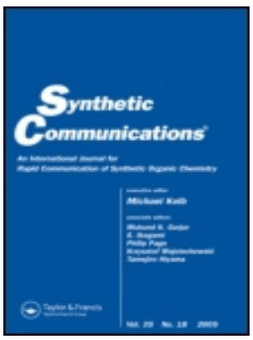

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Unexpected C-C bond cleavage of α-nitroketone in the presence of $TsNBr_2$: A new pathway for C-N bond formation

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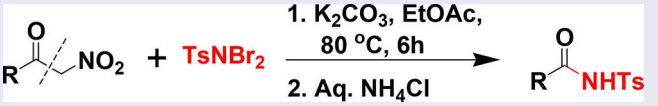
ABSTRACT

A new catalyst-free protocol for C-N bond formation via the cleavage of *α*-nitroketone has been developed. When *α* -nitroketones are treated with $TsNBr_2$ in the presence of potassium carbonate, unexpected cleavage of C(O)-$CHNO_2$ bond of *α* -nitroketone was observed followed by the formation of corresponding amide. Various nitroketones could be converted to corresponding amide using this procedure.

GRAPHICAL ABSTRACT



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Amide; C-C bond cleavage; C-N bond formation; α-nitroketone; $TsNBr_2$

Introduction

Development of a new method for the synthesis of amides is an important pursuit in organic synthesis owing to the prevalence of this linkage in a myriad of biomolecules as well as pharmaceutically important compounds.[1] In the past several years, various reagents such as chloramine-T,[2] bromamine-T,[3] tosyloxycarbamate,[4] and azide[5] have been developed for introducing amine groups because of their greater reactivity profile than normal amino organic compounds. Recently, *N,N*-dibromo-*p*-toluenesoulfonamide ($TsNBr_2$) has also been found to be an effective reagent for introduction of amine functionality in organic framework.[6] $TsNBr_2$ has been found to be useful for different organic transformations, such as oxidation, bromination, and C-H bond activation.[6,7] We have recently established a catalyst-free protocol for C-H amination of alkyl aromatics and aldehydes using $TsNBr_2$ as amine source.[6e] Organic molecules having α-nitroketone subunits can be used as important building blocks for a variety of synthetic transformations.[8] Recently, White and Young developed an efficient method for functionalization of to α-nitroketones using a terminal olefin in the presence of a palladium catalyst (Scheme 1a).[9] In continuation of our earlier protocol of C-H amination reaction (Scheme 1b),[6e] we intended to develop a strategy for introduction of a tosylamide group in the α-position of the nitro ketone using $TsNBr_2$ as an amine source. However, the reaction took a different course, which led to the cleavage of C

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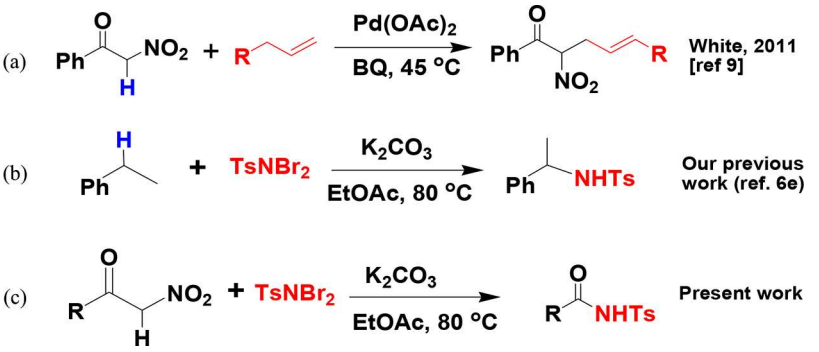


Scheme 1. C-H and C-C bond activation processes.

(O)-$CHNO_2$ bond of α-nitroketone followed by the formation of corresponding amide (Scheme 1c). This report discloses our study on the use of $TsNBr_2$ for the synthesis of *N*-tosyl amides via the C-C bond cleavage of α-nitroketones.

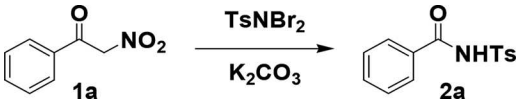
Results and discussion

For the initial survey, the reaction was carried out by considering benzoylnitromethane as a model substrate. In this case, we were expecting the amidation at α-position of α-nitroketones via C-H bond activation. However, the reaction led to the formation of *N*-tosylbenzamide as the sole product. Typically, a mixture of benzoylnitromethane (1 mmol), K_2CO_3 (2 mmol), and *N,N*-dibromo-*p*-toluenesoulfonamide (1 mmol) in ethyl acetate was heated at 80 °C in an inert atmosphere in a tightly capped Schlenk tube. After 16 h of reaction at that temperature, *N*-tosylbenzamide was isolated in 44% yield. The yield of the product could be improved to 76% by increasing the amounts of K_2CO_3 to 3 mmol and $TsNBr_2$ to 2 mmol. Further increasing the amount of K_2CO_3 to 5 mmol and the reaction time did not improve the yield of product. A marginal increment of yield was observed when the amount of $TsNBr_2$ was increased to 2.5 mmol. Reaction in different solvents such as acetonitrile and carbon tetrachloride could not improve the results. Finally, the use of 3 equiv of K_2CO_3 and 2 equiv of $TsNBr_2$ in 2 mL ethyl acetate was considered as optimum amounts for further studies at 80 °C.

After optimizing the reaction condition (Table 1), the procedure was extended to various α-nitroketones, which are summarized in Table 2. It can be seen from the table that both aromatic as well as aliphatic nitroketones could to transformed into corresponding tosyl amide effectively. It was observed that the yield of the reaction is lower in the case of aliphatic α-nitroketones as compared to aromatic α-nitroketones. *Ortho*-substituted aromatic α-nitroketones were found to be less active for this reaction. On the other hand, electronic effect of substituents on the aromatic ring was not found to be very significant. In all cases, moderate yield of corresponding tosylamide was observed.

The feasibility of this protocol was further examined for α-substituted α-nitroketones. When 1-(4-chlorophenyl)-2-nitropropan-1-one is treated with $TsNBr_2$ under the same reaction condition, corresponding 4-chloro-*N*-tosylbenzamide was isolated in 45% yield (Scheme 2).

Table 1. Optimization of reaction condition for amidation.[a]



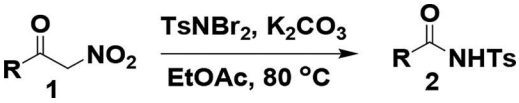
Entry	K_2CO_3 (mmol)	$TsNBr_2$ (mmol)	Time (h)	Solvent	Yield (%)[b]
1	2	1	16	EtOAc	44
2	3	1	12	EtOAc	50
3	3	2	6	EtOAc	76
4	3	2.5	6	EtOAc	78
5	3	2	6	MeCN	30
6	3	2	6	CCl_4	48

[a]Reaction condition: α-nitroketones (1 mmol), solvent (2 mL), N_2 atmosphere, 80 °C.
[b]Isolated yields after chromatographic purification.

The possible mechanistic pathway for the reaction is shown in Scheme 3. Usually, α-nitroketone prefers to stay in the form of β-hydroxy nitroolefin[10] because the enol form is stabilized by intramolecular hydrogen bond. Addition of a base led to abstraction of Br^+ species from $TsNBr_2$. The reaction is believed to proceed via initial attack of *N*-nucleophile to α-nitroketone. Subsequently the reaction undergos successive protonation-deprotonaiton steps in the presence of water, which led to elimination of nitromethane, resulting in the formation of the tosyl amide.

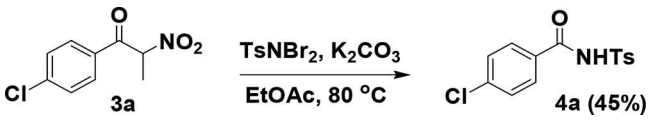
Thereafter we have examined the possibility of cleavage of different 1,3-diketone such as diethyl melonate, ethyl acetoacetate, methyl acetoacetate, and ethyl cyanoacetate under the same reaction condition. However, this procedure was found to be ineffective for C-C cleavage of 1,3-diketones.

Table 2. Synthesis of amides from various nitroketones.[a]

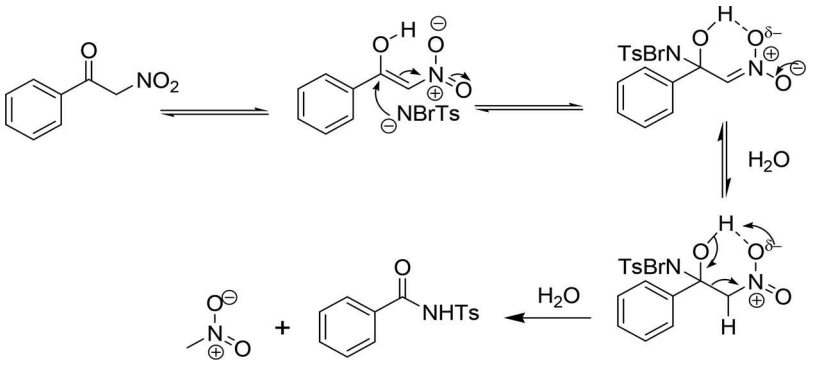


Entry	R	Product	Yield (%)[b]
1	C_6H_5 (1a)	**2a**	76
2	4-Br-C_6H_5 (1b)	**2b**	71
3	4-Cl-C_6H_5 (1c)	**2c**	74
4	4-Me-C_6H_5 (1d)	**2d**	76
5	4-MeO-C_6H_5 (1e)	**2e**	72
6	3-Cl-C_6H_5 (1f)	**2f**	68
7	3-Br-C_6H_5 (1 g)	**2g**	66
8	3-NO_2-C_6H_5 (1 h)	**2h**	65
9	2-MeO-C_6H_5 (1i)	**2i**	53
10	2-F-C_6H_5 (1j)	**2j**	57
11	2-Br-C_6H_5 (1k)	**2k**	56
12	2-Naphthyl (1 l)	**2l**	70
13	$C_6H_5CH_2CH_2$ (1 m)	**2m**	65
14	*n*-C_7H_{15} (1n)	**2n**	61

[a]Reaction condition: α-nitroketones (1 mmol), K_2CO_3 (3 mmol), EtOAc (2 mL), $TsNBr_2$ (1 mmol), N_2 atmosphere, 80 °C.
[b]Isolated yields.



Scheme 2. Cleavage of α-methyl α-nitroketones.



Scheme 3. Possible mechanism.

Conclusions

In summary, a new method has been developed for the formation of C-N bond via C-C bond cleavage using $TsNBr_2$ as a nitrogen source. Reaction of $TsNBr_2$ with α-nitroketones in the presence of K_2CO_3 results in the formation of *N*-tosyl amides in moderate yield. This C-N bond-forming process is effective in ethyl acetate at 80 °C without any catalyst.

Experimental

All reagents and starting materials were purchased from commercial sources. The solvents were purified through distillation prior to use. Nitroketons are synthesized by oxidation of corresponding nitroalcohols, which were prepared following a procedure reported earlier.[11] The amine source $TsNBr_2$ was synthesized from chloramine-T · $3H_2O$ using a literature procedure.[12,7a] ^1H and ^{13}C NMR were recorded using Bruker Ultrashield 300-MHz spectrometer at 300 and 75 MHz respectively using $CDCl_3$ as solvent. Chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (*J*) were reported in hertz. Infrared (IR) spectra were recorded on an Affinity-1 (Shimadzu) spectrometer.

$TsNBr_2$ (2 mmol) was added to a mixture of α-nitroketone (1 mmol) and K_2CO_3 (3 mmol) in dry EtOAc (2 mL) in a Schlenk tube. The tube was then tightly capped and heated at 80 °C for 6 h. After completion of the reaction, the reaction mixture was washed with saturated NH_4Cl solution and finally 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.

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