300–400 mesh silica gel. All reagents were purchased from commercial suppliers and used without further purification.

3-Iodoimidazo[1,2-*a*]pyridine (8a). Method I. A mixture of imidazo[1,2-*a*]pyridine (**7a**) (10.00 g, 84.71 mmol) and NIS (22.86 g, 101.65 mmol) in acetonitrile (100 ml) was stirred at room temperature for 8 h. The reaction mixture was poured into water (150 ml) and then extracted with EtOAc (3×150 ml). The combined organic phase dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (eluent petroleum ether – EtOAc, 1:1) to give the desired product.

Method II. A mixture of imidazo[1,2-*a*]pyridine (**7a**) (10.00 g, 84.71 mmol), morpholine (14.75 g, 169.42 mmol), and I_2 (43.00 g, 169.42 mmol) in MeOH (100 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water (150 ml) and then extracted with EtOAc (3×150 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (eluent petroleum ether – EtOAc, 1:1) to give the desired product. Yield 14.88 g (72%, method I), 14.26 g (69%, method II), yellow solid, mp 118.4–119.8°C (167°C[12a]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.13 (1H, dt, *J* = 6.9, *J* = 1.1, H Ar); 7.71 (1H, s, H Ar); 7.61 (1H, dt, *J* = 9.1, *J* = 1.0, H Ar); 7.23 (1H, ddd, *J* = 9.1, *J* = 6.8, *J* = 1.2, H Ar); 6.93 (1H, td, *J* = 6.8, *J* = 1.0, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 146.9; 139.7; 126.5; 125.1; 117.1; 113.5; 64.4. Mass spectrum, *m*/*z* (I_{rel}, %): 245 [M+H] (100).

3-Iodo-6-(trifluoromethyl)imidazo[1,2-*a*]pyridine (8b). Method I. A mixture of 6-(trifluoromethyl)imidazo[1,2-*a*]-pyridine (**7b**) (10.00 g, 53.75 mmol) and NIS (14.51 g, 64.50 mmol) in acetonitrile (100 ml) was stirred at room temperature for 8 h. The reaction mixture was poured into water (150 ml) and then extracted with EtOAc (3×80 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (eluent petroleum ether – EtOAc, 1:1) to give the desired product.

Method II. A mixture of 6-(trifluoromethyl)imidazo[1,2-*a*]-pyridine (**7b**) (10.00 g, 53.75 mmol), morpholine (9.36 g, 107.50 mmol), and I_2 (27.29 g, 107.50 mmol) in MeOH (100 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water (150 ml) and then extracted with EtOAc (3×150 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (eluent petroleum ether – EtOAc, 1:1) to give the desired product. Yield 12.41 g (74%, method I), 10.90 g (65%, method II), yellow solid, mp 156.4–157.9°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.58 (1H, s, H Ar); 7.87 (1H, s, H Ar); 7.79 (1H, d, *J* = 9.4, H Ar); 7.51 (1H, d, *J* = 9.4, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 146.7; 141.7; 125.7; 124.9; 120.4; 118.3; 116.0; 67.7. Mass spectrum, *m*/*z* (I_{rel}, %): 313 [M+H] (100).

3-Iodo-6-nitroimidazo[1,2-*a*]pyridine (10). A mixture of 6-nitroimidazo[1,2-*a*]pyridine (**9**) (10.00 g, 61.34 mmol) and NIS (16.56 g, 73.61 mmol) in acetonitrile (100 ml) was stirred at room temperature for 8 h. The reaction mixture was poured into water (150 ml) and then extracted with EtOAc (3×150 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (eluent petroleum ether – EtOAc, 1:1). Yield 13.30 g (75%), yellow solid, mp 213.2–214.9°C. IR spectrum, ν, cm^{-1}: 3106, 1640, 1548, 1523, 1497, 1353, 1090, 896, 868. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.14 (1H, s, H Ar); 7.99 (1H, d, *J* = 9.9, H Ar); 7.95 (1H, s, H Ar); 7.77 (1H, d, *J* = 9.8, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 147.6; 143.6; 137.9; 127.4; 119.4; 117.4; 69.8. Mass spectrum, *m*/*z* (I_{rel}, %): 290 [M+H] (100).

8-Iodo-6-nitroimidazo[1,2-*a*]pyridine (11). A mixture of 6-nitroimidazo[1,2-*a*]pyridine (**9**) (10.00 g, 61.34 mmol), morpholine (10.68 g, 122.68 mmol), and I_2 (31.14 g, 122.68 mmol) in MeOH (100 ml) was stirred at room temperature for 6 h. The reaction mixture was poured into water (150 ml) and then extracted with EtOAc (3×150 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (eluent petroleum ether – EtOAc, 1:1). Yield 11.86 g (67%), yellow solid, mp 263.4–265.2°C. IR spectrum, ν, cm^{-1}: 3141, 1626, 1547, 1512, 1493, 1358, 1088, 901, 854. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.90 (1H, d, *J* = 2.1, H Ar); 8.35 (2H, dd, *J* = 5.3, *J* = 1.6, H Ar); 7.83 (1H, d, *J* = 1.2, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 144.9; 137.1; 136.6; 128.7; 127.2; 118.9; 84.6. Mass spectrum, *m*/*z* (I_{rel}, %): 289 $[M]^+$ (100).

X-ray structural study of compounds 10 and 11. The X-ray diffraction data was recorded on a Bruker P4 X-diffractometer using a fine-focus sealed tube graphite-monochromated MoKα radiation (λ 0.71073 Å) at 296 K in the range of 2.74≤θ≤25.21°. The crystals of compounds **10** and **11** were grown by slow evaporation of DMF solution under ambient conditions. The measured values reveals that compound **10** crystallizes in the orthorhombic crystal system with the *Pnma* space group (unit cell: *a* 13.9233(6),

b 6.4117(3), *c* 9.9957(4) Å) in the range of $2.51 \leq \theta \leq 25.19°$. Compound **11** possesses orthorhombic crystal system having *Pnma* space group (unit cell: *a* 8.359(5), *b* 6.670(4), *c* 14.881(9) Å). Crystallographic data of compounds **10** and **11** have been deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1545842 and CCDC 1545844, respectively).

Computational calculations were performed by the B3LYP hybrid electron density functional[13] and the 6-311G(d,p) basis set.[14] All the calculations were performed using the Gaussian 09 program package[15] with the default convergence criteria without any constraint on the geometry.

The Supplementary information file containing ^{1}H and ^{13}C NMR, MS spectra of all synthesized compounds, IR spectra of compounds **10**, **11**, as well as ORTEP diagrams, the crystallographic and refinement data and selected geometry parameters of compounds **10**, **11** is available at the journal website at http://link.springer.com/journal/10593.

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