

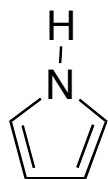
## ***Chapter 44 — Aromatic heterocycles: synthesis***

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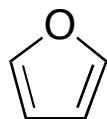
- Making pyrroles, furans, thiophenes by condensation (1185–1191)
- Pyrazoles and pyridazines from hydrazine (1195–1198)
- Synthesis of a complex drug: Viagra (1196–1198)
- Cycloadditions for heterocycle synthesis: triazoles and tetrazoles (1202–1203)

# Heterocycles from the 3 major synthetic approaches

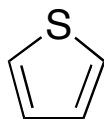
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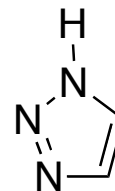
pyrroles



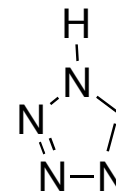
furans



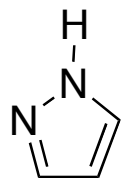
thiophenes



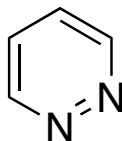
1,2,3-triazoles



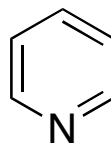
tetrazoles



pyrazoles



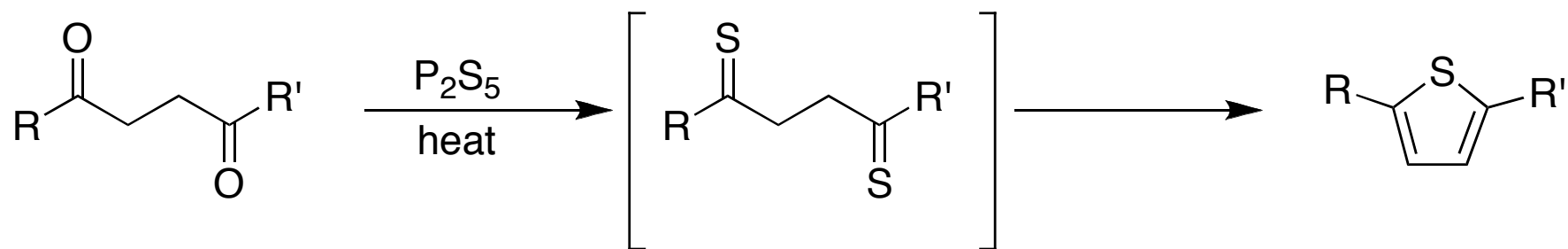
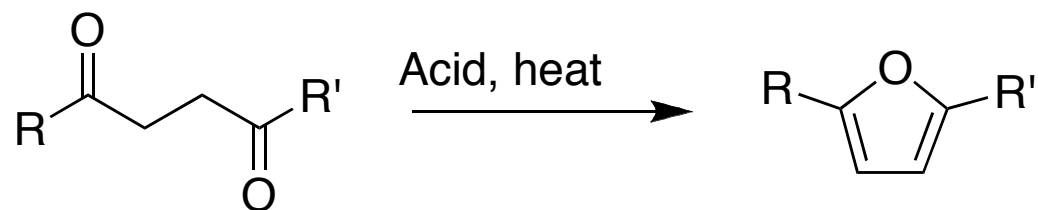
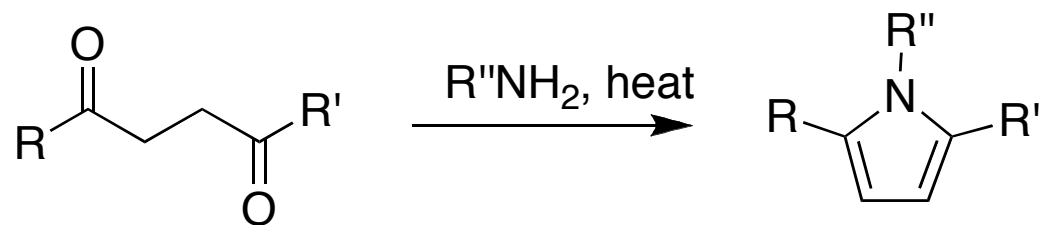
pyridazines



pyridines

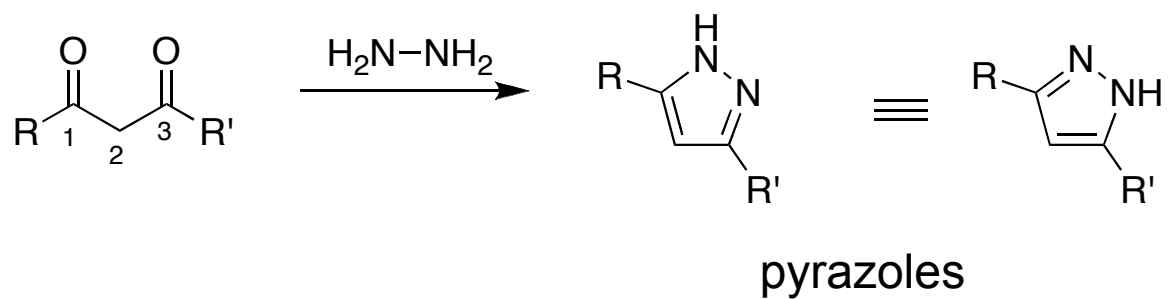
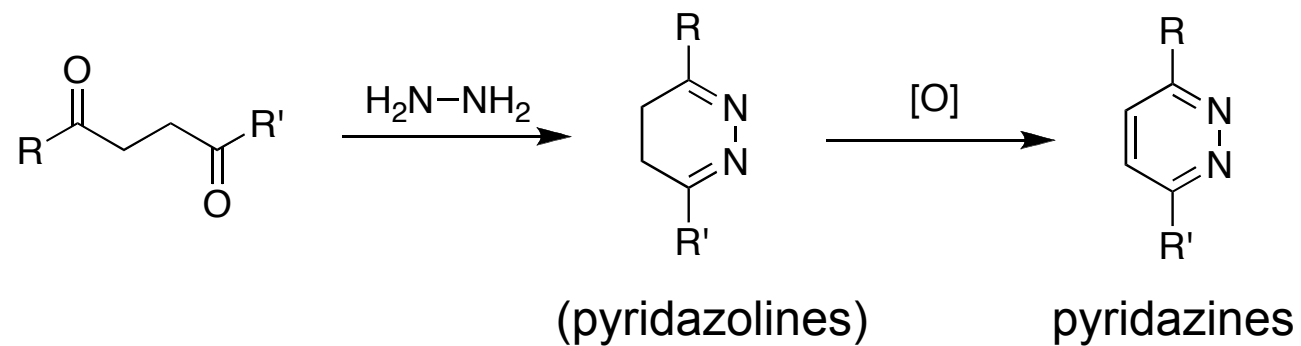
## Heterocycles from condensations of 1,4 dicarbonyls

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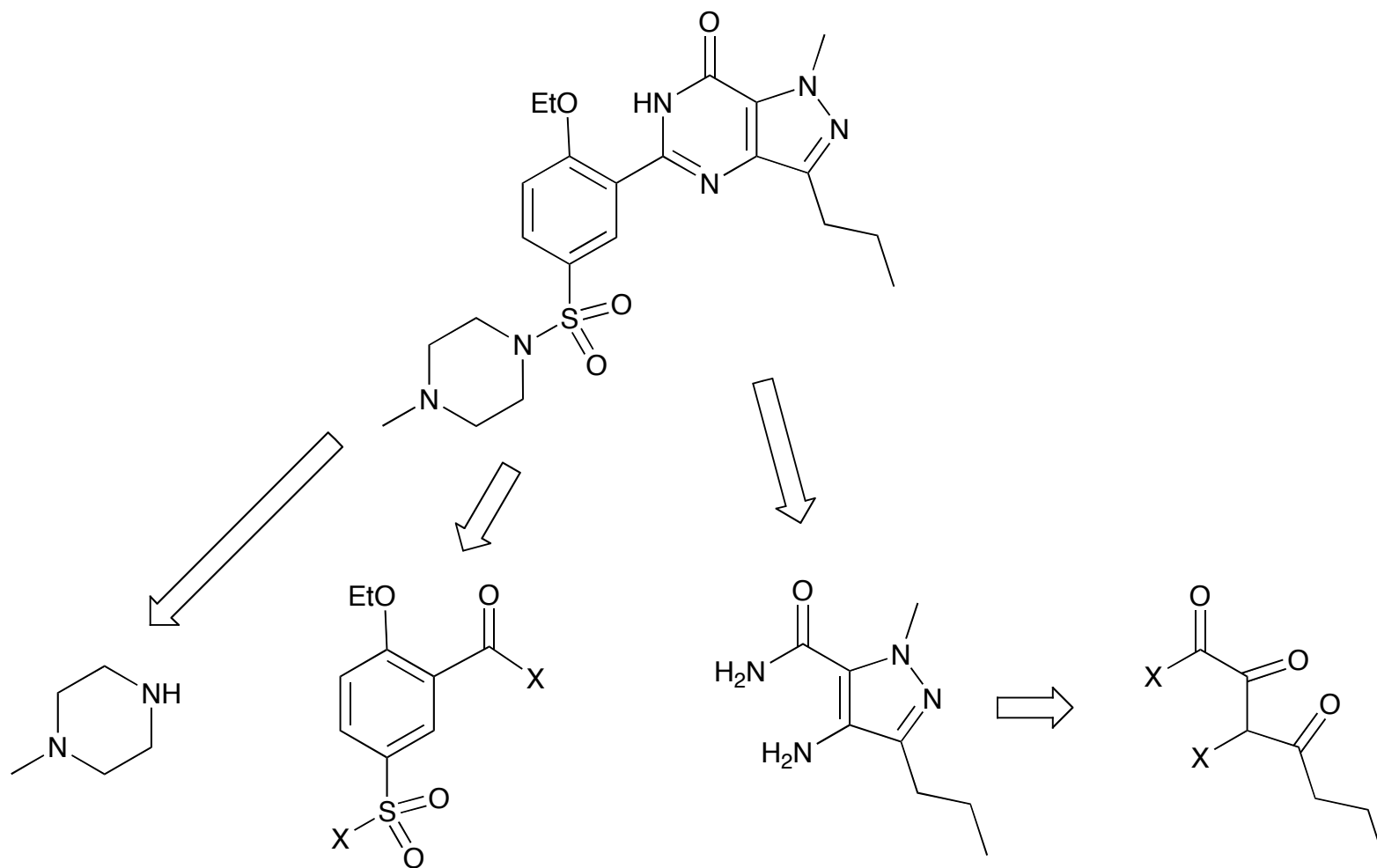


## Hydrazine is a double nucleophile

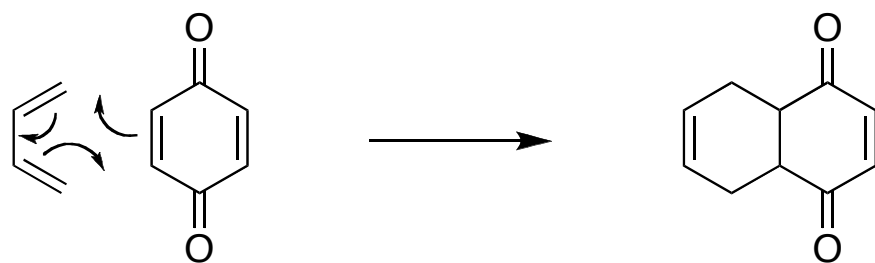
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# Easy disconnections for a complex drug synthesis

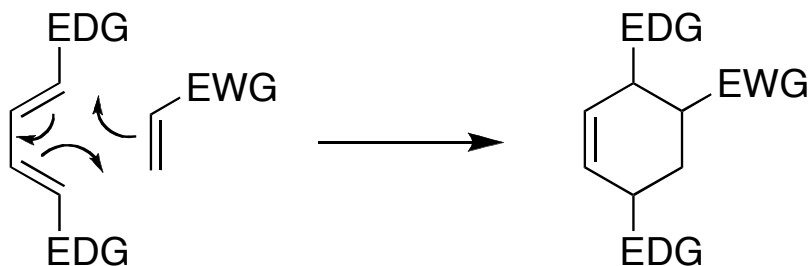


## 4 + 2 cycloadditions (a la Diels-Alder)



Diene      Dienophile

$4 \pi e^-$        $2 \pi e^-$



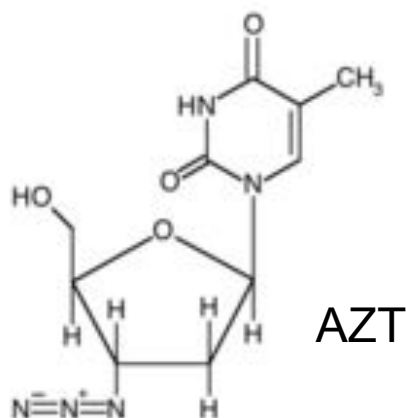
Otto Diels and Kurt Alder "Syntheses in the hydroaromatic series" *Justus Liebigs Annalen der Chemie* **1928**, 460, 98.

*"Wir behalten uns die Anwendung der von uns gefundenen Reaktionene zur Lösung derartiger Probleme ausdrücklich vor."*

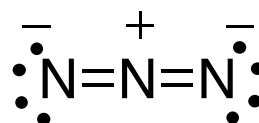
**"We reserve for ourselves explicitly the future study and use of the reaction we've discovered."**

## The Azide functional group

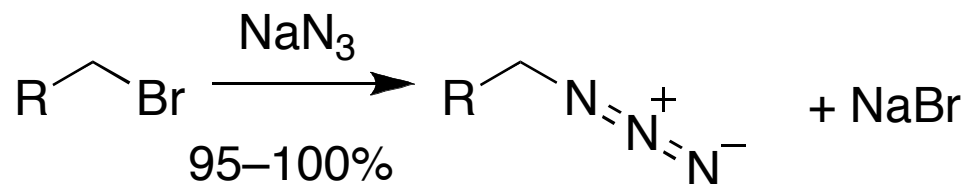
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Sodium azide = Na<sup>+</sup> N<sub>3</sub><sup>-</sup>



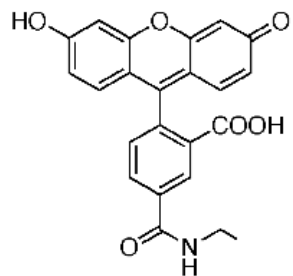
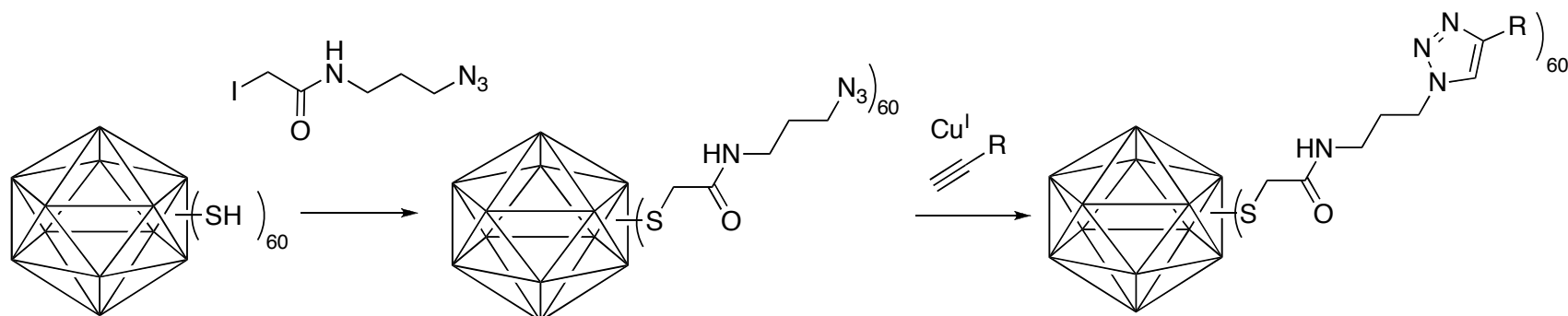
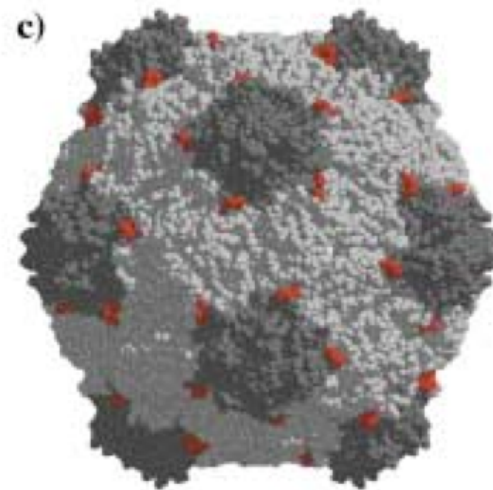
Azide anion (N<sub>3</sub><sup>-</sup>) is a potent nucleophile (one of the most reliable in organic synthesis)



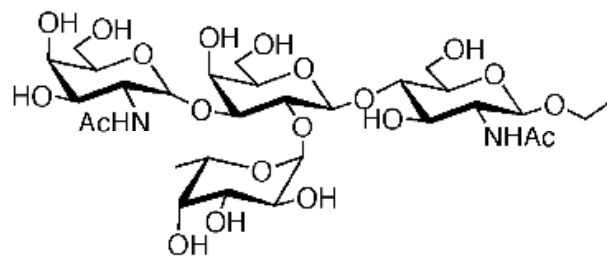
# Azide-acetylene cycloadditions create triazole biochemical linkers

A viral protein shell can be linked to almost any chemical entity using azide-alkyne cycloadditions

*All biochemical functional groups remain untouched!*



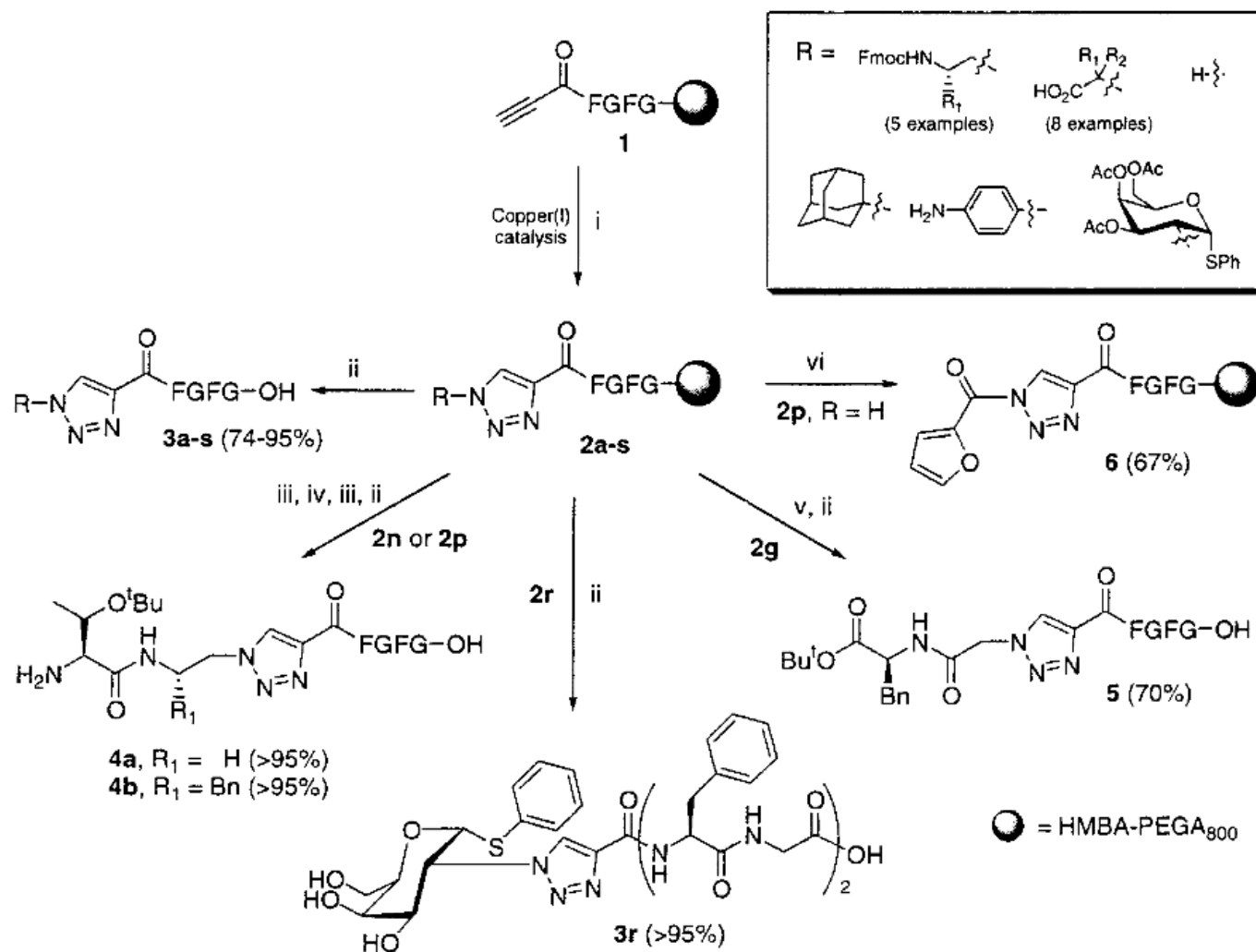
fluorescent dyes



complex carbohydrates



# More triazole biochemical linker examples



<sup>a</sup> Reported purities (xx%) are from analytical HPLC traces (215 nm), and conversions were in all cases quantitative. (i) R-N<sub>3</sub>, DIPEA, CuI; (ii) 0.1 M NaOH (aq); (iii) 20% piperidine/DMF; (iv) Fmoc-Thr(<sup>t</sup>Bu)-OPfp, Dhbt-OH; (v) H-Phe-O<sup>t</sup>Bu-HCl, PyAOP, HOAt, DIPEA; (vi) 2-furoyl chloride, DIPEA.

## Azide-nitrile 4+2 cycloadditions make tetrazoles

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