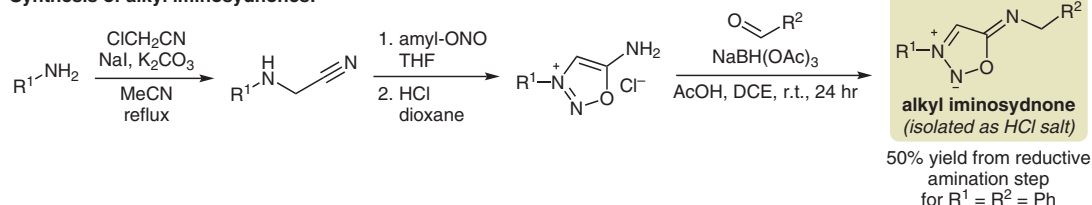


M. RIBÉRAUD, K. PORTE, A. CHEVALIER, L. MADEGARD, A. RACHET, A. DELAUNAY-MOISAN, F. VINCHON, P. THUÉRY, G. CHIAPPETTA, P. A. CHAMPAGNE, G. PIETERS, D. AUDISIO, F. TARAN\* (UNIVERSITÉ PARIS SACLAY, GIF-SUR-YVETTE, FRANCE)

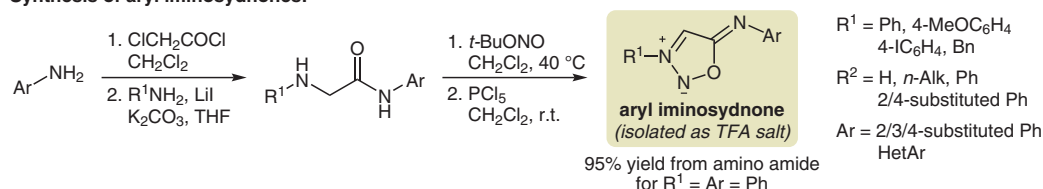
Fast and Bioorthogonal Release of Isocyanates in Living Cells from Iminosydones and Cycloalkynes  
*J. Am. Chem. Soc.* **2023**, *145*, 2219–2229, DOI: 10.1021/jacs.2c09865.

## Bioorthogonal “Click-and-Release” of Iminosydones to Give Water-Stable Isocyanates

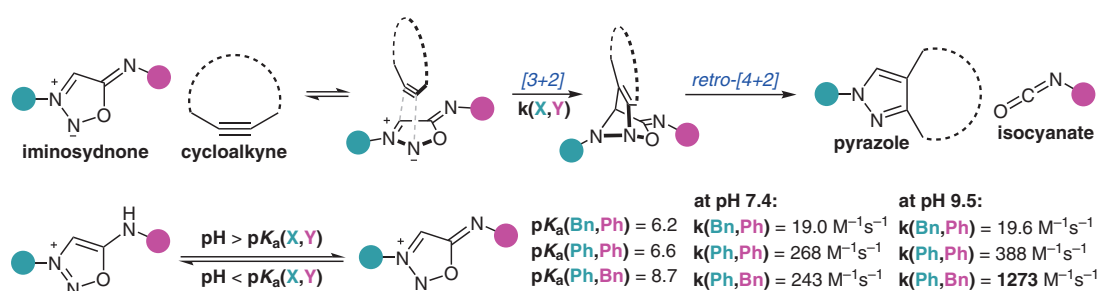
### Synthesis of alkyl iminosydones:



### Synthesis of aryl iminosydones:



### Strain-promoted iminosydnone–cycloalkyne cycloaddition:



**Significance:** Bioorthogonal click-and-release is one strategy for targeted drug delivery. For this method to be effective, high reaction rates are required. Taran and co-workers demonstrate that alkyl and aryl iminosydones (referring to the substituent on the exocyclic imine nitrogen atom), which were never previously synthesized, have high rates ( $>100 \text{ M}^{-1}\text{s}^{-1}$ ) of click-and-release with cycloalkynes. This releases alkyl or aryl isocyanates respectively, which can subsequently react with intracellular thiol nucleophiles. The initial [3+2] cycloaddition only occurs in the neutral 1,3-dipole form of the iminosydnone. With  $pK_a$  values near neutrality ( $pK_a[\text{alkyl}] \sim 8.5$ ,  $pK_a[\text{aryl}] \sim 6.5$ ) these iminosydones offer an inherent mechanism of rate control based on  $pK_a$  vs intracellular pH.

**Comment:** Prior to this work, only iminosydones with electron-withdrawing substituents on the exocyclic nitrogen atom had been investigated. These have low rates of addition to cycloalkynes. Furthermore, upon click-and-release, the resulting isocyanate would be too electrophilic to be captured by an endogenous nucleophile before undergoing hydrolysis. By developing syntheses of alkyl and aryl iminosydones, Taran and co-workers have introduced a method for the intracellular delivery of isocyanates that can be captured by biochemical nucleophiles of interest, such as cysteine residues in glutathione or human serum albumin.

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