The assembly of fused pyridazines *via* one-pot sequence IEDDA reaction, scope and limitations

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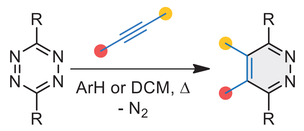
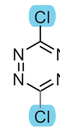
Background and aim of the project

- 1,2,4,5-tetrazines are well known electron deficient dienes in IEDDA reactions, giving highly functionalized pyridazines

The first experimental demonstration of the inverse electron demand Diels-Alder (IEDDA) reaction
[CARBONI & LINDSEY, *JACS*, 1959]



COMMONLY
R = H, Alk, Ar, Het
TOTAL SYNTHESES
R = CO_2Me
SOLID PHASE REACTIONS
R = SMe

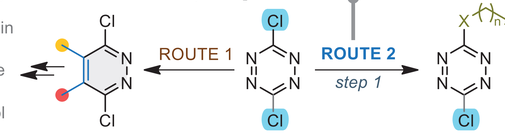


→ offers more synthetic flexiblity
→ commercially available substrate

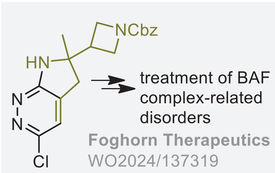
[SPAREY & HARRISON, *TETRAHEDRON LETT.*, 1998]

THIS WORK: ● optimization ● substrate scope ● scaling-up

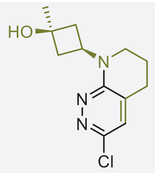
→ numerous precendents in research papers
→ more or less clear range of applicable alkynes
→ recognized practical tool



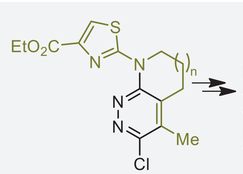
→ no research reports
→ elegant access to condensed pyridazine carcasses
→ **much attention from big pharma**



treatment of BAF complex-related disorders
Foghorn Therapeutics
WO2024/137319



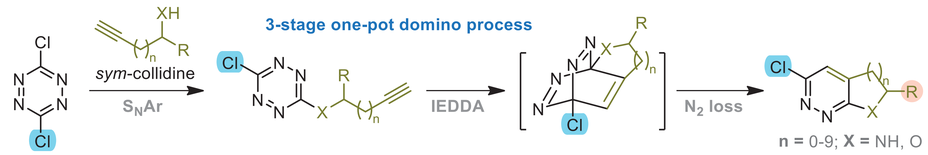
inhibitors of nod-like receptor protein 3
MERCK
WO2024/137319



Bcl-xL inhibitor antibody-drug conjugates
NOVARTIS
WO2023/225320

Outline of the synthetic results

Principal synthetic scheme used in the research



→ **NO** intermediate isolation
→ **NO** chromatography purification
→ post modifications

- **the elaborated method avoids drawbacks of protocols available in patent literature**, namely a low yield and chromatographic purification of the final product, and stepwise workflow with the isolation of the intermediate (which can spontaneously release nitrogen followed by polymerization, making it difficult to scale up the reaction)
- **in the case of but-3-yn-1-ol the formation of the target products occurs almost instantly, with vigorous nitrogen release;** therefore, the former was added over the course of an hour at 0°C
- **starting from the pyran ring, room temperature was insufficient,** so the solvent was replaced with the higher-boiling 1,2-DCE
- **the base – 2,4,6-trimethylpyridine,** 1.0 equiv for O-nucleophiles and 2.0 equiv for N-nucleophiles (used as salts)

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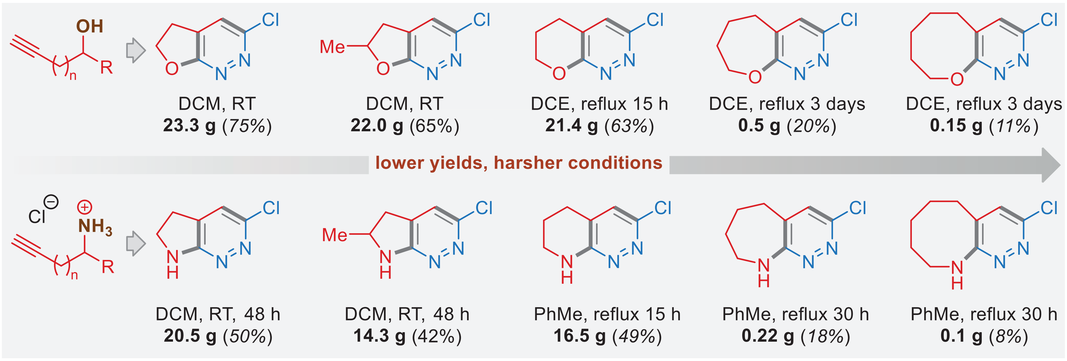
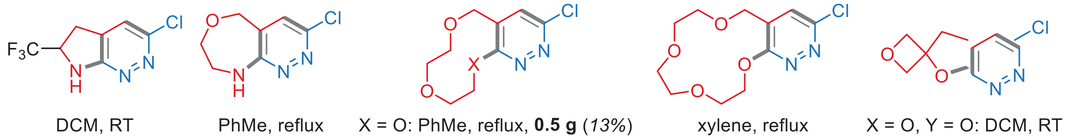
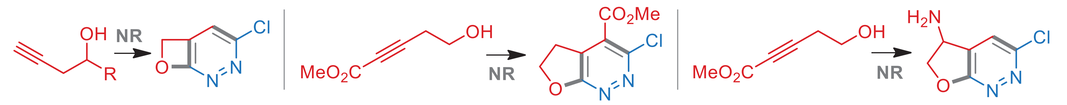
Scope, yields, and scales for simple alcohols and amines



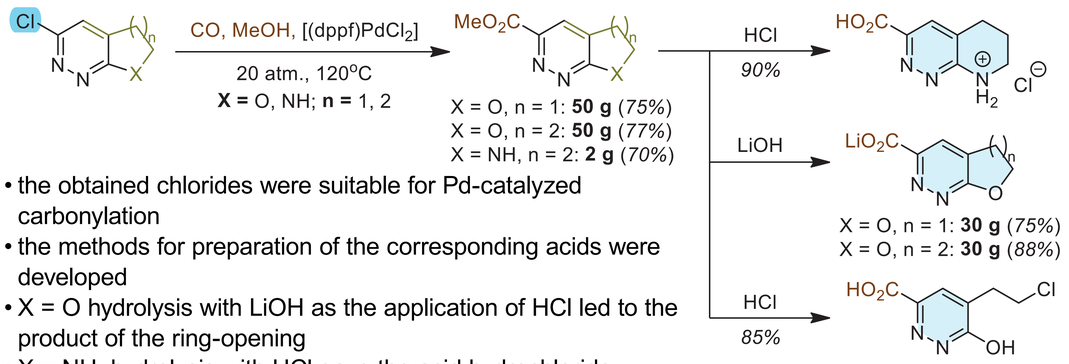
Further exploration of the reaction boundaries



CURRENT LIMITATIONS OF THE METHOD



Post-synthetic modifications



- the obtained chlorides were suitable for Pd-catalyzed carbonylation
- the methods for preparation of the corresponding acids were developed
- X = O hydrolysis with LiOH as the application of HCl led to the product of the ring-opening
- X = NH hydrolysis with HCl gave the acid hydrochloride