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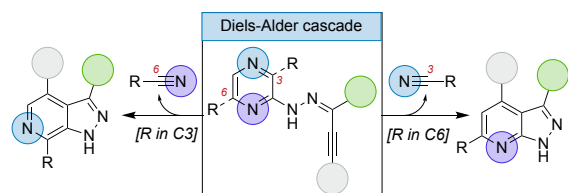
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Divergent Synthesis of 6- or 7-Aza-Indazoles Via Intramolecular Diels-Alder Cascade of Pyrazines

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ABSTRACT: Pyrazines are reactive 4π partners in intermolecular Diels Alder cycloaddition with exceptionally activated dienophiles or in intermolecular version at elevated temperatures. Herein it is shown that an intramolecular cascade could occur even at room temperature, delivering a collection of 6- or 7-aza-indazoles. An interesting substituent effect of the cycloaddition precursor on the product distribution was uncovered and *in situ* NMR studies were conducted to gain insights into this unexpected selectivity.

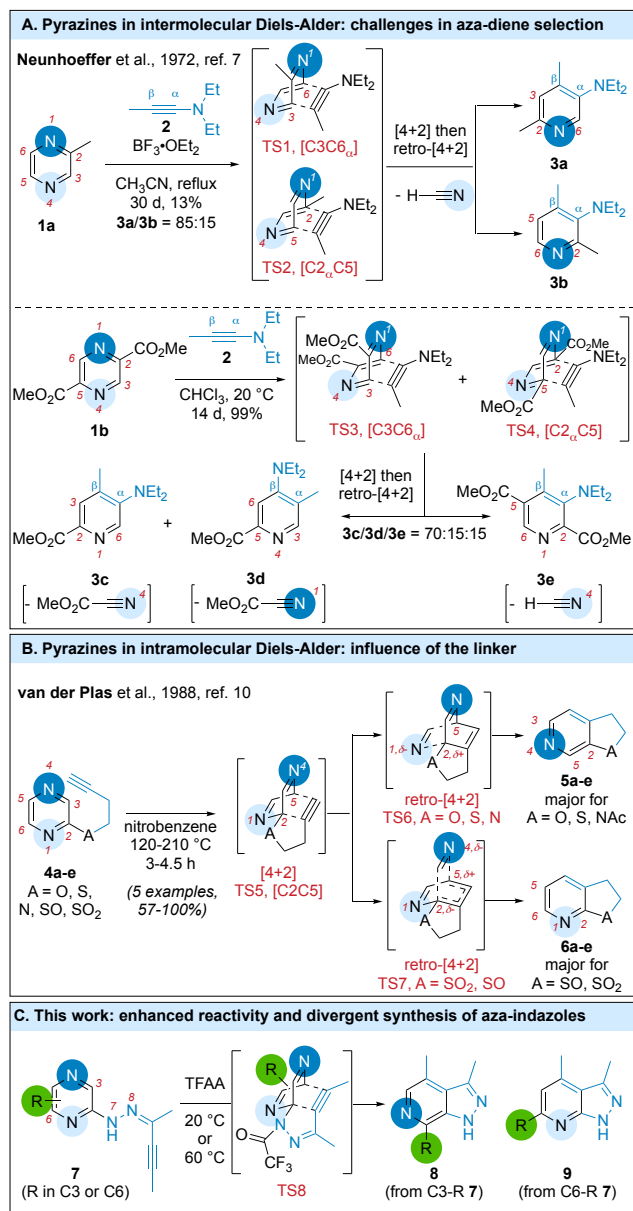
Due to their inherent electron-deficiency, pyrazines can engage in inverse-electron demand Diels-Alder cycloadditions with electron-rich dienophiles, leading to valuable N-heterocycles after a spontaneous retro-Diels-Alder step.¹⁻⁵ Recent theoretical studies highlighted the crucial role of the two nitrogen atoms (N1 and N4) which contributed to the overall reactivity by lowering the distortion energy and increasing the orbital interaction energy required to reach the transition state of the initial [4+2] cycloaddition.⁶ In a seminal report by Neunhoeffer, the intermolecular cycloaddition of 2-methylpyrazine **1a** with ynamine **2**, an electron-rich dienophile, led to a very low yield of 3-aminopyridines **3a** and **3b** in a 85:15 ratio, after a month at reflux in acetonitrile (Scheme 1, A).⁷ Two transition states of the initial [4+2] could be invoked to rationalize this product distribution: **TS1** which engages the C3C6 portion of **1a** and **TS2** which engages the C2C5 portion. In addition to this site-selectivity of pyrazine **1a**, the unsymmetrical dienophile **2** also presents some α/β -selectivity challenges. Increased reactivity was observed with pyrazine **1b** substituted by two esters, as a Diels-Alder cascade with **2** was observed at room temperature, without boron trifluoride. After two weeks, a quantitative yield of three pyridines, **3c**, **3d** and **3e**, was obtained in a 70:15:15 ratio. This product distribution can be attributed to the same classes of transition states, **TS3** and **TS4**, with two divergent retro-Diels-Alder pathways in the case of the former (elimination of 2 different methylcyanoformates).

Due to these multiple site-selectivities in the initial intermolecular [4+2] cycloaddition but also in the retro-[4+2] cycloaddition, only a handful of investigations have been reported.¹⁻⁷ In contrast, intramolecular versions have been more developed with insightful studies from van der Plas in the 1980s (Scheme 1, B).^{8,9} Pyrazines **4a-e** substituted in the C2-position by an ω -alkynyl side chain undergo a Diels-Alder cascade when heated

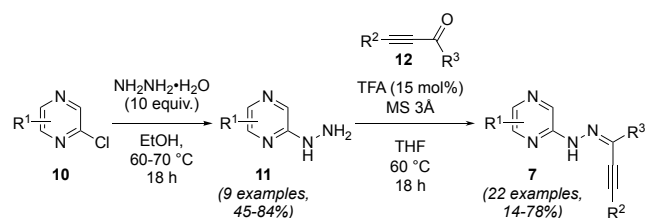
at 120-210 °C in nitrobenzene.¹⁰ *c*-Fused pyridines **5** or *b*-fused pyridines **6** are obtained as the major cycloadducts depending on the nature of the A group in the linker. Interestingly, a small but not negligible solvent effect was observed ($t_{1/2}$ in *p*-cymene 1.0, in *p*-bromotoluene 1.7 and in nitrobenzene 2.9), which led van der Plas to consider that the transition states of the retro-[4+2] might have some ionic character. It was therefore postulated that the nitrogen atom eliminated (N1, light blue) possesses a partial negative charge. As a consequence, substituents A able to stabilize a partial positive charge at C2, such as oxygen/sulfur atoms or N-acetyl, favor **TS6** and thus *c*-fused pyridines **5**. On the other hand, strongly electron-withdrawing substituents A, such as SO₂, favor **TS7** and thus the formation of *b*-fused pyridines **6**. Intriguingly, opposite trends have been reported by the same group when A is a methylene group or when the pyrazine is quaternarized by Meerwein reagent.¹¹ This brief literature overview demonstrates that pyrazine Diels-Alder cycloadditions present multiple challenges in terms of reactivity and selectivities, challenges that have not found a general solution yet.¹²

Inspired by our recent investigations on Diels-Alder cascade of pyrimidines,¹³⁻¹⁶ we report herein the straightforward synthesis of 6-aza-indazoles **8** or 7-aza-indazoles **9** as the major to exclusive cycloadducts via an intramolecular Diels-Alder cascade of pyrazine **7** (Scheme 1, C). Compared to the current state-of-the-art, this reaction sequence is characterized by mild reaction conditions and a predictable selectivity depending on the nature of the pyrazine's substitution. In addition, various substituents are tolerated, including halides, alkyls, fluoroalkyls, cycloalkyls, alkenyls, aryls, heteroaryls, alkoxy, protected alcohols and amines.

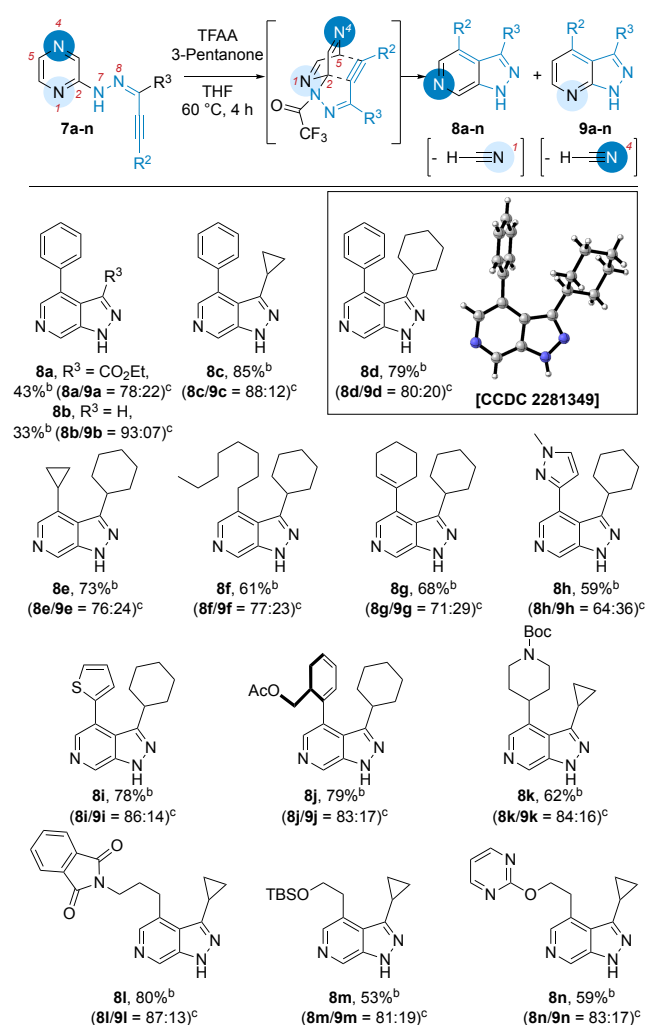
Scheme 1. Challenges of Pyrazines as dienophiles in Diels-Alder cycloaddition/retro-cycloaddition.



Scheme 2. Synthesis of Diels-Alder cascade precursors.



Scheme 3. Scope of Diels-Alder cascade of pyrazines **7**.^a



^a Reactions were performed using **7**, TFAA (1.5 equiv), 3-pentanone (3 equiv) under nitrogen in THF (0.5 M) at 60 °C for 4 h. ^b Isolated yield. ^c **8/9** ratio determined by ¹H NMR.

We then turned our attention to the reactivity of **7** in Diels-Alder cascades (Scheme 3). Based on our previous activation strategy for pyrimidines,^{13,14} we anticipated that acylation of the N7-atom from the hydrazone function with trifluoroacetic anhydride should trigger a conformational switch of the side chain, bringing the 2-azadiene (the C2C5 moiety of the pyrazine ring) in close proximity to the alkynyl dienophile, thus favoring the initial [4+2] cycloaddition. Indeed, upon treatment of **7a** by trifluoroacetic anhydride and 3-pentanone (acting as a trap for the HCN liberated during the retro-[4+2] step, leading to the corresponding cyanohydrin)^{17,18} in THF at 60 °C for 4 h, 6-aza-indazole **8a** and 7-aza-indazole **9a** were produced in a 78:22 ratio (after aqueous hydrolysis). These two heterocycles were easily separated by chromatography, and **8a** was isolated in a moderate 43%. The fact that **8a** is the major cycloadduct is consistent with previous studies from van der Plas⁸⁻¹⁰ and implies an initial [4+2] cycloaddition via **TS8**. This Diels-Alder cascade has a general character as R³ can be a hydrogen atom (**8b**, 33% isolated yield), a cyclopropyl (**8c**, 85%) or a cyclohexyl (**8d**, 79%) while keeping R² as phenyl. When R³ is a cyclohexyl, R² can be cyclopropyl (**8e**, 73%), a linear alkyl chain (**8f**, 61%), a

cyclohexenyl (**8g**, 68%) or a *N*-methyl pyrazole (**8h**, 59%). A 2-thienyl substituent (**8i**, 78%) or an ortho-substituted phenyl (**8j**, 79%) are also tolerated in the R² position. Finally, substituent containing heteroatoms could also be included in the R² substituent, such as a *N*-Boc piperidine (**8k**, 62%), a *N*-propyl phthalimide (**8l**, 80%), a (*tert*-butyldimethylsilyloxy)ethyl (**8m**, 53%) or (2-pyrimidinyl)oxy)ethyl (**8n**, 59%). In all these 14 examples, the major cycloadduct is the expected 6-aza-indazole **8** as determined from the ¹H NMR analysis of the crude reaction mixture, in ratio ranging from 64:36 to 93:7, independently of the electronics or steric parameters of the R² and R³ substituents of the alkynyl-hydrazone side chain.

We next focused on the influence of substituents of the pyrazine on the efficiency and product distribution of this Diels-Alder cascade (Scheme 4). Cycloaddition precursor **7d** was selected as a reference substrate leading, as discussed above, to an **8d/9d** ratio of 80:20. Interestingly, when TFAA was substituted by Boc₂O, an increased ratio was observed between the 6-aza-indazole **8d-Boc** and the 7-aza-indazole **9d-Boc** (**8d-Boc/9d-Boc** = 95:5), which might be attributed to a more sterically demanding acyl group. To probe substituent effects, conditions A were selected for the rest of the studies. Thus, substitution of the pyrazine core of **7d** in the C3 position was first investigated under standard conditions, with a methyl group (**7o**), a methoxy (**7p**), a chlorine (**7q**) and a trifluoromethyl (**7r**) (Scheme 3, B). These substituents of opposed steric and electronic requirements all favor the formation of the 6-aza-indazoles **8o-r** as the major cycloadduct, via **TS9** as the transition state for the retro-[4+2] step. Quite remarkably, when the R⁴ substituent is electron-withdrawing (and independently of its mesomeric character), only the 6-aza-indazole could be detected in the crude reaction mixture as can be seen when R⁴ is a halide (**7q** leading to **8q**) or a trifluoromethyl group (**7r** leading to **8r**).

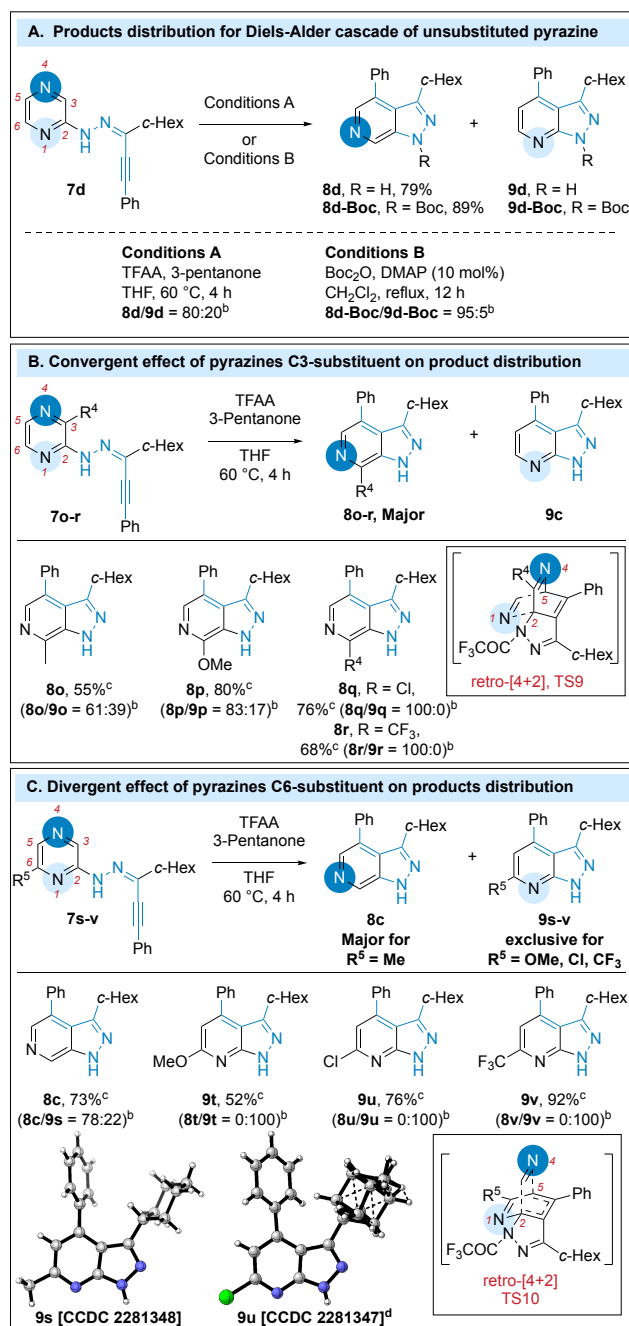
This convergent effect of the pyrazine C3-substituent on product distribution, enhancing the intrinsic preference of **7** for the 6-aza-indazole cycloadduct **8**, was not observed in the case of C6-substituents (Scheme 3, C). Four cycloaddition precursors were prepared with R⁵ being a methyl group (**7s**), a methoxy (**7t**), a chlorine (**7u**) and a trifluoromethyl (**7v**). C6-substitution by an alkyl group led to the 6-aza-indazole **8c** as the major cycloadduct (73% isolated yield), the 7-aza-indazole **9s** being present only in 22% in the crude reaction mixture. On the other hand, the exclusive formation of 7-aza-indazoles **9t-v** was observed for the other substituents, independently of the steric or electronics. This outcome can be rationalized by **TS10** for the retro-[4+2] step.

The observed convergency and divergency in product distribution raises the question of an eventual protonation effect of one of the different nitrogen atoms of the pyrazine core.¹¹ Indeed, upon trifluoroacetylation of the hydrazone nitrogen atom of **7** with trifluoroacetic anhydride, one equivalent of trifluoroacetic acid is released. The latter might protonate one or several nitrogen atoms of the cycloaddition precursor, in turn affecting the outcome of the retro-Diels-Alder step. Protonation of pyrazines has been reported in a handful of studies, and characteristic ¹³C NMR chemical shifts of the C2/C6 and C3/C5 atoms allow for the attribution of the protonated nitrogen.¹⁹⁻²¹ A systematic NMR study of the effect of two different acids differing by their H₀ acidity function (TFA, -3.03 and 98% H₂SO₄, -10)²² was conducted on three different model compounds, **7d**, **7q** and **7u**

in the absence or presence of trifluoroacetic anhydride, at 20 and 60 °C in THF-*d*8.²³

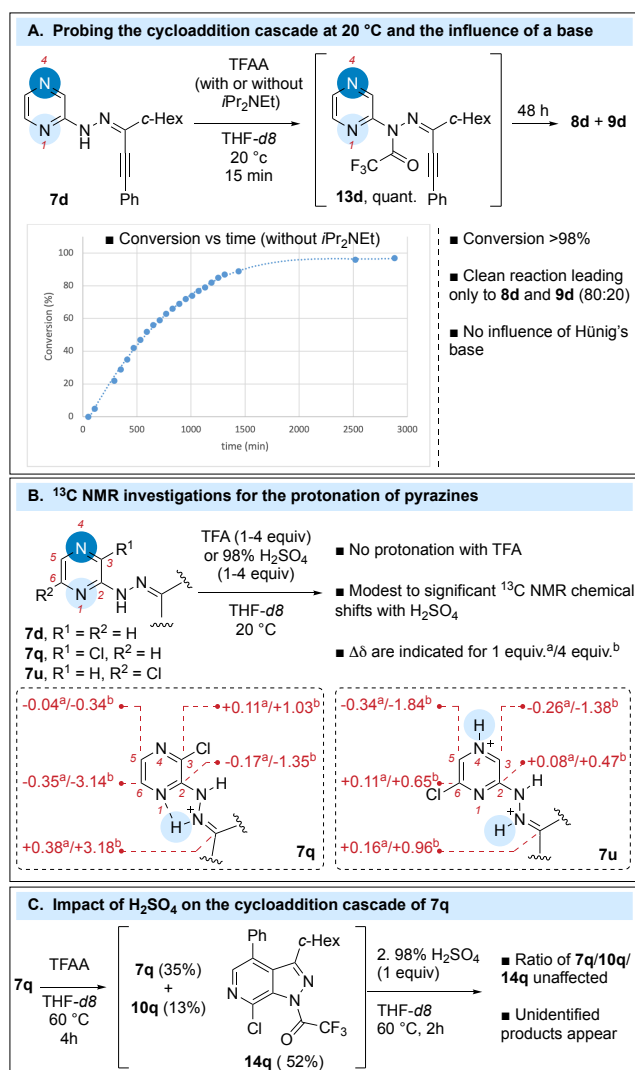
First, a kinetic profile at 20 °C for the cycloaddition cascade of **7d** demonstrated that the reaction was highly efficient, an almost complete conversion being obtained after 24h (Scheme 5, A, *cf.* conversion vs. time curve). The exact same conversion and product distribution was observed when the cycloaddition cascade was conducted in the presence of an organic base (iPr₂EtN) for 24h.

Scheme 4. Convergent and divergent substituent effects.^a



^a Reactions were performed using **7**, TFAA (1.5 equiv), 3-pentanone (3 equiv) under nitrogen in THF (0.5 M) at 60 °C for 4 h. ^b **8/9** ratio determined by ¹H NMR. ^c Isolated yield. ^d C14-18 methyl- enes are disordered over two positions with an occupancy ratio of 0.55/0.45.

Scheme 5. ¹³C NMR studies for the protonation of **7**.^a



The influence of acids on **7d**, **7q** and **7u** was then evaluated in the absence of trifluoroacetic anhydride (Scheme 5, B). It appeared that TFA was not able to protonate cycloaddition precursors **7** at 20 °C or 60 °C. This first series of experiments therefore ruled out the protonation of **7** (and hence *a fortiori* of **13d**) with TFA as one of the factors influencing the product distribution when standard cycloaddition conditions are employed (TFAA, 3-pentanone, THF).

On the other hand, the addition of H₂SO₄ to **7q** and **7u** led to small (for 1 equivalent) to significant (for 4 equivalents) ¹³C NMR chemical shifts, indicating that protonation occurs first on the nitrogen atom of the hydrazone, potentially assisted by N1 in the case of **7q** (Scheme 5, B, left).²⁴⁻²⁶ For **7u** and in the presence of 4 equivalents of H₂SO₄, the second protonation occurs at N4 (Scheme 5, B, right). Then, the influence of H₂SO₄ in the cycloaddition cascade conditions (TFAA, 60 °C) was evaluated for **7q** (Scheme 5, C). When it was present at the outset of the reaction, the trifluoroacetylation could not proceed. When it was added after 4 hours of reaction at 60 °C (65% conversion), the presence of H₂SO₄ immediately led to a plateau and to unidentified products. Although the presence of a strong acid such as H₂SO₄ could protonate **7** and thus contribute to the electrodeficiency of the pyrazine, it was detrimental to the cycloaddition reaction. Eventually, the impact of the C3- or C6-

substitution of the pyrazine core on the cycloadduct distribution might be explained by the nature of the retro-Diels-Alder products. In all cases, the major to exclusive elimination leads to HCN which either spontaneously polymerizes under thermal conditions²⁷ or is trapped by 3-pentanone to the corresponding cyanohydrine.¹⁷ The gaseous nature of HCN might thus provide a highly favorable thermodynamic driving force in this Diels-Alder cascade, as is usually observed for 1,2,4-triazines or 1,2,4, 5-tetrazines cycloadditions.¹⁻³

In conclusion, we have disclosed that pyrazines substituted by an alkynylhydrazone could undergo intramolecular Diels-Alder cascade even at room temperature. A collection of diversely substituted 6- or 7-aza-indazoles was obtained in moderate to good yields. Interestingly, an influence of the pyrazine substitution on the cycloadduct distribution was observed. Mechanistic investigations have shown that protonation of the cycloaddition precursors with the *in situ* generated TFA do not account for this observed divergency. Current studies aim at further exploring the selective protonation of pyrazines with strong Brønsted acids as modulators of cycloaddition reactivity.

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