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TBCA mediated microwave-assisted Hofmann rearrangement

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ABSTRACT

A protocol for the microwave-assisted Hofmann rearrangement mediated by TBCA/KOH/MeOH was developed. Under these conditions high yields and short reaction times were observed for aromatic benzamides.

Tribromoisocyanuric acid (TBCA) is an efficient source of electrophilic bromine (Br^+) that has been used for the bromination of 1,3-dicarbonyl compounds,[1] activating aromatic rings,[2] dibromination and cobromination of alkenes,[3] and also in diverse oxidation reactions.[4] TBCA is a stable solid that can be easily synthesized from isocyanuric acid and NaBr in the presence of oxone.[3] It has advantage in comparison to similar systems such as *N*-bromosuccinimide (NBS) and 3,3-dibromo- 5,5-dimetilidantoin (DBH): in the case of NBS a maximum of only 45% of its mass can be transferred in halogenation reactions, while in comparison to TBCA it represents 66% of its mass, such a higher mass transfer leads to a greener reagent in terms of the concept of mass efficiency of the reaction.[5] Furthermore, in the reactions involving TBCA, isocyanuric acid is left as a by-product at the end of the reaction that can be easily recovered by filtration and reused to produce more TBCA, leading to a completely green protocol. So far, transformations mediated by TBCA are usually carried out with electrophilic activation and no information concerning its ability to act as an electrophilic halogen in basic medium exists in the literature. To test the TBCA behavior as an electrophilic bromine donor in basic media we performed the Hofmann rearrangement under microwave irradiation.

Recently, several publications have shown that microwave irradiation can accelerate the rate of chemical reactions[6] often with increased yields leading to cleaner and enhanced chemical processes. In our continuous work on the development of processes under microwave irradiation,[7] here in, we present a microwave-assisted procedure for the Hofmann Rearrangement mediated by TBCA, compatible with electron-poor aromatic benzamides.

The Hofmann rearrangement (HR) in its classical form, as developed by Hofmann, is the conversion of primary amides to primary amines through the intermediary of isocyanates using bromine under basic conditions.[8] The trapping of the intermediate isocyanates with alcohol leads to the corresponding carbamates.[9e,f] For the classic HR protocol, several experimental conditions can be found within the literature,[9] as well as for a non classical HR, known as the oxidative Hofmann rearrangement.[10]

Reactions were initially performed with DBU as base, in methanol under microwave irradiation. Reactions were also performed with NBS for sake of comparison and because the best of our knowledge there is no precedent works on microwaves in the context of the Hofmann rearrangement in the literature.

These experiments were performed using an Anton-Paar Monowave 300 microwave reactor. With this reactor the temperature was simultaneously monitored by infrared sensor (IR) and ruby thermometer (RT), and no significant difference was observed between both measured temperatures, validating the data on the microwave experiment. The microwave power applied was at a temperature controlled mode by the ruby thermometer.

Results obtained are shown in Table 1. Reactions were performed at 60 °C, under microwave heating protocols. A heating ramp time of 11 s was observed in all cases at 'as soon as possible' method, offered by the Monowave 300 software. Temperature, pressure and power profile during the ramp time are shown in Supplementary material.

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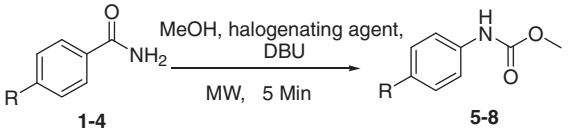
Table 1
Results on the MW assisted NBS or TBCA mediated Hofmann rearrangement with DBU



1-4 5-8

Entry	R	Halogenating reagent	Temperature (°C)	GC conversion (%)
1	H (**1**)	NBS	60	80 (**5**)
2	NO_2 (**2**)	NBS	60	20 (**6**)
3	OMe (**3**)	NBS	60	>99 (**7**)
4	Cl (**4**)	NBS	60	90(**8**)
5	H (**1**)	TBCA	60	50 (**5**)
6	NO_2 (**2**)	TBCA	60	10 (**6**)
7	OMe (**3**)	TBCA	60	91 (**7**)
8	Cl (**4**)	TBCA	60	66 (**8**)

A hold time of 5 min was chosen to monitor the conversion to the desired carbamates. Under these conditions, a complete conversion of 4-methoxybenzamide to the corresponding methyl carbamate was observed with the use of NBS (Table 1), once the 4-methoxybenzamide could not be detected in the crude reaction mixture. In the case of benzamide and 4-chlorobenzamide, high conversions were also observed with NBS (entries 1 and 4). In the case of the 4-nitrobenzamide only 20% conversion was obtained (entry 2), and no improvement was observed with increasing reaction time.

Gratifyingly the reaction performed with TBCA afforded the desired carbamates with the same conversion pattern as for NBS, however with lower conversions (entries 5–8). This lower TBCA performance can be explained by the concurrent reaction with the DBU base. In the case with the electron withdrawing substituted benzamides where a slower rearrangement rate is expected the decomposition of DBU is responsible for the low yields.

In order to circumvent this problem, the reaction with TBCA was performed in the presence of KOH; results are shown in Table 2.

As can be observed in Table 2, using a reaction system comprised of TBCA/KOH/MeOH/MW high conversions could be obtained for all cases studied including the less reactive 4-nitrobenzamide in only 5 min. Control experiments using conventional heating afforded good yields only after 90 min (see Supplementary data) It should be noted that no bromination was observed during reactions. This is a very important observation, since carbamate bromination derived from 4-methoxybenzamide could be expected once the anisole ring can be easily brominated by TBCA.

In conclusion it was demonstrated that TBCA is effective in the Hofmann rearrangement conducting to the methylcarbamates in high isolated yields under microwave irradiation. Under these conditions the reagent showed that high chemo-selectivity for no brominated products could be detected.

Table 2
Results on the MW assisted HR mediated by TBCA/KOH

4-7 8-11

Entry	R	Product	GC conversion (%) (isolated yields)
1	H (**1**)	**5**	>99% (85%)
2	NO_2 (**2**)	**6**	80% (75%)
3	OMe (**3**)	**7**	>99% (95%)
4	Cl (**4**)	**8**	97% (90%)

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.126.

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