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Metal-Free [2 + 1 + 2]-Cycloaddition of Tosylhydrazones with Hexahydro-1,3,5-triazines To Form Imidazolidines

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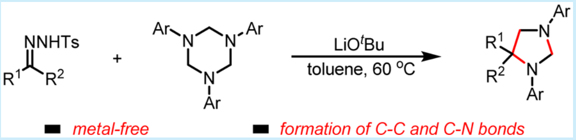
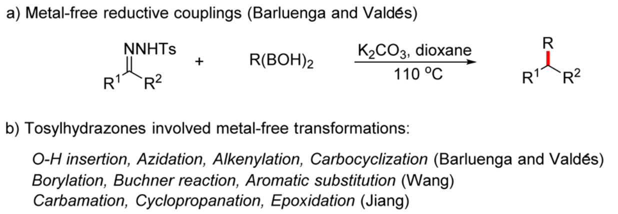
Supporting Information

ABSTRACT: A novel protocol toward imidazolidines has been accomplished using tosylhydrazones and hexahydro-1,3,5-triazines as the substrates under metal-free reaction conditions. Importantly, the role of LiO^{t}Bu has been confirmed not only to release the diazo but also to promote the cycloaddition. Further mechanistic investigations reveal that the reaction proceeds through a stepwise [2 + 1 + 2] process.



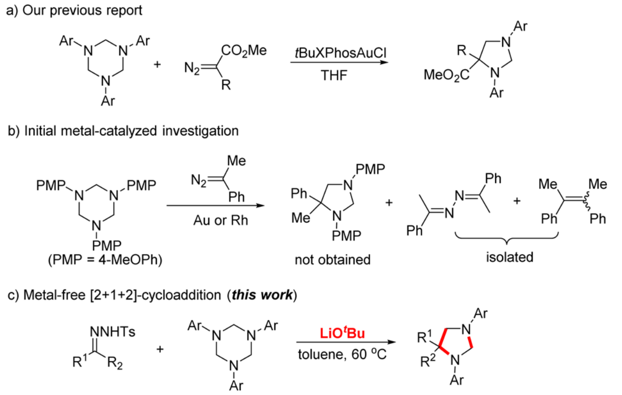
As stable and readily available starting materials, tosylhydrazones have been extensively employed as diazo precursors to synthesize structurally diverse molecules in modern organic synthesis.[1] Not surprisingly, generation of a diazo moiety in situ from tosylhydrazones has enabled the development of versatile novel reactions under transition-metal catalysis,[2,3] or even more appealing, under metal-free reaction conditions.[4−8] For example, in 2009, Barluenga and Valdés demonstrated an elegant C−C bond formation by reductive coupling of boronic acids and tosylhydrazones under metal-free conditions (Scheme 1a).[4] Later, they further extended this protocol to forge C−C, C−O, and C−N bonds.[5] Wang and coworkers successfully developed metal-free C−B and C−Si bonds formation by using tosylhydrazones as ideal substrates.[6] The Jiang group also reported tosylhydrazones involved metal-free carbamation and cyclopropanation (Scheme 1b).[7] Despite these advances, new reactions using tosylhydrazones as starting materials under metal-free conditions are still needed from the viewpoints of cost and sustainability.

Scheme 1. Previous Reports



Recently, we reported a gold-catalyzed cycloaddition of donor/acceptor diazo compounds with hexahydro-1,3,5-triazines[9] to prepare five-membered N-heterocycles (Scheme 2a).[10a] Unfortunately, this protocol was not applicable to donor/donor diazo substrates. Under gold catalysis, the expected cyclization product was not obtained but rather the coupling products azine and olefin (Scheme 2b). Moreover, the use of rhodium complexes also did not produce the desired heterocycle. The initial unsuccessful attempts prompted us to develop an effective protocol to circumvent this challenge. In continuation of our ongoing interest in diazo chemistry and triazine involved cycloadditions,[10] we report here a base-promoted cycloaddition from tosylhydrazones via a [2 + 1 + 2] process under metal-free reaction conditions (Scheme 2c).

Scheme 2. Initial Attempts and Our Strategy



At the outset, we utilized tosylhydrazone **1a** and hexahydro-1,3,5-triazine **2a** as model substrates to establish the optimal reaction conditions (Table 1). When the reaction was performed in toluene at 60 °C, the use of 2 equiv of Cs_2CO_3 afforded **3a** in 40% yield associated with a small amount of azine **4a** (entry 1), while K_2CO_3 gave a much lower yield (entry 2). Gratifyingly, when LiO^{t}Bu was employed, **3a** was obtained in 84% yield (79% isolated yield) together with a 7% yield of **4a** (entry 3). Switching the base to KO^{t}Bu, NaO^{t}Bu, and NaH resulted in moderate yields (entries 4−6), while the use of KOH and NaOMe gave very low yields (entries 7 and 8). Then, the solvent was screened. First, the formation of similar

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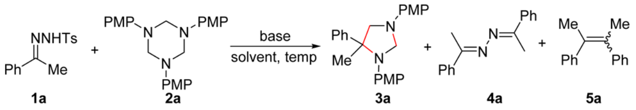
Table 1. Optimization of Reaction Conditions[a]



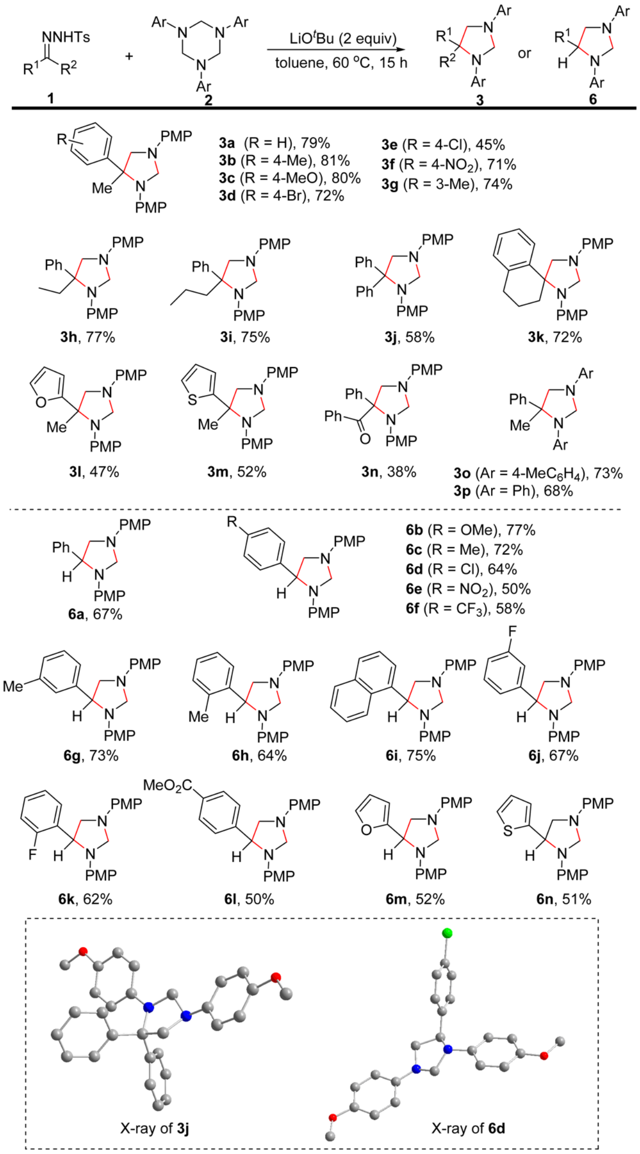
entry	base	solvent	t (°C)	yield (%)^b 3a/4a/5a
1	Cs_2CO_3	toluene	60	40/6/<5
2	K_2CO_3	toluene	60	25/4/<5
3	LiO^{t}Bu	toluene	60	84(79)/7/<5
4	KO^{t}Bu	toluene	60	48/5/4
5	NaO^{t}Bu	toluene	60	43/19/<5
6	NaH	toluene	60	40/5/0
7	KOH	toluene	60	12/0/0
8	NaOMe	toluene	60	18/3/0
9	LiO^{t}Bu	dioxane	60	46/41/5
10	LiO^{t}Bu	DCE	60	65/18/4
11	LiO^{t}Bu	CH_2Cl_2	60	54/4/0
12	LiO^{t}Bu	THF	60	38/7/5
13	LiO^{t}Bu	*p*-xylene	60	75/12/6
14	LiO^{t}Bu	toluene	110	28/64/7
15	LiO^{t}Bu	toluene	80	68/16/5
16	LiO^{t}Bu	toluene	25	<5/<5/0

[a] The reactions were carried out with **1a** (0.2 mmol), **2a** (0.24 mmol), and base (0.4 mmol) in solvent (5 mL) at 60 °C for 15 h. [b] NMR yield. The number in parentheses is the isolated yield.

amounts of **3a** and **4a** were observed when the reaction was conducted in dioxane, while 1,2-dichloroethane (DCE) provided **3a** and **4a** in 65% and 18% yield, respectively (entry 10). The use of dichloromethane and THF afforded **3a** in moderate yields with a small amount of **4a** (entries 11 and 12), while *p*-xylene furnished **3a** in 75% yield associated with a 12% yield of **4a** (entry 13). As a result, toluene was the best solvent regarding reactivity and selectivity. It should be noted that high temperature is detrimental to the reaction. A larger amount of **4a** formed when the reaction was conducted at high temperature (entries 14 and 15). Moreover, the reaction was sluggish under low temperature (entry 16).

With the optimal conditions in hand, we turned our attention to the scope of this base-promoted cycloaddition. Gratifyingly, aromatic ketone/aldehyde derived tosylhydrazones with different substitution patterns could be employed in this reaction, providing the corresponding imidazolidines in moderate to good yields (Scheme 3). Both electron-rich and -deficient substrates were tolerated. Notably, this cycloaddition tolerates various functional groups on the aromatic ring of the tosylhydrazones, including F, Cl, Br, NO_2, CF_3, and CO_2Me, providing potential application for further transformations. Moreover, tosylhydrazones bearing electron-donating substituents furnished the corresponding products in higher yields than those with electron-withdrawing groups. For bis-phenyl substituted tosylhydrazone, the cycloaddition proceeded well to afford **3j** in 58% yield. Interestingly, heteroaromatic derived tosylhydrazones were also tolerated and the corresponding products were obtained in moderate yields (**3l**, **3m** and **6m**, **6n**). Notably, benzil derived tosylhydrazone smoothly underwent the cycloaddition to give the desired product **3n** in 38% yield. Next, different aryl substituted hexahydro-1,3,5-triazines were examined and the corresponding products (**3o** and **3p**) were obtained in moderate yields. Unfortunately, aliphatic ketone/aldehyde derived tosylhydrazones were not applicable to this reaction. The structures of **3j** and **6d** were confirmed by X-ray analysis.

Scheme 3. Substrate Scope[a,b]

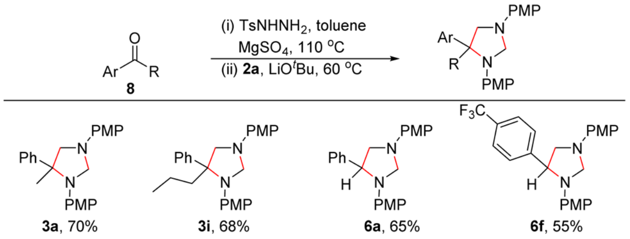


[a] All reactions were performed with **1** (0.2 mmol), **2** (0.24 mmol), and LiO^{t}Bu (0.4 mmol) in toluene (5 mL) at 60 °C for 15 h. [b] Isolated yields.

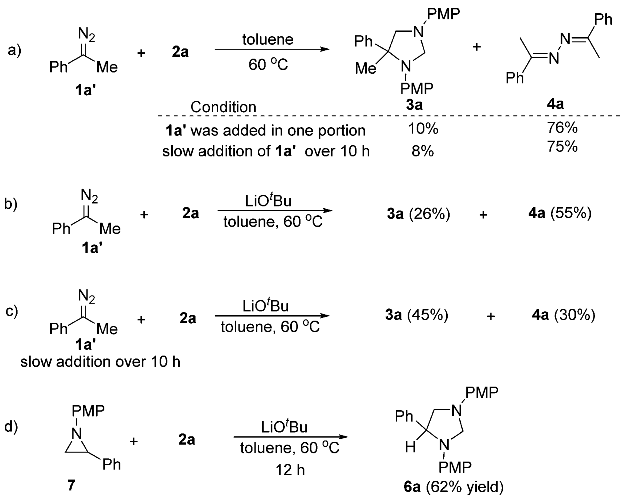
As observed, the condensation of carbonyl compounds with tosylhydrazines cleanly furnished the corresponding tosylhydrazones in quantitative yields in toluene. Thus, we attempted to combine the condensation and cycloaddition in one pot, which can be considered a formal reductive coupling of a carbonyl group to an sp^3-carbon atom with the concurrent construction of C−C and C−N bonds. Indeed, with the addition of anhydrous $MgSO_4$ to the reaction system, the one-pot two-step reactions proceeded well and gave the corresponding products in acceptable yields (Scheme 4). It should be noted that the presence of $MgSO_4$ is essential to remove the water generated in situ during the condensation process. Otherwise, the anticipated cycloaddition would not occur.

To understand the possible role of LiO^{t}Bu, control experiments were conducted. The reaction of **1a′** with **2a** was

Scheme 4. One-Pot Reaction from Ketones/Aldehydes



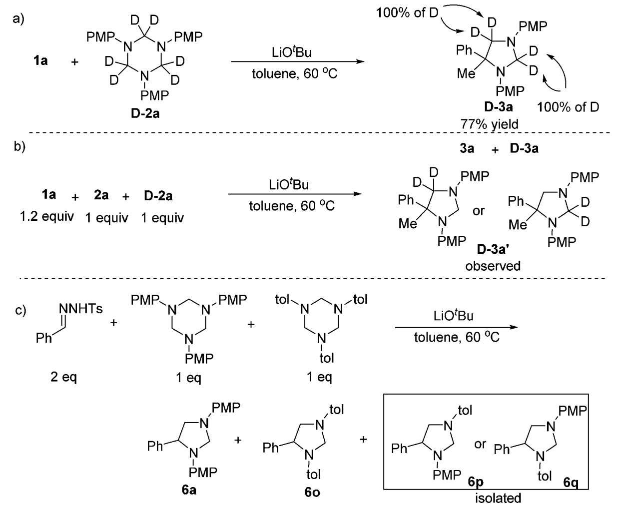
Scheme 5. Control Experiments



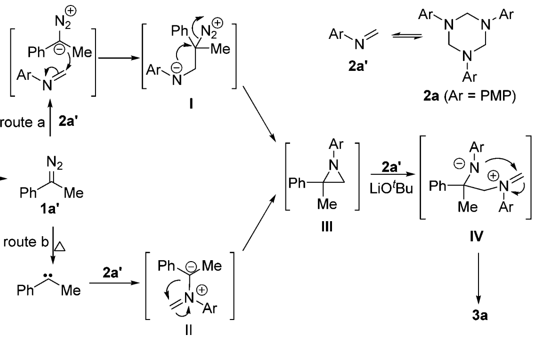
performed and only a small amount of desired product **3a** was detected, instead of the formation of **4a** (76% yield). Moreover, when **1a′** was slowly added by a syringe pump over 10 h, **3a** was still obtained in low yield (Scheme 5a). Clearly, there is no difference between one-portion and slow addition of **1a′**, indicating that the role of LiO^{t}Bu is far beyond just releasing the diazo from tosylhydrazone. Next, the reaction of **1a′** and **2a** with LiO^{t}Bu provided **3a** in 26% yield associated with the 55% yield of **4a** (Scheme 5b). Furthermore, the slowly addition of **1a′** to the mixture of **2a** and LiO^{t}Bu provided **3a** in 45% yield and the yield of **4a** decreased to 30% (Scheme 5c). Furthermore, Lewis or Brønsted acid catalyzed reaction of diazo compounds with imine usually leads to the formation of aziridines.[12] Thus, the cycloaddition might proceed through the initial aziridination followed by ring opening with another molecule of hexahydro-1,3,5-triazine.[13] So we run the reaction of aziridine **7** with **2a** in the presence of LiO^{t}Bu. As a result, **6a** was obtained in 62% yield (Scheme 5d). The control experiments revealed that LiO^{t}Bu worked not only as a base to slowly generate the diazo from tosylhydrazone but also to promote the cycloaddition process.

Next, deuterium labeling experiments were performed. First, the reaction of **1a** with **D-2a** furnished fully deuterated product **D-3a** in 77% yield (Scheme 6a). The reaction of **1a** with **2a** and **D-2a** afforded not only **3a** and **D-3a** but also the cross-deuterated product **D-3a′** (Scheme 6b), which could be further confirmed by HRMS analysis (see Supporting Information for details). Moreover, a cross reaction involving different hexahydro-1,3,5-triazines was conducted, and **6p**/**6q** were observed (Scheme 6c, see Supporting Information). The incorporation of two different formaldimines indicated the reaction probably proceeded via a stepwise [2 + 1 + 2] process.

Scheme 6. Deuterium-Labelling and Cross Experiments



Scheme 7. Proposed Reaction Mechanism



Based on the former results, a plausible reaction mechanism has been proposed (Scheme 7). First, diazo **1a′** is slowly released from tosylhydrazone **1a** by LiO^{t}Bu. The cycloaddition would be initiated by the first nucleophilic addition between diazo and formaldimine **2a′**, generating aziridine intermediate **III** through transition state **I** or **II**. Then, a base-promoted ring-opening reaction of aziridine by another molecule of **2a′** occurs and delivers the final product **3a** via intermediate **IV**.

In summary, we have developed a metal-free [2 + 1 + 2]-cycloaddition reaction between tosylhydrazones and hexahydro-1,3,5-triazines in the presence of LiO^{t}Bu, affording imidazolidines in moderate to good yields under mild reaction conditions. The construction of C−N and C−C bonds has been realized under metal-free conditions. Moreover, the isolation of tosylhydrazones is not necessary and the reaction can be performed in one pot directly from carbonyl compounds. Notably, the dual roles of LiO^{t}Bu were proven either to release the diazo or to promote the cycloaddition.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00600.

Experimental procedures along with characterizing data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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