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Sulphur promoted C(sp^3)–C(sp^2) cross dehydrogenative cyclisation of acetophenone hydrazones with aldehydes: efficient synthesis of 3,4,5-trisubstituted 1*H*-pyrazoles†

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A novel strategy for the cross dehydrogenative coupling (CDC) of acetophenone hydrazones and aldehydes has been developed for the synthesis of highly substituted pyrazoles. This work, for the first time, uses elemental sulfur as a promoter as well as a hydrogen acceptor in effecting the Csp^3–Csp^2 bond formation *via* C–H activation.

Pyrazoles constitute an important class of heterocyclic compounds exhibiting a wide range of biological activities such as antibacterial,[1] antiobesity,[2] antitumor,[3] antileukemic,[4] anti-inflammatory,[5] and analgesic.[6] They also act as vital building blocks of many pharmaceuticals and natural products.[7] The contemporary pyrazole syntheses involve the reaction of hydrazines with 1,3-dicarbonyl compounds/unsaturated hydrocarbons,[8,9] and 1,3-dipolar cycloaddition of diazoalkanes with alkenes or alkynes,[10] besides some other strategies.[11] Yet, novel, atom economic and environmentally benign methodologies, involving readily available starting materials, are highly desirable.

The development of advanced and ecologically benevolent means to achieve C–C and C–X bond formation is of great topical interest. In the present synthesis scenario, the development of cross-coupling methods involving unactivated C–H precursors has captured a great deal of attention.[12] In this perspective, the direct catalytic coupling termed as cross-dehydrogenative coupling (CDC) of unfunctionalized C–H bonds has particularly emerged as a powerful tool for the synthesis of diverse compounds.[13] Most of the CDC reactions developed so far have been nicely applied for the formation of C–C (sp–sp, sp–sp^2 and sp^2–sp^2) bonds, but the formation of a Csp^3–C bond *via* CDC is yet underdeveloped and more challenging.[13g] Furthermore, most of the explored Csp^3–C bond forming reactions are limited to the coupling of C–H bonds adjacent to a heteroatom[14] and a carbonyl group,[15] besides allylic, benzylic,[16] and alkane C–H bonds.[17] Also, many of the CDC reactions require transition metal catalysts and oxidants such as oxygen or peroxides as hydrogen acceptors.

The first CDC approach was reported by Miura and co-workers involving the coupling of *N*,*N*-dimethylanilines with alkynes.[14a] Li *et al.* and others have subsequently enriched this area by expanding the substrate scope.[14–17] An "iminium ion" intermediate is assumed to be formed *via* amine oxidation by a copper source in the presence of an oxidant using a single electron transfer (SET) process, which subsequently acts as an electrophile for the nucleophilic addition (intermolecular approaches). Ge *et al.* have successfully applied this strategy to an intramolecular CDC approach using hydrazones as potential substrates for the synthesis of pyrazoles.[18]

In view of the above and as a part of our interest in C–H activation,[19] and development of practical protocols,[20] we describe herein an unprecedented intramolecular cross dehydrogenative cyclisation of acetophenone hydrazones with aldehydes for the valuable synthesis of substituted pyrazoles. This work, for the first time, uses sulphur as a promoter as well as a hydrogen acceptor for the formation of a C(sp^3)–C(sp^2) bond *via* the CDC approach. An illustration of the related reports and the present strategy involving C–H activation is summarized in Scheme 1.

The investigation commenced with a model reaction employing acetophenone hydrazone and *p*-tolualdehyde in the presence of $Pd(OAc)_2$ as a catalyst and *t*-butyl hydrogen peroxide (TBHP, 70% aq.) as an oxidant in *t*-butanol at 120 °C for 24 h. In conformity with the earlier reports,[21] we envisioned the formation of product **I** *via* dehydrogenative coupling of imine–H and aromatic–H (Fig. 1, path A). Surprisingly, but to our utmost delight, unique formation of pyrazole **II** (74%, path B) was exclusively observed involving intramolecular cross-dehydrogenative cyclisation of Csp^3–H with imine–H under the investigated conditions.

Having observed this distinctive one pot intramolecular CDC result, the studies were directed towards the optimization of reaction conditions and the findings are presented in Table 1. To improve the reaction profile, different parameters such as catalysts, additives, oxidants and solvents were screened. Out of the different catalysts tried, only $Pd(OAc)_2$ and $Cu(OAc)_2$ could perform well (entries 1 and 2). Remarkably, addition of a base

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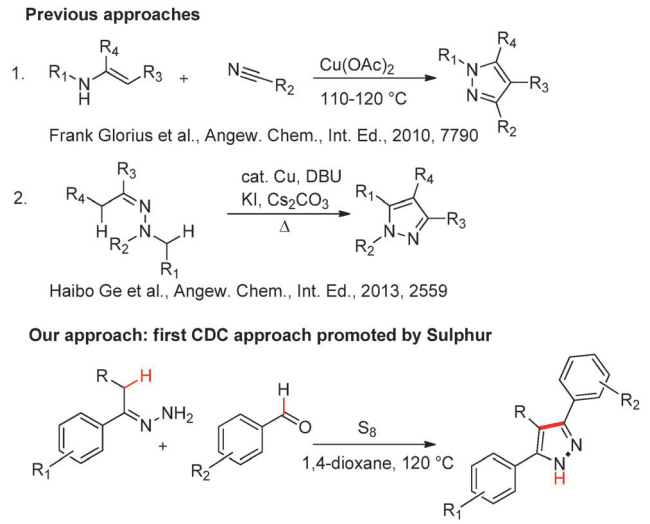
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds. CCDC 1027771. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc08210a



Scheme 1 Related reports and the present strategy.

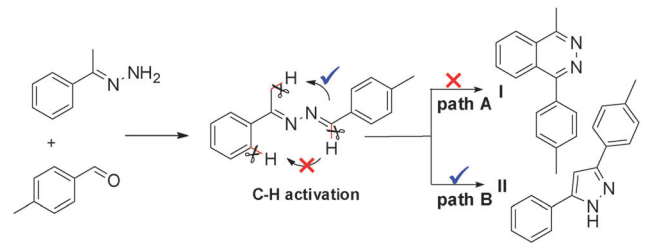
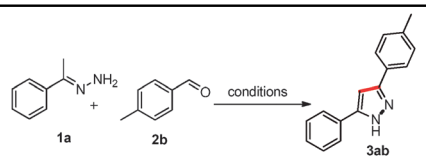


Fig. 1 Selective sp^3 C–H bond cleavage.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst/ promoter	Additive	Oxidant	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	—	TBHP	*t*-BuOH	74
2	$Cu(OAc)_2$	—	TBHP	*t*-BuOH	65
3	$Pd(OAc)_2$	K_2CO_3	TBHP	*t*-BuOH	0
4	$Pd(OAc)_2$	DBU	TBHP	*t*-BuOH	30
5	$Pd(OAc)_2$	—	TBHP	DCE	0
6	$Pd(OAc)_2$	—	TBHP	DMF	0
7	$Pd(OAc)_2$	—	TBHP	DMSO	0
8	$Pd(OAc)_2$	—	$K_2S_2O_8$	*t*-BuOH	78
9	$Pd(OAc)_2$	—	—	*t*-BuOH	0
10	S_8	—	—	*t*-BuOH	82
11	—	—	TBHP	*t*-BuOH	0
12	S_8	—	—	1,4-Dioxane	85
13	S_8	K_2CO_3	—	1,4-Dioxane	0
14	S_8	—	—	DMF	0
15	S_8	—	—	DMSO	0
16	S_8	—	—	—	65
17	S_8	—	—	Toluene	59
18	S_8	—	—	Water	55
19	S_8	—	—	Chlorobenzene	71

[a] Reaction conditions: **1a** (0.5 mmol), **2b** (1 mmol), catalyst (10 mol%), oxidant (1 mmol), additive (1 mmol), S_8 (1 mmol), solvent (0.75 mL), 120 °C, 24 h. [b] Isolated yield.

like K_2CO_3 or DBU either blocked the reaction or diminished the product yield (entries 3 and 4). Replacement of TBHP by $K_2S_2O_8$ brought about a modest improvement in the yield (entry 8), but the use of solvents such as DCE, DMF and DMSO as alternatives to *t*-butanol proved to be completely ineffective (entries 5–7). The reaction employing $Pd(OAc)_2$ without the oxidant also proved to be worthless (entry 9).

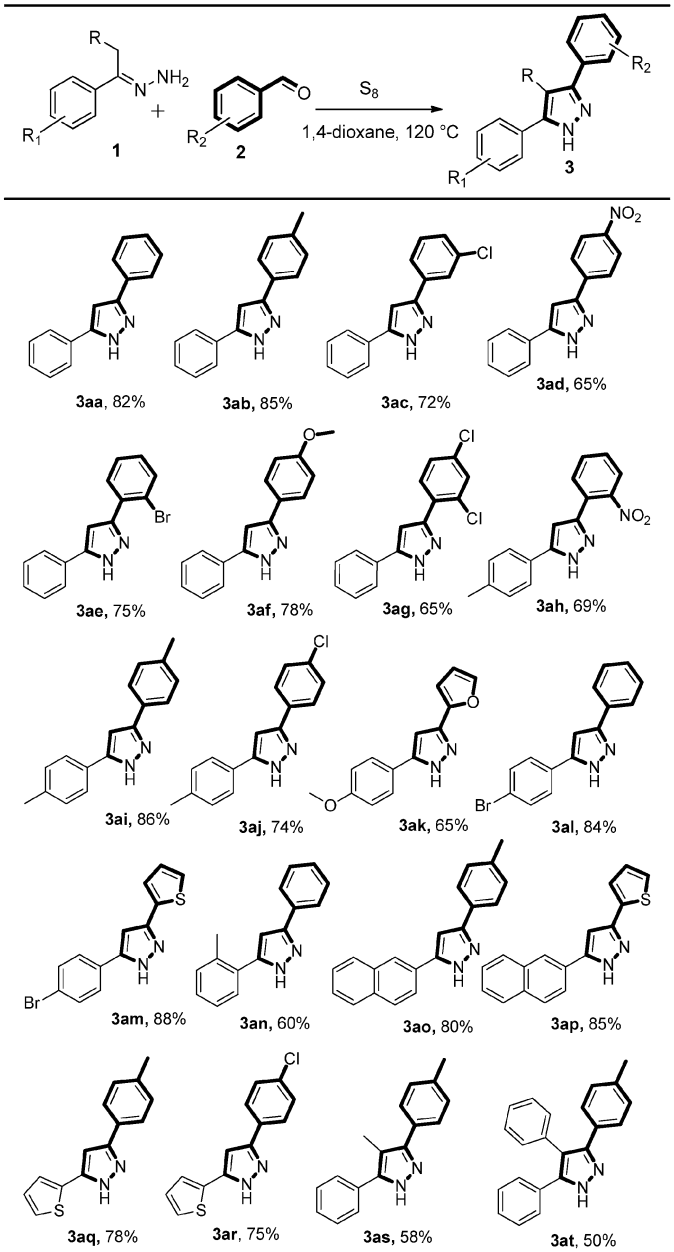
A cognizance of the Willgerodt–Kindler reaction reveals the formation of an ''enamine'' intermediate to activate elemental sulfur, which in turn stimulates the adjoining methyl group.[22] Keeping this clue in mind, the formation of an enamine type intermediate in the presence of S_8 in the present investigation was assumed to cause activation of the sp^3 C–H bond. In order to validate the idea, sulfur powder (S_8, mol. wt 32) was used to test its efficacy as a promoter as well as an oxidant, and to our aspiration, a considerably enhanced yield of the product was observed (entry 10). Changing the solvent to 1,4-dioxane in the presence of S_8 without an additive and an oxidant resulted in further improvement of the yield (85%, entry 12), but the use of solvents such as DMF and DMSO proved to be ineffective (entries 14 and 15). Solvent-free conditions as well as the use of solvents such as toluene, water and chlorobenzene also promoted the reaction to a good extent (entries 16–19) under similar conditions. The use of TBHP without the catalyst or the promoter (entry 11) and the addition of K_2CO_3 in the presence of S_8 (entry 13) were, however, unsuccessful.

With the optimized conditions in hand, the generality of the reaction was examined using diversely substituted acetophenone hydrazones and various aldehydes to provide the corresponding 3,4,5-trisubstituted 1*H*-pyrazoles in reasonably high yields. The outcome is recapitulated in Table 2. The reactions underwent smoothly with acetophenone hydrazones having different aromatic substitutions and aldehydes bearing various steric and electronic properties. Hydrazones bearing heteroaromatic and bicyclic moieties also participated well in the reaction. However, the reaction required the addition of TFA to achieve adequate conversion to the products **3as** and **3at**. The use of an aliphatic aldehyde *viz.* heptanal failed to give the product. The structure of a representative product **3ao** has been conclusively proved by the X-ray crystal structure (Fig. 2).[23]

Based on the existing literature[22] and isolation of products, a plausible mechanism is outlined in Fig. 4. It is worthwhile to mention that the formation of intermediate **I** (Fig. 3) was immediately observed during the reaction of acetophenone hydrazone and *p*-tolualdehyde, even at room temperature without the addition of S_8. The formation of thioamide intermediate **II** was, however, not noticed during the entire course of standard conditions, thereby discarding this pathway.

The formation of an ''enamine'' type intermediate **Ia**, analogous to the ''iminium ion'' reported by Miura and Li, may therefore be postulated for the reaction. The existence of **Ia** is assumed to activate sulfur as in the case of Willgerodt Kindler reaction to afford **Ib**, which may eventually lose H_2S and rearrange to give product **3**. In order to explore the radical pathway, some radical trapping experiments were also conducted using BHT and TEMPO as radical scavengers, which did

Table 2 Reaction scope and versatility[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), S_8 (1 mmol), 1,4-dioxane (0.75 mL), 120 °C, 24 h. Yields refer to isolated products. Addition of TFA (1.2 equiv.) was required for **3as** and **3at**.

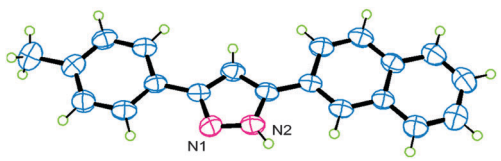


Fig. 2 X-ray crystal structure of the product **3ao**.

not inhibit the reaction, albeit the product yield was somewhat lowered.

In conclusion, we have developed a novel CDC approach *via* sulfur-promoted C–H activation for the formation of a less explored Csp^3–Csp^2 bond. The present study comprehends and demonstrates the innovative dual use of sulfur as a promoter as well as an oxidant in cross dehydrogenative cyclisation of acetophenone hydrazones and aldehydes.

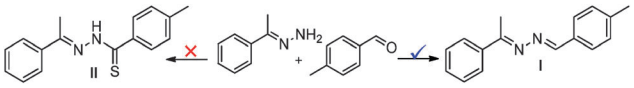


Fig. 3 Mechanistic study.

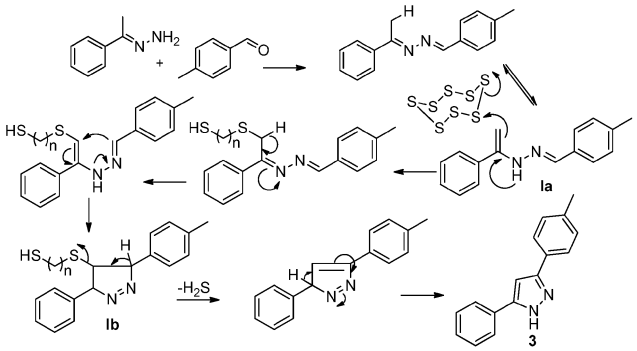


Fig. 4 Proposed mechanism.

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23 Crystallographic data for compound **3ao** CCDC 1027771.

