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N-Alkylation of tosylhydrazones via a metal-free reductive coupling procedure

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ABSTRACT

A simple metal-free route for the N-alkylation of tosylhydrazones is described via the NaOMe-promoted reductive coupling of tosylhydrazones under mild conditions. A wide variety of N-alkylated tosylhydrazones were obtained in moderate to good yields.

Tosylhydrazones represent a useful class of synthons that can be further converted into numerous pharmaceutical and biologically active compounds.[1] One example is PIK-75, a preferential inhibitor of the p110α/γ forms of phosphatidylinositol 3-kinase (PI3K) (Fig. 1).[2] The efficient syntheses of N-alkylated sulfonylhydrazones are of interest to medicinal chemistry and the synthesis of screening libraries. The most common route for their preparation is through nucleophilic substitution of tosylhydrazones with alkyl halides.[1b] Furthermore, tosylhydrazones can substitute alcohol under Mitsunobu reaction conditions (DEAD/PPh_3) (Scheme 1a).[3a] Tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] catalyzed reactions of alcohols with tosylhydrazones have also been reported.[3b]

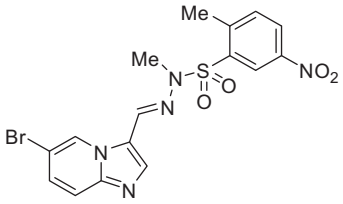
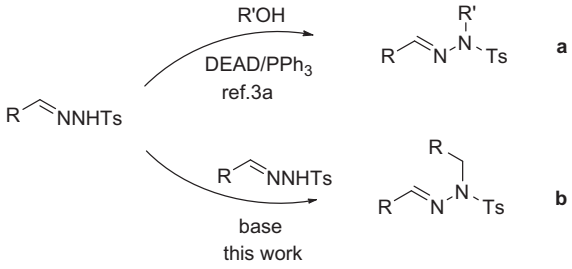


Figure 1. Structure of PIK-75.

Tosylhydrazones are widely used as precursors of diazo compounds and carbenes,[4] which are valuable and readily available reagents in C–C,[5] C–O,[6] C–N,[7] C–S,[8] and C–B[9] bond-forming reactions through both metal-catalyzed and metal-free processes. In particular, metal-free reactions have attracted widespread attention in recent years. Barluenga et al. reported a new metal-free carbon–carbon bond-forming reaction between tosylhydrazones and boronic acids.[5e] Subsequently, Barluenga et al. and Ding et al. developed procedures that can insert the incipient carbenes into the O–H bond and S–H bond to prepare ethers[6] and thioethers[8c] via metal-free reductive coupling of tosylhydrazones with alcohols or thiols. Recently, a metal-free reaction to convert tosylhydrazones into pinacol boronates was explored by Wang and co-workers.[9]



Scheme 1. (a) Mitsunobu reaction of tosylhydrazones and alcohols. (b) Metal-free reductive coupling of tosylhydrazones discussed in this work (Ts = tosyl).

Although Shi and co-workers used *N*-tosylhydrazones as nucleophiles in Michael addition,[10] the reductive coupling reaction using *N*-tosylhydrazone as nucleophile remains less developed.[11] In view of tosylhydrazone's nucleophilicity and ability to generate carbene in situ, a direct nucleophilic substitution reaction between tosylhydrazone and its in situ-generated carbene may result in N-alkylated tosylhydrazone (Scheme 1b). Further research may lead

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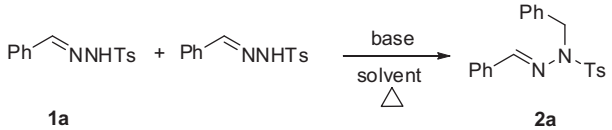
Table 1
Influences of the reaction conditions on the formation of N-alkylated tosylhydrazone **2a**[a]



1a **2a**

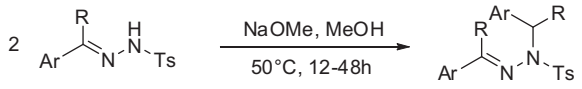
Entry	Base	Solvent	*T* (°C)	Yield[b] (%)
1	K_2CO_3	Dioxane	110	56
2	DBU	Dioxane	110	43
3	Na_2CO_3	Dioxane	110	48
4	KOH	Dioxane	110	21
5	K_2CO_3	Dioxane	100	55
6	K_2CO_3	Dioxane	70	37
7	NaOMe	Dioxane	110	64
8	NaOMe	MeOH	65	78
9	NaOEt	EtOH	80	70
10	*t*BuOK	*t*BuOH	80	45
11	**NaOMe**	**MeOH**	**50**	**83**
12[c]	NaOMe	MeOH	50	82
13[d]	NaOMe	MeOH	50	70
14	NaOMe	MeOH	25	67
15	NaOMe	THF	50	59
16	NaOMe	CH_3CN	50	45
17	K_2CO_3	MeOH	50	Trace

The bold values indicated the optimal reaction conditions and the best result.
[a] Reaction conditions: **1a** (0.3 mmol), base (1.5 equiv), solvent (2 mL), 12 to 48 h.
[b] Isolated yield.
[c] NaOMe (2.0 equiv).

to the development of highly efficient metal-free N-alkylation reaction of tosylhydrazones, which represents a novel access to these compounds.

To test our hypothesis, we selected tosylhydrazone **1a** derived from benzaldehyde as the model substrate for reaction condition screening. The results were summarized in Table 1. Initially, we examined the reaction of tosylhydrazone **1a** (0.3 mmol) in the presence of K_2CO_3 (1.5 equiv) in dioxane at 110 °C. To our delight, the expected N-alkylated tosylhydrazone **2a** was obtained in 56% yield (Table 1, entry 1). Encouraged by this result, we screened a variety of bases for this reaction. Slightly lower yields were obtained when DBU and Na_2CO_3 were employed as the bases (Table 1, entries 2 and 3). In the presence of KOH, the reaction proceeded less efficiently. The reductive coupling product **2a** produced a yield of 21% (Table 1, entry 4). Lowering the temperature produced no better results (Table 1, entries 5 and 6). Further evaluation showed that NaOMe was the best base for this transformation because it afforded the desired product **2a** in 83% yield (Table 1, entry 11). Increasing the amount of base loading to 2.0 equiv resulted in a comparable yield (Table 1, entry 11 vs entry 12). However, a significant drop in yield was observed when 1.0 equiv of NaOMe was used (Table 1, entry 13). Different solvents were subsequently screened, and methanol proved to be the most efficient solvent (Table 1, entries 15 and 16). The yield was strongly dependent on the base used, as evidenced by the observed trace target product in MeOH with K_2CO_3 even with prolonged reaction time (Table 1, entry 17).

Table 2
Reductive coupling of tosylhydrazone 1[a]



1 **2**

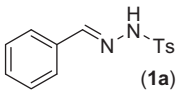
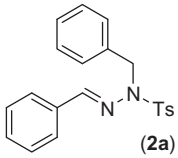
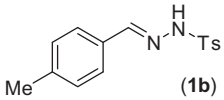
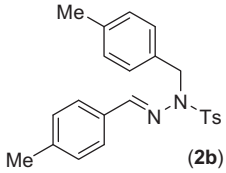
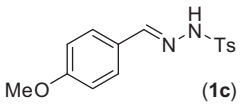
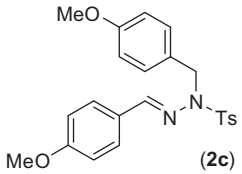
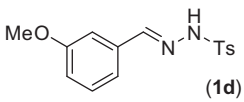
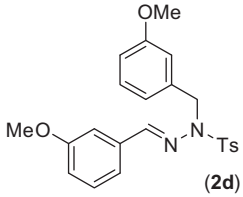
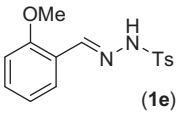
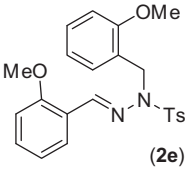
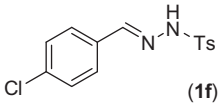
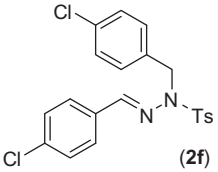
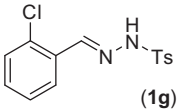
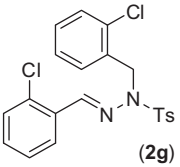
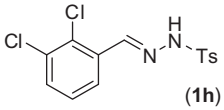
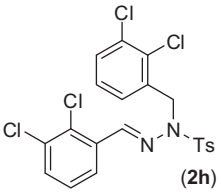
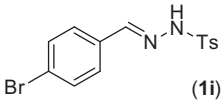
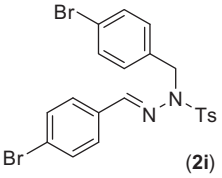
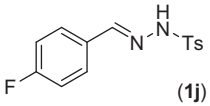
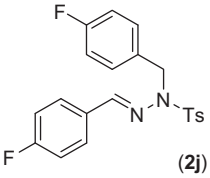
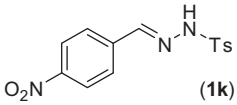
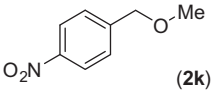
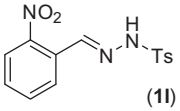
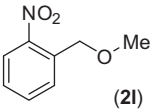
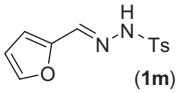
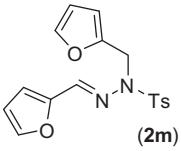
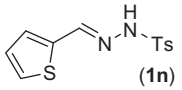
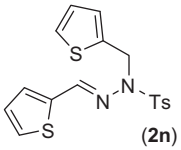
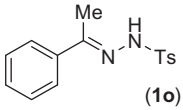
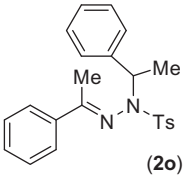
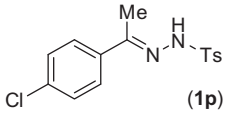
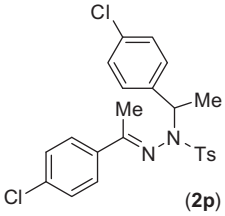
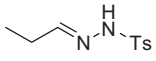
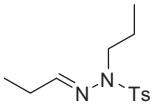
Entry	Tosylhydrazone	Product	Yield[b] (%)
1	 (**1a**)	 (**2a**)	83
2	 (**1b**)	 (**2b**)	86
3	 (**1c**)	 (**2c**)	81
4	 (**1d**)	 (**2d**)	70

Table 2 (*continued*)

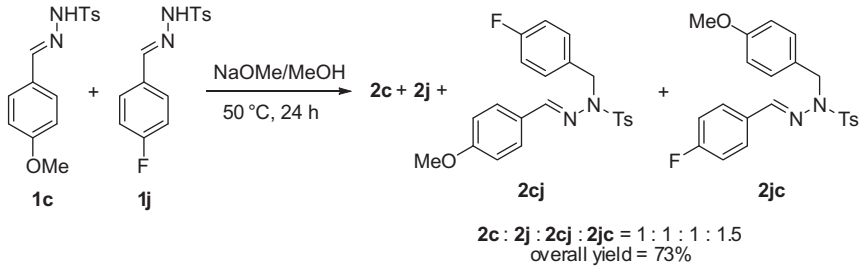
Entry	Tosylhydrazone	Product	Yield[b] (%)
5	 (**1e**)	 (**2e**)	74
6	 (**1f**)	 (**2f**)	76
7	 (**1g**)	 (**2g**)	57
8	 (**1h**)	 (**2h**)	69
9	 (**1i**)	 (**2i**)	74
10	 (**1j**)	 (**2j**)	85
11	 (**1k**)	 (**2k**)	91
12	 (**1l**)	 (**2l**)	89
13	 (**1m**)	 (**2m**)	64

(*continued on next page*)

Table 2 (*continued*)

Entry	Tosylhydrazone	Product	Yield[b] (%)
14	 (**1n**)	 (**2n**)	82
15[c]	 (**1o**)	 (**2o**)	52
16[c]	 (**1p**)	 (**2p**)	50
17	 (**1q**)	 (**2q**)	–

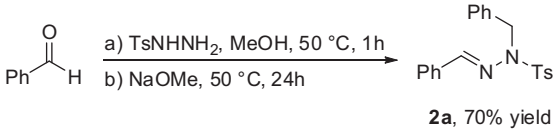
[a] Reaction conditions: **1** (0.3 mmol), NaOMe (1.5 equiv), MeOH (2 mL), 50 °C, 12 h to 48 h.
[b] Isolated yield.
[c] 60 °C.



Scheme 2. The reductive coupling between **1c** and **1j**.

After the optimal conditions were obtained (1.5 equiv of NaOMe, MeOH as solvent, 50 °C), we explored the generality and scope of the reductive coupling of tosylhydrazones. The results were presented in Table 2. The reaction could be performed through hydrazones derived from both aldehydes and ketones. For instance, tosylhydrazones **1b** and **1c** with electron-donating groups could be successfully converted into the desired products in high yields (Table 2, entries 2 and 3). Slightly lower yields were obtained with tosylhydrazones **1d** and **1e** for their larger steric hindrances of methoxy substituents (Table 2, entries 4 and 5). Halogen substituents on phenyl rings (Table 2, entries 6–10) were observed to be tolerant in this reaction, which enabled further derivation of the adducts through various cross-coupling techniques. Interestingly, when substrates **1k** and **1l** were used, the desired products were not detected, but methyl ethers for the participation of MeOH were isolated in 91% and 89% yields, respectively (Table 2, entries 11 and 12). Not only aryl-substituted but also heteroaryl-substituted tosylhydrazones gave high yields (Table 2, entries 13 and 14). In the case of ketone-derived substrates such as tosylhydrazones **1o** and **1p**, higher temperature was needed because of the large steric hindrance of the substrates (Table 2, entries 15 and 16). The alkyl-substituted tosylhydrazone **1q** derived from propanal was completely inert in this reaction (Table 2, entry 17).

We have also tried the reductive coupling reaction between different tosylhydrazones as **1c** (with electron-donating substitute) and **1j** (with electron-withdrawing substitute), and obtained a mixture of N-alkylated tosylhydrazones **2c**, **2j**, **2cj**, and **2jc** with the ratio of 1:1:1:1.5 (Scheme 2). The current chemoselectivity was poor, and we are still screening the reaction conditions in detail to further improve the chemoselectivity and to explore its practical applications in organic synthesis.



Scheme 3. One-pot synthesis of *N*-benzyl tosylhydrazone **2a**.

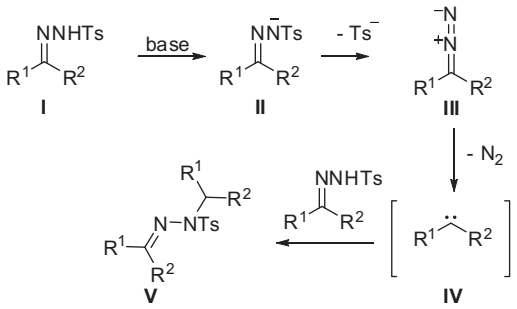


Figure 2. Proposed mechanism.

To further simplify the reaction procedure, we carried out a one-pot synthesis of tosylhydrazone **2a** starting from benzaldehyde (Scheme 3) and obtained the desired product in a slightly lower yield.

A possible mechanism for this reaction was also proposed, which involved the formation of a diazo compound **III** by decomposition of the tosylhydrazone salt **II** (Fig. 2).[4,5e] A carbene **IV**, generated from the diazo compound **III** by thermally induced N_2 release, could then be inserted into the N–H bond of tosylhydrazone, giving rise to the corresponding N-alkylated tosylhydrazone **V**.

In summary, we have described a new method for the synthesis of N-alkylated tosylhydrazone by a metal-free reductive coupling procedure. In the presence of NaOMe, a variety of N-alkylated tosylhydrazones were obtained in moderate to high yields under a simple and mild condition. Efforts are underway to extend the scope of the reaction between different tosylhydrazones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.124.

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