Organic LETTERS

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I_2–TBHP-Catalyzed Oxidative Cross-Coupling of *N*-Sulfonyl Hydrazones and Isocyanides to 5-Aminopyrazoles

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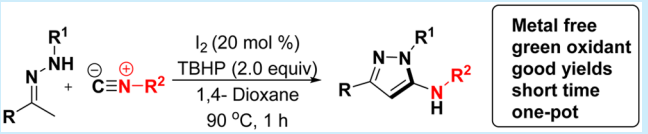
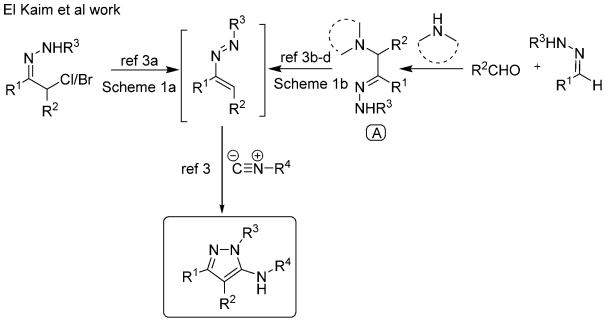
Supporting Information

ABSTRACT: I_2–TBHP-catalyzed oxidative cross coupling of *N*-sulfonyl hydrazones with isocyanides has been realized for the synthesis of 5-aminopyrazoles through formal [4 + 1] annulation via in situ azoalkene formation. Notable features are the metal/alkyne-free strategy, C–C and C–N bond formation, atom economy, catalytic I_2, broad functional group tolerance, good reaction yields, shorter time, and also applicability to one-pot methodology.



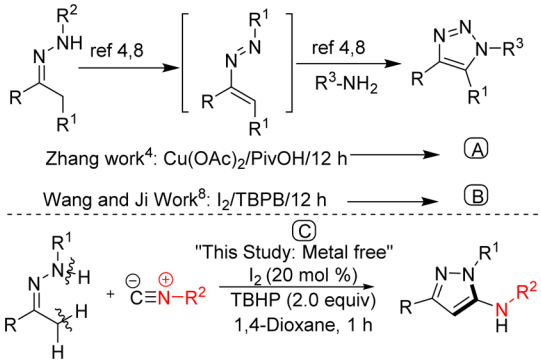
Hydrazones are important precursors in synthetic chemistry owing to their high reactivity.[1] In particular, the formation of 1,2-diaza-1,3-dienes (azo-alkenes) from dehydrohalogenation of hydrazones has emerged as a powerful tool for the synthesis of nitrogen-containing heterocycles.[2] In this context, El Kaim et al. developed an elegant approach to construct aminopyrazoles from α-halo ketohydrazones and isocyanides in the presence of base via an azo-alkene intermediate (Scheme 1a),[3a] but the lack

Scheme 1. Previous Approaches to 5-Aminopyrazoles



of readily available starting material and utilization of activated hydrazones are drawbacks of this method. Later, the same group developed an improved protocol for starting material synthesis from the Mannich reaction of hydrazones with aldehydes and amines to afford the azo-alkene precursor **A** (Scheme 1b).[3b−d] Despite their remarkable advances, they also suffer from certain limitations such as prefunctionalized hydrazones, limited substrate scope, and the need for a stoichiometric base. To overcome these issues, Zhang et al. disclosed a facile oxidative C–H functionalization approach to beget azo-alkenes from hydrazones for the first time mediated by $Cu(OAc)_2$/PivOH, which was then trapped with anilines for the synthesis of 1,2,3-triazoles (Scheme 2A).[4] On the other hand, oxidative C–H

Scheme 2. Previous Approaches and Present Study



functionalization by metal-free versions has become very popular for avoiding expensive metals and environmental hazards.[5] In this view, the I_2/oxidant combination has become an efficient method for the construction of various C–C[6] or C–N[7] bonds. These metal-free advancements prompted Wang and Ji to establish a practical and simple I_2–TBPB-mediated azo-alkene generation through an α-halo ketohydrazone intermediate from hydrazones, which was also trapped with anilines to afford 1,2,3-triazoles (Scheme 2B).[8] Based on the above study and to the best of our knowledge, there is no literature precedence to afford 5-aminopyrazoles by direct oxidative α-C_{sp^3}–H functionalization[5d] of hydrazones with isonitriles. As part of our continuing interest in iodine[9a−c] and isocyanide[9d] chemistry, we herein

Received: February 6, 2015

DOI: 10.1021/acs.orglett.5b00398
Org. Lett. XXXX, XXX, XXX−XXX

report an environmentally benign I_2–TBHP-catalyzed oxidative cross-coupling of *N*-sulfonyl hydrazones with isocyanides through conjugate (C–C bond) and zwitterionic (C–N bond) bond formation via in situ generated azoalkenes (Scheme 2C).

5-Aminopyrazoles are one of the privileged classes of nitrogen heterocycles, and they find extensive application in pharmaceutical chemistry[10] and possess versatile biological properties (Figure 1), for example, as positive allosteric modulators

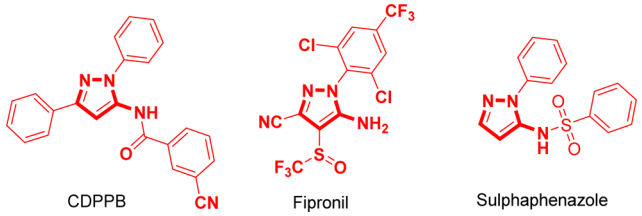


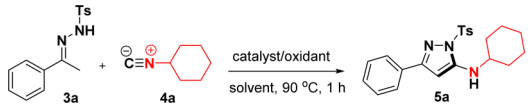
Figure 1. Examples of 5-aminopyrazoles.

(CDPPB),[11a] insecticides (fipronil),[11b] sulfonamide antibacterials (sulfaphenazole),[11c,d] etc. They also represent a potential building block for the synthesis of various fused *N*-heterocycles.[12] Therefore, the development of non-prefunctionalized, green, efficient, and especially catalytic metal/base-free synthetic routes toward pyrazoles is highly desirable for the synthetic community.

We began our investigation reaction between 4-methyl-*N*′-(1-phenylethylidene)benzenesulfonylhydrazide **3a** and cyclohexyl isocyanide **4a** as the model substrate with a stoichiometric amount of I_2 (2.0 equiv) in 1,4-dioxane at 90 °C for 16 h, but the desired compound **5a** was unsuccessful (Table 1, entry 1). Next, the feasibility of reaction was tested with various oxidants (Table 1, entries 2–9) and catalytic I_2 (20 mol %). To our surprise, the desired compound **5a** was achieved in 85% in 1 h using TBHP (5–6 M) in decane (Table 1, entry 9). The reaction failed to proceed in the absence of I_2 or TBHP (Table 1, entries 10 and 11), suggesting that both I_2 and TBHP are very crucial for the formation of compound **5a**. Several other iodide sources such as KI, NaI, NIS, TBAI, and PIDA in the presence of TBHP (Table 1, entries 12–16) as an oxidant revealed NIS as the best choice among them by affording 84% of 5-aminopyrazoles **5a** (entry 14). Replacing NIS with NBS as the "Br" source failed to proceed with the remaining starting material (Table 1, entry 17). We have selected I_2 as compared with NIS for further optimization by considering the benefits like the environmentally benign nature of I_2 and cost-effectiveness.[13] The solvent study revealed 1,4-dioxane (Table 1, entry 9) as the best solvent (Table 1, entries 18–22). Furthermore, the lower loading of I_2 (10 mol %) showed a decreased reaction yield for **5a** (74%) and no significant change on higher loading of I_2 (Table 1, entries 23 and 24). Finally, the effect of time and temperature was examined, and it was found that longer time (Table 1, entry 27) and lower temperature (Table 1, entry 25) reduced the yield of compound **5a** and led to no substantial change at 100 °C (Table 1, entry 26). Thus, the reaction parameters given in Table 1, entry 9, were the optimal reaction conditions.

With the optimal reaction conditions, we decided to examine the scope of this conversion with a diverse set of *N*-sulfonyl hydrazones and isocyanides (Schemes 3 and 4). As shown in Scheme 3, a variety of *N*-tosyl hydrazones **3a–q** reacting with cyclohexyl isocyanide **4a** were first investigated for the formation of 5-aminopyrazoles. If the *R*-position of *N*-sulfonyl hydrazones is attached to a phenyl ring, both electron-donating groups and electron-withdrawing groups such as *p*-Me, *p*-MeO, *m*-Br, *m*-I, *p*-

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant[g]	solvent	yield[b] (%)
1[c]	I_2		1,4-dioxane	0
2[d]	I_2	Oxone	1,4-dioxane	trace
3[d]	I_2	$K_2S_2O_8$	1,4-dioxane	trace
4[e]	I_2	H_2O_2	1,4-dioxane	0
5	I_2	BPO[l]	1,4-dioxane	71
6[d]	I_2	Tempo	1,4-dioxane	<10
7[d]	I_2	DTBP	1,4-dioxane	trace
8[f]	I_2	TBHP	1,4-dioxane	80
9	**I_2**	**TBHP**	**1,4-dioxane**	**85**
10[d]		TBHP	1,4-dioxane	0
11[d]	I_2		1,4-dioxane	trace
12	KI	TBHP	1,4-dioxane	70
13	NaI	TBHP	1,4-dioxane	72
14	NIS	TBHP	1,4-dioxane	84
15	TBAI	TBHP	1,4-dioxane	17
16	PIDA	TBHP	1,4-dioxane	0
17	NBS	TBHP	1,4-dioxane	0
18	I_2	TBHP	CH_3CN	24
19	I_2	TBHP	1,2-DCE	0
20	I_2	TBHP	toluene	59
21	I_2	TBHP	DMSO	<10
22	I_2	TBHP	DMF	42
23[h]	I_2	TBHP	1,4-dioxane	74
24[i]	I_2	TBHP	1,4-dioxane	87
25[j]	I_2	TBHP	1,4-dioxane	78
26[k]	I_2	TBHP	1,4-dioxane	84
27[d]	I_2	TBHP	1,4-dioxane	70

[a]Reaction conditions: **3a** (0.175 mmol), **4a** (0.190 mmol), catalyst (20 mol %), oxidant (0.346 mmol), solvent (0.7 mL), time (1 h), temp (90 °C). [b]Isolated yields. [c]I_2 (2.0 equiv) and stirred for 16 h. [d]For 16 h. [e]H_2O_2 (30% in water). [f]TBHP (70% aqueous). [g]TBHP (5–6 M in decane). [h]I_2 (10 mol %). [i]I_2 (30 mol %). [j]At 70 °C. [k]At 100 °C. [l]BPO (benzoyl peroxide).

CF_3, 3,4-dichloro, *p*-CN, and *p*-COOMe were well tolerated to give the corresponding target compounds **5b,c,e–l,k** in 72–80% yields. In the case of the *p*-F substituent (**5d**), NIS was used as a catalyst due to the low yield and complex mixture with iodine. The reaction was also successful with heterocyclic and cycloalkanones derivatives such as furyl and α-tetralone by affording the desired final compounds **5m** and **5n** in 63–68% yields, respectively, except for the 6-MeO-α-tetralone, which resulted in the inseparable mixture after purification.[14a] However, hydrazones such as *p*-$CONH_2$, *p*-COOH, and α-substituted and aliphatic *N*-sulfonyl hydrazones did not create the required pyrazole compounds **5j,l,p,q**.[14b]

To further explore the synthetic potential of this methodology, several isocyanides as well as hydrazone groups were investigated as substrates under the optimized reaction conditions (Scheme 4). Tertiary and benzyl isocyanides were converted to the corresponding products **6a,c,d** in high yields (70–88%), except the compound **6b** (60%), which may attribute to the steric hindrance of the methoxy group at the *ortho* position. Aryl isocyanide substrates bearing an electron-donating group on the benzene ring gave a higher yield (**6e** and **6f**) than the electron-withdrawing group (**6h** and **6i**). In the case of *p*-fluoro isocyanide substituent (**6g**), I_2 was replaced by NIS because of the complex

DOI: 10.1021/acs.orglett.5b00398
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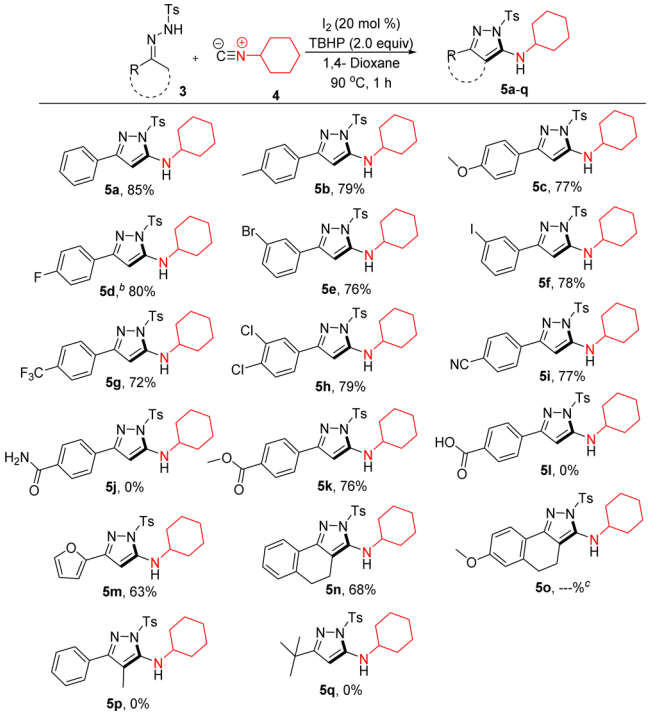
Scheme 3. Scope of I_2–TBHP-Catalyzed Synthesis of 5-Aminopyrazoles with Various *N*-Tosyl Hydrazones and Cyclohexyl Isocyanide[a]



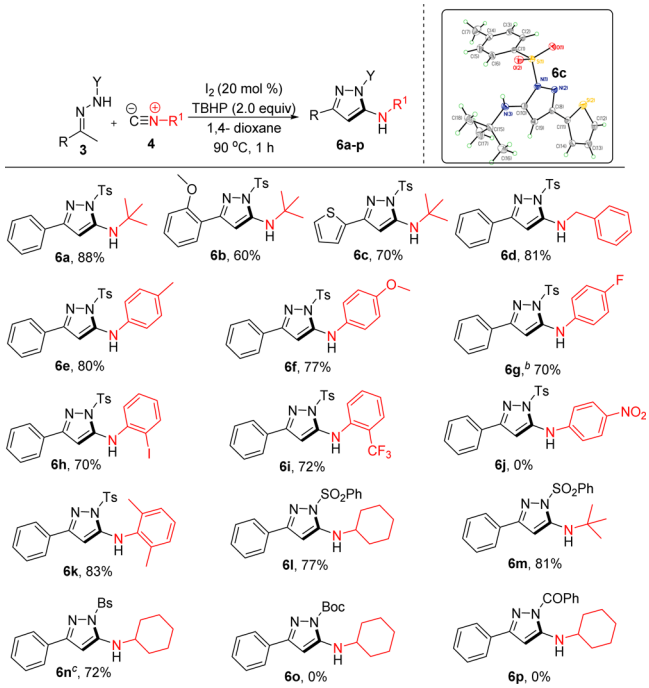
[a]Reaction conditions: compound **3a-q** (0.5 mmol), cyclohexyl isocyanide **4a** (0.55 mmol), I_2 (20 mol %), TBHP (1.0 mmol), 1,4-dioxane (2.0 mL), 90 °C, 1 h. [b]NIS was used instead of I_2. [c]The exact yield of the compound could not be determined due to the inseparable mixture along with desired compound.

mixture and low reaction yield. In addition, the scope of reaction worked well with simple benzenesulfonyl and 4-bromobenzenesulfonyl by obtaining the respective aminopyrazoles derivatives **6l–n** in 72–81% yields. On the other hand, replacing *N*-sulfonyl hydrazones with tertiary butyl carbazate and benzoyl hydrazides did not produce the desired final compounds **6o** and **6p**. The structures of compound **6c** and **6g** were confirmed by X-ray analysis.

To check the feasibility of the reaction in a one-pot strategy, we initially examined tosyl hydrazine **2**, acetophenone **1a**, and cyclohexyl isocyanide **4a** in a 1/1.1/1.1 ratio under the optimized conditions for 1 h (Scheme 5), and to our surprise, the desired compound **5a** was obtained in 40% yield. The reason for the low yield could be the shorter reaction time and the presence of unreacted hydrazone intermediate **3**. On the basis of this result, when the reaction was heated for longer time (12 h), the yield decreased with the complex mixture.[Ts] To further explore the scope of the one-pot reaction, some of the representative ketones and isocyanides were tested, and all of them resulted in the desired products **5f,6a,k,l** albeit in low to average reaction yields.

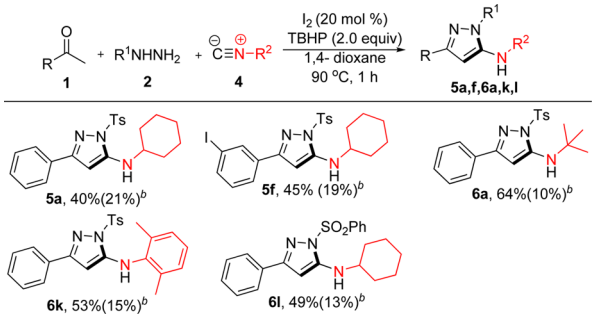
From the obtained results and previous literature reports,[3,4,8] a plausible mechanism was proposed as shown in Scheme 6. The *N*-sulfonyl hydrazones **3** were converted to *α*-iodo hydrazones **A** in the presence of catalytic iodine, and subsequently, the intermediate **A** was transformed to the azoalkene **B** by the elimination of HI. The probable reason for this elimination may be attributed to weak nucleophilicity of isocyanides to displace the aliphatic iodide of intermediate **A**. The eliminated HI was oxidized to I_2 in the presence of TBHP, and the catalytic cycle

Scheme 4. Scope of Isocyanides and Hydrazones[a]



[a]Reaction conditions: compound **3a,o–s** (0.5 mmol), cyclohexyl isocyanide **4a** (0.55 mmol), I_2 (20 mol %), TBHP (1.0 mmol), 1,4-dioxane (2.0 mL), 90 °C, 1 h. [b]NIS was used instead of I_2. [c]Bs (brosyl).

Scheme 5. One-Pot Reaction of Aryl Methyl Ketones, Tosylhydrazines, and Isocyanides[a]



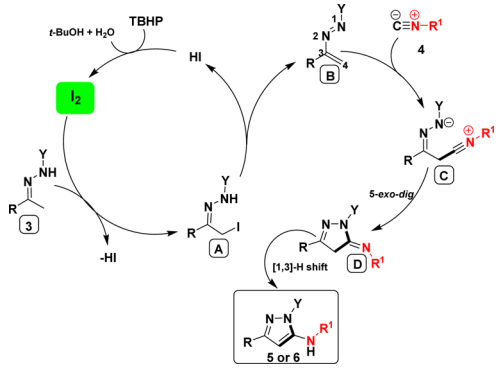
[a]Reaction conditions: compound **2a,b** (0.53 mmol), compound **1a,f** (0.59 mmol), isocyanide **4** (0.59 mmol), I_2 (20 mol %), TBHP (1.06 mmol), 1,4-dioxane (2.0 mL), 90 °C, 1 h. [b]Isolated yields of *N*-sulfonyl hydrazones **3**.

was regenerated.[8] Then the reaction of isocyanide **4** with highly electrophilic C-4 carbon[2a] of azo-alkene **B** gave zwitterion intermediate **C** through the conjugate addition (C–C bond).[3] Finally, the desired aminopyrazoles were obtained by zwitterionic 5-*exo-dig* cyclization (C–N bond) of intermediate **C** followed by [1,3]-H shift.[9d]

In summary, we have developed the first example of I_2–TBHP-catalyzed formal [4 + 1]-annulation of *N*-sulfonyl hydrazones with isocyanides for the synthesis of 5-aminopyrazole via in situ generation of azo-alkene. This metal-free approach is realized through conjugate addition (C–C bond formation) and zwitterionic cyclization (C–N bond formation). The key features of this work include environmentally benign catalytic I_2, applicable to one-pot methodology, atom-econom-

DOI: 10.1021/acs.orglett.5b00398
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 6. Plausible Reaction Mechanism



ical, broad functional group compatibility, good reaction yields, and shorter time.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and spectral data of the starting materials and final products. X-ray structures of compound **6c** (CCDC No. 1038285) and **6g** (CCDC No. 1048006). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge funding from the Ministry of Science and Technology (MOST), Taiwan.

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(13) The price of I_2 was comparatively 5 times lesser than NIS. For example, I_2 (25 g, 99.8% purity) is $20 USD and NIS (25 g, 99.8% purity) is $95 USD.

(14) (a) The reaction worked to afford the desired compound, but after the column purification NMR spectra showed an inseparable mixture (see the Supporting Information, **5o**). (b) The starting material was analyzed by TLC to isolate other unidentified compounds instead of the desired pyrazoles.

(15) At this stage, the yield of the one-pot reaction was found to be lower. We are currently working on ways to optimize the one-pot strategy and extend this application of our work.

DOI: 10.1021/acs.orglett.5b00398
Org. Lett. XXXX, XXX, XXX−XXX