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Synthesis of Spirobicyclic Pyrazoles by Intramolecular Dipolar Cycloadditions/[1s, 5s] Sigmatropic Rearrangements

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Abstract

Formation of fused pyrazoles via intramolecular 1,3-dipolar cycloadditions of diazo intermediates with pendant alkynes are described. A subsequent thermal [1s, 5s] sigmatropic shift of these pyrazole systems resulted in a ring contraction to form spirocyclic pyrazoles. The limitations of this rearrangement were explored by chang-ing the substituents on the non-migrating aromatic ring and by using substrates lacking an aromatic linkage to the propargyl group.

Keywords

dipolar cycloaddition; spirocycles; pyrazole; sigmatropic rearrangement

Pyrazoles are common heterocyclic cores in many approved drugs and pharmaceutical lead compounds.[1–3] The majority of these heterocycles are made by one of two methods: 1) the Knorr condensation of a hydrazine with a 1,3-diketone or 2) dipolarcycloaddition (DPC) of a diazoalkanes with alkynes.[4–7] Pyrazoles resulting from the latter method with two carbon substituents on an sp^3-hybridized carbon adjacent to nitrogen can undergo migration to form either 1*H*-or 4*H*-pyrazoles. This process was first noted by van Alphen and the mechanism later explored by Hüttel (Figure 1).[8–15] The most heavily explored variant involves cyclic acceptor-substituted diazo compounds, which predictably undergo migration of the acyl group to the neighboring nitrogen.[16–19] Recently, focus has turned to similar migrations of alkyl groups on bicyclic or fused pyrazole systems.[17,20–25] Padwa showed that spirocyclic pyrazoles could be formed, and then a thermal rearrangement would cause a ring expansion to a fused system.[26] Valdés has recently explored the migration process in pyrazoles not fused to another ring.[20,27] Methods to synthesize spiropyrazoles remain limited, with many requiring the use of transition metal catalysts.[28–32] We discovered an approach to this core structure involving ring *contraction* following an intramolecular DPC reaction. During the final stages of our work, a similar sequence was reported by Xu using an alternative precursor to the requisite diazo substrates.[21]

During investigations into C–H insertion reactions of donor/donor metal carbenes, we noticed a competing pathway of an intramolecular 1,3-dipolar cycloaddition of the diazo

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intermediate in the absence of a rhodium catalyst (Scheme 1).[33] It was previously known that diazo intermediates could be trapped in the presence of unsaturated alkenes and alkynes.[34–38] Following our standard procedure, hydrazone **2a** was made by condensing hydrazine onto the corresponding ketone. Once the hydrazone was oxidized by manganese dioxide, the resulting diazo compound (**2a'**) reacted immediately with the propargylic ether (Scheme 1).[39–41] The new cycloaddition product **3a** was isolated and the structure was determined by NMR spectroscopy. Compound **3a** then underwent partial conversion to **4a** during recrystallization at ambient temperature.[8–11]

Computed transition states for the various migration pathways are consistent with the observed ring contraction. In previous studies, similar [1s, 5s] sigmatropic shifts proceed to give products of ring expansion.[42] The rearrangement of **3a** favors formation of the spirobicyclic pyrazole **4a** over phenyl migration to either nitrogen or carbon (**33** and **34**; Figure 2). Results of density functional theory calculations (M062X/6–31+G(d,p)[43]) reveal that after the dipolar cycloaddition has taken place, **3a** forms spirocycle **4a** with an energy penalty of only 25.3 kcal/mol (TSBE) compared to the barriers of 27.8 and 31.8 kcal/mol for TSBC and TSBD, respectively. This preference is likely a result of orbital alignment leading to the newly formed σ-bond, this alignment is poorest at TSBD where the phenyl substituent migrates towards the nitrogen atom; in this system the phenyl group moves into the plane of the heterocycle rather than migrating over it[44].

While the oxidation and DPC reactions occur readily at room temperature, various conditions were explored for the subsequent rearrangement. Heating to 80 °C for 12–18h provided full conversion. The temperature and time required were insensitive to the polarity of the solvent, including protic solvents. Acetonitrile was optimal for solubility and appropriate reflux temperature. These optimized conditions were applied to a variety of substrates (Figure 3). Changing $\mathbf{R^2}$ from a phenyl to methyl (**4e** and **4h**, Figure 3) produced only small changes in yield relative to **4d** and **4g**, suggesting that this substituent has little impact on the migration step. When a terminal alkyne was used ($\mathbf{R^2}$**=H**), the rearrangement product **4c** was not stable to purification. When $\mathbf{R^1}$ was changed from H to CN, the rearrangement proceeded smoothly and the product (**4f**) was isolated in 88% yield. Alternatively, when $\mathbf{R^1}$ was changed to OCH_3, the terminal alkyne ($\mathbf{R^2}$**=H**) did not survive the harsher conditions needed for hydrazone formation. Changing the heteroatom from O to NTs (**3a** to **3j**) did not negatively impact the DPC or rearrangement reactions.

Substrates that would produce heterocycles lacking a fused benzene ring were also explored. Although the oxidation and DPC both proceed smoothly, producing **16** in 71% yield (Figure 4) as a 91:9 mixture of diastereomers, the rearrangement required much higher temperature when compared to a similar fused substrate (**3b**). Upon heating to reflux in acetonitrile, only alcohol **19**[45] was isolated, which is attributed to the expected rearrangement to **17** followed by acid-catalyzed hydrolysis *via* oxocarbenium ion **18**.

Two nitrogen-tethered substrates lacking a fused benzene ring were also investigated (Figure 5). Upon oxidation, sulfonamide **21** underwent facile dipolar cycloaddition, producing **22** in 80% yield. As with the oxygen-tethered substrate **15**, the subsequent rearrangement proved more difficult. Rearrangement product **23** was isolated in only 17% yield from a complex

mixture of unidentifiable by-products after employing microwave heating in acetonitrile to 150 °C. The addition of various Lewis acids, including $MgBr_2$, $Sc(OTf)_3$, BF_3•OEt and PPTS failed to facilitate the rearrangement at a lower temperature as did the use of several other solvents (methanol, dichloroethane, HFIP and toluene). Substrate **25** was prepared in order to examine the influence of the stereogenic center on the dipolar cycloaddition/ rearrangement sequence. As with previous substrates, the cycloaddition occurred readily upon oxidation of hydrazone **25** with modest diastereoselectivity favoring cis isomer **26a** relative to trans isomer **26b**. Although **26a** is formed via a chair like transition state with the methyl group in an axial position, this transition state structure is predicted to be favored by 1 kcal/mol, since a 1,2 diequatorial interaction of the protecting group and the methyl is avoided.[43] Isomers **26a** and **26b** performed differently when heated. Cis isomer **26a** did not undergo rearrangement after prolonged heating at 210 °C, whereas trans isomer **26b** behaves similarly to **22**, eventually producing **27** in modest yield. While the computed barrier for rearrangement of **26a** is higher than that for rearrangement of **26b**, these differ by <1 kcal/mol at the level of theory used,[43] indicating that either a different method is needed to rationalize the experimental result or the experimental situation is more complicate than expected (e.g., explicit solvent effects are important).

We have discovered a tandem DPC/rearrangement sequence that produces spirocyclic pyrazoles from hydrazone precursors. Although three different rearrangement pathways have been observed with acyclic pyrazoles, we observe only one pathway for substrates with benzene-fused tethers leading to spirocyclic products, which aligns well with computed transition state energies. Substrates derived from benzophenones with a variety of substituents perform well with either oxygen or nitrogen linkages to the pendant alkyne. Substrates leading to spirocycles lacking a fused benzene ring undergo smooth oxidation and dipolar cycloaddition while exhibiting significantly higher barriers to rearrangement.

Experimental Section

Experimental procedures and compound characterization can be found in the Supporting Information (PDF). ^1H and ^{13}C NMR spectra for all new compounds (PDF). X-ray data for compound 4a (CIF) and 26a (CIF).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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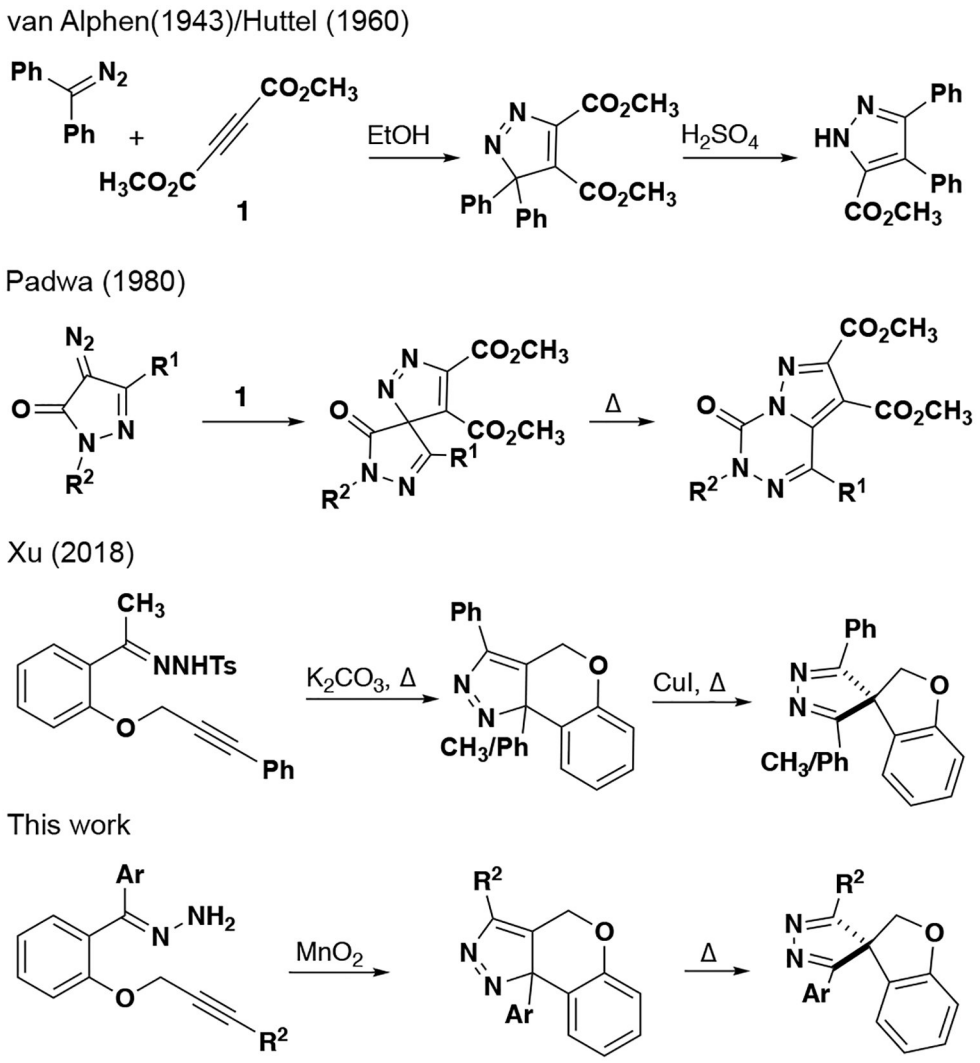


Figure 1.
Dipolar cycloaddition rearrangement reactions.

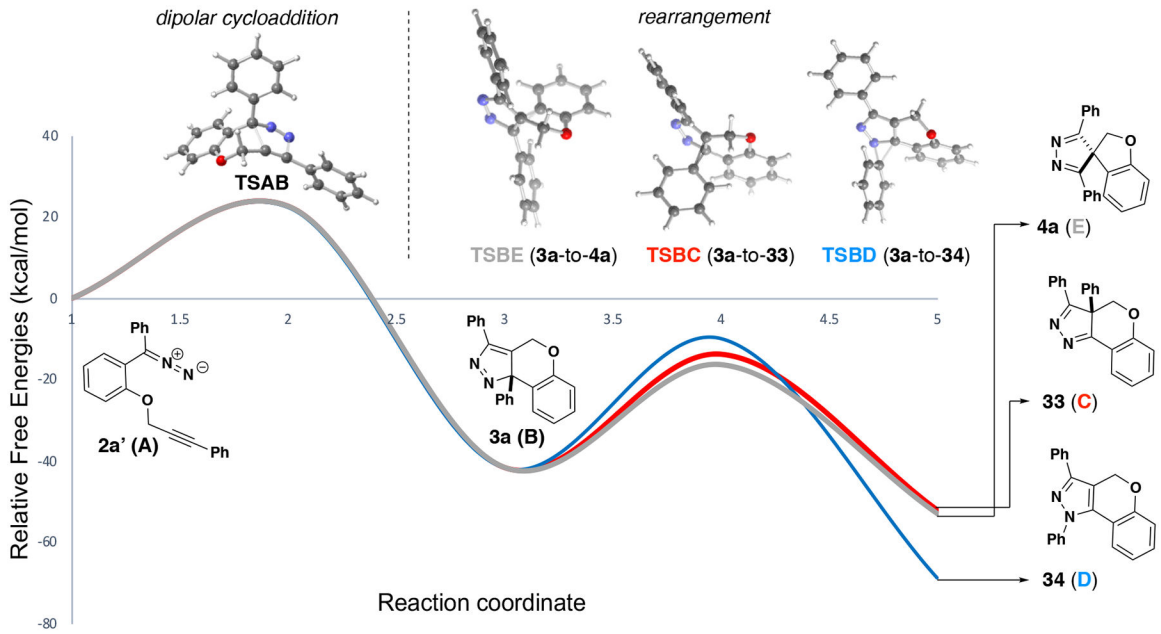
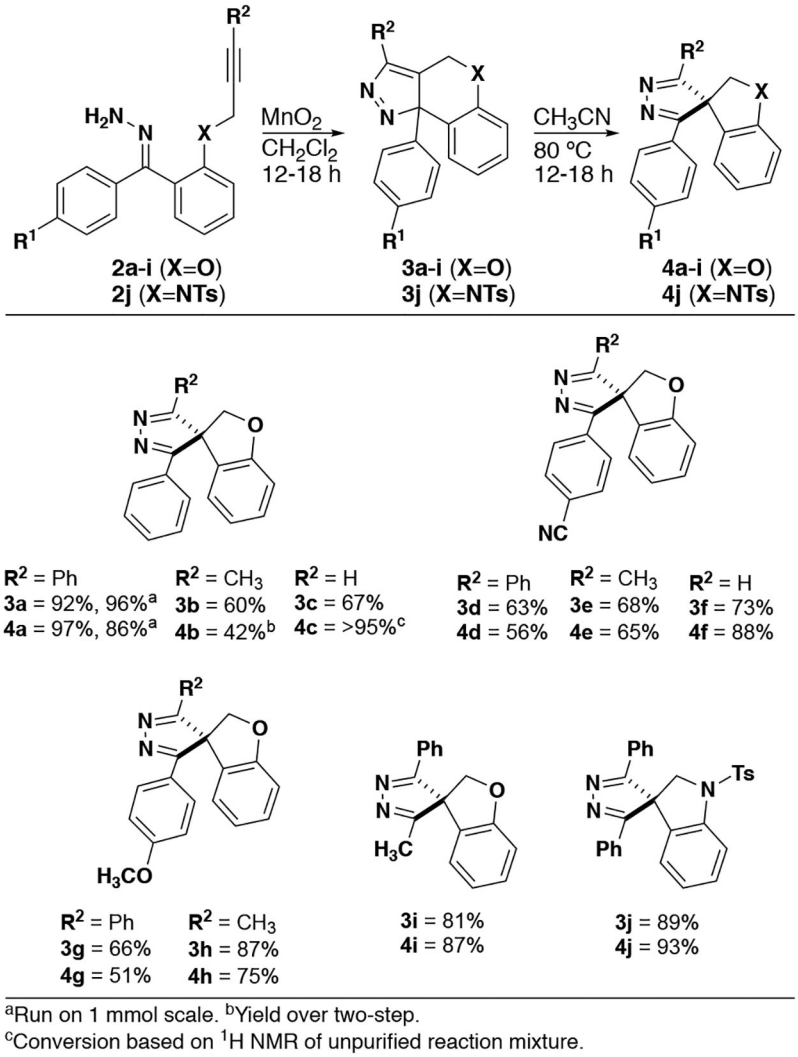


Figure 2.

Predicted (M062X/6–31+G(d,p)) reaction profile for compound **2a'**, based on free energies of minima and transition state structures.



[a]Run on 1 mmol scale. [b]Yield over two-step.
[c]Conversion based on ^{1}H NMR of unpurified reaction mixture.

Figure 3.
Benzophenone derived spiropyrazoles.

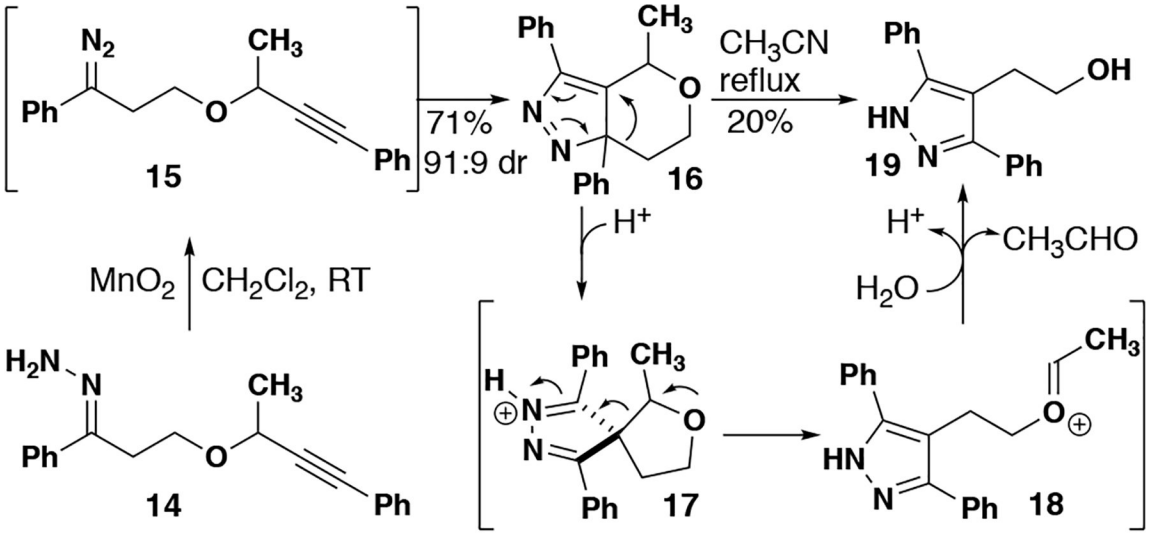


Figure 4.

Oxygen tethered substrate **14** leading to alcohol **19** by rearrangement and hydrolysis after the DPC reaction.

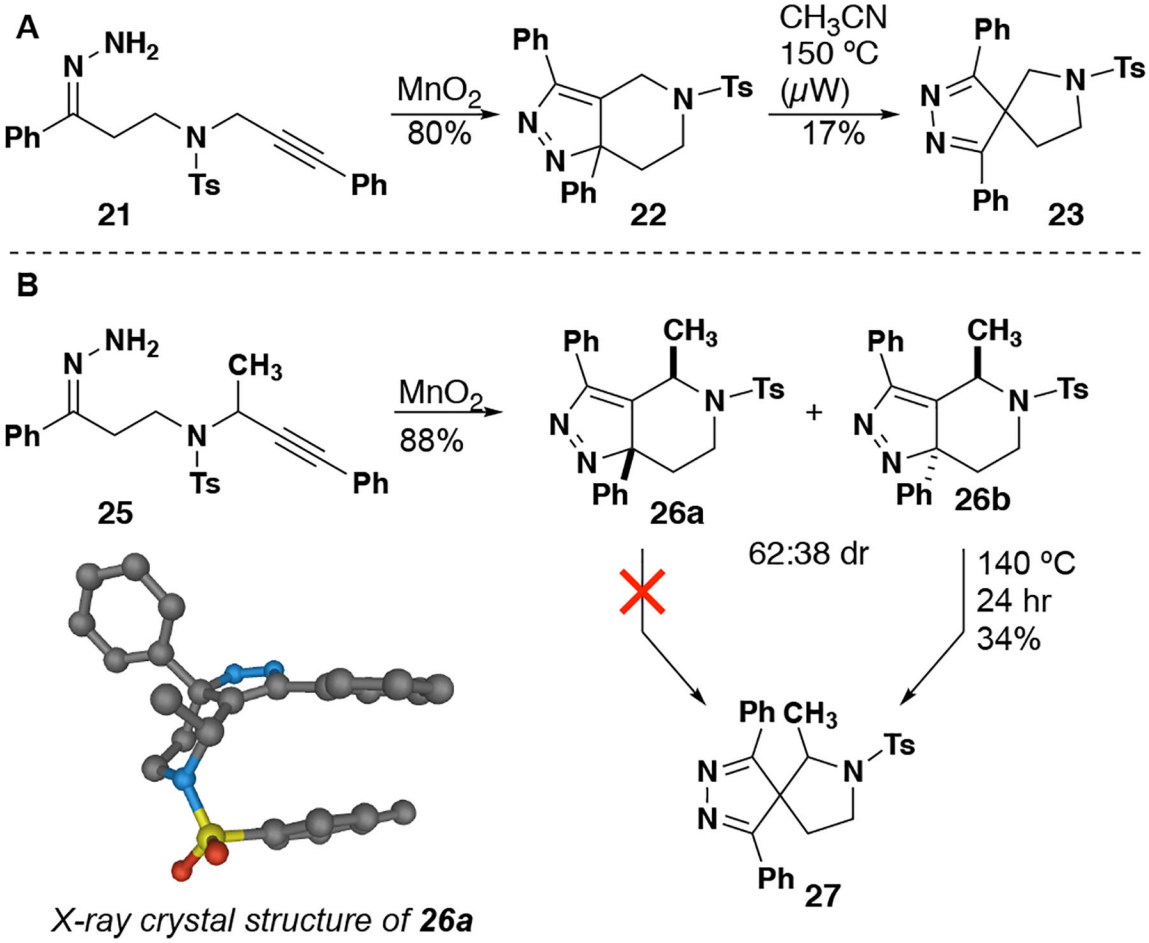
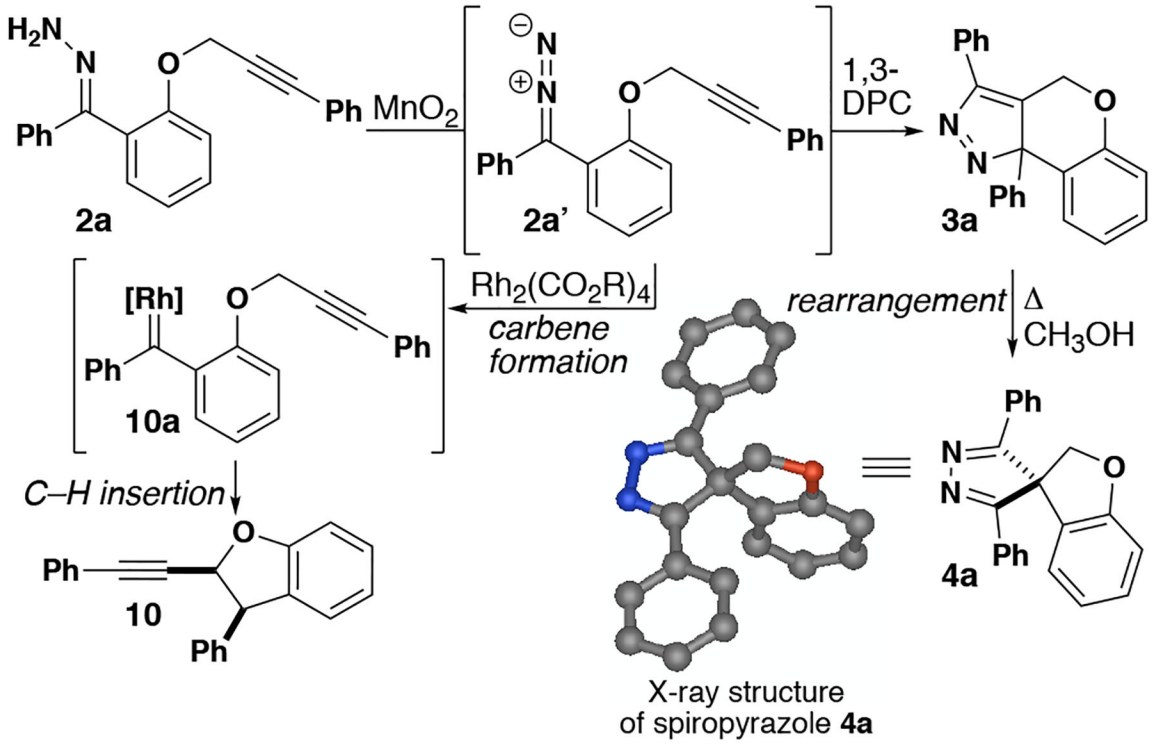


Figure 5.
Nitrogen-tethered substrates leading to spirocyclic pyrrolidines.



Scheme 1.
Reactions of propargylic hydrazones.