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A New Cyclization to Fused Pyrazoles Tunable for Pericyclic or Pseudopericyclic Route: An Experimental and Theoretical Study

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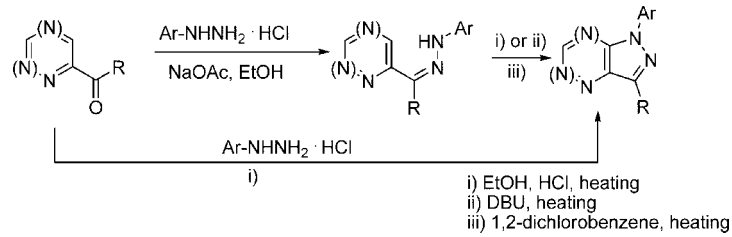

2-Pyrazinyl (**2**) and 3-pyridazinylketone arylhydrazones (**6**) and their benzologues undergo a ring closure reaction to yield pyrazolo[3,4-*b*]pyrazines (**4**) and pyrazolo[4,3-*c*]pyridazines (**7**), respectively, in acceptable to good yields. The reaction was found to be accelerated by using acidic or basic conditions. Quantum chemical calculations suggest the key step of the mechanism to be a direct cyclization; analysis of aromaticity based on computed magnetic properties revealed its medium-dependent pericyclic or pseudopericyclic character. The cyclization reaction has also been extended for the synthesis of related ring systems (**9**, **12**, **14**).

Introduction

Some years ago we reported[1] that [1,2,3]triazolo[1,5-*a*]pyrazinium salt **c** (Figure 1), accessible by oxidative cyclization of the 4-chlorophenylhydrazone (**b**) obtained from the appropriate ketone (**a**), easily undergoes thermal rearrangement to yield the reactive valence bond isomeric diazaallenium cation (**d**), which species spontaneously cyclizes either on the phenyl substituent or the pyrazine ring. Thus, accordingly, formation of an indazole (**e**) and pyrazolo[3,4-*b*]pyrazine (**f**) has been experienced.

In the course of detailed experimental research of these transformations, chromatographic analysis of the reaction mixture of transformation **a**→**b** indicated, quite unexpectedly, the presence of **f** as a side product in variable amounts. Careful isolation and comparison of this side product formed besides **b** and one of the main products (**f**) obtained from **c** via **d** unambiguously supported their structural identity, and thus, further investigation of the transformation **a**→**f** seemed of particular interest.

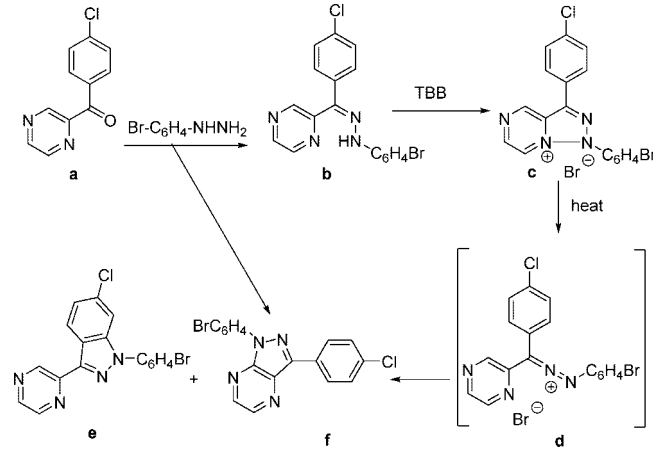

FIGURE 1. Chart of different reaction pathways leading to pyrazolo[3,4-*b*]pyrazines (**f**).

Results and Discussion

Results of experiments with transformation **1**→**2** carried out under various reaction conditions revealed that under the earlier established conditions (sodium acetate in ethanol) the hydrazone (**2**) is the main product, whereas under acidic conditions a

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(1) Béres, M.; Hajós, Gy.; Riedl, Zs.; Soós, T.; Timári, G.; Messmer, A. *J. Org. Chem.* **1999**, *64*, 5499.

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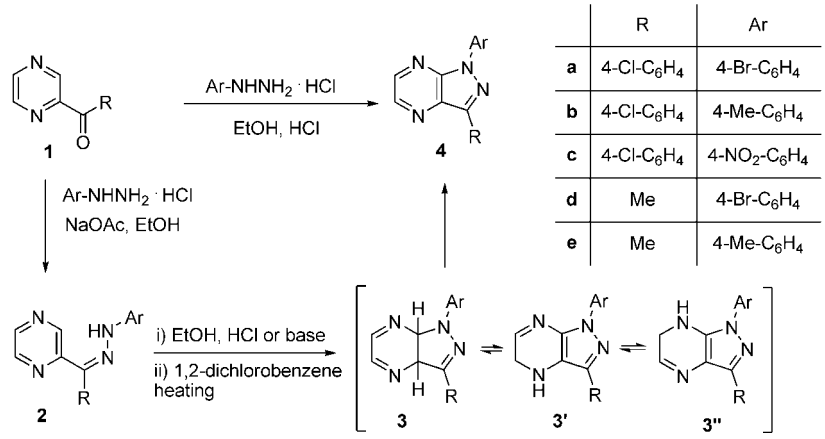
SCHEME 1



	R	Ar
a	4-Cl-C_6H_4	4-Br-C_6H_4
b	4-Cl-C_6H_4	4-Me-C_6H_4
c	4-Cl-C_6H_4	4-NO_2-C_6H_4
d	Me	4-Br-C_6H_4
e	Me	4-Me-C_6H_4

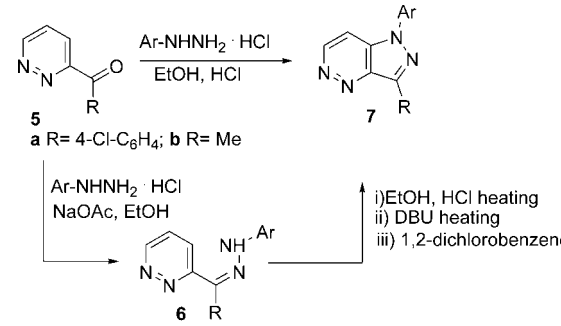
dramatic change occurs and the fused pyrazole **4** is only formed in moderate to good yields (Scheme 1). When some selected hydrazones were treated under acidic conditions, that is, with application of the same conditions as that used with the successful synthesis of **4** from **1**, the same pyrazolo[3,4-*b*]pyrazines were obtained, which strongly supports the fact that hydrazones **2** are intermediates along the pathway **1**−**4**. This cyclization provides a simple, general approach to pyrazolo[3,4-*b*]pyrazine derivatives, which were earlier available only by more sophisticated methods.[1,2]

Concerning the reaction mechanism of this ring closure, several possibilities can be outlined. The fact that the pyrazole ring closure is successful in the presence of acid suggests that the main ring closing step might be a nucleophilic attack of the hydrazone-*N* atom at the pyrazine ring activated by protonation to give the dihydro intermediate **3** (which can exist in some of the possible tautomeric forms, e.g. **3**, **3′**, or **3″**),[3] and then areal oxidation could lead to the heteroaromatic product (**4**). Similar activation at the hydrazone site of the molecule was also found successful: when **2a** or **2b** was treated with DBU and, thus, a powerful negatively charged nitrogen nucleophile was formed, the same ring closure took place and **4a** or **4b**, respectively, was obtained in good yield.

Although all of these mechanistic considerations seemed to be in accordance with the experimental finding, another explanation should also be considered: inspection of the double bonds and lone pair of the hydrazone-nitrogen atom in **2** reveals that these three electron pairs could also interact in a pericyclic manner. To find experimental support for this supposition, hydrazone **2a** was heated in pure 1,2-dichlorobenzene without the presence of any acid or base. Under somewhat more forced conditions (at 140 °C, for 12 h), the ring closure was successful, and **4a** was obtained in the same yield as under acidic conditions.

The ring closure methodology was also successfully extended for pyridazines (Scheme 2). Thus, pyridazinyl ketone (**5a**), when reacted with arylhydrazines in the presence of acid, gave rise to pyrazolo[4,3-*c*]pyridazines (**7a**, **7b**). To the best of our knowledge, only a few representatives of this ring system have been synthesized before by using different approaches.[4] Similar to the analogous pyrazine derivatives, also this transformation proceeds via formation of the hydrazones (**6**), which can be isolated when **5** is reacted with an arylhydrazine under buffered conditions. Transformation of **6** to **7** under thermal conditions has also been accomplished: heating **6c** in dichlorobenzene (at 140 °C) for 12 h gave rise to formation of **7c** in medium yield. Our efforts to carry out analogous pyrazole-fusion to pyrimidines, unfortunately, failed and only decomposition was experienced.

SCHEME 2



	R	Ar
a	4-Cl-C_6H_4	4-Br-C_6H_4
b	4-Cl-C_6H_4	4-Me-C_6H_4
c	Me	4-Br-C_6H_4

After the successful cyclizations with two diazines, the question arose if similar transformation could also be carried out with pyridinylhydrazones. In the case of 2-pyridylketone hydrazone, the reactivity of position 3 against a nucleophile is obviously much less than that of diazines; however, the pericyclic route could, in principle, be realized. In accordance with these considerations, treatment of the hydrazone **8** either with acid or with base did not result in any ring closure. Heating

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(3) Our efforts to detect the intermediate formation of this dihydro species by NMR spectrosopy, unfortunately, failed.

(4) (a) Baig, G. U.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1424. (b) Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3721.

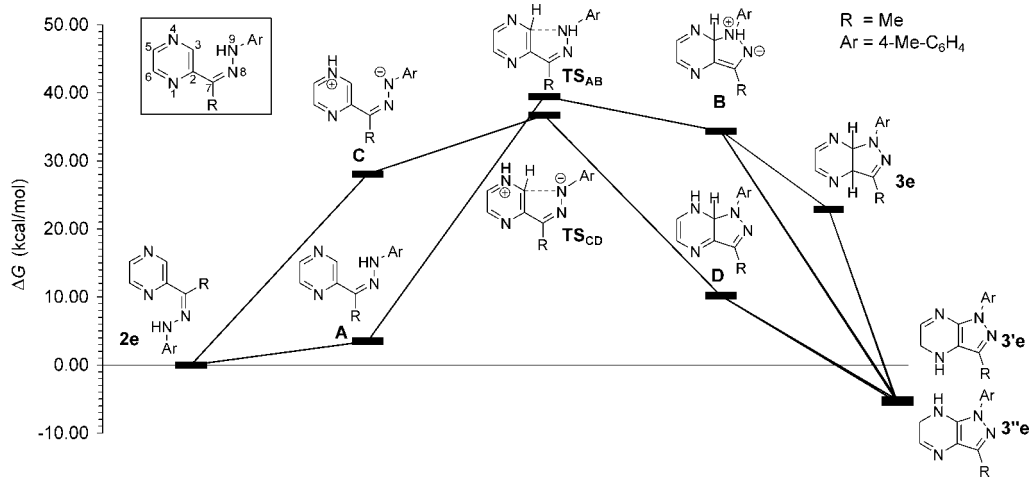
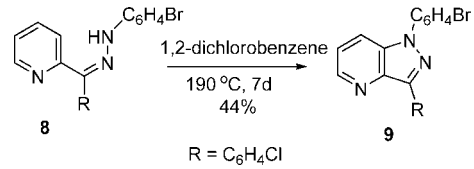


FIGURE 2. Proposed reaction mechanism and energetics for the cyclization of **2e** in apolar solvent. (Inset) Arbitrary atom numbering used in text.

in dichlorobenzene at 190 °C, in turn, proved to be suitable for the cyclization, and **9** was isolated in medium yield (Scheme 3).[5]

SCHEME 3



To unravel the mechanism of the ring closure, quantum chemical calculations have been carried out for the cyclization of **2e**.[6] As the investigated hydrazones are air-stable compounds, it was assumed that ring closure precedes oxidation. The latter, being probably an exergonic, multistep radical reaction with molecular oxygen, has not been studied; neither has the formation of the *Z* geometric isomer of the hydrazone required for the cyclization.

In apolar solvents, the most stable form of the *Z*-hydrazone is predicted to be the one having an internal N9−H···N1 hydrogen bond, which must be broken to achieve the conformation **A** suitable for the ring closure (Figure 2). Direct cyclization to intermediate **B** is feasible; the overall barrier of this process is high (39.5 kcal/mol), which explains the need for elevated temperature to accomplish this transformation. **B** is thermodynamically unstable, lying 34.3 kcal/mol above **2e**, but its rearomatization to **3′e** or **3′′e** via tautomerization might be the next step rendering already the ring closure exergonic; the above proposed structure **3e** might be an intermediate here. An alternative route might start with the formation of the zwitterionic tautomer **C**, which can then cyclize through a slightly lower barrier (36.7 kcal/mol) to another unstable intermediate **D**. Oxidation might proceed directly from intermediates **B** or **D**, or from any one of their tautomers (including **3e**, **3′e**, and **3′′e**).

For the catalyzed cases only (de)protonated species were compared to each other. Deprotonation of the attacking N9 nitrogen atom of **2e** precludes the formation of the N9−H···N1 hydrogen bond, the ring closure can therefore proceed directly from the most stable conformer having C3−H···N9 contact. Protonation of **2e** can occur at several positions but the N4 protonated form is predicted to be most stable and to have the lowest cyclization barrier. For both acid and base catalysis, the energy profile of the reaction is similar to the neutral case, but the ring closure requires significantly less activation free energy (24.8 kcal/mol in acidic, 21.7 kcal/mol in basic medium), in accordance with experimental results. Cyclization of the neutral **2e** to **B** is endothermic, with late transition state as predicted by the Hammond postulate. In this step, catalytic effect of both acids and bases is therefore mainly based on stabilizing the zwitterionic product **B** as compared to the respective form of the hydrazone. Acid catalysis is most effective at N4, which is expected and has been indeed calculated to be the most basic site in **B**.

The investigated ring closure proceeds via reorganization of electrons around the perimeter of the forming heterocycle. Such reactions may have cyclic orbital overlap in their transition states, in which case they follow appropriate stereochemistry to achieve aromaticity with the given number of electrons (pericyclic reactions).[7,8] However, ring atoms (usually heteroatoms) may participate with more than a single orbital in the reaction, which means disconnection in the cyclic overlap, and therefore, absence of aromaticity and stereochemical requirements (pseudopericyclic reactions).[9–14] The nonuniqueness of the MO picture can make distinction based on involved orbitals ambigous;[10,11] therefore, other means have been proposed to classify reactions as pericyclic or pseudopericyclic. Among

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(6) For detailed energetics, see Supporting Information.

(7) (a) Evans, M. G.; Warhurst, E. *Trans. Faraday. Soc.* **1938**, *34*, 614. (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781. (c) Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 272. (d) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761. (e) See special issue 5 dedicated to aromaticity: *Chem. Rev.* **2001**, *101*.

(8) Herges, R.; Jiao, H.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1376.

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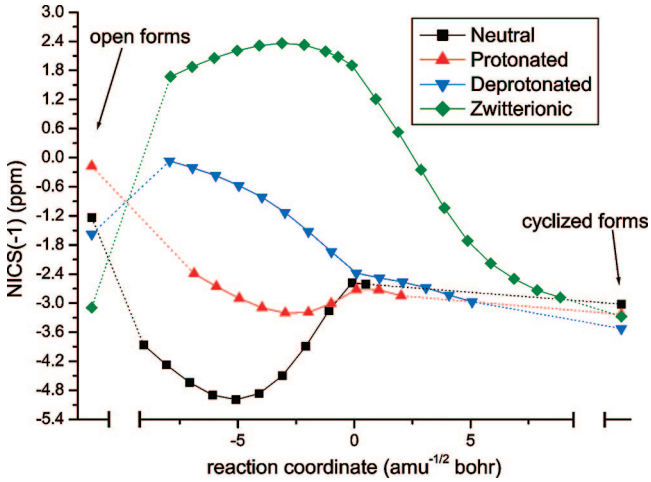


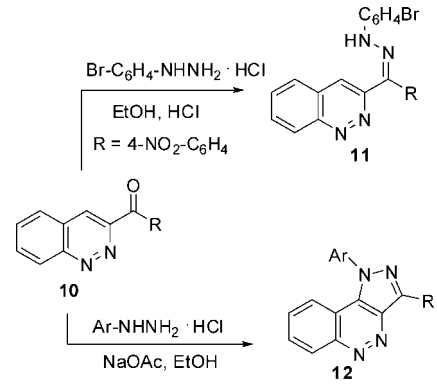
FIGURE 3. NICS values calculated along the IRC paths.

others,[13,15] characteristic magnetic properties of aromatic systems have been shown to be useful for this purpose.[8,16,17] For instance, strong magnetic shielding caused by aromatic ring currents can be detected by calculating nucleus independent chemical shift (NICS) values[18] near the center of the forming ring.

Following literature recommendations, we calculated NICS values at the center of the ring as well as 0.5 Å and 1 Å above and below along the intrinsic reaction coordinate (IRC) path of the ring closure step.[12,19] Presence of a minimum with large negative values in these curves points to enhancement of aromaticity, characteristic for pericyclic reactions. After observing atomic motions along the IRC, for drawing conclusions we have chosen the data calculated 1 Å away from the center on the side from which the pyrazine ring is attacked, as cyclic overlap of the *p* orbitals is supposed to be the largest, influence of localized σ bonds the smallest here.[12,19,20] All calculated curves are given in the Supporting Information.

Geometric and magnetic aspects (Figure 3) both support that cyclization of the neutral molecule is a pericyclic disrotatory electrocyclization, which is a thermally allowed process for such $10e^-$ systems according to the Woodward−Hoffmann rules. Cyclization of the N4 protonated form has less expressed pericyclic character. While both HOMO and LUMO of the neutral system spread to both the aromatic ring and the hydrazone side chain, protonation causes the HOMO to be more localized on the side chain, LUMO on the pyrazine ring (see Figure 4). Electrocyclization character is therefore decreased in favor of aromatic nucleophilic addition. However, removing the proton from N9 (either via deprotonation by base or in tautomerization to the zwitterionic **C**) leads to a completely different picture. One of its two lone pairs can remain conjugated with the π system during the whole course of the cyclization, whereas the other one attacks the carbon atom. Involvement of two orbitals of N9 suggests orbital disconnection preventing aromatization, which is clearly demonstrated by the NICS curve. These reaction routes can therefore be classified as pseudopericyclic.

SCHEME 4



12	R	Ar
a	C_6H_5	4-Br-C_6H_4
b	4-Cl-C_6H_4	4-Br-C_6H_4
c	4-Br-C_6H_4	4-Br-C_6H_4
d	4-NO_2-C_6H_4	4-Br-C_6H_4
e	4-MeO-C_6H_4	4-Br-C_6H_4

The relatively mild reaction conditions and the acceptable yields supported the preparative importance of the experienced ring closure and, thus, extension of this methodology for benzologues of the above-discussed azines has been decided.

Our literature survey indicated that similar ring closure with quinoxalines have been described: Boguslavskiy et al.[21] described that treatment of 2-quinoxalylketone hydrazones with diluted sulfuric acid on air resulted in fused pyrazoles, whereas Sarodnick et al. carried out similar ring closure in xylene at high temperature in the presence of chloranil.[22]

In one of our recent publications,[23] we have reported on difficulties with transformation of 3-cinnolylketones (**10**) to hydrazones, and only the 4-nitrophenyl derivative (**11**) could be isolated. We have now found that with treatment of the majority of these ketones with arylhydrazines, a spontaneous ring closure to pyazolo[4,3-*c*]cinnolines (**12**) occurs (Scheme 4). The facile cyclization found under acidic conditions is obviously caused by the enhanced sensitivity of position 4 against nucleophiles due to the presence of the fused benzene ring. A different ring closure starting from 4-hydroxy substituted cinnolinylketone hydrazones to related substances has also been reported.[24]

Presence of the fused benzene ring in 3-isoquinolinylketone hydrazones was found not effective enough to facilitate the pyrazole formation and treatment of 3-isoquinolylketones with arylhydrazines under acidic conditions gave only hydrazones. Application of the thermal ring closure technique, however,

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(24) Youssef, M. S. K.; El-Dean, A. M. K.; Abbady, M. S.; Hassan, K. M. *Collect. Czech. Chem. Commun.* **1991**, *56*, 8.

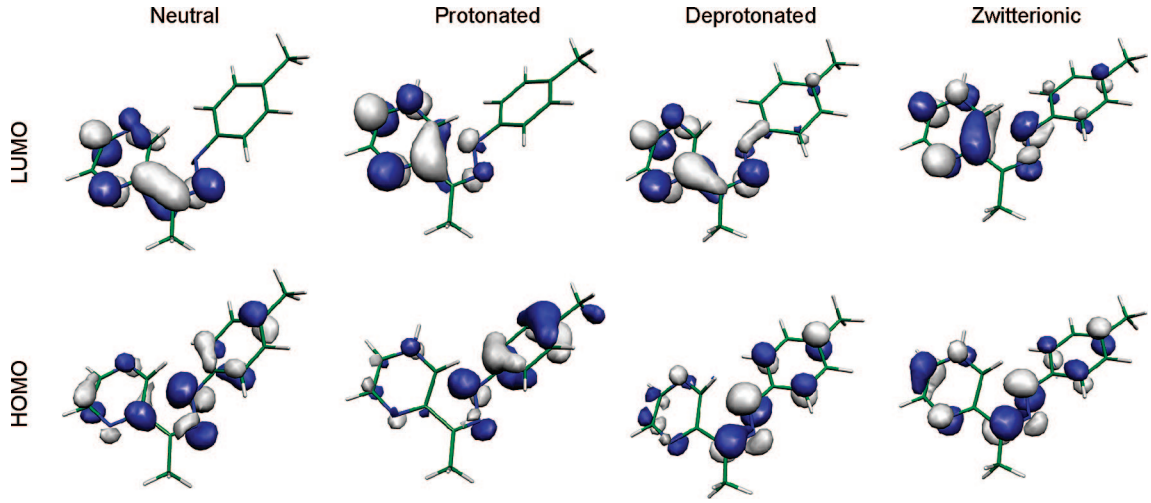
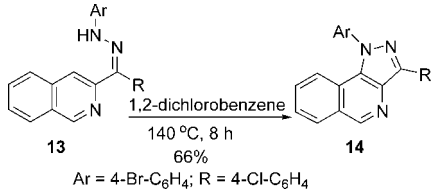


FIGURE 4. Molecular orbitals of various forms of *Z*-**2e** at *d*(C3−N9) = 2.21 Å.

SCHEME 5



proved to be successful: heating of hydrazone **13** in dichlorobenzene for 6 h resulted in formation of the pyrazolo[4,3-*c*]isoquinoline derivative **14** (Scheme 5). This tricyclic product proved to be identical with those obtained by us earlier via a different reaction pathway.

Conclusion

Our findings reveal that azinyl and diazinyl ketone hydrazones are suitable starting materials for ring closure to fused pyrazoles. Quantum chemical calculations reveal that the mechanism of these cyclizations specifically depend on the applied reaction conditions: under thermal conditions, the transformation is clearly of pericyclic nature, and under acidic conditions, where the nucleophilic character of the hydrazone side chain is obviously decisive, the pericyclic character of the cyclization is still present. In the presence of a strong base, the ring closure can also be carried out, and the calculations suggest that pseudoelectrocyclization takes place in this case.

Experimental Section

Computational Details. The Gaussian and Turbomole software packages[25] were used throughout this study. Stationary points of the potential energy surface were located at the B3LYP/6−31G* density functional level of theory,[26,27] and their nature (minimum or first-order saddle point) was confirmed by harmonic vibrational analysis at the same level (having 0 and 1 imaginary frequency, respectively). Thermodynamic corrections were estimated from unscaled frequencies, using standard formulas in the ideal gas approximation as implemented in Gaussian, and refer to 298.15 K and 1 atm. Relative electronic energies were determined using single-point spin component scaled MP2 (SCS-MP2) method[28] employing the aug-cc-pVTZ basis set[29] with the resolution of identity (RI) integral approximation.[30] Free energies of solvation were estimated[31] from the conductor-like polarizable continuum model[32] (CPCM) with HF wave function and the 6−31+G** basis set,[27,33] using the in vacuo optimized geometries and van der Waals radii from Bondi.[34] Toluene, ethanol, and THF were used as solvent for the neutral case, acid, and base catalysis, respectively. Reported energy values refer to relative Gibbs free energies of solvated species. Transition states were further analyzed by intrinsic reaction coordinate (IRC) calculations[35] at the B3LYP/6−31G* level. These usually failed before reaching the respective minima, but they revealed a significant portion of the path. Aromaticity was studied using NICS values[16,18] calculated at the geometrical centers of the forming rings, as well as 0.5 and 1 Å above and below. The GIAO-B3LYP/6−31+G* method[36] was used for this purpose.

Syntheses of 2-(4-chlorobenzoyl)pyrazine[38] (**1a**), acetylpyrazine[38] (**1b**), 3-(4-chlorobenzoyl)pyridazine (**5a**),[37] 3-acetylpyridazine (**5b**),[37] 2-(4-chlorobenzoyl)pyridine[39] (*E*)-2-((2-(4-bromophenyl)hydrazono)-(4-chlorophenyl)methyl)pyrazine (**2a**),[38] (*E*)-2-(1-(2-(4-bromophenyl)-hydrazono)ethyl)pyrazine (**2d**),[38] 3- (*E*)-[2-(4-bromophenyl)hydrazinylidene](4-chlorophenyl)methyl]pyridazine (**6a**),[37] (*E*)-3-(1-(2-(4-bromophenyl)-hydrazono)ethyl)pyridazine (**6c**),[37] 1-(4-bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (**4a**),[38] and cinnolylketones (**10**)[40] have been published earlier.

General Procedure for Hydrazones 2, 6, and 8. A mixture of the appropriate ketone (**1, 5** or 2(4-Cl-benzoyl)pyridine 5 mmol), substituted phenylhydrazine hydrochloride (6.1 mmol), and NaOAc (4.9 g, 60 mmol) was stirred in a mixture of ethanol (15 mL) and

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chloroform (10 mL) at rt. The progress of the reaction was monitored by TLC. After disappearance of the starting material, water (100 mL) and saturated $NaHCO_3$ solution (pH = 7−8) were added. The organic layer was separated, and the aqueous phase was extracted with chloroform (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The crude product was subjected to flash chromatography over silica by using hexane/EtOAc = 4:1 as eluent. The product was recrystallized from ethanol.

(*E*)-2-((4-Chlorophenyl)(2-p-tolylhydrazono)methyl)pyrazine (2b). This compound was obtained from 2-(4-chlorobenzoyl)pyrazine (**1a**, 5.0 mmol, 1.10 g) and 4-methylphenylhydrazine hydrochloride (6.1 mmol, 0.95 g) to give the title compound (1.20 g, 75%) as yellow crystals, mp 184−185 °C; IR (KBr) ν_{max}: 3163, 3031, 1512, 1402, 1248, 1011, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.29 (3H, s, C<u>H</u>$_3$), 7.00−7.18 (4H, m, H2″+H3″+H5″+H6″), 7.32 (2H, m, H3′+H5′), 7.58 (2H, m, H2′+H6′), 7.86 (1H, s, N<u>H</u>), 8.36 (2H, m, H5+H6), 9.45 (1H, d, J = 1.1 Hz, H3);. ^{13}C NMR ($CDCl_3$) δ (ppm): 20.6 (<u>C</u>H$_3$″), 113.4 (C2″+C6″), 129.9 (C3″+C5″), 130.0 (C2′+C6′), 130.8 (C3′+C5′), 135.6 (C4″), 139.6 (C1″), 141.0 (C6), 141.6 (C3), 142.0 (C5), 142.9 + 143.0 (C1′+C4′), 145.7 (*C*═N), 151.8 (C2). Anal. Calcd for $C_{18}H_{15}ClN_4$ (322.10): C, 66.98; H, 4.68; N, 17.36; Found: C, 66.97; H, 4.71; N, 17.20.

(*E*)-2-((4-Chlorophenyl)(2-(4-nitrophenyl)hydrazono)methyl)pyrazine (2c). This compound was obtained from 2-(4-chlorobenzoyl)pyrazine (**1a**, 5.0 mmol, 1.10 g) and 4-nitrophenylhydrazine hydrochloride (6.1 mmol, 1.15 g) to give 1.42 g of product (81%) as yellow crystals; mp 210−215 °C.

(*E*)-2-(1-(2-*p*-Tolylhydrazono)Ethyl)Pyrazine (2e). This compound was obtained from acetylpyrazine (**1b**, 5.0 mmol, 0.61 g) and *p*-tolylhydrazine hydrochloride (6.1 mmol, 0.95 g) to give 0.96 g of the product (85%) as deep-red crystals, mp 155 °C.

(*E*)-3-((4-Chlorophenyl)(2-*p*-tolylhydrazono)methyl)pyridazine (6b). This compound was obtained from 3-*p*-chlorobenzoylpyridazine (**5a**, 5.0 mmol, 1.10 g) and *p*-tolylhydrazine hydrochloride (6.1 mmol, 0.95 g) to give 1.24 g of the product (77%) as pale-yellow crystals, mp 187−192 °C; IR (KBr) ν_{max}: 3278, 1613, 1558, 1519, 1430, 1252, 1141, 1090, 1013 cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.20 (3H, s, C<u>H</u>$_3$″), 7.05 (2H, m, H2″+H6″), 7.23 (2H, m, H3″+H5″), 7.38 (2H, m, H3′+H5′), 7.60 (2H, m, H2′+H6′), 7.66 (1H, dd, J = 6.0 + 3.2 Hz, H5), 8.35 (1H, d, J = 6.0 Hz, H4), 9.04 (1H, d, J = 3.2 Hz, H6), 9.53 (1H, s, N<u>H</u>); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.2 (<u>C</u>H$_3$″), 114.6 (C2″+C6″), 124.4 (C4), 127.7 (C5), 129.9 (C3″+C5″), 130.1 (C4″), 130.3 (C3′+C5′), 131.9 (C4′), 132.6 (C2′+C6′), 134.3 (C1′), 139.2 (C1”), 143.3 (*C*═N), 151.0 (C6), 159.8 (C3). HRMS (EI): M^+, found 322.0983. $C_{18}H_{15}ClN_4$ requires 322.0985.

(*E*)-2-((2-(4-Bromophenyl)Hydrazono)(4-chlorophenyl)methyl)pyridine (8). This compound was obtained from 2-(4-chlorobenzoyl)pyridine (5.0 mmol, 1.08 g) and (4-bromophenyl)hydrazine hydrochloride (6.1 mmol, 1.35 g) to give 1.58 g (82%) of **8**; yellow crystals, mp 186−190 °C; IR (KBr) ν_{max}: 3277, 1592, 1560, 1494, 1426, 1242, 1132, 1070, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 7.00 (2H, m, H3′+H5′), 7.17 (1H, m, H5), 7.31 (2H, m, H2″+H6″), 7.36 (2H, m, H3″+H5″), 7.56 (2H, m, H2′+H6′), 7.68 (1H, s, N<u>H</u>), 7.72 (1H, m, H4), 8.15 (1H, d, J = 8.1 Hz, H3), 8.48 (1H, d, J = 4.2 Hz, H6); ^{13}C NMR ($CDCl_3$) δ (ppm): 112.8 (C4″), 114.8 (C2″+C6″), 120.6 (C3), 122.5 (C5), 128.5 (C1′), 129.9 (C2′+C6′), 130.7 (C3′+C5′), 132.1 (C3″+C5″), 135.4 (C4), 136.1 (C4′), 143.0 (C1″), 143.7 (*C*═N), 148.9 (C6), 155.9 (C2). Anal. Calcd for $C_{18}H_{13}BrClN_3$ (385.00): C, 55.91; H, 3.39; N, 10.87; Found: C, 55.77; H, 3.33; N, 10.86.

General Procedure for the Synthesis of Pyrazoles 4 and 7 from Ketones under Acidic Conditions. A mixture of the appropriate ketone (10 mmol), arylhydrazine (12 mmol), saturated HCl in ethanol (0.5 mL), and ethanol (30 mL) was refluxed for 4−24 h. The progress of the reaction was monitored by TLC. After disappearance of the starting material water (50 mL) was added, and the solution was made basic (pH = 8) with 1 M NaOH. The reaction mixture was extracted with chloroform, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was flash chromatographed over silica by using chloroform as eluent. The product was recrystallized from acetonitrile.

3-(4-Chlorophenyl)-1-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (4c). This compound was obtained from 2-(4-chlorobenzoyl)pyrazine (**1a**, 10 mmol, 2.19 g) and (4-nitrophenyl)hydrazine hydrochloride (12 mmol, 2.27 g) to give the title compound (1.93 g, 55%) as brown crystals, mp 182−184 °C;. IR (KBr) ν_{max}: 1596, 1515, 1503, 1401, 1342, 1201, 1111, 1091, 958, 854 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 7.52 (2H, m, H3′+H5′), 8.41 (2H, m, H3″+H5″), 8.55 (2H, m, H2′+H6′), 8.72 (2H, m, H2″+H6″), 8.64 + 8.77 (2H, 2×d, J = 2.2 Hz, H5+H6); ^{13}C NMR ($CDCl_3$) δ (ppm): 120.0 (C2″+C6″), 125.4 (C3″+C5″), 129.0 (C2′+C6′), 129.4 (C3′+C5′), 129.5 (C3a), 135.0 (C1′), 135.9 (C4′), 142.4 (C5), 143.5 (C6), 144.1 (C7a), 144.2 (C4″), 145.2 (C1″), 145.3 (C3). Anal. Calcd for $C_{17}H_{10}ClN_5O_2$ (351.05): C, 58.05; H, 2.87; N, 19.91; Found: C, 58.12; H, 2.65; N, 19.67.

3-(4-Chlorophenyl)-1-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyrazine (4b). This compound was obtained from 2-(4-chlorobenzoyl)pyrazine (**1a**, 10 mmol, 2.19 g) and *p*-tolylhydrazine hydrochloride (12 mmol, 1.91 g) to give 1.98 g of the product (62%) as yellow crystals, mp 160−161 °C.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (4a). This compound was obtained from 2-(4-chlorobenzoyl)pyrazine (**1a**, 10 mmol, 2.19 g) and (4-bromophenyl)hydrazine hydrochloride (12 mmol, 2.68 g) to give **4a** (2.35 g, 61%) as orange crystals, mp 202−203 °C.

1-(4-Bromophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyrazine (4d). This compound was obtained from acetylpyrazine (**1b**, 10 mmol, 1.22 g) and (4-bromophenyl)hydrazine hydrochloride (12 mmol, 2.68 g) to give 1.67 g of the product (58%); orange crystals, mp 134−136 °C.

3-Methyl-1-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyrazine (4e). This compound was obtained from acetylpyrazine (**1b**, 10 mmol, 1.22 g) to and *p*-tolylhydrazine hydrochloride (12 mmol, 1.91 g) to give 1.32 g of the product (59%) as brown crystals, mp 83−84 °C.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]pyridazine (7a). This compound was obtained from 3-(4-chlorobenzoyl)pyridazine (**5a**, 10 mmol, 2.19 g) and (4-bromophenyl)hydrazine hydrochloride (12 mmol, 2.68 g) to give 2.63 g (68%) of **7a** as pale-yellow crystals, mp 212−214 °C; IR (KBr) ν_{max}: 3079, 2919, 1589, 1574, 1492, 1394, 1093, 1072, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 7.52 (2H, m, H3′+H5′), 7.65 (2H, m, H3″+H5″), 7.72 (2H, m, H2″+H6″), 7.78 (1H, d, J = 6.2 Hz, H7), 8.50 (2H, m, H2′+H6′), 9.22 (1H, d, J = 6.2 Hz, H6); ^{13}C NMR ($CDCl_3$) δ (ppm): 106.3 (C7), 121.3 (C4″), 123.4 (C2″+C6″), 128.8 (C3a), 129.1 (C2′+C6′), 129.2 (C3′+C5′), 131.5 (C1′), 133.0 (C3″+C5″), 136.0 (C4′), 137.7 (C7a), 145.2 (C3), 145.6 (C6), 147.1 (C1″). Anal. Calcd for $C_{17}H_{10}BrClN_4$ (383.98): C, 52.95; H, 2.61; N, 14.53; Found: C, 52.95; H, 2.49; N, 14.25.

3-(4-Chlorophenyl)-1-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]pyridazine (7b). This compound was obtained from 3-*p*-chlorobenzoylpyridazine (**5a**, 10 mmol, 2.19 g) *p*-tolylhydrazine hydrochloride (12 mmol, 1.91 g) to give 2.28 g of the product (71%) as yellow crystals, mp 185−187 °C.

General Procedure for the Synthesis of 4 and 7 under Basic Medium. A mixture of the appropriate hydrazone (0.5 mmol), DBU (1 mL), and THF (20 mL) was refluxed for 4−8 h. The progress of the reaction was monitored by TLC. After disappearance of the starting material, water (50 mL) was added, the solution was extracted with chloroform, and the organic layer was dried over

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Na_2SO_4 and evaporated. The residue was flash chromatographed over silica by using hexane/EtOAc = 4:1 as eluent.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (4a). This compound was obtained from (*E*)-2-((2-(4-bromophenyl)hydrazono)(4-chlorophenyl)methyl)pyrazine (**2a**) (0.5 mmol, 0.193 g) to give 0.139 g (72%) of product. Physical and spectroscopic data (mp, IR, NMR) of this product were identical with **4a**, which was earlier isolated from 2-(4-chlorobenzoyl)pyrazine and (4-bromophenyl)hydrazine hydrochloride under acidic conditions.

3-(4-Chlorophenyl)-1-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyrazine (4b). This compound was obtained from (*E*)-2-((4-chlorophenyl)(2-*p*-tolylhydrazono)methyl)pyrazine (**2b**) (0.5 mmol, 0.162 g) to give **4b** (0.121 g, 76%). Physical and spectroscopic data (mp, IR, NMR) of this product were identical with **4b**, which was earlier isolated from 2-(4-chlorobenzoyl)pyrazine and *p*-tolylhydrazinehydrochloride under acidic conditions.

3-(4-Chlorophenyl)-1-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]pyridazine (7b). This compound was obtained from (E)-3-((4-chlorophenyl)(2-*p*-tolylhydrazono)methyl)pyridazine (**6b**) (0.5 mmol, 0.162 g) to give title compound **7b** (0.114 g, 70%). Physical and spectroscopic data (mp, IR, NMR) of this product were identical with **7b**, which was earlier isolated from 2-(4-chlorobenzoyl)pyridazine and *p*-tolylhydrazine hydrochloride under acidic conditions.

General Procedure for Pyrazole Formation from Hydrazones in 1,2-Dichlorobenzene. A mixture of the appropriate hydrazone (**2**, **6**, **8**, and **13**, 1 mmol) and 1,2-dichlorobenzene (15 mL) was stirred at 140 °C for 12−18 h. The progress of the reaction was monitored by TLC. After disappearance of the starting material, the reaction mixture was evaporated under reduced pressure at 140 °C and the residue was flash chromatographed over silica by using hexane/EtOAc = 4:1 as eluent.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (4a). This compound was obtained from (*E*)-2-((2-(4-bromophenyl)hydrazono)(4-chlorophenyl)methyl)pyrazine (**2a**) (1 mmol, 0.388 g) to give 0.251 g (65%) of **4a**. Physical and spectroscopic data (mp, IR, NMR) of this product were identical with **4a**, which was earlier isolated from 2-(4-chlorobenzoyl)pyrazine and (4-bromophenyl)hydrazine hydrochloride under acidic reaction conditions.

1-(4-Bromophenyl)-3-methyl-1*H*-pyrazolo[4,3-*c*]pyridazine (7c). This compound was obtained from (*E*)-3-(1-(2-(4-bromophenyl)-hydrazono)ethyl)pyridazine (**6c**) (0.345 mmol, 0.1 g) to give 0.078 g of product (79%) as brown crystals, mp 192−196 °C.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*b*]pyridine (9). This compound was obtained from (*E*)-2-((2-(4-bromophenyl)hydrazono)(4-chlorophenyl)methyl)pyridine (**8**, 2 mmol, 0.77 g), at 190 °C to give 0.340 g (44%) of **9** as white crystals, mp 159−162 °C; IR (KBr) ν_{max}: 3064, 1589, 1494, 1425, 1399, 1302, 1090, 947, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 7.38 (1H, dd, J = 8.4, 4.2 Hz, H6), 7.48 (2H, m, H3′+H5′), 7.68 (4H, m, H3″+H5″, H2″+H6″), 8.03 (1H, d, J = 8.4 Hz, H7), 8.57 (2H, m, H2′+H6′), 8.72 (1H, d, J = 4.2 Hz, H5); ^{13}C NMR ($CDCl_3$) δ (ppm): 118.3 (C6), 120.4 (C4″), 121.5 (C7), 123.6 (C2″+C6″), 128.7 (C2′+C6′), 128.9 (C3′+C5′), 130.2 (C1′), 132.8 (C3″+C5″), 134.6 (C4′), 138.7 (C7a), 140.0 (C3), 141.1 (C1″), 144.1 (C3a), 146.3 (C5). Anal. Calcd for $C_{18}H_{11}BrClN_3$ (382.98): C, 56.20; H, 2.88; N, 10.92; Found: C, 56.23; H, 2.64; N, 10.92.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]isoquinoline (14). This compound was obtained from (*E*)-3-((2-(4-bromophenyl)hydrazono)(4-chlorophenyl)methyl)isoquinoline (**13**, 1 mmol, 0.435 g) to give title compound **14** (0.273 g, 63%) as white crystals. All physical and spectroscopic data of this product were identical with the literaturic data.

General Procedure of Preparation of Pyrazolo[4,3-*c*]cinnolines (12). A mixture of the appropriate cinnolinylketone (**10**, 5.0 mmol) ethanol (50 mL), (4-bromophenyl)hydrazine hydrochloride or *p*-tolylhydrazine hydrochloride (1.67 g, or 1.20 g, respectively, 7.5 mmol), and 5N hydrochlorid acid in ethanol (1.27 mL) was refluxed for 4.5 h. The mixture was cooled, and the precipitated solid was collected. The crystals were suspended in water and extracted with chloroform, and the organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was boiled in ethanol (20 mL), the mixture was cooled, and the crystalline product was filtered off and recrystallized from dimethyl formamide.

3-(4-Nitrophenyl)-1-*p*-tolyl-1*H*-pyrazolo[4,3-*c*]cinnoline (12d). This compound was obtained from cinnolin-3-yl(4-nitrophenyl)-methanone (**10d**, 1.40 g), and *p*-tolylhydrazine hydrochloride to give 0.97 g (51%) of **12d** as pale-yellow crystals, mp 288−289 °C; ν_{max}: 3073, 2922, 1600, 1509, 1346, 836, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.6 (3H, s, Me), 7.5 (2H, m, H3′+H5′), 7.62 (2H, m, H2′+H6′), 7.77 (2H, m, H8+ H9), 7.95 (1H, m, H7), 8.38 (2H, m, H2″+ H6″), 8.76 (1H, d, J = 8.0 Hz, H6), 9.0 (2H, m, H3″+H5″); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4 (CH_3), 112.9 (C9a), 120.8 (C9), 123.8 (C2″+C6″), 126.4 (C2′+C6′), 128.5 (C3″+C5″), 128.6 (C3a), 130.1 (C7), 130.5 (C3′+C5′), 131.0 (C6), 131.5 (C8), 137.2 (C3), 137.4 (C1′), 139.3 (C1a), 140.6 (C4′), 143.2 (C4″), 146.3 (C5a), 147.8 (C1″); Anal. Calcd for $C_{22}H_{15}N_5O_2$ (381.39): C, 69.28; H, 3.96; N, 18.36; Found: C, 69.28; H, 3.96; N, 18.36.

1-(4-Bromophenyl)-3-phenyl-1*H*-pyrazolo[4,3-*c*]cinnoline (12a). This compound was obtained from cinnolin-3-yl(phenyl)methanone (**10a**, 1.17 g), and (4-bromophenyl)hydrazine hydrochloride to give 1.0 g (45%) of product as white crystals, mp 287−289 °C.

1-(4-Bromophenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]cinnoline (12b). This compound was obtained from (4-chlorophenyl)(cinnolin-3-yl)methanone (**10b**, 1.34 g) and (4-bromophenyl)hydrazine hydrochloride to give 1.12 g (52%) of product as white crystals, mp > 300 °C.

1,3-Bis(4-bromophenyl)-1*H*-pyrazolo[4,3-*c*]cinnoline (12c). This compound was obtained from (4-bromophenyl)(cinnolin-3-yl)methanone (**10c**, 1.57 g), and (4-bromophenyl)hydrazine hydrochloride to give 1.0 g (42%) of product as white crystals, mp > 300 °C.

1-(4-Bromophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]cinnoline (12e). This compound was obtained from cinnolin-3-yl(4-methoxyphenyl)methanone (**10e**, 1.32 g), and (4-bromophenyl)hydrazine hydrochloride to give 1.18 g (55%) of product as yellow crystals, mp 255−260 °C.

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Supporting Information Available: More detailed information, copy of NMR spectra of all compounds, ^1H NMR data (Tables S1−3), elemental analysis (Table S4), and data of computation; full references of software packages, all calculated NICS curves (Figure S1); detailed energetics for the cyclization of **2e** (Tables S5−7); total electronic energies (Tables S8−10); Cartesian coordinates of all calculated stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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