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Efficient synthesis of methyl carbamate via Hofmann rearrangement in the presence of $TsNBr_2$

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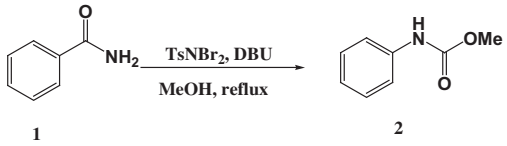
ABSTRACT

An efficient method has been developed for the synthesis of carbamates from the corresponding amides via the Hofmann rearrangement using *N,N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) in the presence of DBU in methanol. The reaction goes into completion in 10–20 min at 65 °C to produce the corresponding carbamate in excellent yield.

Hofmann reaction is a well known useful method for the synthesis of amines or carbamates from primary carboxamides.[1] Classical Hofmann rearrangement was carried out by using aqueous NaOH and bromine.[1] However this method is not always effectively applicable to all kinds of substrates. Therefore, several modifications have been initiated to improve the reaction conditions which include important examples such as hypervalent iodine species,[2] lead tetra acetate,[3] benzyltrimethylammonium tribromide,[4] NBS-$(HgOAc)_2$,[5] NBS-NaOMe,[6] NBS-DBU,[7] MeOBr,[8] TBA-Br_3,[9] and $NaBrO_2$-NaBr.[10] Many of the reported methods suffer from drawbacks such as requirement of a large excess of oxidizing agent, over oxidation of the carbamate products, and substrate scope limitation. However, by introducing modified protocols, these drawbacks have been minimized to different extents. Recently Miranda et al. reported a microwave assisted Hofmann rearrangement mediated by tribromoisocyanuric acid (TBCA).[11] As a part of our ongoing work on the development of synthetic methods using *N,N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$),[12] we report herein a fast and efficient method for Hofmann rearrangement of carboxamides using $TsNBr_2$ in the presence of DBU in MeOH for the synthesis of carbamates (Scheme 1).

N,N-Dibromo-*p*-toluenesulfonamide is known for a long time in organic synthesis. Since the discovery of the reagent by Kharasch,[13] it has been utilized for a variety of organic transformations.[14] $TsNBr_2$ employed for this purpose was prepared from Chloramine-T by following literature procedure.[15]



1 2

Scheme 1. Hofmann rearrangement using $TsNBr_2$.

To begin with, a study was carried out to check the feasibility of the method using benzamide as the model substrate. The results are summarized in Table 1. The reaction was carried out by adding $TsNBr_2$ (1 mmol) to a solution of benzamide (1 mmol) and DBU (3 mmol) in methanol (10 mL). Initial experiment at room temperature afforded 88% yield of the corresponding carbamate after 12 h of reaction. To improve the rate of the reaction, we have investigated the reaction at reflux temperature (65 °C). Interestingly, we found that the reaction works excellently and completes in 10 min with an improved yield of 95%. Further investigation by lowering the amount of $TsNBr_2$ to 0.5 mmol produced 76% of the corresponding carbamate after 30 min of reaction at reflux temperature. Finally, 1 equiv of $TsNBr_2$ was considered to be the optimum amount at reflux temperature of methanol.

After finding the optimum condition, we have extended the reaction to a variety of amides. The results are summarized in Table 2. The reaction was carried out by refluxing a mixture of amide (1 mmol), $TsNBr_2$ (1 mmol), and DBU (3 mmol) in methanol (10 mL).[16] Initially, we have screened several aromatic carboxamides to examine the scope of the reaction which produced the corresponding methyl carbamate in excellent yield (Table 2, entries 1–6). Thereafter, a few amides

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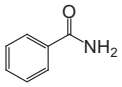
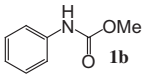
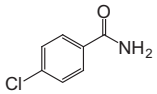
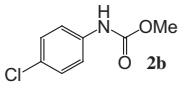
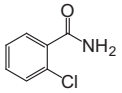
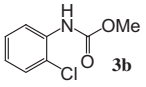
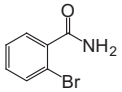
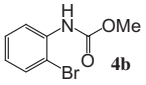
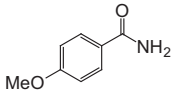
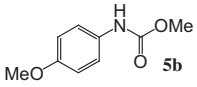
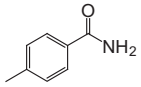
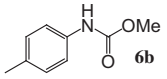
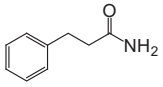
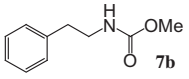
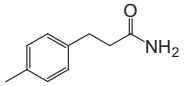
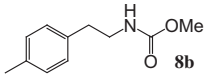
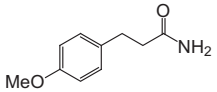
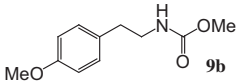
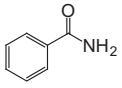
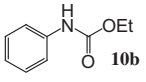
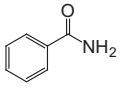
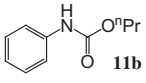
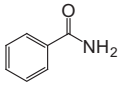
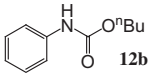
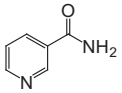
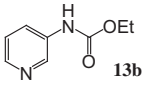
Table 1
Hofmann rearrangement of benzamide under different conditions[a]

Entry	$TsNBr_2$ (mmol)	Temp (°C)	Time	Yield[b] (%)
1	1	rt	12 h	88
2	1	65	10 min	95
3	0.5	65	30 min	76

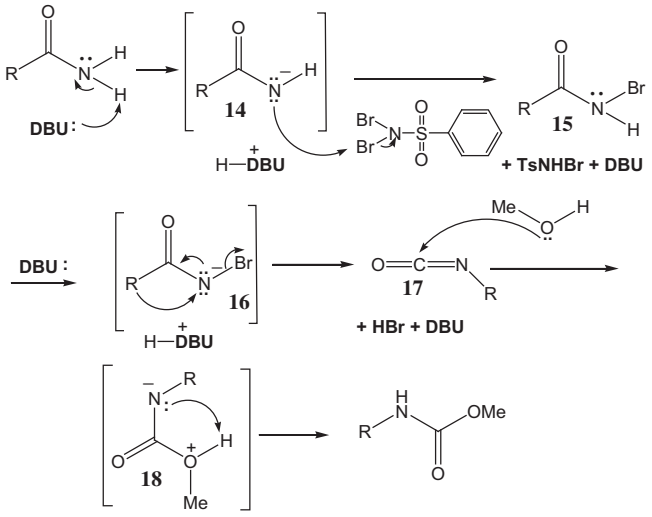
[a] Reaction condition: Benzamide (1 mmol), DBU (3 mmol), methanol (10 mL).
[b] Isolated yield.

bearing aliphatic chain were screened. Excellent yields were obtained in these cases also (Table 2, entries 7–9). In general, this procedure works well for a variety of aromatic as well as aliphatic amides to produce the corresponding carbamate in excellent yield.[16] The reaction time for the rearrangement could be significantly shortened (10–20 min) by increasing the reaction temperature. After being successful in producing methyl carbamate, the reaction was further extended to other alcohols as solvents. The reaction also works well for primary alcohols such as ethanol (Table 2, entry 10), *n*-propanol (Table 2, entry 11), and *n*-butanol (Table 2, entry 12). However secondary alcohols such as isopropanol, cyclohexanol, and *tert*-butanol failed to produce the desired product. Our effort to extend the procedure for 2-(trimethylsilyl)ethanol was found to be negative. This may be due to the strong oxidizing nature of the reagent.[12c] We have also examined the scope of the reaction for a heteroaromatic substrate, nicotinamide which produced the desired product in excellent yield (Table 2, entry 13).

Table 2
Synthesis of methyl carbamates via Hofmann rearrangement in the presence of $TsNBr_2$

Entry	Substrate (a)	Alcohol	Product (b)	Time (min)	Yield[a] (%)	Mp (°C)	
						Obsd	Lit.
1		MeOH	 **1b**	10	95	46–47	47–49[7]
2		MeOH	 **2b**	20	97	113–115	115–117[7]
3		MeOH	 **3b**	20	90	Oil	–
4		MeOH	 **4b**	20	97	Oil	–
5		MeOH	 **5b**	20	94	88–90	88–89[7]
6		MeOH	 **6b**	20	97	97–99	99–101[7]
7		MeOH	 **7b**	20	92	Semi solid	–
8		MeOH	 **8b**	20	92	38–40	–
9		MeOH	 **9b**	20	92	58–60	–
10		EtOH	 **10b**	10	85	47–49	49–50[9]
11		*n*-PrOH	 **11b**	10	86	52–54	54–55[9]
12		*n*-BuOH	 **12b**	10	82	60–62	62[9]
13		EtOH	 **13b**	20	78	81–83	84[1e]

[a] Isolated yield after chromatographic purification.



Scheme 2. Probable mechanistic pathway.

A probable mechanistic pathway to explain the rearrangement process is depicted in Scheme 2.[17] Initial step of the reaction is the deprotonation of the NH_2 group by the non-nucleophilic base DBU. The resulting *N*-based anion (**14**) subsequently picks up Br^+ ion from $TsNBr_2$. Since, $TsNBr_2$ is an excellent source of Br^+ species,[12e] formation of an intermediate *N*-bromoamide (**15**) is very facile in this case. In the next step, the bromoamide anion (**16**) formed in a DBU-promoted proton loss, undergoes an intramolecular Hofmann rearrangement via a nitrene intermediate, to form the corresponding isocyanate (**17**). Finally, the electrophilic cyanate group is trapped by methanol to form the carbamate.

In conclusion, an efficient protocol for Hofmann rearrangement reaction of various amides has been established by using *N,N*-dibromo-*p*-toluenesulfonamide in the presence of DBU. Although the reaction works well at room temperature, use of a higher temperature could push the reaction forward at a much faster rate. The procedure is very fast, easy to perform, and applicable to various aromatic, aliphatic, and heteroaromatic amides to produce the corresponding carbamates in excellent yields.

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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.2012.04.011.

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16. *Experimental procedure for the synthesis of carbamate*: To a solution of amide (1 mmol) in methanol (10 mL) was added DBU (0.5 mL). To this solution $TsNBr_2$ (1 mmol) was added. The reaction mixture was heated under reflux condition for a period of 10–20 min (TLC). After completion of the reaction (TLC) methanol was evaporated under reduced pressure. The crude mixture was then dissolved in EtOAc. This solution was washed with 5% HCl and then with saturated Na_2CO_3 solution. The organic extracts were separated and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography using petroleum ether and ethyl acetate (4:1) as eluent to get the pure carbamate product.
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