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Oxidative ring-opening of 1*H*-pyrazol-5-amines and its application in constructing pyrazolo-pyrrolo-pyrazine scaffolds by domino cyclization

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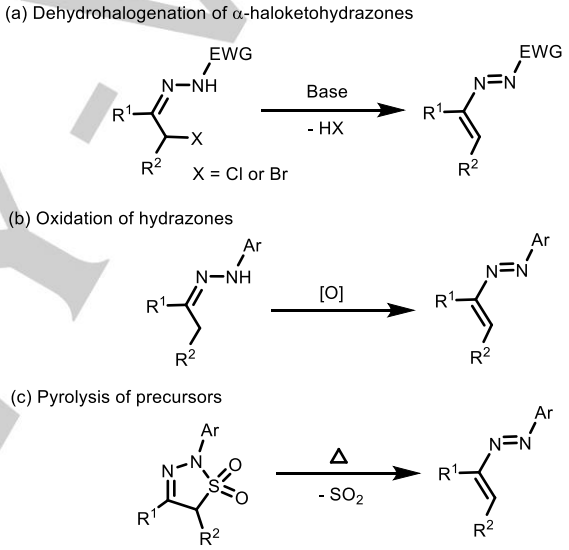
Abstract: Herein oxidative ring-opening of 1*H*-pyrazol-5-amines to form 3-diazenylacrylonitrile derivatives under mild and transition-metal-free conditions is described. In addition, the nucleophilic addition of deprotonated 1*H*-pyrrole-2-carbaldehydes to the vinyl moiety of the yielded 3-diazenylacrylonitriles could trigger domino cyclization to afford the 3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine derivatives. Computational studies suggest that the oxidation of 1*H*-pyrazol-5-amines in the presence of PhIO is through the formation of a hydroxylamine intermediate followed by elimination of H_2O to result in the ring-opening product. The detailed domino cyclization pathway leading to the pyrazolo-pyrrolo-pyrazine scaffolds is revealed.

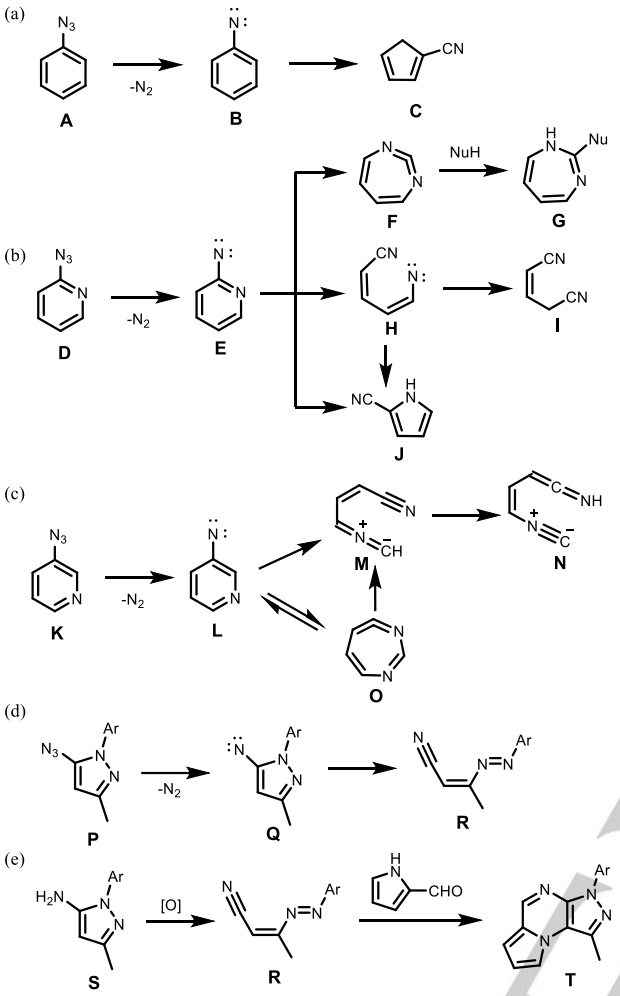
Introduction

Nitrogen-containing heterocycles are usually considered as significant motifs in bio-active compounds. Developing concise and efficient approaches to synthesize nitrogen-containing heterocycles continue to attract significant research interests.[1] In this context, azoalkenes are one of valuable building blocks in constructing multi-nitrogen-containing scaffolds via cycloaddition reactions.[2] For instance, azoalkenes involved formal [2 + 2],[3] [3 + 2],[4] [4 + 1],[5] [4 + 2],[6] and [4 + 3][7] cycloaddition reactions to access various multi-nitrogen-containing frameworks have been extensively investigated. The commonly employed method to generate azoalkenes *in situ* is through the base induced dehydrohalogenation of α-halohydrazones (Scheme 1a).[8] In addition, azoalkenes can be formed by the oxidation of hydrazones with oxidizing agents, such as I_2, HgO, and TEMPO (Scheme 1b).[9] Moreover, the pyrolysis of precursors, such as 2,5-dihydro-1,2,3-thiadiazole-1,1-dioxides and analogues, can also lead to the formation of azoalkene intermediates (Scheme 1c).[10]

The conversions of (hetero)aromatic nitrenes have been documented by Wentrup and co-workers.[11] For instance, the N_2 dissociation of phenyl azide (**A**) can produce phenylnitrene (**B**), which could undergo direct ring contraction to afford 1-cyanocyclopentadiene (**C**) (Scheme 2a). Interestingly, for 2-pyridylnitrene (**E**), the formation of ring expansion intermediate (**F**) has been established under the conditions of flash vacuum thermolysis or photolysis. In the presence of nucleophiles, the preparation of diazepines (**G**) has been realized as the application of aryl nitrene rearrangement in organic synthesis (Scheme 2b). Alternatively, **E** might undergo the ring-opening or ring contraction reactions, leading to **I** or **J**, respectively. In addition, for 3-pyridylnitrene (**L**), the generation of nitrile ylides via the ring-opening reaction has been reported (Scheme 2c). In particular, it would be reasonable to propose that 1*H*-pyrazol-5-azide derivatives (**P**) might undergo N_2 elimination to form **Q**. For the formed special hetero-aromatic nitrene intermediate **Q**, in which there is an *ortho*-(1,2)-relationship between a nitrene center and a ring heteroatom, the subsequent rearrangement might result in ring-opening to form cyano-containing azoalkene derivative, 3-diazenylacrylonitrile (**R**) (Scheme 2d).

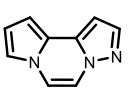


Scheme 1. The reported methods to generate azoalkenes.

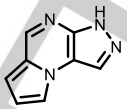


Scheme 2. Rearrangements of aryl nitrenes.

On the other hand, the oxidation of primary amines in the presence of appropriate hypervalance iodine compounds could lead to the dehydrogenation intermediate, which might behave as nitrene precursors to undergo C—H insertion[12] and aziridination reactions[13]. Guided by this strategy, we propose that 1*H*-pyrazol-5-amine derivatives (**S**) might undergo ring opening to form **R** after the dehydrogenation of the primary amino group in the presence of appropriate oxidants (Scheme 2e). In this work, a convenient approach to generate 3-diazenylacrylonitrile derivatives (**R**) is realized by the aforementioned approach. In particular, the nucleophilic addition of deprotonated 1*H*-pyrrole-2-carbaldehydes to the vinyl moiety of **R** could trigger domino cyclization to construct a novel pyrazolo-pyrrolo-pyrazine fused heterocycles (**T**). To our knowledge, the synthetic methodologies to access the pyrazolo-pyrrolo-pyrazine frameworks are very limited. In 2012, Stanforth and co-workers reported the formation of pyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine skeleton as an unexpected product.[14] In 2015, Balci and co-workers disclosed a $AuCl_3$-catalyzed cyclization of the *N*-propargyl pyrazoles to synthesize pyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine derivatives.[15] Herein, we describe a concise and efficient approach to construct a novel 3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine scaffold under mild and transition-metal-free conditions.



pyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine

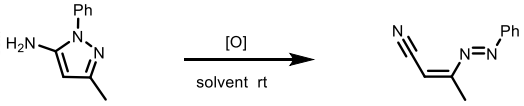


3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine

Results and Discussion

Our initial studies focus on the exploration of optimal conditions to enable the dehydrogenation of the primary amino group of 1*H*-pyrazol-5-amine (**1a**) in the presence of appropriate oxidizing agent. We are pleased to find that, when 1 equiv iodosobenzene (PhIO) is employed as the oxidant in toluene solvent, 70% yield of the proposed product (*Z*)-3-diazenylacrylonitrile derivative (**2a**), confirmed by single-crystal X-ray diffraction analysis[16], is obtained at room temperature (entry 1, Table 1). Using CH_3CN as solvent, the yield of **2a** can increase to 75% (entry 2). When the amount of PhIO increases to 2 equiv, excellent yield (90%) of the desired product is obtained (entry 9). Other oxidants, such as $PhI(OAc)_2$, $K_2S_2O_8$, and TBHP, however, are less efficient or ineffective in driving this transformation.

Table 1. Optimization of the reaction conditions for the oxidative ring-opening of **1a** [a]



1a **2a**

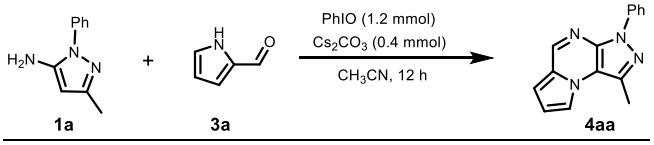
Entry	Solvent	Oxidant (equiv.)	Time (h)	Yield [b] (%)
1	Toluene	PhIO (1.0)	12	70
2	CH_3CN	PhIO (1.0)	12	75
3	DCE	PhIO (1.0)	12	71
4	^{i}PrOH	PhIO (1.0)	12	63
5	DMF	PhIO (1.0)	12	trace
6	DMSO	PhIO (1.0)	12	trace
7	NMP	PhIO (1.0)	12	trace
8	CH_3CN	PhIO (1.0)	1	75
9	CH_3CN	PhIO (2.0)	1	90
10	CH_3CN	$PhI(OAc)_2$ (2.0)	12	58
11	CH_3CN	KIO_4 (2.0)	12	trace
12	CH_3CN	$K_2S_2O_8$ (2.0)	12	trace
13	CH_3CN	TBHP (2.0)	12	trace

[a] Reaction conditions: **1a** (0.2 mmol), solvent (1 mL). [b] Isolated yield.

Next, the isolated **2a** was tried to react with 1*H*-pyrrole-2-carbaldehyde (**3a**) in the presence of base. Interestingly, a cyclization to construct a novel pyrazolo-pyrrolo-pyrazine fused heterocycle, 3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine (**4aa**), was found. The employment of base, Cs_2CO_3, in CH_3CN solvent is more operative (Table S1). We envision whether the reaction could proceed in one pot. To our delight, the desired product

4aa is obtained in 41% yield using **1a** and **3a** as reagents, PhIO and Cs_2CO_3 as additives (entry 1, Table 2). Significantly, increasing the amount of **1a** to 2 equiv, the yield of **4aa** is improved to 58% (entry 2). We also screen other bases, such as K_3PO_4, NaOH and CH_3ONa (entries 3−5), which are less effective than Cs_2CO_3. Subsequently, we continue to increase the amount of **1a** to 3 equiv, the desired product **4aa** is obtained in 62% yield (entry 6). Moreover, when **3a** and Cs_2CO_3 are added after the conversion of **1a**, the yield of **4aa** can increase to 74% via a "one-pot two steps" manner (entry 7). The change of temperature is not effective to enhance the yield (entries 8-12). This reaction is allowed to proceed for one hour with similar yield of **4aa** (entry 13). It should be noted that the reaction can be carried out on gram scale with good yields.[17]

Table 2. Optimization of the domino cyclization to afford **4aa** [a]



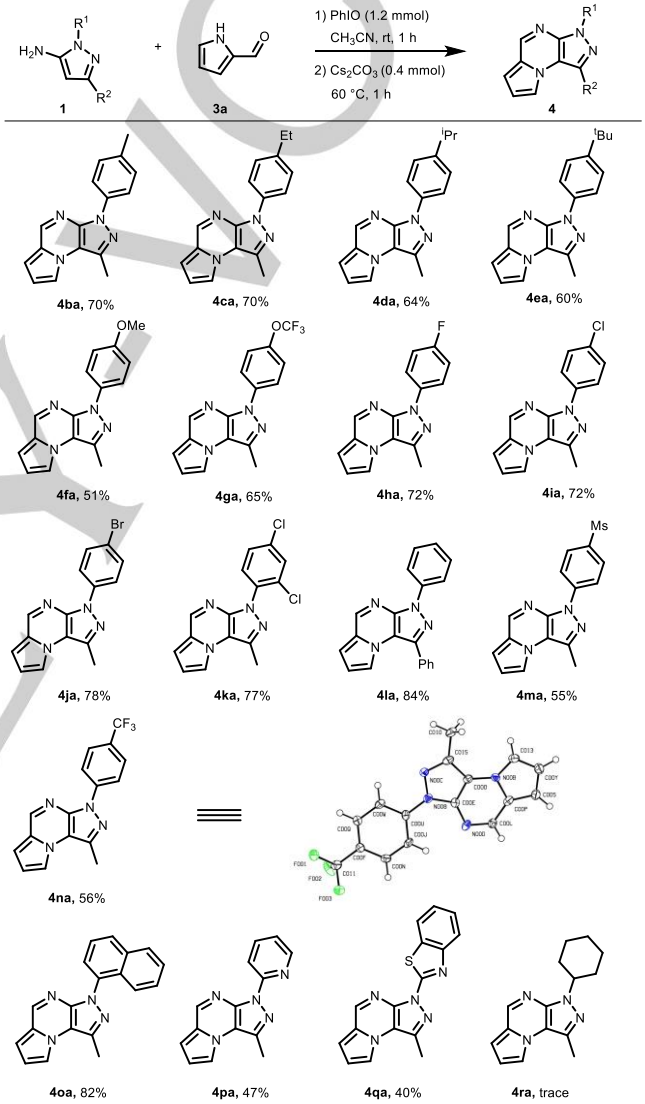
1a **3a** **4aa**

Entry	Ratio (**1a**/**3a**)	Base	T (℃)	Yield [b] (%)
1	1:1	Cs_2CO_3	60	41
2	2:1	Cs_2CO_3	60	58
3	2:1	K_3PO_4	60	45
4	2:1	NaOH	60	44
5	2:1	CH_3ONa	60	53
6	3:1	Cs_2CO_3	60	62
7 [c]	3:1	Cs_2CO_3	60	74(72) [d]
8 [c]	3:1	Cs_2CO_3	30	68
9 [c]	3:1	Cs_2CO_3	40	69
10 [c]	3:1	Cs_2CO_3	50	71
11 [c]	3:1	Cs_2CO_3	70	68
12 [c]	3:1	Cs_2CO_3	80	62
13 [c,e]	3:1	Cs_2CO_3	60	74

[a] **1a** (0.6 mmol), **3a** (0.2 mmol), PhIO (1.2 mmol) and base (0.4 mmol) in CH_3CN (1 mL) were heated to 60 ℃ for 12 h. [b] Determined by ^1H NMR with dibromomethane as internal standard. [c] A suspension solution of PhIO (1.2 mmol) in CH_3CN (5 mL) was added over 30 min to a mixture of **1a** (0.6 mmol) in CH_3CN (5 mL) at rt, after 1 h, filtrated and concentrated in 1mL, then **3a** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were added, heated for 12 h. [d] Isolated yield. [e] Reaction for 1 h.

With the optimized conditions in hand, the scope of the cyclization reaction with respect to 1*H*-pyrazol-5-amine derivatives was examined (Table 3). A series of aryl group (R^1) bearing electron-donating groups, such as Me, Et, ^{i}Pr, ^{t}Bu, and OMe, are well tolerated in the reaction of **1** with **3a**, giving the corresponding products (**4ba-4fa**) in moderate to good yields. When R^1 is OCF_3 group, the corresponding product **4ga** is obtained in 65% yield. The substrates with halogen-containing aryl groups in **1** also show good reactivity, affording the desired products (**4ha-4ka)** in good yields. Moreover, when R^2 is replaced by a phenyl group, the expected product **4la** is given in 84% yield. For the substrates with electron-withdrawing groups at the aryl group, such as trifluoromethyl and sulfonyl groups, moderate yields of the desired product are isolated (**4ma-4na**). When R^1 is 1-naphthyl (**1o**), the corresponding product **4oa** is afforded in good yield of 82%. Furthermore, for 1-pyridineyl and 1-benzothienyl pyrazoles, the yields of corresponding products **4pa** and **4qa** are isolated in 47% and 40%, respectively. Unfortunately, the 1-cyclohexyl pyrazole fails to undergo this transformation to give the product **4ra**. A possible explanation is given in the computational studies below.

Table 3. Substrate scope of substituted 1*H*-pyrazol-5-amines. [a]

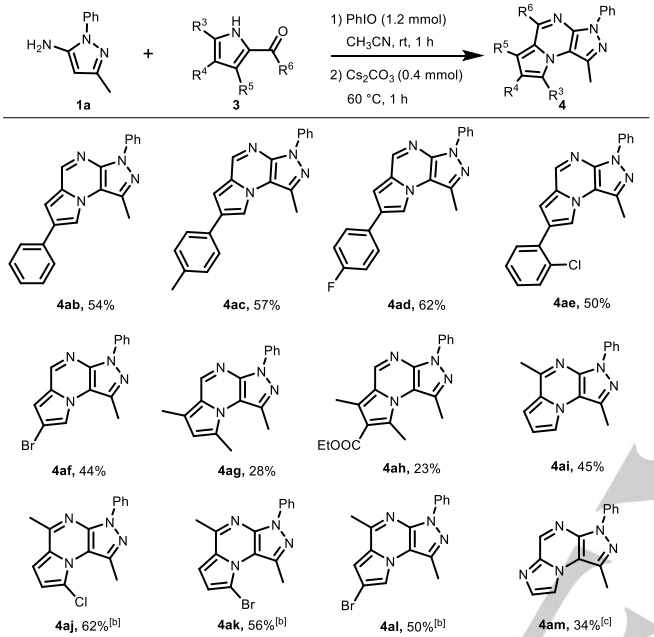


[a] Reaction conditions: a suspension solution of PhIO (1.2 mmol) in CH_3CN (5 mL) was added over 30 min to a mixture of **1** (0.6 mmol) in CH_3CN (5 mL) at rt, after 1 h, filtrated and concentrated in 1 mL, then **3a** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were added and heated to 60 ℃ for 1 h; isolated yield.

Next, we explored the substrate scope of 1*H*-pyrrole-2-carbaldehydes (**3**) (Table 4). A variety of 4-aryl-substituted 1*H*-pyrrole-2-carbaldehyde (**3b**-**3e**) can undergo the reaction with **1a** to afford the corresponding products in moderate yield (**4ab-4ae**). The 4-Br-substituted pyrrole aldehyde can also react with **1a** to afford **4af** in moderate yield. When 3,5-dimethylpyrrole

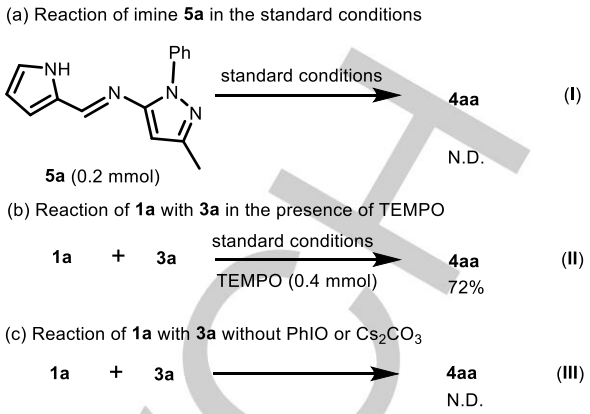
aldehydes (**3g** and **3h**) are tried to react with **1a**, the corresponding products, **4ag** and **4ah**, are obtained in low yields, which might be due to the steric hindrance caused by the 3,5-dimethyl groups attached to the pyrrole moiety. Encouragingly, a series of ketone derivatives of **3** (R^6 = Me) are tolerated in this reaction with **1a**, giving the corresponding products (**4ai-4al)** in moderate yields. Apart from the pyrrole aldehyde substrates, analogous 1*H*-imidazole-2-carbaldehyde (**3m**) can also react with **1a**, although only 34% yield of the product **4am** is obtained.

Table 4. Substrate scope of substituted 1*H*-pyrrole-2-carbaldehydes. [a]



[a] Reaction conditions: a suspension solution of PhIO (1.2 mmol) in CH_3CN (5 mL) was added over 30 min to a mixture of **1a** (0.6 mmol) in CH_3CN (5 mL) at rt, after 1 h, filtrated and concentrated in 1 mL, then **3** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were added and heated to 60 ℃ for 1 h; isolated yield. [b] Reaction for 12 hours. [c] Using K_3PO_4 (0.6 mmol) instead of Cs_2CO_3, reaction for 12 hours.

As proposed and experimentally verified previously, the (*Z*)-3-diazenylacrylonitrile (**2a**) is suggested to be the key intermediate in the formation of the desired product. Nevertheless, when the reaction is carried out in a one-pot manner, one may hypothesize alternative mechanistic pathways via an imine intermediate to afford the final product, which are independent on the formation of **2a**. The imine intermediate **5a**, which might be formed by the condensation of **1a** with **3a** in the reaction, was prepared to test the possibility in leading to the final product. When **5a** is treated under the standard conditions, the desired product **4aa** is not found (Scheme 3a). Consequently, the possible imine intermediate could be ruled out to play a critical role in this reaction. When TEMPO is added in this reaction, the yield of **4aa** is almost unchanged, implying that this reaction is not a radical process (Scheme 3b). In the absence of PhIO or Cs_2CO_3, no desired product is observed, indicating that these two additives are indispensable (Scheme 3c). Overall, the formed (*Z*)-3-diazenylacrylonitrile molecule via the dehydrogenation of the primary amino group of **1a** is the key intermediate in leading to the final product.



Scheme 3. Control experiments.

Computational studies were carried out to gain mechanistic insights into the formation of **2a** and subsequent transformation to afford the product **4aa**. Initially, the ring-opening of **1a** in the presence of PhIO to generate **2a** was explored. After the formation of an initial complex **INT1** via H-bonding interaction between **1a** and PhIO, a transition state of proton migration from the amino group of **1a** to PhIO was located as **TS1**, in which the N...H bond length is lengthened to 1.34 Å while the O...H bond length is shortened to 1.11 Å. In addition, the O...I distance is lengthened to 2.15 Å. The process of proton migration leads to the formation of hydroxylamine intermediate (**INT2**) and PhI. The dehydration of **INT2** with the assistance of two water molecules[18] could result in the ring-opening of the five-membered ring and lead to the formation of **2a** in a concerted manner. It should be noted that the oxidation of **1a** is through the formation of a hydroxylamine intermediate followed by elimination of H_2O, instead of the formation of any nitrene intermediate, which may account for the experimental result that the reaction is not sensitive to TEMPO.

The substrate **3a** could undergo deprotonation in the presence of base, Cs_2CO_3, to form **INT4** (Figure S1). The consequent nucleophilic addition of **INT4** to the alkenyl carbon of **2a** could occur to form the adduct **INT5** and the corresponding transition state is located as **TS3**. The optimized **TS3** is characterized by the shortening of the N...C distance to 2.09 Å. The predicted free energy barrier is 27.4 kcal/mol for this addition step relative to separated **INT4** and **2a** (Figure 1). It should be noted that the negatively charged N^1 in **INT5** could be stabilized by the attached phenyl group while such stabilization effect is absent for the 1-cyclohexyl pyrazole substrate (**1r**), which might account for the failure of the formation of **4ra**. Subsequently, an intramolecular nucleophilic addition of **INT5** via N^1 to the carbon of cyano group could follow to form the cyclized intermediate **INT6**. The optimized **TS4** features the shortening of C…N^1 distance to 1.97 Å. Due to the presence of Cs cation, the formed imino group in **INT6** could be stabilized to some extent. Afterwards, the second cyclization via intramolecular nucleophilic addition of the formed imino group to the carbon of aldehyde moiety could take place via **TS5** to form the framework of the fused ring. Subsequent protonation of the oxygen atom in **INT7** could lead to the formation of **INT8**. Finally,

the dehydration of **INT8** facilitated by two water molecules could lead to the final product **4aa**. Overall, a feasible domino cyclization pathway is suggested to produce **4aa** after the nucleophilic addition of deprotonated **3a** to the vinyl moiety of the key **2a** intermediate.

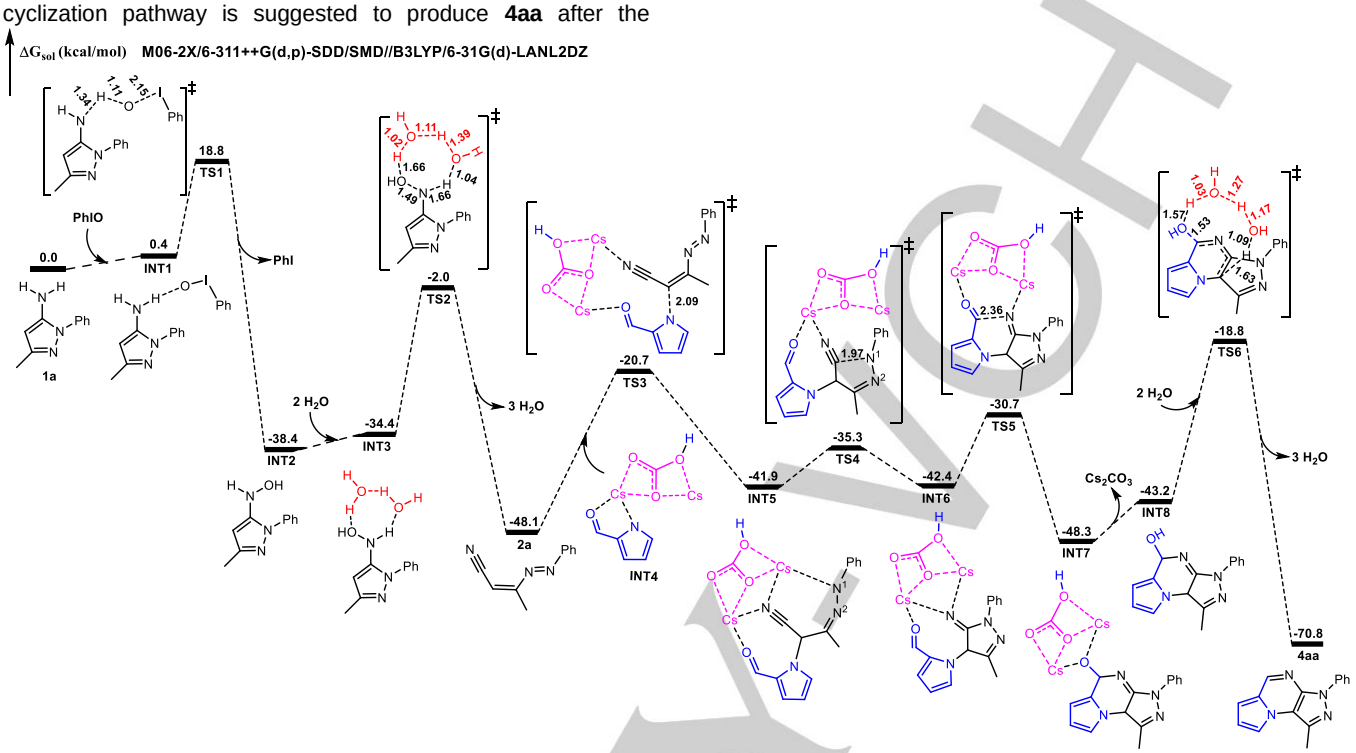


Figure 1. Energy profiles (in kcal·mol^{-1}) for the formation of final product **4aa**. Bond distances are given in Å.

Conclusion

In conclusion, the oxidative ring-opening of 1*H*-pyrazol-5-amines to form 3-diazenylacrylonitrile derivatives is realized in the presence of PhIO. Computational studies suggest that the oxidation of 1*H*-pyrazol-5-amines is through the formation of a hydroxylamine intermediate followed by elimination of H_2O to afford the ring-opening product. Interestingly, the nucleophilic addition of deprotonated 1*H*-pyrrole-2-carbaldehydes to the vinyl moiety of the formed 3-diazenylacrylonitriles could trigger domino cyclization followed by dehydration to afford the 3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine derivatives under mild and transition-metal-free conditions. Other reaction types related to the formed 3-diazenylacrylonitriles, which could be a useful building block in organic synthesis, are currently under exploration in our laboratory.

Experimental Section

General Procedure: A round bottom flask equipped with a magnetic stirrer bar was charged with PhIO (1.2 mmol, 264 mg), CH_3CN (5 mL), then the suspension solution was added over 30 min to a mixture of 1*H*-pyrazol-5-amine (**1**) (0.6 mmol) in CH_3CN (5 mL). The mixture was stirred for 1 h at room temperature. Upon completion, the mixture was filtrated and concentrated in 1 mL, then 1*H*-pyrrole-2-carbaldehyde (**3**) (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were added and heated for the given time at 60 ℃. Finally, the reaction mixture was quenched with saturated solution of brine and extracted with EtOAc (3 × 10 mL). The combined organic layer was then dried over Na_2SO_4 and concentrated under vacuum to give a residue, which was purified by flash column chromatography to give the product 3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine (**4**).

Computational details: The B3LYP density functional method (DFT)[19] was employed to carry out all the geometry optimizations. The LANL2DZ basis set in conjunction with the LANL2DZ pseudopotential[20] was used for Cs and I atoms. The 6-31G(d)[21] basis set was used for other atoms. Vibrational frequency analyses at the same level of theory were performed on all the optimized geometries to characterize stationary points as local minima (no imaginary frequency) or transition states (one imaginary frequency). In addition, intrinsic reaction coordinate (IRC) calculations were used to verify that the transition state connects with appropriate reactant and product[22]. The gas-phase Gibbs free energies for all species were obtained at 298.15 K and 1 atm at their respective optimized structures. To consider the effect of solvation, M06-2X functional[23] with the SMD[24] continuum solvation model (in acetonitrile solvent) was used in single-point energy calculations. A larger basis set, SDD[25] for Cs, I atoms and 6-311++G(d,p) for the remaining atoms, was utilized for such single-point energy calculation. The solvation Gibbs free energy was used for discussion and its value was obtained from the addition of solvation single-point energy and gas-phase thermal correction to Gibbs free energy. All calculations were carried out with the Gaussian 09 suite of programs[26].

Acknowledgements

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Keywords: Ring-opening • domino cyclization • N-heterocycle • DFT calculation

[1] For select examples, see: a) N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso, A. F. Trindade, *Chem. Rev*. **2009**, *109*, 2703; b) N. Krause, C. Winter, *Chem. Rev*. **2011**, *111*, 1994; c) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev*. **2011**, *111*, 2937; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev*. **2013**, *113*, 1; e) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev*. **2013**, *113*, 3084; f) L. Ackermann, *Acc. Chem. Res*. **2014**, *47*, 281; g) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, *Chem. Rev*. **2015**, *115*, 1622; h) P. Ruiz-Castillo S. L. Buchwald, *Chem. Rev*. **2016**, *116*, 12564; i) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Org. Biomol. Chem*. **2019**, *17*, 3670; j) J. S. Zhu, M. J. Haddadin, M. J. Kurth, *Acc. Chem. Res*. **2019**, *52*, 2256.

[2] a) J. S. Smolen, A. L. Pangan, P. Emery, W. Rigby, Y. Tanaka, J. I. Vargas, Y. Zhang, N. Damjanov, A. Friedman, A. A. Othman, H. S. Camp, S. Cohen, *The Lancet*, **2019**, *393*, 2303; b) M. C. Bryan, N. S. Rajapaksa, *J. Med. Chem*. **2018**, *61*, 9030; c) J. Schoepfer, W. Jahnke, G. Berellini, S. Buonamici, S. Cotesta, S. W. Cowan-Jacob, S. Dodd, P. Drueckes, D. Fabbro, T. Gabriel, J.-M. Groell, R. M. Grotzfeld, A. Q. Hassan, C. Henry, V. Iyer, D. Jones, F. Lombardo, A. Loo, P. W. Manley, X. Pellé, G. Rummel, B. Salem, M. Warmuth, A. A. Wylie, T. Zoller, A. L. Marzinzik, P. Furet, *J. Med. Chem*. **2018**, *61*, 8120; d) C. J. Menet, *J. Med. Chem*. **2018**, *61*, 8594; e) S. T. Wrobleski, *J. Med. Chem*. **2019**, *62*, 8973.

[3] S. Sommer, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 58.

[4] S. Sommer, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 695.

[5] a) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres, C. Bolm, *J. Am. Chem. Soc*. **2012**, *134*, 6924; b) O. A. Attanasi, L. D. Crescentini, G. Favi, F. Mantellini, S. Mantenuto, S. Nicolini, *J. Org. Chem*. **2014**, *79*, 8331; c) R. Huang, H.-Y. Tao, C.-J. Wang, *Org. Lett*. **2017**, *19*, 1176; d) Z. Wang, Y. Yang, F. Gao, Z. Wang, Q. Luo, L. Fang, *Org. Lett*. **2018**, *20*, 934; e) J. Shao, W. Chen, M. Zhao, K. Shu, H. Liu, P. Tang, *Org. Lett*. **2018**, *20*, 3992.

[6] Selected examples: a) S. Gao, J.-R. Chen, X.-Q. Hu, H.-G. Cheng, L.-Q. Lu, W.-J. Xiao, *Adv. Synth. Catal*. **2013**, *355*, 3539. b) M. C. Tong, X. Chen, J. Li, R. Huang, H. Y. Tao, C. J. Wang, *Angew. Chem. Int. Ed*. **2014**, *53*, 4680; *Angew. Chem*. **2014**, *126*, 4768; c) X. Li, K. Gai, Z. Yuan, J. Wu, A. Lin, H. Yao, *Adv. Synth. Catal.* **2015**, *357*, 3479; d) L. Wei, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 15374. e) X. Zhong, J. Lv, S. Luo, *Org. Lett.* **2015**, *17*, 1561.

[7] a) X.-Q. Hu, J.-R. Chen, S. Gao, B. Feng, L.-Q. Lu, W.-J. Xiao, *Chem. Commun*. **2013**, *49*, 7905; b) C. Guo, B. Sahoo, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc*. **2014**, *136*, 17402; c) H.-W. Zhao, H.-L. Pang, T. Tian, B. Li, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-Y. Liu, Y.-D. Zhao, *Adv. Synth. Catal*. **2016**, *358*, 1826; d) L. Wei, L. Yao, Z.-F. Wang, H. Li, H.-Y. Tao, C.-J. Wang, *Adv. Synth. Catal*. **2016**, *358*, 3748; e) L. Wei, Z.-F. Wang, L. Yao, G. Qiu, H. Tao, H. Li, C.-J. Wang, *Adv. Synth. Catal.* **2016**, *358*, 3955; f) L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2016**, *55*, 11110; *Angew. Chem*. **2016**, *128*, 11276.

[8] Selected examples: a) B. T. Gillis, J. D. Hagarty, *J. Am. Chem. Soc.* **1965**, *87*, 4576; b) L. Caglioti, G. Rosini, F. Rossi, *J. Am. Chem. Soc.* **1966**, *88*, 3865; c) L. Caglioti, G, Roaini, P. Tundo, A. Vigevani, *Tetrahedron Lett*, **1970**, *11*, 2349; d) O. Attanasi, P. Filippone, A. Mei, F. Serra-Zanetti, *J. Heterocycl. Chem.* **1985**, *22*, 1341.

[9] a) J. Schantl, *Tetrahedron Lett.* **1971**, *12*, 153; b) J. Schantl, *Monatsh. Chem*. **1972**, *103*, 1705; c) X.-L. Yang, X.-X. Peng, F. Chen, B. Han, *Org. Lett.* **2016**, *18*, 2070.

[10] a) R. K. Boeckman, Jr, P. Ge, J. E. Reed, *Org. Lett*. **2001**, *3*, 3651; b) H.-T. Yang, G.-W. Wang, Y. Xu, J.-C. Huang, *Tetrahedron Lett*. **2006**, *47*, 4129; c) N. A. Al-Awadi, Y. A. Ibrahim, E.John, A. Parveen, *Tetrahedron*. **2011**, *67*, 1298.

[11] a) C. Wentrup, *Acc. Chem. Res*. **2011**, *44*, 393. b) C. Wentrup, *Chem. Rev*. **2017**, *117*, 4562.

[12] Selected examples: a) S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung, C.-M. Che, *J. Am. Chem. Soc*. **1999**, *121*, 9120; b) X.-G. Zhou, X.-Q. Yu, J.-S. Huang, C.-M. Che, *Chem. Commun*. **1999**, 2377; c) S.-M. Au, J.-S. Huang, C.-M. Che, W.-Y. Yu, *J. Org. Chem*. **2000**, *65*, 7858; g) h) J.-L. Liang, J.-S. Huang, X.-Q. Yu, N. Zhu, C.-M. Che, *Chem. Eur. J*. **2002**, *8*, 1563; d) M. R. Fructos, S. Trofimenko, M. M. D. Requejo, P. J. Pérez, *J. Am. Chem. Soc*. **2006**, *128*, 11784; e) Z. Li, C. R. Rahaman, C. He, *Angew. Chem. Int. Ed*. **2007**, *46*, 5184; *Angew. Chem.* **2007**, *119*, 5276.

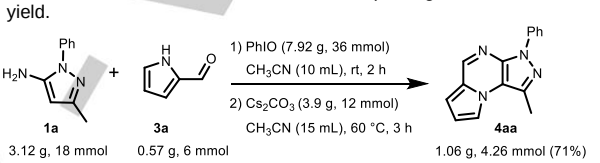
[13] Selected examples: a) P. J. Pérez, M. Brookhart, J. L. Templeton, *Organometallics* **1993**, *12*, 261; b) D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Am. Chem. Soc*. **1994**, *116*, 2742; c) P. Müller, C. Baud, Y. Jacquier, *Tetrahedron* **1996**, *52*, 1543; d) S.-M. Au, W.-H. Fung, M.-C. Cheng, C.-M. Che, S.-M. Peng, *Chem. Commun*. **1997**, 1655; e) A. N. Vedernikov, K. G. Caulton, *Org. Lett*. **2003**, *5*, 2591; f) L. D. Amisial, X. Dai, R. A. Kinney, A. Krishnaswamy, T. H. Warren, *Inorg. Chem*. **2004**, *43*, 6537; g) B. P. Gómez-Emeterio, J. Urbano, M. M. Díaz-Requejo, P. J. Pérez, *Organometallics* **2008**, *27*, 4126.

[14] R. W. Harrington, S. P. Stanforth, *Tetrahedron Lett*. **2012**, *53*, 2111.

[15] S. Basceken, M. Balci, *J. Org. Chem*. **2015**, *80*, 3806.

[16] CCDC 1974130 (**2a**) and 1974127 (**4na**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] The reaction of **1a** with **3a** could be scaled up in a gram scale with 71% yield.



[18] Additional computational results suggest that one water molecule assisted dehydration of **INT2** requires to overcome a much higher energy barrier than two water molecules (Figure S2). The formation of five-membered ring transition state for dehydration (**TS2'**) with one water is less favourable than the seven-membered ring **TS2** with the assistance of two water molecules. Similar results can also be obtained for the dehydration of **INT8** (Figure S3).

[19] a) A. D. Becke, *J. Chem. Phys*. **1993**, *98*, 5648; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B*, **1988**, *37*, 785.

[20] P. J. Hay, W. R. Wadt, *J. Chem. Phys*. **1985**, *82*, 299.

[21] P. C. Hariharan, J. A. Pople. *Theor. Chim. Acta.* **1973**, *28*, 213.

[22] K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363.

[23] a) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res*. **2008**, *41*, 157; b) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc*. **2008**, *120*, 215.

[24] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B*, **2009**, *113*, 6378.

[25] a) M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys.* **1987**, *86*, 866. b) D. Andrae, U. Häußermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta.* **1990**, *77*, 123.

[26] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision C.01, Gaussian, Inc., Wallingford CT, 2010.

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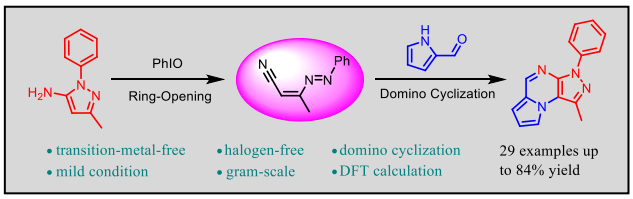
Key Topic: N-heterocycle



A concise approach to synthesize 3*H*-pyrazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine derivatives via oxidative ring-opening of 1*H*-pyrazol-5-amines under mild and transition-metal-free conditions is described herein.