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RESEARCH ARTICLE

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Taming the 1,5-sigmatropic shift across protonated spirocyclic 4*H*-pyrazoles

Brian J. Levandowski | **Brian J. Graham** | **Nile S. Abularrage** | **Ronald T. Raines**

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

Correspondence
Brian J. Levandowski and Ronald T. Raines, Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139-4307, USA.
Email: levandbj@ucla.edu and rtraines@mit.edu

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[Correction added on 2 July 2024, after first online publication: the Schemes 1-4 have been corrected in this version].

Abstract

The condensation of 1,3-diketones with hydrazine to access 4*H*-pyrazoles is a well-established synthetic route that travels through a 4*H*-pyrazol-1-ium intermediate. In the route to a 3,5-diphenyl-4*H*-pyrazole containing a cyclobutane spirocycle, density functional theory calculations predict, and experiments show that the protonated intermediate undergoes a rapid 1,5-sigmatropic shift to form a tetrahydrocyclopenta[*c*]pyrazole. Replacing the 3,5-diphenyl groups with 2-furanyl groups decreases the calculated rate of the 1,5-sigmatropic shift by 6.2×10^5-fold and enables the isolation of new spirocyclic 4*H*-pyrazoles for click chemistry.

KEYWORDS

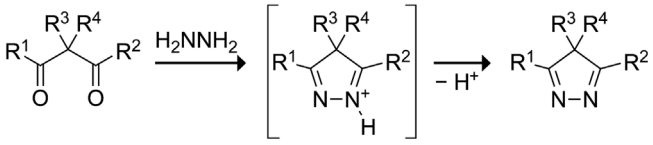
4*H*-pyrazole, density functional theory, pericyclic reaction, sigmatropic shift, spiroconjugation

1 | INTRODUCTION

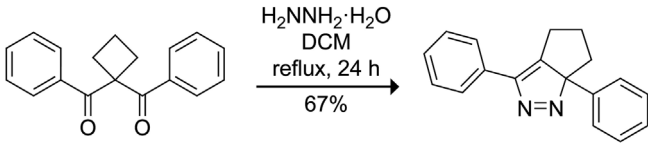
5-Membered dienes such as 4*H*-pyrazoles are rapidly emerging as useful click reagents.[1,2] Spirocyclization provides an effective means to increase the Diels–Alder reactivity of 4*H*-pyrazoles by circumventing the disrupting effects of geminal repulsion in acyclic geminally substituted 5-membered dienes.[3–6] Although 4*H*-pyrazoles containing five-membered spirocycles have been previously synthesized, they are predicted to be less reactive as Diels–Alder dienes than four-membered spirocycles.[5,6] Accordingly, a synthetic route to four-membered spirocyclic 4*H*-pyrazoles is of particular interest.

The general synthetic route to 4*H*-pyrazoles involves treating a 1,3-diketone with hydrazine (Scheme 1).[7,8] This condensation reaction proceeds through a protonated 4*H*-pyrazole (that is, a 4*H*-pyrazol-1-ium) intermediate. Our attempts to synthesize a 4*H*-pyrazole containing a cyclobutane spirocycle via hydrazine condensation with a diphenyl 1,3-diketone resulted in a 1,5-sigmatropic shift to form a tetrahydrocyclopenta[*c*]pyrazole as the major product (Scheme 2). Developing methods to prevent or slow the 1,5-sigmatropic shift across the 4*H*-pyrazole scaffold would significantly expand their utility as click reagents.

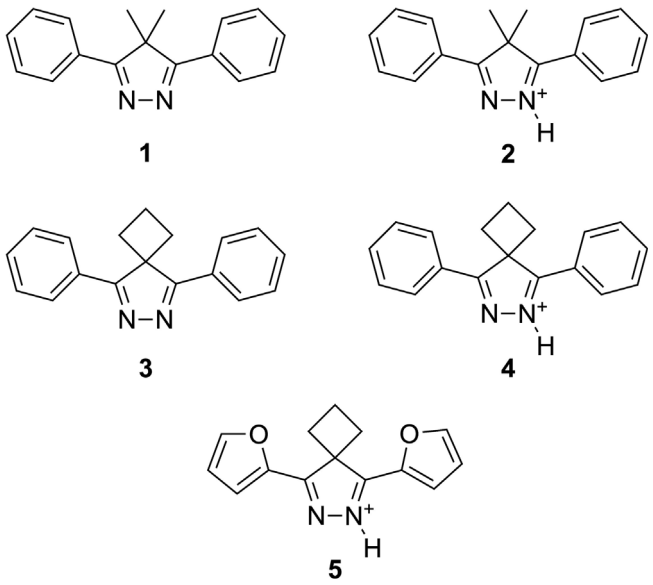
Although it is experimentally known that protonating a 4*H*-pyrazole accelerates their Diels–Alder reactivity,[9,10]



SCHEME 1 Hydrazine condensation of a 1,3-diketone to access 4*H*-pyrazoles via a 4*H*-pyrazol-1-ium intermediate.



SCHEME 2 Reaction of a spirocyclic diphenyl 1,3-diketone with hydrazine.



SCHEME 3 Structures of 4*H*-pyrazoles **1**–**5**.

how protonation affects the rate of the undesirable 1,5-sigmatropic shift has yet to be explored. This knowledge gap led us to computationally investigate the 1,5-sigmatropic shift of 4*H*-pyrazoles **1**–**5** (Scheme 3). Here, we identify a means to stabilize the 4*H*-pyrazol-1-ium intermediate and enable the synthesis of a 4*H*-pyrazole containing a cyclobutane spirocycle.

2 | COMPUTATIONAL METHODS

We computationally explored the 1,5-sigmatropic shifts of the 4*H*-pyrazole systems using density functional theory (DFT). The M06-2X functional was used to calculate both the geometries and energies.[11] Geometry optimizations were carried out in Gaussian 16 rev. C[12] with the 6-31G(d) basis set. Energetic data were obtained from single-point energy calculations with the 6-311++G(d,p) basis set. The SMD solvation model for water was applied to both the geometry and single-point energy calculations.[13] All calculations were performed in the gas phase, assuming a standard state of 1 M at 298 K and 1 atm.

3 | RESULTS AND DISCUSSION

The calculated Gibbs activation energies for the 1,5-sigmatropic shift across 4*H*-pyrazoles **1**–**4** are shown in Figure 1. The barrier to the 1,5-sigmatropic shift of dimethyl 4*H*-pyrazole **1** was calculated to be 34.9 kcal/mol. The 4*H*-pyrazol-1-ium **2** has an activation energy of 28.1 kcal/mol. The spirocyclic 4*H*-pyrazole **3** and the spirocyclic 4*H*-pyrazol-1-ium **4** have computed activation energies of 21.6 and 14.1 kcal/mol, respectively. Thus, the

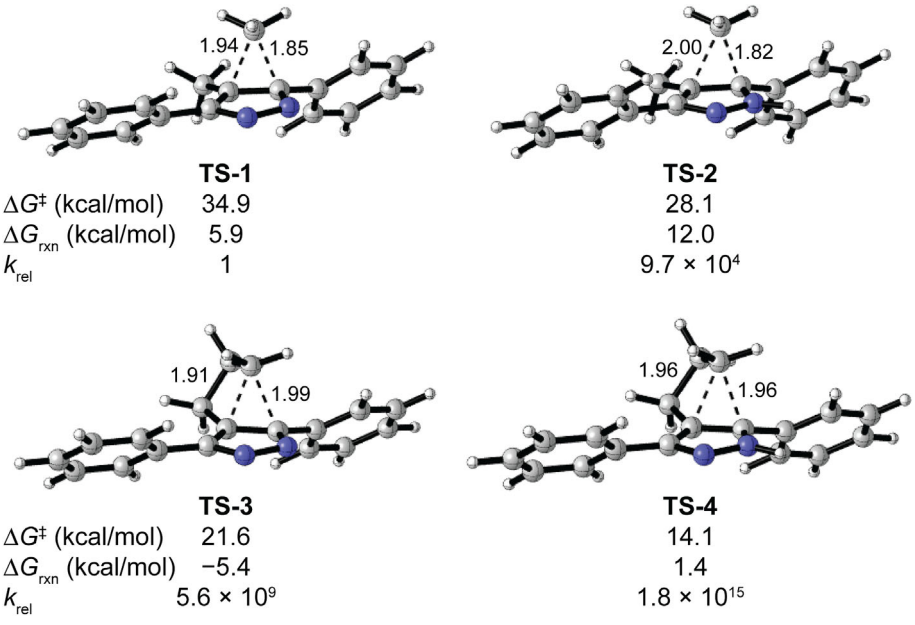


FIGURE 1 Transition state structures and Gibbs activation free energies for the 1,5-sigmatropic shifts of 4*H*-pyrazoles **1**–**4**. Relative rate constants at 298 K were obtained from the Arrhenius equation. Forming bond lengths are reported in Ångstroms.

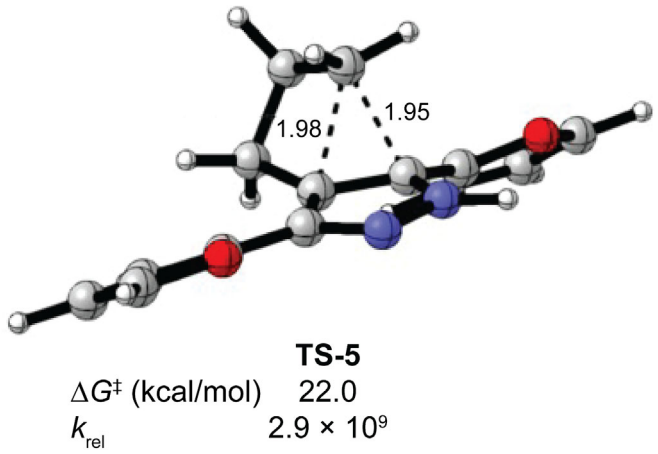
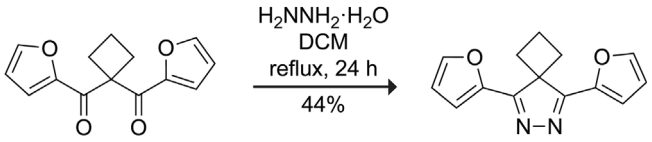


FIGURE 2 Transition state structure and Gibbs activation free energy (kcal/mol) for the 1,5-sigmatropic shift of difuranyl 4*H*-pyrazol-1-ium **5**. The rate constant at 298 K relative to 4*H*-pyrazol-1-ium **1** (Figure 1) was obtained from the Arrhenius equation. Forming bond lengths are reported in Ångstroms.



SCHEME 4 Reaction of a spirocyclic difuranyl 1,3-diketone with hydrazine.

protonation of 4*H*-pyrazoles **1** and **3** results in a 9.7×10^4 and 3.2×10^5 increase in reactivity, respectively.

Spirocyclization enhances the rate of the 1,5-sigmatropic shift by 5.6×10^9 in the neutral state and 1.9×10^{10} in the protonated state. Together, the spirocyclization and protonation result in 1.8×10^{15} rate enhancement of the 1,5-sigmatropic shift. This large rate enhancement upon spirocyclization and protonation is consistent with the experimental difficulty of accessing 3,5-diphenyl-4*H*-pyrazole containing a cyclobutane spirocycle (Scheme 2).

Spirocyclization of the 4*H*-pyrazole lowers the reaction energy of the 1,5-sigmatropic shift by 11.4 kcal/mol in the neutral state and 10.6 kcal/mol in the protonated state. These decreases parallel the trend in the activation energies, suggesting that the accelerated reactivity is promoted by strain release of the 4-membered ring in the spirocycle.

Next, we sought to stabilize the 4*H*-pyrazol-1-ium scaffold and slow the 1,5-sigmatropic shift. We hypothesized that the 4*H*-pyrazol-1-ium intermediate could be stabilized by replacing the two phenyl groups with a more electron-rich aryl moiety. We discovered that 2-furanyl groups exert a remarkable increase to activation energy for the 1,5-sigmatropic shift (Figure 2). Specifically, the 1,5-sigmatropic shift of difuranyl 4*H*-pyrazol-1-ium **5** is predicted to decrease by a factor of 6.2×10^5 relative to

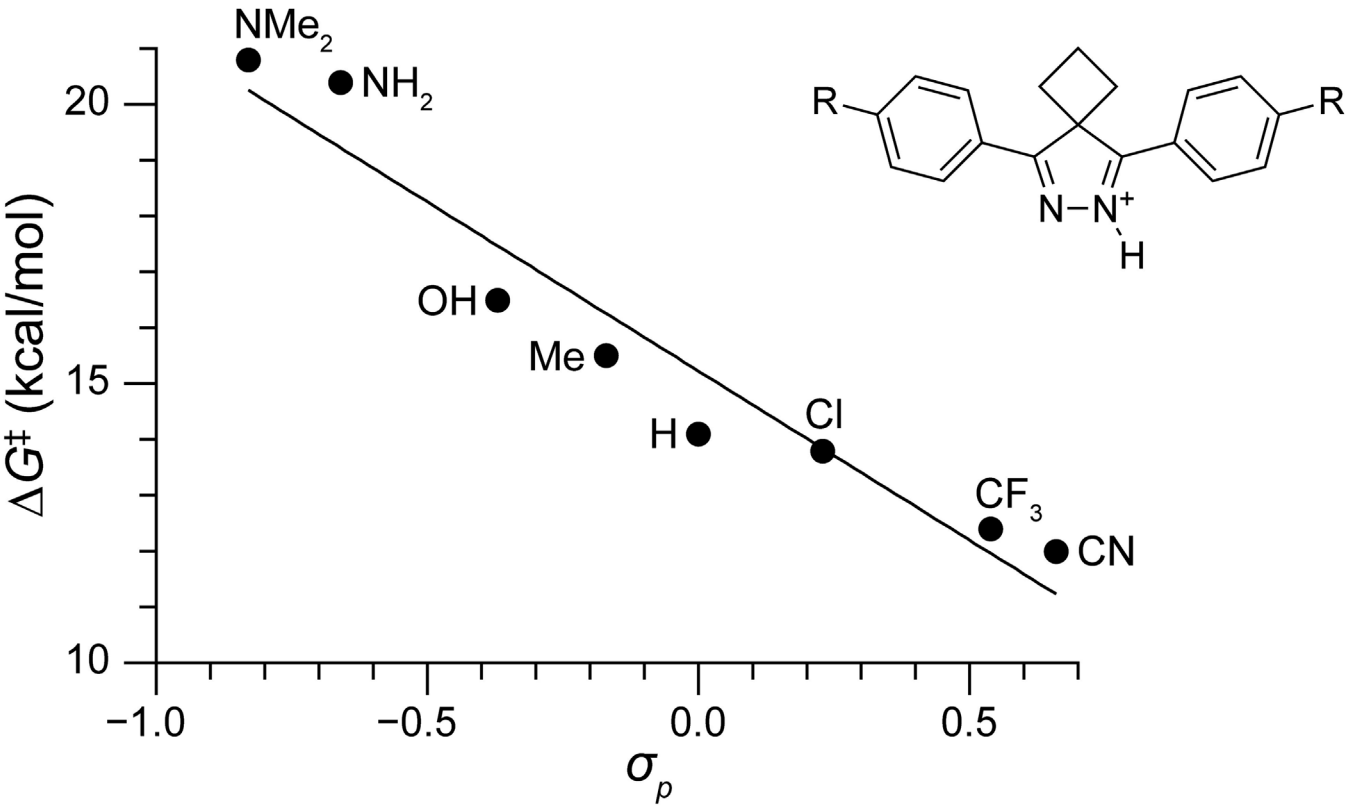


FIGURE 3 Hammett plot showing the linear free-energy relationship between calculated activation energies for the 1,5-sigmatropic shift of *para*-disubstituted derivatives of Compound **4** and σ_p. A linear least-square fit gives $\Delta G^{\ddagger}$ (kcal/mol) $= -6.1\sigma_p + 15.2$ with $R^2 = 0.93$. The value of $\Delta G^{\ddagger} = 14.1$ kcal/mol for R = H (Compound **4**) is also listed in Figure 1.

that of diphenyl 4*H*-pyrazol-1-ium **3**. Consistent with the calculations, we were able to synthesize a 4*H*-pyrazole containing a cyclobutane spirocycle via hydrazine condensation of a difuranyl 1,3-diketone (Scheme 4).

To further our understanding of the relationship between the reactivity and the electronic nature of the aryl groups, we decorated the *para* position of the phenyl group in Compound **4** with a range of electron-donating and electron-withdrawing groups and calculated the activation energies of the 1,5-sigmatropic shifts. Those activation energies range from 12.0 kcal/mol (R = CN) to 20.8 kcal/mol (R = NMe_2). A Hammett plot[14,15] shows a strong linear free-energy relationship between the activation energies and the σ_p Hammett constants (Figure 3).[16] Thus, the 1,5-sigmatropic shift is tied to the electronic nature of the aryl group: Electron-donating substituents increase the activation energy and slow the rate of the shift. Conversely, electron-withdrawing substituents lower the activation energy, accelerating the 1,5-sigmatropic shift.

4 | CONCLUSIONS

The spirocyclization of geminally substituted 5-membered cyclic dienes is known to enhance their Diels–Alder reactivity. The four-membered spirocycles are predicted to be the most reactive but are difficult to synthesize because the 4*H*-pyrazol-1-ium intermediates are prone to rearrange. Replacing the phenyl groups in a spirocyclic 3,5-diphenyl-4*H*-pyrazole with 2-furanyl groups stabilizes the 4*H*-pyrazol-1-ium intermediate enough to allow for the first isolation of a spirocyclic 4*H*-pyrazole containing a cyclobutane spirocycle.

AUTHOR CONTRIBUTIONS

Brian J. Levandowski: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; validation; formal analysis; project administration; funding acquisition. **Brian J. Graham:** Investigation; methodology; validation; writing—review and editing. **Nile S. Abularrage:** Writing—review and editing; investigation; methodology; validation. **Ronald T. Raines:** Supervision; data curation; funding acquisition; writing—review and editing; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting information of this article.

ORCID

Brian J. Levandowski https://orcid.org/0000-0002-8139-9417
Brian J. Graham https://orcid.org/0000-0001-9985-3553
Nile S. Abularrage https://orcid.org/0000-0002-3112-2591
Ronald T. Raines https://orcid.org/0000-0001-7164-1719

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