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A facile and expeditious approach to substituted 1*H*-pyrazoles catalyzed by iodine

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ABSTRACT

A facile and expeditious method for the synthesis of 1*H*-pyrazoles by the reaction of α,β-unsaturated aldehydes/ketones and sulfonyl hydrazide catalyzed by as low as 2 mol% I_2 has been demonstrated. This synthetic system features simple operation and mild reaction conditions, and displays a broad functional group tolerance furnishing good to excellent yields.

Introduction

While the relative incapacity of Nature to cope with the N-N bond results in pyrazole containing natural products a real infrequency, such heterocycles, which are not only of considerable application but also a perennial source of fascination and inspiration to scientists for more than a century, represent a diverse array of significantly functional compounds of unnatural origin abundantly featured in agrochemicals, pharmaceuticals, material and synthetic chemistry.[1] Compounds bearing the pyrazole nucleus, in particular, have exhibited a wide spectrum of therapeutic application and a plethora of drugs have progressed to the market,[2,3] such as lonazolac,[2b] fipronil,[2c] Viagra,[2d] celecoxib,[2e] and many others. Pyrazoles also constantly act as essential building blocks of ligands for transition metals, supermolecules and liquid crystals.[4] Owing to their multifarious and prominent properties, the discovery of environmentally benign, efficient and practical approaches for the construction and functionalization of pyrazole cores, especially in a regioselective manner, has always been an active field of research of high impact in synthetic chemistry.[5]

The most commonly used approaches for the acquisition of substituted pyrazoles include: 1) condensation of hydrazines with 1,3-dicarbonyl compounds or their synthetic equivalents,[6] 2) condensation of α,β-unsaturated carbonyl compounds with hydrazines followed by dehydrogenation,[7] 3) [3 + 2] cycloadditions of 1,3-dipoles to dipolarophiles like alkenes and alkynes,[5g] 4) the nucleophilic attack of hydrazines to flavones, chromones, or isoxazoles.[8] Although appealingly general, these approaches have their own safety, eco-friendliness, scope or efficiency limitations. For instance, formation of two regioisomers by the condensation routes is an inevitable drawback and methods based on nucleophilic reactions necessitate multistep procedures to secure the starting material, while methodologies depending on dipolar cycloaddition reactions usually characterize regioselective disadvantages, and diazo compounds are considered to be poisonous and potentially explosive.

Among these popular procedures for pyrazole synthesis, hydrazine hydrate is applied as a predominant nitrogen source, nevertheless, most of these transformations are dependent on a large excess amount of hydrazine hydrate and oxidant or base. In 1987, Shechter et al. published the early report in which only 1.1 eq. of tosyl hydrazide with unsaturated ketone was used as nitrogen source for the preparation of 1*H*-cyclooctapyrazoles.[9] Then, a remarkable number of novel 1*H*-pyrazoles synthesis using substituted hydrazides, especially sulfonyl hydrazides as nitrogen transfer reagents have been reported. In 2011, Yu and co-workers established a highly efficient and eco-friendly protocol for the preparation of substituted 1*H*-pyrazoles by one-pot condensation reaction of α,β-unsaturated carbonyl compounds with tosyl hydrazide promoted by stoichiometric tetrabutylammonium bromide in water (Scheme 1).[10] In 2014, Chang et al. developed an efficient method for regioselective pyrazole preparation from α,β-unsaturated aldehydes/ketones and hydrazines through I_2-promoted oxidative intramolecular C−N bond formation (Scheme 1).[7c] Although these approaches resolved some of the conventional problems inherent in the cycloaddition of diazo compounds to α,β-unsaturated carbonyl

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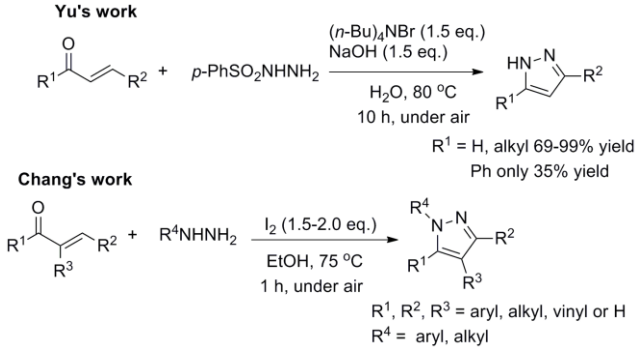
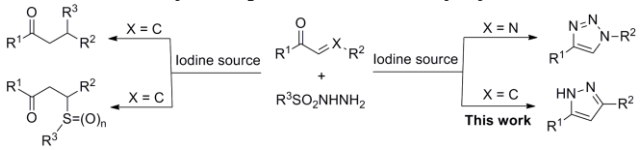
Scheme 1 Methods toward the preparation of substituted pyrazoles between α,β-unsaturated carbonyl compounds and substituted hydrazides



Scheme 2 Iodine source promoted reactions between α,β-unsaturated carbonyl compounds and sulfonylhydrazides



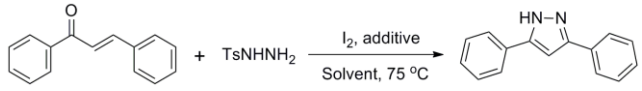
compounds, the existing methodologies hereinabove suffer from the requirement of metal salts, stoichiometric additives as well as strong bases.

According to the published literature, sulfonyl hydrazides constantly served for the construction of C-S bond with α,β-unsaturated carbonyl compounds mediated by iodine source, however, such preeminent transformations for the generation of C-C bond or two C-N bonds remain comparatively infrequent to date (Scheme 2).[11] To the best of our knowledge, however, there is no precedent study enabling the preparation of 1*H*-pyrazoles from readily available α,β-unsaturated carbonyl compounds and *p*-toluenesulfonyl hydrazide catalyzed by iodine. Herein, we report the first example of an efficient and generally applicable route for the construction of diversely substituted 1*H*-pyrazoles via the annulation of α,β-unsaturated aldehydes/ketones along with *p*-toluenesulfonyl hydrazine with a broad substrate scope, simple reaction conditions and excellent yields. Notably, the utilization of EtOH as a green medium and only 2 mol% iodine as a highly efficient catalyst to prepare the pyrazole moiety in a one-pot sequence make this reaction a green procedure.

Results and discussion

The investigation commenced with a model reaction employing chalcone **1a** and *p*-toluenesulfonyl hydrazide in the presence of various additives and solvents using iodine as the selected catalyst to acquire the optimized reaction conditions, and the results are summarized in Table 1. In consideration of dehydrogenation of the 4,5-dihydro-1*H*-pyrazole formed by condensation/Michael addition sequence, the initial optimization was screened between different oxidants and bases. Disappointedly, addition of different kinds of oxidants to the reaction system did not lead to dramatically increased yields. Then, we turned to bases, and thankfully, K_2CO_3 exhibited the best performance to produce 3,5-diphenyl-1*H*-pyrazole **2a** in 75% yield at 75 °C under air, which indicated that deprotonation by base had absolute predominance compared with oxidative dehydrogenation via oxidant (Table 1, entry 3). Encouraged by the primary result, the influence of other common solvents such as EtOAc, H_2O, EtOH, DMSO, DCE and THF were tested (Table 1, entries 7−12), and the best result (93%) was acquired in EtOH (Table 1, entry 9). Most unexpectedly, reducing the loading of I_2

Table 1 Optimization of reaction conditions [a]



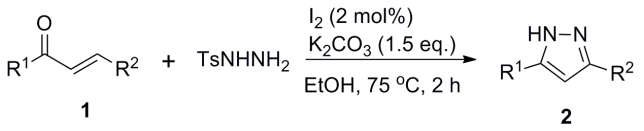
Entry	Additive	Solvent	t (h)	Yield[b] (%)
1	TBHP	MeCN	8	49
2	H_2O_2	MeCN	8	53
3	K_2CO_3	MeCN	3	75
4	Na_2CO_3	MeCN	8	36
5	CH_3COONa	MeCN	8	Trace
6	KOH	MeCN	3	72
7	K_2CO_3	EtOAc	3	75
8	K_2CO_3	H_2O	8	Trace
9	K_2CO_3	EtOH	1.5	93
10	K_2CO_3	DMSO	1.5	84
11	K_2CO_3	DCE	3	78
12	K_2CO_3	THF	3	88
13[c]	K_2CO_3	EtOH	1.5	95
14[d]	K_2CO_3	EtOH	2	95
15[e]	K_2CO_3	EtOH	2	71
16[f]	K_2CO_3	EtOH	2	Trace
17	---	EtOH	8	23
18[g]	K_2CO_3	EtOH	8	76

[a] Reaction conditions: benzylidenacetone **1a** (0.50 mmol), $TsNHNH_2$ (1.2 mmol), iodine (0.1 mmol), additive (1.5 mmol), solvent (2.0 mL), 75 °C, open to air. [b] Isolated yield. [c] 5 mol% I_2 was used. [d] 2 mol% I_2 was used. [e] 1 mol% I_2 was used. [f] No catalyst. [g] At 60 °C.

to 2 mol% made no difference to the yield, while 1 mol% iodine resulted in the decreasing yield of the pyrazole (Table 1, entries 14-15). Trace amount of the product was generated without iodine catalyst on account of the difficult formation of the tosyl hydrazone only in the presence of K_2CO_3, which indicated that iodine was crucial to the condensation between α,β-unsaturated carbonyl compounds and $TsNHNH_2$ (Table 1, entry 16). By assessing the base loading and temperature, it was found that both were critical to this transformation (Table 1, entries 17-18).

Based on the optimal conditions, the scope and generality of this transformation was conducted with an array of α,β-unsaturated carbonyl compounds. As outlined in Table 2, a vast variety of substitution patterns and functional groups smoothly tolerated iodine-catalyzed conditions with $TsNHNH_2$ to afford the 1*H*-pyrazole products in high yields with excellent regioselectivity. Satisfactorily, chalcones bearing functional groups like -OH, -OMe, -Me, -X, and $-NO_2$ were commendably applied to the established reaction conditions to furnish the desired products in satisfactory yields (Table 2, **2b**-**2l**). Of note was that *o*-hydroxyphenylpyrazole (Table 2, **2b**), which is conventionally synthesized by treatment of chromone, alkynone or 1,3-diketone with hydrazine, and possesses broad bioactivities, could be easily obtained in high yield.[1a,1o] The steric hindrance was studied and proved to be all but negligible (Table 2, **2d** and **2o**). Meanwhile, significant electronic effects of the substituents on the reactivity were observed. The result revealed that slightly lower yields for substrates with strongly electron-withdrawing or electron-donating substitutions, such as -OH and $-NO_2$, in the R^2 ring were got (Table 2, **2b** and **2l**), and the electronic effect of substituent groups on the benzoyl ring has an insignificant impact on the yields. It is worth mentioning that thienyl and naphthyl substituted chalcones efficiently reacted with $TsNHNH_2$ to afford the corresponding pyrazoles under present catalytic conditions (Table 2, **2m, 2n and 2r**). Furthermore, we were delighted to disclose that gratifying yield was also acquired from cinnamyl

Table 2 Synthesis of pyrazoles from α,β-unsaturated carbonyl compounds and $TsNHNH_2$ [a]



entry	R^1	R^2	2	yield (%)[b]
1	Ph	Ph	**2a**	95
2	Ph	2-HOC_6H_4	**2b**	70
3	Ph	4-$MeOC_6H_4$	**2c**	86
4	Ph	2-$MeOC_6H_4$	**2d**	93
5	Ph	3-MeC_6H_4	**2e**	94
6	Ph	4-MeC_6H_4	**2f**	96
7	Ph	4-FC_6H_4	**2g**	93
8	Ph	4-ClC_6H_4	**2h**	93
9	Ph	3,4-$Cl_2C_6H_3$	**2i**	95
10	Ph	2-BrC_6H_4	**2j**	91
11	Ph	4-BrC_6H_4	**2k**	96
12	Ph	4-$NO_2C_6H_4$	**2l**	79
13	Ph	2-Naphthyl	**2m**	92
14	Ph	2-Thienyl	**2n**	88
15	2-MeC_6H_4	Ph	**2o**	88
17	3-BrC_6H_4	Ph	**2p**	94
18	3- $NO_2C_6H_4$	Ph	**2q**	96
19	1-Naphthyl	Ph	**2r**	89
19	H	Ph	**2s**	96
20	Me	Ph	**2t**	81

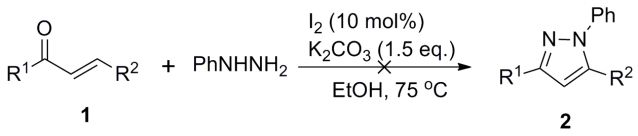
[a] Reaction conditions: **1** (0.5 mmol), $TsNHNH_2$ (0.6 mmol), I_2 (2 mol%), K_2CO_3 (0.75 mmol), EtOH (2 mL) under air. Isolated yield.

aldehyde (Table 2, **2s**). More importantly, 81% yield of 5-methyl-3- phenyl-1*H*-pyrazole was observed when benzalacetone was subjected to the standard condition (Table 2, **2t**).[13] By comparing with previously published results, it could be easily discerned that the new method not only saliently reduced the reaction time, but above all successfully avoided the use of strong base and excess additives.[10]

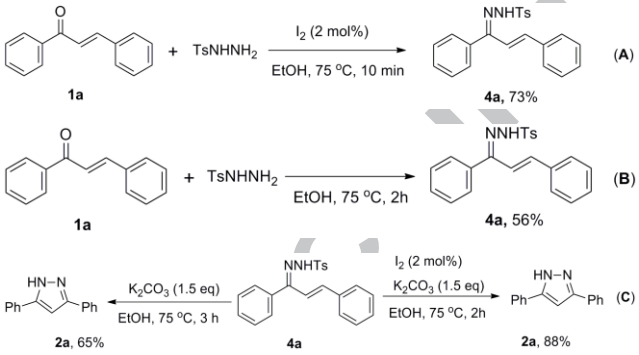
Considering these inspiring results, further investigations of this facile protocol were initiated with α,β-unsaturated aldehydes/ketones and phenylhydrazine. Surprisingly, no anticipated products were detected, which strongly displayed that an alternative reaction mechanism for our process might exist in contrast with Chang's speculation (Scheme 3).[7c]

Then, several control experiments were carried out to discern the probable mechanistic pathway thoroughly of this developed protocol, as shown in Scheme 4. Firstly, chalcone (**1a**) was treated with $TsNHNH_2$ (1.2 eq.) in EtOH at refluxing temperature in the presence of 2 mol% iodine and hydrazone (**4a**) was formed in 73% yield in 10 minutes by way of condensation (Scheme 4,

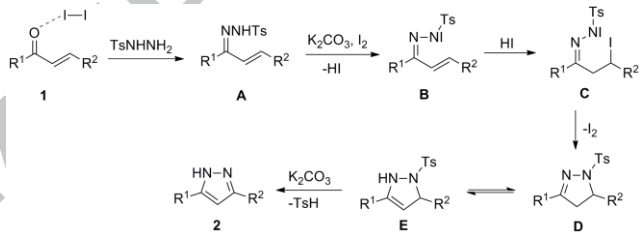
Scheme 3 Synthesis of pyrazoles from α,β-unsaturated carbonyl compounds and $PhNHNH_2$



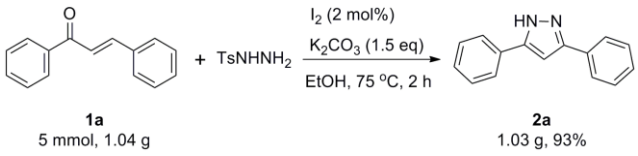
Scheme 4 Control Experiments



Scheme 5 Proposed mechanism



Scheme 6 Gram-Scale Reaction



A). It is noteworthy that the condensation reaction proceeded faster than iodine-free procedure, which indicates that condensation between α,β-unsaturated carbonyl compounds and $TsNHNH_2$ can be dramatically promoted by iodine (Scheme 4, B). In a further experiment hydrazone (**4a**) was subjected to the standard conditions and the relevant derivative (**2a**) was finally found in 88% yield (Scheme 4, C). Nevertheless, there was moderate yield of desired product formed without iodine, which thereby suggests that iodine is of great importance to the intramolecular cyclization of hydrazones.

In light of the above experimental results and previously published examples,[7c,11a,12] a plausible reaction mechanism is finally proposed (Scheme 5). At first, hydrazone (**A**) is generated via condensation of α,β-unsaturated carbonyl compounds and $TsNHNH_2$ by the activation of iodine. Then, N-I bond (**B**) is formed under K_2CO_3 followed by HI addition to the C-C double bond and subsequent intramolecular cyclization to yield 4,5-dihydro-1*H*-pyrazole **D**. Elimination of TsH from intermediate **E** under the mediation of K_2CO_3 results in the formation of the target product **2**. Further investigations on the more detailed mechanism are in progress in our laboratory.

We performed the reaction on a much larger scale to demonstrate the practical applicability of the one-pot sequence and a gram-scale synthesis of **2a** was subjected to the our developed experimental conditions. To our delight, the reaction

proceeded smoothly, and the expected product **2a** was isolated in 93% yield (Scheme 6).

Conclusions

In summary, a simple, green and practical system for the regioselective preparation of 1*H*-pyrazole derivatives in the presence of 2 mol% iodine using $TsNHNH_2$ as nitrogen-transfer reagent in EtOH under mild conditions has been demonstrated. In contrast with reported procedures, the present procedure is applicable and highly efficient, and has the advantage of short reaction time and high yields. Moreover, the utilization of catalytic amounts of iodine as an efficient catalyst to synthesize pyrazole moiety in a one-pot condensation and cyclization manner has been testified to be reliable. Last but not the least, the present transformation proceeds in good yields and commendably tolerates a wide range of functional groups, which paves the way for the synthesis of 1*H*-pyrazoles and will gain much attention in multidisciplinary fields for the preparation of potentially bioactive derivatives.

Acknowledgments

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13. Compound **2t** was purified by column chromatography on neutral Al_2O_3.

Graphical Abstract

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A facile and expeditious approach to substituted 1*H*-pyrazoles catalyzed by iodine

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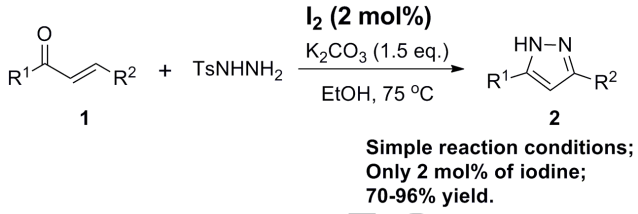

Highlights

- A facile and expeditious approach to 1*H*-pyrazoles is developed.
- Starting materials are α,β-unsaturated ketones/aldehydes and sulfonyl hydrazide.
- The reaction is catalyzed by as low as 2 mol% I_2.
- The process features simple conditions, high yield, and broad substrate scope.