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PIDA-mediated oxidative aromatic C—N bond cleavage: Efficient methodology for the synthesis of 1,2-diaza-1,3-dienes under ambient conditions

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ABSTRACT

A series of functionalized 1,2-diaza-1,3-diene derivatives were synthesized from 5–aminopyrazoles *via* oxidative cleavage of the aromatic C—N bond under transition metal-free conditions. A control experiment revealed that the presence of a free NH_2 group on the 5–aminopyrazole is important for the reaction. The utility of this valuable synthon for building diverse heterocyclic structures is also presented, which otherwise would be difficult to access using conventional methods.

Azo compounds are ubiquitous in both medicinal and synthetic chemistry (Fig. 1) [1]. More specifically, 1,2-diaza-1,3-dienes are versatile synthetic intermediates with numerous applications for the assembly of heterocyclic compounds and in the target-oriented synthesis of bioactive compounds [2,3].

In the last few decades, 1,2-diaza-1,3-dienes have gained significant attention due to their versatile reactivity and applications in various synthetic transformations [4]. However, only a few strategies have been developed to prepare these valuable intermediates.

Traditionally, 1,2-diaza-1,3-dienes are generated *in situ* from α-halohydrazones using commercially available bases [5,6]. Nenajdenko and co-workers have developed a one-pot copper-catalyzed coupling of *N*-substituted hydrazones with polyhalogenated compound to synthesize various polyhalogenated 1,2-diaza-1,3-dienes (Scheme 1a) [7].

Despite the utility of the reported methods, these reactions often suffer from disadvantages such as (i) the requirement for pre-functionalized starting materials, (ii) multiple reaction steps, (iii) harsh reaction conditions, (iv) use of bases (v) low selectivity, and (vi) poor atom economy. Thus, an efficient one-step method to access these valuable 1,2–diaza-1,3-dienes is highly desirable.

Pyrazoles are heterocycles characterized by a five-membered ring containing three carbon atoms and two adjacent nitrogen atoms [8]. Pyrazoles are known to require high dissociation energy for ring-opening of the seemingly unreactive C—N bond [9,10]. Interestingly, Smith and co-workers have demonstrated the first N_2 dissociation of azide from pyrazoles to produce heteroaromatic nitrene intermediates, which were further converted into 1,2-diaza-1,3-dienes (Scheme 1b) [11]. Recently, Bao and co-workers reported the oxidative ring-opening of 5–aminopyrazoles to produce the corresponding 1,2-diaza-1,3-dienes as well as their applications in constructing diverse heterocyclic scaffolds *via* domino cyclization (Scheme 1c) [12].

In this context, we report the regioselective ring-opening of 5-aminopyrazoles in the presence of hypervalent iodine (PIDA), affording 1,2-diaza-1,3-dienes (Scheme 1d). The utility of this strategy to build diverse, complex structures from simple starting materials is also demonstrated.

Results and discussion

We started our investigation using commercially available 5-amino-3-methyl-1-phenylpyrazole **1a** as a model substrate. Initially, we explored the reaction in DCE at 25 °C for 30 min, in the

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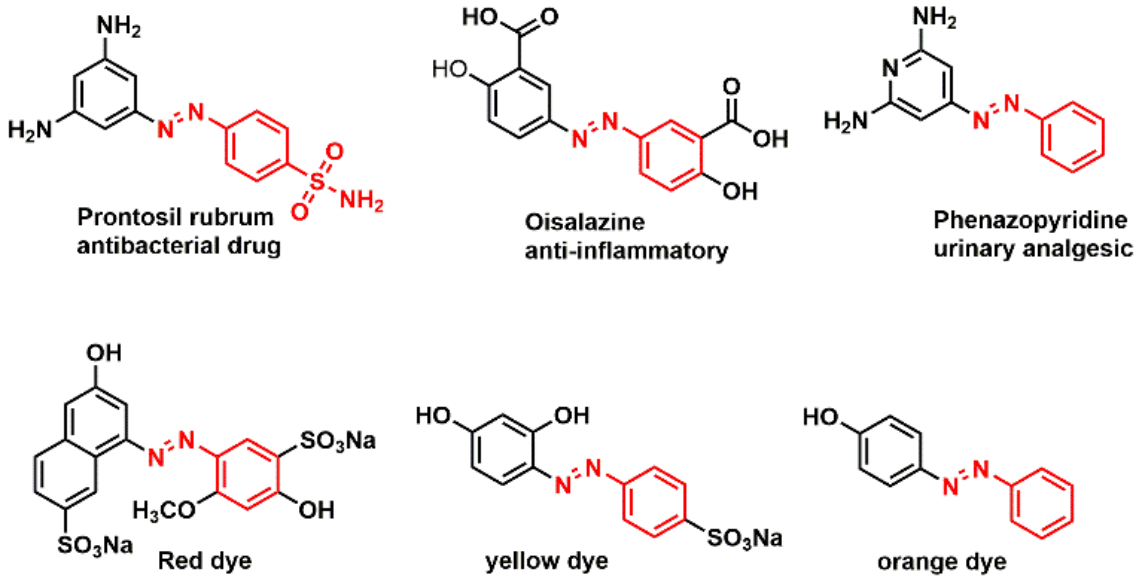
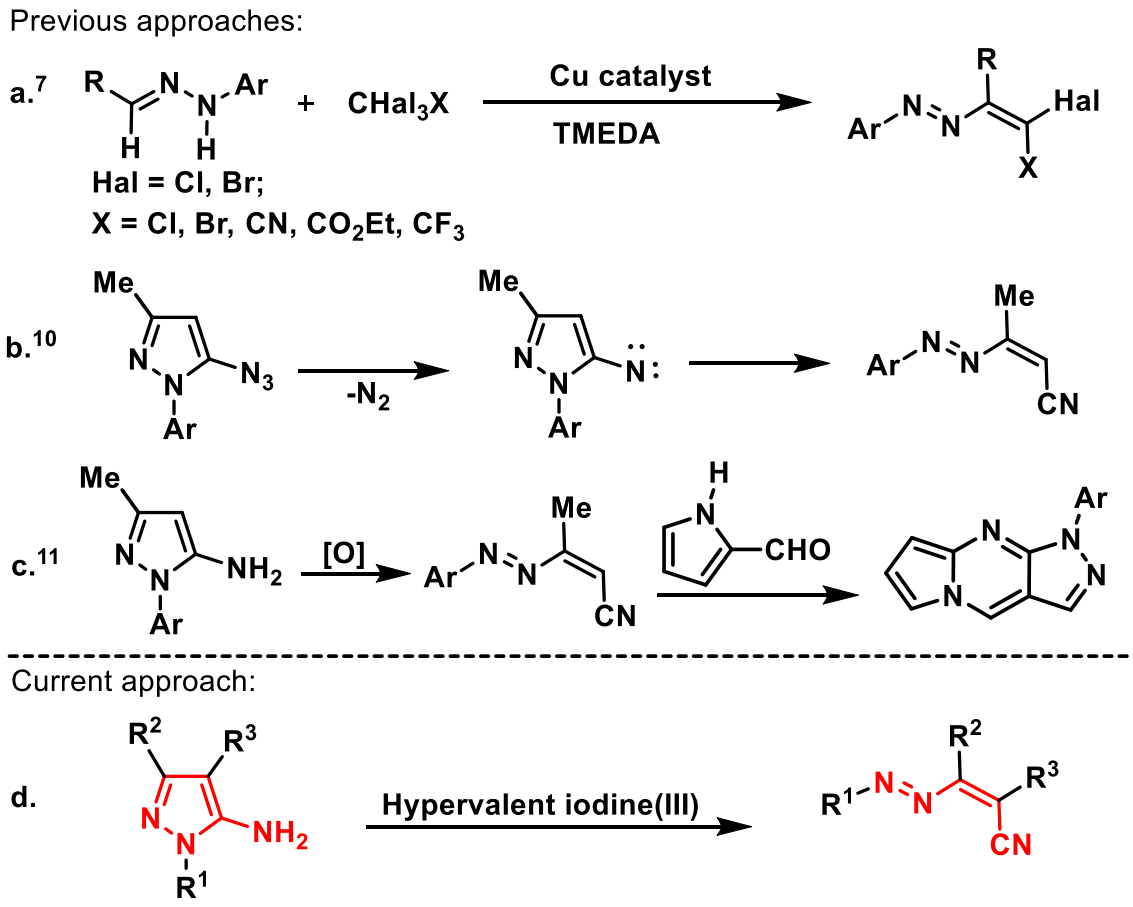


Fig. 1. Representative examples of azo containing compounds.



Scheme 1. Synthesis of 1,2-diaza-1,3-dienes.

presence of inexpensive PIDA (1.5 equiv.) as an oxidant, which gave **2a** in 90% yield.

Inspired by this result, we screened the effect of various aprotic solvents such as DMF, toluene, THF, $CHCl_3$, and 1,4-dioxane (Table S1, ESI). 1,4-Dioxane was the best solvent and gave the desired product in 96% yield after 30 min. Lower yields were obtained in protic solvents such as ethanol and water. Other oxidants such as PIFA, I_2, KI, $PhI(OPiv)_2$, and HTIB were ineffective and provided low yields (Table S2, ESI). Decreased yields were also observed with lower equivalents of PIDA. Finally, the reaction was

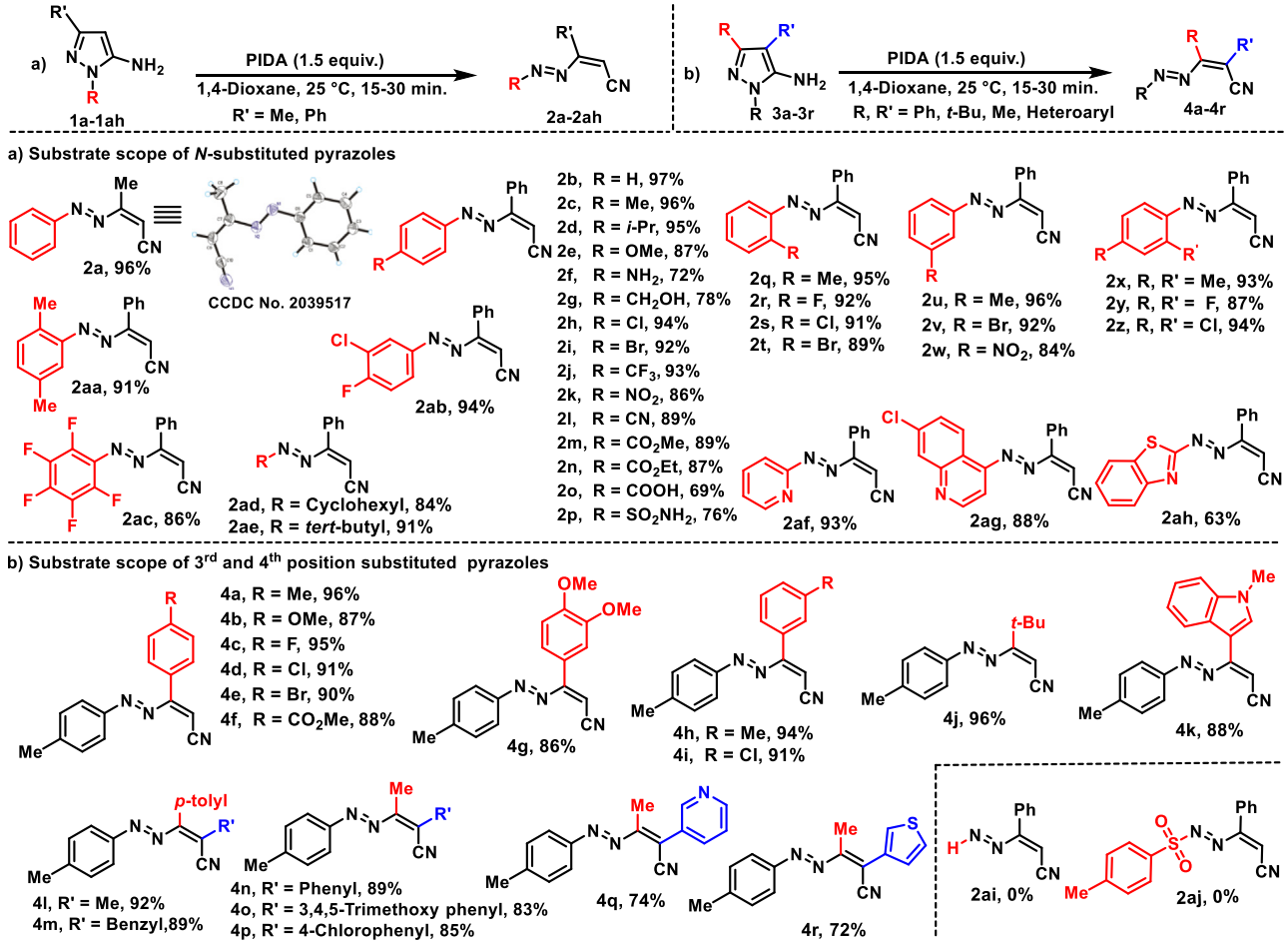
performed without PIDA; in this case, no product was obtained. The structure of **2a** was elucidated based on spectroscopic data and X-ray crystallographic analysis [13].

With the optimized reaction conditions in hand, we systematically investigated the reaction scope starting with different *N*-substituted pyrazole derivatives bearing electron-donating, -neutral, and -withdrawing groups (Scheme 2a). Aromatic rings with electron-donating groups **2b-2g** such as Me, *i*Pr, OMe, NH_2, CH_2OH, and electron-withdrawing groups **2h-2p** at the *para* position such as Cl, Br, CF_3, NO_2, CN, CO_2Me, CO_2Et, COOH, SO_2NH_2, were all tolerated and afforded the desired products in 69–97% yield. Substitution at the *ortho* and *meta* positions with electron-donating groups **2q**, **2u** or electron-withdrawing groups **2r-2w** as well as *o*-*m* **2x-2z**, *m*-*p* **2ab**, and *p*-*o* **2aa** di-substituted arene rings were also tolerated and gave the desired products in good to excellent yields. Additionally, a substrate bearing pentafluoro substitution on the aromatic ring afforded the corresponding product **2ac** in 86% yield. Notably, aliphatic **2ad-2ae** and heteroarene motifs such as pyridine **2af**, quinoline **2ag**, or thiazole **2ah** were also suitable substrates, affording the azadiene derivatives in good to excellent yields.

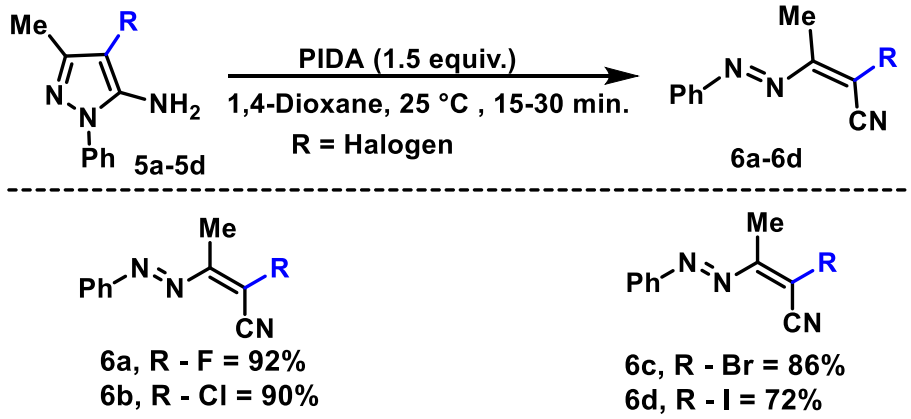
Next, we examined the substitution pattern on the third and fourth positions of the 5-amino-1-phenylpyrazoles (Scheme 2b). A wide variety of substrates possessing electron-donating and electron-withdrawing groups on the arene rings such as *p*-Me, *p*-OMe, *p*-F, *p*-Cl, *p*-Br, *p*-CO_2Me **4a-4f** and *m*-Me, *m*-Cl **4h-4i**, afforded the corresponding products in 88–95% yield. The reactions with di-substituted and *meta* substituted phenyl rings **4g-4i** gave the desired products in 86–94% yield. Furthermore, substrates with sterically hindered aliphatic motifs such as *tert*-butyl or indolylpyrazole at the third position of the 5-amino-1-phenylpyrazole **4j-4k** afforded the corresponding azadiene derivatives in excellent yields. Interestingly, substrates containing aromatic and aliphatic groups on the third and fourth positions of 5-amino-1-phenylpyrazoles **4l-4p** were also suitable substrates, affording the desired products in 83–92% yield. Notably, heterocyclic pyrazoles with pyridine and thiophene substituents were compatible with the reaction conditions and gave the corresponding azadienes **4q-4r** in 72–74% yield.

Since halogenated compounds are important in the production of biologically active compounds, the introduction of halogen atoms was attempted. Thus, 5-amino-1-phenylpyrazoles bearing halogen substitution at the fourth position were employed under the optimized reaction conditions (Scheme 3). Fluoro-substituted 5-amino-1-phenylpyrazole **6a** afforded the desired product in excellent yield. The reaction also proceeded well with the other halogen substituents **6b-6d** such as chloro, bromo, and iodo to give the desired products in good yields.

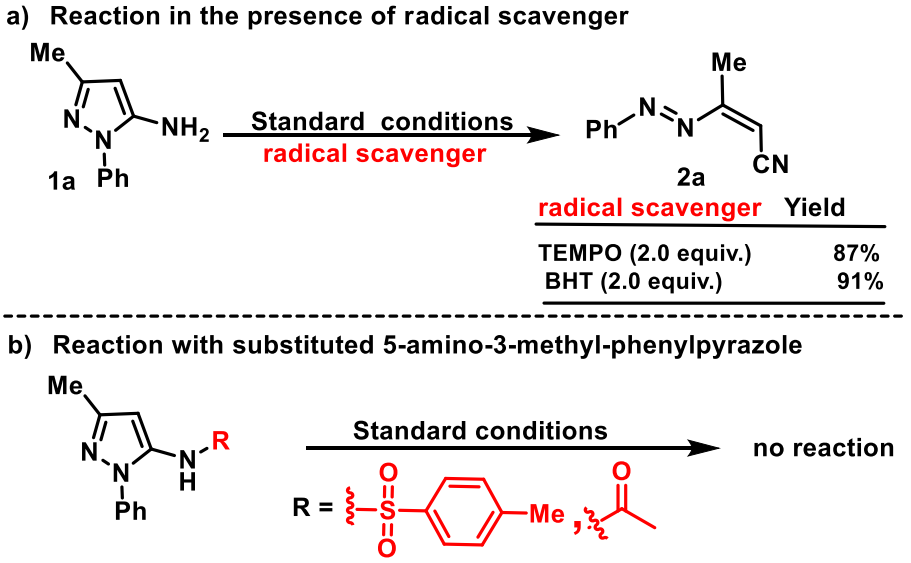
A series of control experiments were conducted to gain insight into the possible mechanism of this formal C—N bond cleavage (Scheme 4). The use of radical scavengers (TEMPO and BHT, 2.0 equiv.) under the optimized reaction conditions gave the desired product **2a** in 87% and 91% yield, respectively, which indicated the absence of radical pathways. Furthermore, the reaction did not take place when *N*-substituted sulfonyl and acyl substituted



Scheme 2. Substrate scope for the synthesis of azadienes.[a,b] [a]Reagents and conditions: **1a** (0.15 mmol), PIDA (1.5 equiv.), 1,4-dioxane (2.0 mL), 25 °C, 15–30 min. [b]Isolated yields.



Scheme 3. Substrate scope for the synthesis of halo azadienes.[a,b] [a]Reagents and conditions: **1a** (0.15 mmol), PIDA (1.5 equiv.), 1,4-dioxane (2.0 mL), 25 °C, 15–30 min. [b] Isolated yields.



Scheme 4. Control experiments.

5-amino-3-methyl-1-phenylpyrazoles were utilized, which underscores the importance of the free NH_2 group for the reaction.

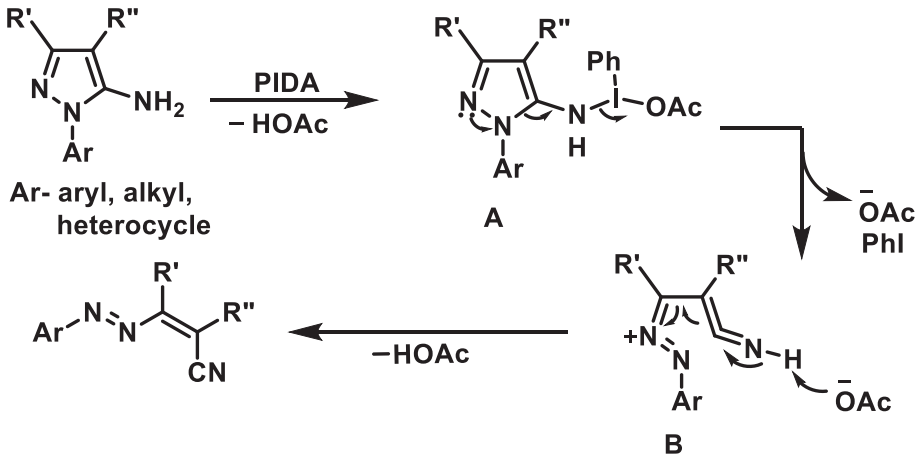
Based on the control experiments and previous literature [12,14,15], a plausible reaction mechanism was proposed (Scheme 5). Initially, $PhI(OAc)_2$ (PIDA) coordinates with 5-aminopyrazoles to give the electrophilic *N*-iodo species **A**. Next, intermediate **A** is converted into intermediate **B** by oxidative ring-opening of the pyrazole with the elimination of iodobenzene and an acetate group. Subsequently, proton abstraction from **B** leads to rearranged 1,2-diaza-1,3-dienes.

Next, various synthetic manipulations were conducted to explore the utility and reactivity of these highly versatile 1,2-diaza-1,3-dienes (Scheme 6).

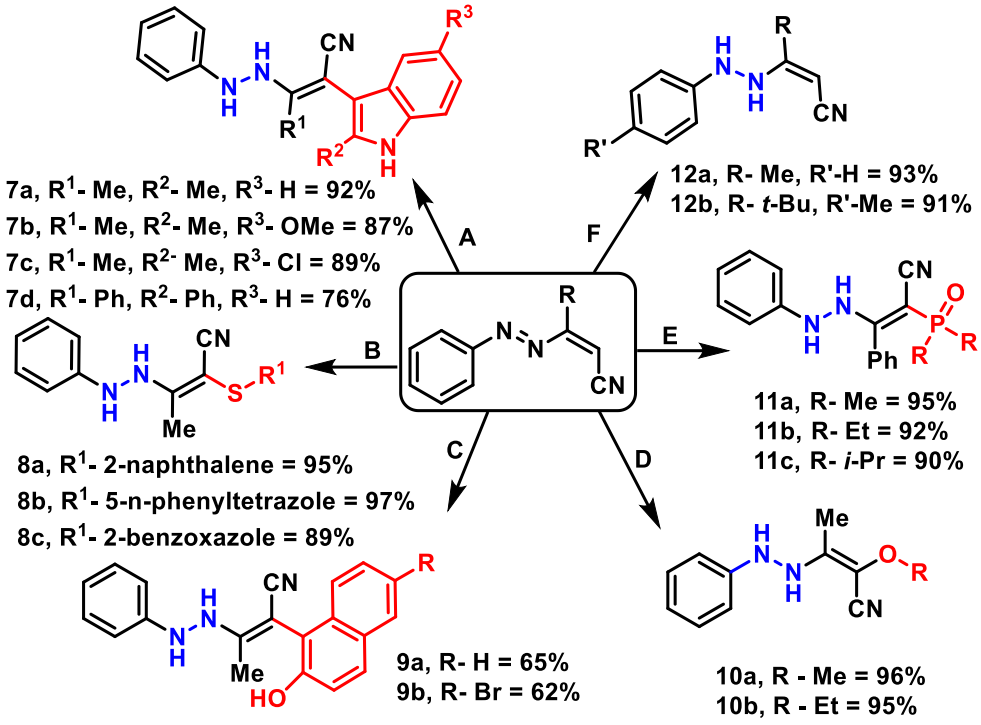
Accordingly, several nucleophiles were reacted with the olefinic carbon of selected 1,2-diaza 1,3-dienes. Interestingly, a variety of nucleophiles including substituted indoles (A), thionaphthols, heteroaromatic thiols (B), and naphthols (C), underwent 1,4-Michael addition with the olefinic carbon of the 1,2-diaza-1,3-dienes in the presence of catalytic diphenyl phosphate (10 mol%) in good to excellent yields. Furthermore, primary alcohols (D) were reacted with 1,2-diaza-1,3-dienes in the presence of K_3PO_4 (0.5 equiv.) in good yields. Also, 1,2-diaza 1,3-dienes were reacted with trialkyl phosphites (E) and NH_2-NH_2·H_2O (F) in ethanol in 90–96% yield.

Conclusion

We have developed a simple and efficient method for preparing 1,2-diaza-1,3-dienes utilizing an inexpensive hypervalent iodine (PIDA) catalyst. This reaction represents the first example of the oxidative ring-opening of C—N bonds under metal-, photocatalyst-, and light-free conditions. Control experiments revealed that the free NH_2 group is important for the reaction. The synthetic utility of these 1,2-diaza-1,3-dienes was demonstrated by the reactions with diverse nucleophiles which readily provided access to a variety of functionalized scaffolds.



Scheme 5. Plausible reaction mechanism.



Scheme 6. Synthetic utility of substituted 1,2-diaza-1,3-dienes. Reagents and conditions: (A) 2-substituted indoles, $(C_6H_5)_2P(O)OH$ (10 mol%), CH_2Cl_2, 25 °C, 2 h; (B) β-substituted thiols, $(C_6H_5)_2P(O)OH$ (10 mol%), CH_2Cl_2, 25 °C, 2 h; (C) β-substituted naphthols, $(C_6H_5)_2P(O)OH$ (10 mol%), CH_2Cl_2, 25 °C, 2–3 h; (D) aliphatic alcohols, K_3PO_4 (0.5 equiv.), 70 °C, 1–2 h; (E) trialkylphosphites, neat, 25 °C, 5–7 h; (F) NH_2-NH_2·H_2O, EtOH, reflux, 1 h.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153252.

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