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 Iminosydnones and Cycloalkynes
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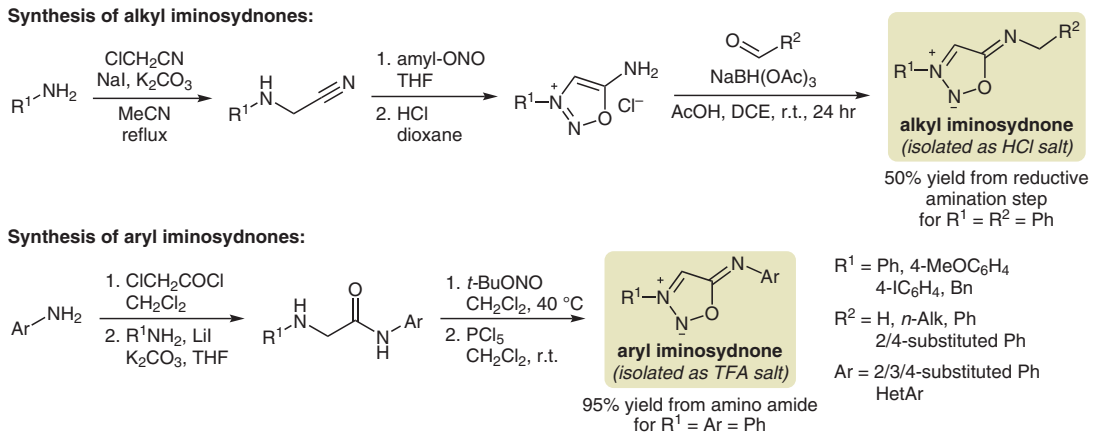
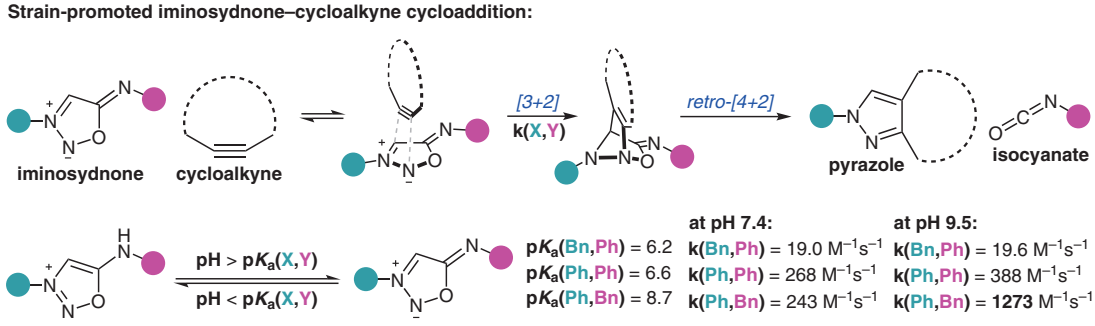
Bioorthogonal "Click-and-Release" of Iminosydnones to Give Water-Stable Isocyanates





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 iminosydnones (referring to the substituent on the exocyclic imine nitrogen atom), which were never previously synthesized, have high rates (>100 $M^{-1}s^{-1}$) 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[alkyl] ~ 8.5, pK_a[aryl] ~ 6.5) these iminosydnones offer an inherent mechanism of rate control based on pK_a vs intracellular pH.

Comment: Prior to this work, only iminosydnones 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 iminosydnones, 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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Category
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Key words
bioorthogonal click-and-release
drug delivery
iminosydnones
isocyanates

Synfact of the Month