

Synthesis of ^{15}N -labeled contrast agents for ^{15}N hyperpolarization by SABRE

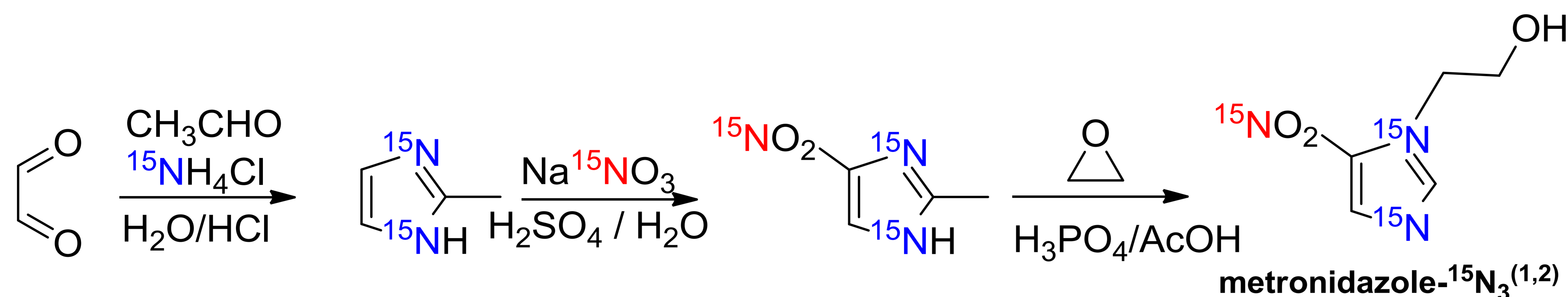
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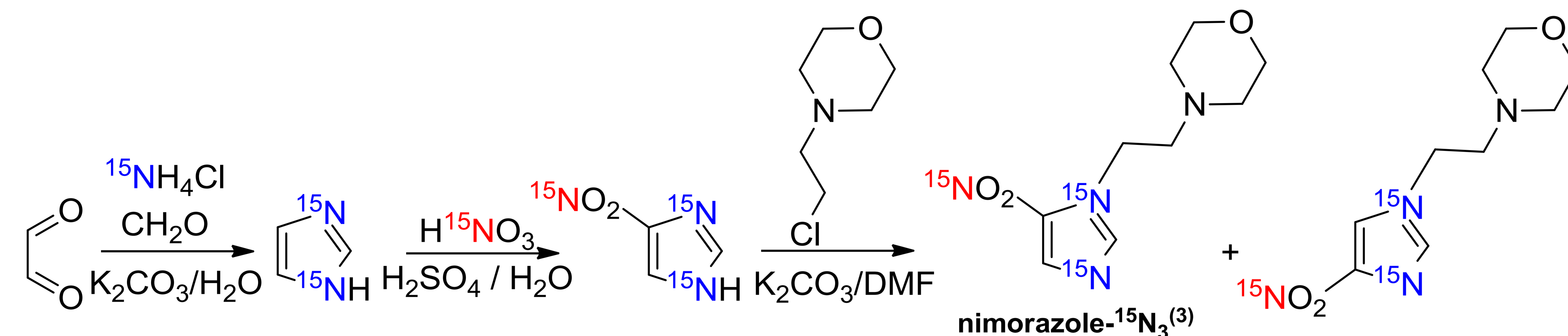
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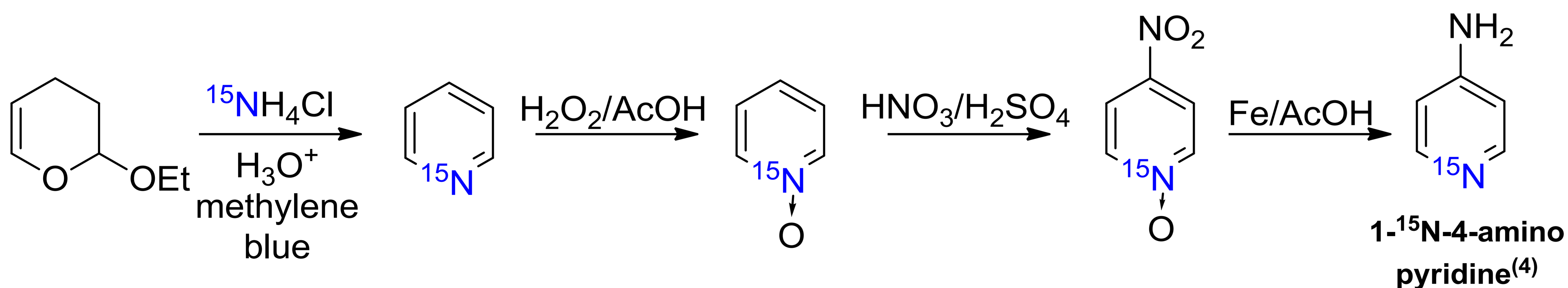
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Metronidazole is an antibiotic that can be safely administered orally and intravenously in large doses. ^{15}N polarizations of up to 34% were obtained for this compound at natural abundance of ^{15}N nuclei using SABRE. Therefore, we developed a synthetic approach for [$^{15}\text{N}_3$]metronidazole using $^{15}\text{NH}_4\text{Cl}$ and $\text{Na}^{15}\text{NO}_3$ as the ^{15}N source. The overall yield over three steps was around 15%.



Nimorazole is a nitroimidazole-based anti-infective which is also being investigated as a radiosensitizing agent for the treatment of head and neck cancer. Therefore, we performed the synthesis of isotopically labeled [$^{15}\text{N}_3$]nimorazole. In the first step, [$^{15}\text{N}_2$]imidazole was prepared with 50–60% yield via condensation of glyoxal, formaldehyde and $^{15}\text{NH}_4\text{Cl}$ used as a source of ^{15}N isotope enrichment. Subsequent nitration with $\text{H}^{15}\text{NO}_3/\text{H}_2\text{SO}_4$ allowed to obtain [$^{15}\text{N}_3$]4(5)-nitroimidazole with 30% yield. Next, this compound was alkylated with 4-(2-chloroethyl)morpholine in the presence of K_2CO_3 forming [$^{15}\text{N}_3$]nimorazole and its isomer in a 1:3 ratio.



4-Aminopyridine is used as a research tool in characterizing subtypes of the potassium channels. It has also been employed as a drug managing some of the symptoms of multiple sclerosis. 4-Aminopyridine was efficiently hyperpolarized by SABRE with ~8% ^{15}N polarization at natural abundance of ^{15}N nuclei. We synthesized [^{15}N]4-aminopyridine using $^{15}\text{NH}_4\text{Cl}$ at the first step to obtain [^{15}N]pyridine which was then converted into the product through the three steps.

¹Shchepin, R. V.; et al., Hyperpolarizing Concentrated Metronidazole (NO_2)-N- ^{15}N Group over Six Chemical Bonds with More than 15 % Polarization and a 20 Minute Lifetime, *Chem. Eur. J.*, 2019, 8829-8836

²Birchall J. R.; et al., Quantifying the Effects of Quadrupolar Sink via ^{15}N Relaxation Dynamics in Metronidazoles Hyperpolarized via SABRE-SHEATH, *Chem. Comm.*, 2020, under review

³Salnikov O. G.; et al., ^{15}N NMR Hyperpolarization of Radiosensitizing Antibiotic Nimorazole via Reversible Parahydrogen Exchange in Microtesla Magnetic Fields, *Angew. Chem. Int. Ed.*, 2020, under review.

⁴Salnikov O. G.; et al., manuscript in preparation.