METHOD of the week

^{15}N Incorporation into Heterocycles

The SARLAH Group

Historical Background

^{15}N enriched compounds were first reported by Urey (Nobel prize 1934 for discovery of deuterium) et al. using ammonia exchange reactions in 1937

> The two runs yielded 61 grams of ammonium chloride containing 2.5 percent N^{15}, 244 grams in which the concentration of N^{15} was better than 2 percent, and 1087 grams in which the concentration of N^{15} ranged between 0.7 percent and 1.5 percent.

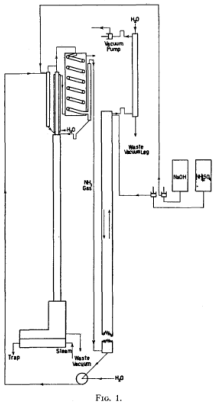
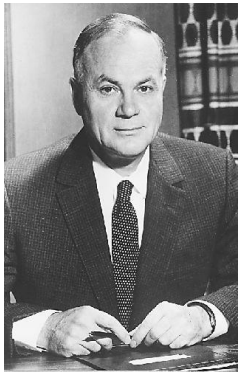


FIG. 1.

Urey, H. *J. Chem. Phys.* **1937**, *5*, 856-868. https://doi.org/10.1063/1.1749954

A Canadian Contribution – Henry G. Thode



B.Sc. University of Saskatchewan (1930)
M.Sc. University of Saskatchewan (1932)
Ph.D. University of Chicago (1934)
Postdoc Columbia University (**1936 – 1938; Urey**)
McMaster University (1939 – 1972; President 1961 – 1972)

- Contributor to first ^{15}N enriched compounds
- Constructed first mass spectrometer in Canada
- Oversaw the construction of the McMaster Nuclear Reactor

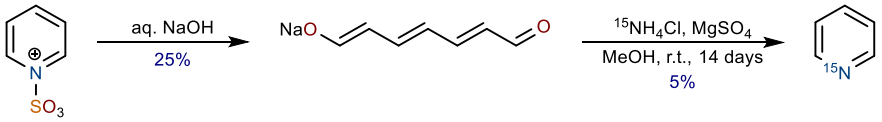
Applications of ^{15}N-labelled Compounds

The applications of ^{15}N enriched compounds were immediately realized.

- 1938: ^{15}N enriched amino acids used to study protein metabolism
- 1938: nuclear spin of ^{15}N determined to be ½
- 1960's: ^{15}N NMR begins to be used
- Modern day: ^{15}N labelled compounds for biological studies commonplace; analysis via MS or NMR. New techniques such as "signal amplification by reversible exchange in shield enables alignment transfer to heteronuclei" (SABRE-SHEATH) increase applicability

Ratner, S. *Science.* **1938**, *88(2295)*, 599-600. https://doi.org/10.1063/1.1750192
Wood, R. *J. Chem. Phys.* **1938**, *6*, 908. https://doi.org/10.1063/1.1750192
Martin, G. *In: ^{15}N-NMR Spectroscopy.* **1981**. https://10.1007/978-3-642-50172-2
Theis, T. *J Am. Chem. Soc.* **2015**, *137(4)*, 1404-1407. https://doi.org/10.1021/ja512242d

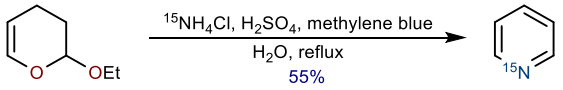
Early Syntheses of ^{15}N-pyridine



The first reported synthesis of ^{15}N-pyridine

- ^{15}N enrichment reported to be 33% in the 30 mg of material obtained

Bak, B. *Acta Chem. Scand.* **1965**, *19*, 2001-2002. https://10.3891/acta.chem.scand.19-2001



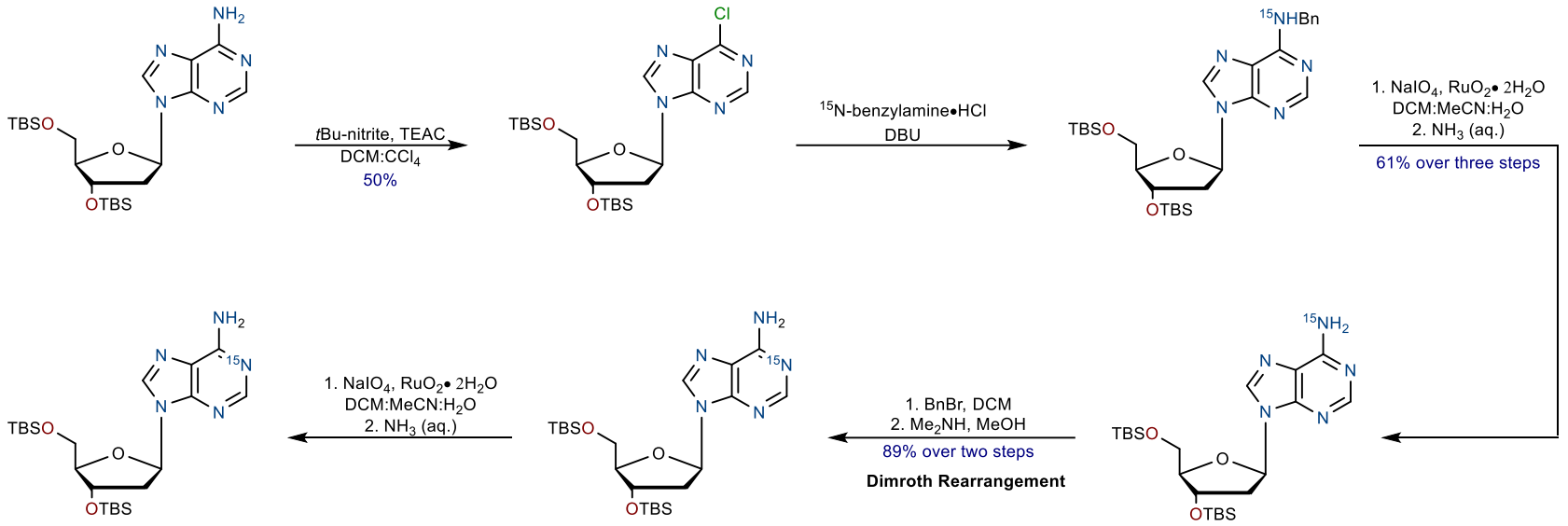
Improved synthesis of ^{15}N-pyridine

- ^{15}N enrichment reported to be 98%
- Gram-scale synthesis

Whaley, T. *J. Label. Compound.* **19674** *10(2)*, 2083-286. https://10.1002/jlcr.2590100212

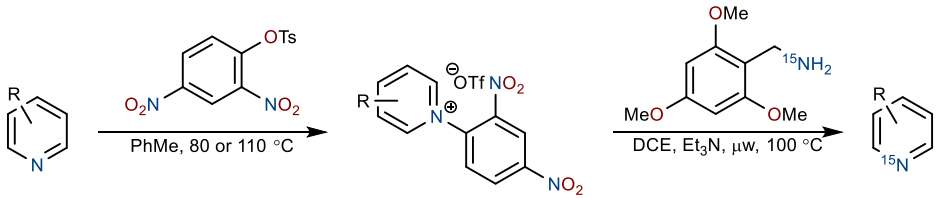
^{15}N Incorporation into Heterocycles

^{15}N-labelled Nucleosides

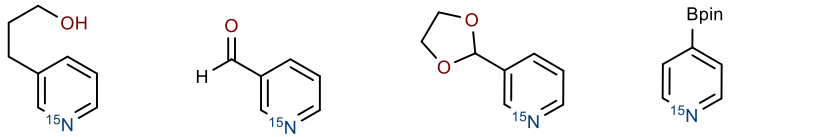


Jones, R. *J. Am. Chem. Soc.* **1987**, *109(4)*, 1275-1278. https://doi.org/10.1063/1.1750192

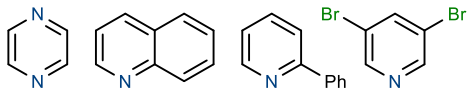
^{15}N-labelled Pyridines via ^{15}NRORC

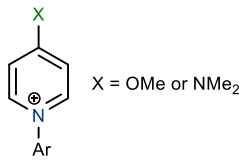


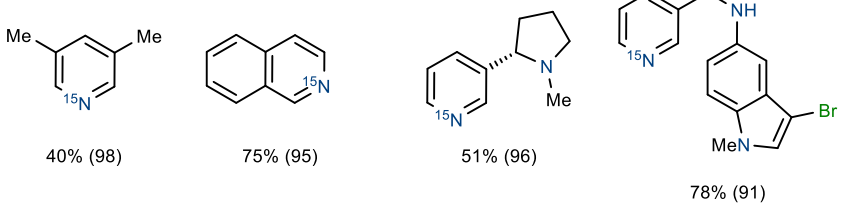
Partial Substrate Scope:



Unsuccessful substrates:



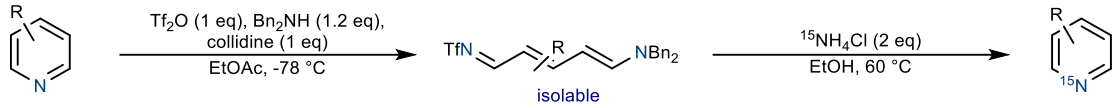


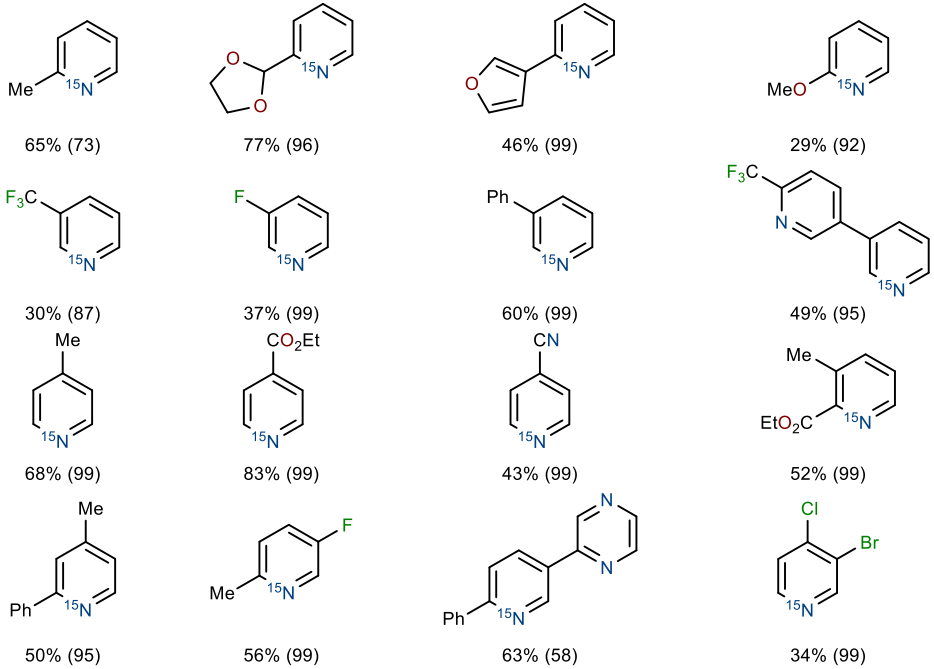


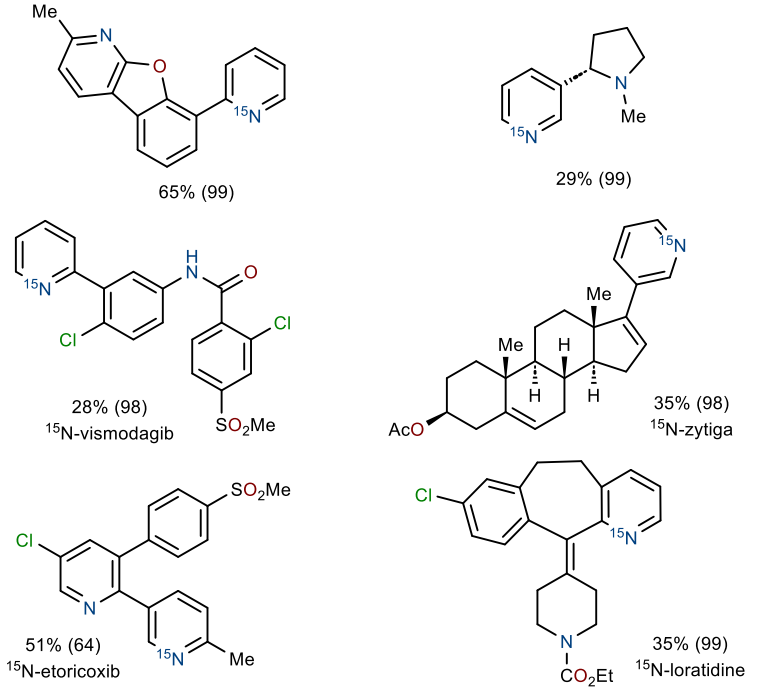
Smith, J. *J. Am. Chem. Soc.* **2024**, *146(5)*, 2939-2943. https://doi.org/10.1021/jacs.3c11618

^{15}N Incorporation into Heterocycles

Synthesis of ^{15}N Pyridines using Zincke Intermediates

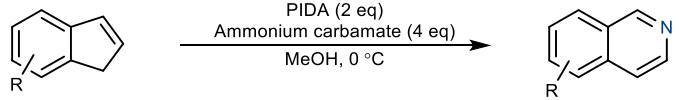




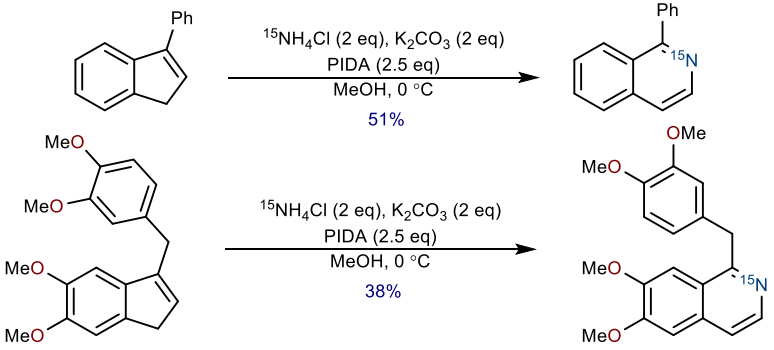


McNally, A. *J. Am. Chem. Soc.* **2024**, *146(5)*, 2944-2949. https://doi.org/10.1021/jacs.3c12445

Indenes to Isoquinolines by Skeletal Editing



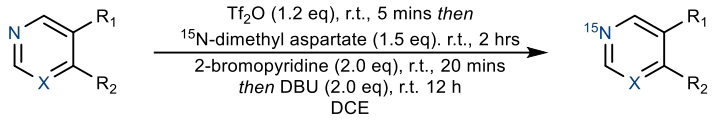
- Scope of ^{14}N insertion is pretty good, but ^{15}N only has the two examples shown to the right

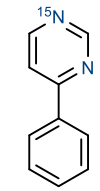


Morandi, B. *Chem . Sci.* **2023**, *14(11)*, 2954-2959. https://10.1039/D2SC06952K

^{15}N Incorporation into Heterocycles

^{14}N to ^{15}N Exchange by Skeletal Editing

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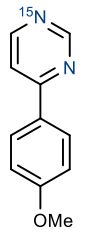
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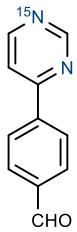
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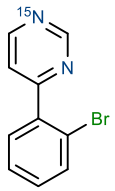
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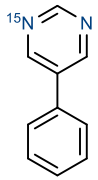
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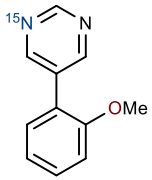
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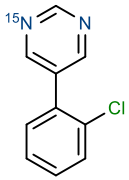
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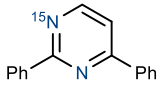
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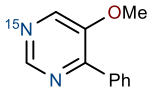
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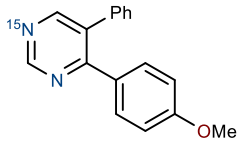
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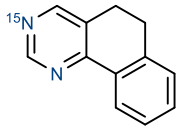
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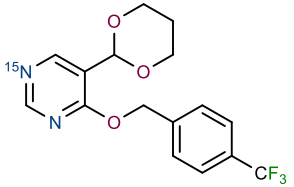
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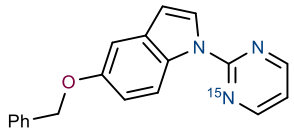
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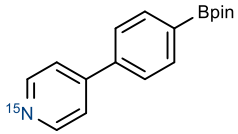
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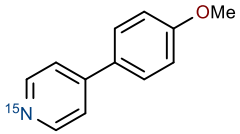
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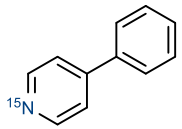
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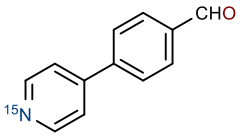
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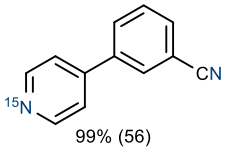
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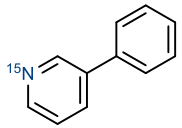
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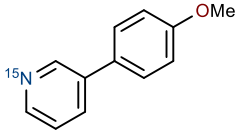
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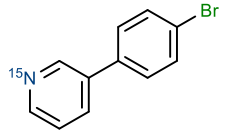
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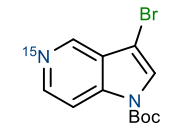
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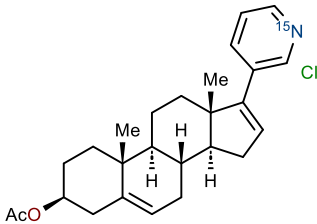
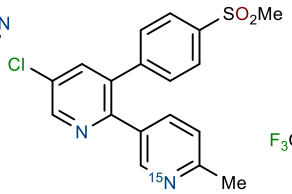
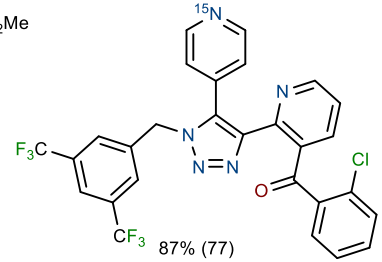

87% (80)
^{15}N-zytiga


83% (16)
^{15}N-etoricoxib


87% (77)
^{15}N-trapipitant

Sarpong, R.. *J. Am. Chem. Soc.* **2024**, *146(5)*, 2950-2958. https://10.1039/D2SC06952K