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COMMUNICATION

A highly efficient catalyst-free protocol for C–H bond activation: sulfamidation of alkyl aromatics and aldehydes†

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A catalyst-free protocol has been developed for amidation of alkyl aromatics and aldehydes using $TsNBr_2$ *via* a nitrene transfer process in the presence of a base in excellent yield within a short time. The reaction was found to be selective for secondary and tertiary benzylic C–H bonds and C–H bonds of aldehydic groups.

Direct *N*-functionalization of saturated C–H bonds is considered as a frontier of organic chemistry due to its potential for achieving synthetically and biologically attractive amino functionality.[1] Nitrene transfer reaction is an attractive tool for introducing such a functionality in the presence of a transition metal catalyst.[1] This field pioneered by Breslow[2] has progressed considerably over the last few years. Iminoiodane derivatives, such as ArI=NTs, have been the most commonly employed reagent in combination with several transition-metal catalysts, including those based on Rh,[3] Ru,[4] Mn,[5] Ag,[6] Cu[7] and Zn.[8] In view of the limitations with the use of hypervalent iodine reagents, efforts have been made for development of new nitrene transfer sources. Thus C–H amidation using *in situ* generated iminoiodane using $PhI(OAc)_2$ has been shown to be catalyzed by Ru,[9,10] Mn,[10] Rh[11] and Ag[12] complexes with sulfonamides, sulfamates or carbamates as nitrene precursors. This field of oxidative amidation process has been boosted by the advent of several metal free protocols and new aminating agents very recently.[13] Other nitrene sources such as chloramine-T,[7a,14] bromamine-T,[15] tosyloxycarbamates[16] and azides[17] have also been employed for amidation reaction in the presence of a metal catalyst.

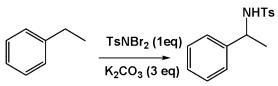
Direct transformation of aldehydes into amides is another important subject in organic synthesis owing to the prevalence of amide linkage in a variety of bioactive compounds. However, there are limited efforts in the literature in this direction. An oxidative C–N bond forming process from aldehydes by using $TsNH_2$ in the presence of a Rh catalyst and $PhI(OC(O)^tBu)_2$ as the oxidant has been reported.[18] Chan *et al.* reported a nitrene insertion into an aldehydic C–H bond using different iminoiodanes in the presence of a Ru, Cu or Fe catalyst.[19] Seo and Marks reported the use of homoleptic lanthanide amido complexes for amidation of aldehydes.[20] NHC catalyzed amidation of aldehydes has been reported by Seayad *et al.*[21] A few other oxidative methods are also known in the literature for amidation of aldehydes.[22]

Recently, we found that *N*,*N*-dibromo-*p*-toluene-sulfonamide ($TsNBr_2$) is a very reactive and efficient reagent for various organic transformations.[23] In this communication, we report a highly efficient amidation reaction of benzylic and aldehydic C–H bonds using $TsNBr_2$ without any catalyst.

Initially we have examined the C–H amidation reaction for alkyl aromatics. The evaluation of the C–H amidation reaction using $TsNBr_2$ as the nitrene source was carried out using ethyl benzene as the model substrate (Table 1). The reaction was carried out by adding $TsNBr_2$ (1 mmol) to a mixture of ethylbenzene (1 mmol) and K_2CO_3 (3 mmol) in ethyl acetate (3 mL) under an inert atmosphere.‡ Initial attempt at room temperature (Table 1, entry 1) did not produce the desired amidated product even after 24 h of reaction. However, the reaction at 80 °C (bath temperature) in a tightly capped Schlenk tube produced the corresponding amidated product in 84% yield after 4 h of reaction. Notably no 1°-C–H insertion product was detected in this case. Longer reaction time did not improve the yield of the reaction (Table 1, entry 3).

Then, the reaction was studied by increasing the amount of $TsNBr_2$ to 1.2 equivalents. However, the yield of the reaction did not improve. Further the use of CCl_4 as the solvent in the reaction also had no effect on the yield. The reaction in acetonitrile did not proceed at all. Finally, the use of 1 equivalent of $TsNBr_2$ (based on the substrate) was found

Table 1 Amidation of ethyl benzene using $TsNBr_2$[a]



Entry	$TsNBr_2$ (mmol)	Solvent	Temp/°C	Time/h	Yield[b] (%)
1	1	EtOAc	RT	24	NR
2	1	EtOAc	80	4	84
3	1	EtOAc	80	15	84
4	1.2	EtOAc	80	4	78
5	1	MeCN	80	12	NR
6	1	CCl_4	80	15	48

[a] Reaction conditions: ethyl benzene (1 mmol), solvent (3 mL), N_2 atmosphere. [b] Isolated yield. NR: no reaction.

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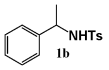
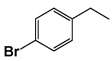
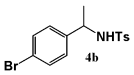
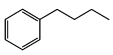
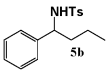
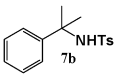
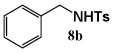
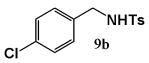
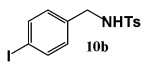
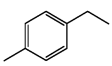
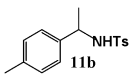
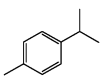
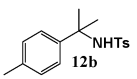
Table 2 Amidation of alkyl aromatics using $TsNBr_2$[a]

Entry	Substrate	Product	Time/h	Yield[b] (%)
1		 **1b**	4	84
2		 **2b**	6	80
3		 **3b**	6	80
4		 **4b**	5	81
5		 **5b**	5	78
6		 **6b**	5	89
7		 **7b**	8	64
8[c]		 **8b**	5	80
9[c]		 **9b**	5	85
10[c]		 **10b**	5	88
11[c]		 **11b**	3	92
12[c]		 **12b**	7	75

[a] Reaction conditions: substrate (1 mmol), $TsNBr_2$ (1 mmol), K_2CO_3 (3 mmol), ethyl acetate (3 mL), 80 °C. [b] Isolated yield. [c] Reaction under solvent-free conditions using 0.5 mL of the reactant.

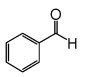
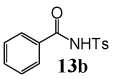
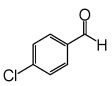
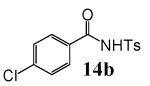
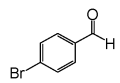
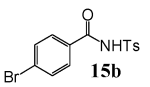
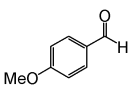
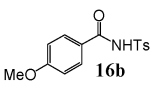
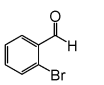
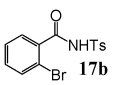
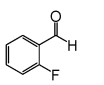
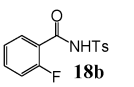
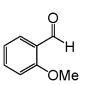
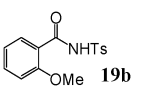
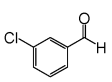
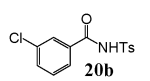
to be the most suitable for optimum yield of the aminated product.

After evaluating the suitable reaction conditions for amidation of ethyl benzene, the process was extended to a variety of substrates (Table 2). It is apparent from Table 2 that different kinds of substrates undergo amidation reaction at the benzylic position in excellent yield with a short reaction time. In the case of 1-(1-bromoethyl)benzene, the reaction produces a substituted (*N*-tosyl)-amino product (Table 2, entry 6) with substitution of Br, which was confirmed by analysis of NMR and mass spectra. In the case of cumene, amidation was observed at the benzylic 3°-C–H bond (Table 2, entry 7).

With a view of expanding the scope of the reaction we attempted amidation of toluene with $TsNBr_2$. Though the reaction failed in ethyl acetate, under solvent free conditions the reaction yielded nearly 80% of the expected sulfamidate product (Table 2, entry 8). In the case of 4-ethyl toluene selective amidation at 2°-benzylic C–H bond was observed (Table 2, entry 11). The same result was observed for *p*-cymene also (Table 2, entry 12), where the tertiary C–H bond was amidated in the presence of the primary one. The attempt for amidation of the allylic C–H bond led to the formation of aziridine as the exclusive product perhaps due to more facile π-insertion of nitrene.[23e] Attempts for amidation of saturated alkanes such as isooctane, 4-methyl cyclohexane and heterocycles such as THF and dioxane were also unsuccessful under these conditions.

The success of the benzylic C–H insertion reactions encouraged us to extend the nitrene insertion reaction to acyl C–H bonds of aldehydes (Table 3). Initial reaction with benzaldehyde as a substrate under the same reaction conditions

Table 3 Amidation of aldehydes using $TsNBr_2$[a]

Entry	Substrate	Product	Time/h	Yield[b] (%)
1		 **13b**	3	85
2		 **14b**	3	84
3		 **15b**	3	80
4		 **16b**	3	88
5		 **17b**	3	78
6		 **18b**	3	80
7		 **19b**	3	88
8		 **20b**	3	84
9		**21b**	3	80
10		**22b**	3	89
11		**23b**	3	90
12		**24b**	3	89
13		**25b**	4	79
14		**26b**	4	87

[a] Reaction conditions: substrate (1 mmol), $TsNBr_2$ (1 mmol), K_2CO_3 (3 mmol), ethyl acetate (3 mL), 80 °C. [b] Isolated yield.

produced the corresponding sulfonamide in 82% yield after 3 h of reaction.

To define the scope of the amidation reaction of aldehydes with $TsNBr_2$, we extended the optimized process to a series of aromatic and aliphatic aldehydes (Table 3). These reactions afforded the corresponding acylsulfonamides in very good yield. Initially, various substituted benzaldehydes were tested for this reaction, which produced high yield of the product irrespective of the substituents present on the benzene ring. The reaction was further extended to aliphatic aldehydes such as *n*-octanal and isobutyraldehyde and was found to be equally efficient. We observed exclusive formation of acylsulfonamides in the case of amidation of *p*-tolualdehyde (Table 3, entry 10) and 3-phenyl propionaldehyde (Table 3, entry 14). However, our attempts for amidation of pyridine 3-carboxaldehyde, 4-hydroxybenzaldehyde, 4-(*tert*-butyldimethyl)silyloxy benzaldehyde were unsuccessful.

Mechanistically, there is a formation of sulfonyl nitrene from *N*,*N*-dibromo-*p*-toluene sulfonamide in the presence of K_2CO_3.[23e] The initial step of the reaction is the abstraction of Br^+ ions by the base which subsequently loses KBr to form the nitrene.[23e] In the final step of the reaction, a C–H σ-insertion of the nitrene leads to the formation of the corresponding sulfonamides as the final product.

In conclusion, an efficient protocol has been developed for direct amidation of benzylic and acyl C–H bonds using $TsNBr_2$ *via* a nitrene transfer process. The amidation process is very facile at 80 °C without a catalyst in the presence of K_2CO_3. The reaction is fast, easy to handle and applicable to various benzylic substrates to give corresponding aminated products in high yield. Moreover, this metal free protocol is highly regioselective for secondary and tertiary benzylic C–H bonds. Selective amidation of aldehydic C–H bonds was also observed.

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Notes and references

‡ General procedure: to a mixture of substrate (1 mmol) and K_2CO_3 (3 mmol) in dry EtOAc (3 mL), in a Schlenk tube, $TsNBr_2$ (1 mmol) was added under a N_2 atmosphere. The tube was then tightly capped and heated at 80 °C. After completion of the reaction, water was added and the reaction mixture was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography using a petroleum ether and ethyl acetate mixture as eluent (4 : 1). Under solvent free conditions, 0.5 mL of substrate was taken for the reaction.

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