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Preparation of Methyl Carbamates via a Modified Hofmann Rearrangement

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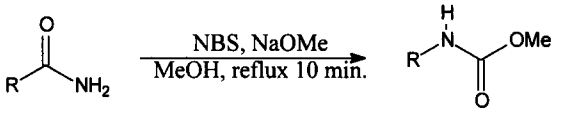
ABSTRACT: Treatment of a series of *para*-substituted aromatic and primary aliphatic carboxamides with NBS and NaOMe in methanol heated to reflux for ten minutes results in the conversion of the carboxamides to their corresponding primary amino methyl carbamates in nearly quantitative yields. The mild oxidative conditions of this modified Hofmann rearrangement are shown to be particularly useful for the preparation of *p*-substituted anilines. Copyright © 1996 Elsevier Science Ltd

The Hofmann rearrangement is the conversion of primary carboxamides to amines using aqueous NaOH and Br_2[1]. Many modifications of this rearrangement have been reported using oxidative reagents including iodine (III) species[2] (such as $PhI(OCOCF_3)_2$, PhI-HCO_2H, PhI(OTs)OH and $PhI(OAc)_4$), lead tetraacetate,[3] benzyltrimethylammonium tribromide,[4] N-bromosuccinimide (NBS)-$Hg(OAc)_2$,[5] and CH_3OBr.[6]

During the synthesis of a series of ^{15}N-labelled *p*-substituted anilines, we encountered some difficulties with the conversion of *p*-methoxybenzamide to anisidine by the Hofmann rearrangement. The use of lead tetraacetate proved unsuccessful, since $Pb(OAc)_4$ is a powerful oxidizing agent, and resulted in the rapid oxidative decomposition of the product anisidine carbamate. Milder oxidative conditions such as NBS-$Hg(OAc)_2$ in methanol have been reported[5] for the conversion of *o*-ethoxybenzamide to the corresponding methyl carbamate. However, upon application of these conditions for the conversion of *p*-methoxybenzamide, the product methyl carbamate (**2a**, Table I) proved to be unstable in the presence of both NBS and $Hg(OAc)_2$ in methanol, although it is stable in the presence of either reagent alone. It was thus necessary to develop a modified procedure that would permit the transformation of the carboxamide **1a** to its methyl carbamate **2a** under reaction conditions that were sufficiently mild to prevent further oxidative decomposition of the product. We found that the combination of NBS and NaOMe in methanol, instead of NBS-$Hg(OAc)_2$, gave an excellent

yield of carbamate **2a**. When *p*-methoxybenzamide was treated with NBS in the presence of NaOMe in methanol at reflux, carbamate **2a** was generated immediately and the reaction was determined to be complete in only ten minutes.



1 **2**

A typical procedure is as follows: A solution of NaOMe was prepared by the addition of $Na_{(s)}$ (0.10 g) to MeOH (5 mL). To this solution was added *p*-methoxybenzamide (50 mg) and NBS (60 mg) and the solution was heated to reflux. After time intervals of three and six minutes, additional portions (30 mg) of NBS were added. After heating for a total of ten minutes, the solvent was removed under reduced pressure. The resulting residue was diluted with 100 mL of EtOAc, washed with H_2O, and dried over $MgSO_4$. Following filtration and removal of EtOAc, a light yellow solid was obtained. The solid was purified by flash column chromatography (silica gel, eluant CH_2Cl_2, followed by 3:1 CH_2Cl_2/EtOAc) to give a white solid (64 mg). Recrystallization from hexane afforded white needles (49 mg, 82 % yield) with a melting point of 88-89 °C (lit.[7] m.p. 88-89 °C). The ^1H NMR spectrum was found to be identical to that previously reported.[7]

As illustrated in Table I, this method was found to be quite general for the transformation of both aromatic and primary aliphatic carboxamides **1a-h** to their methyl carbamates **2a-h** in quantities on the milligram to gram scale. A notable exception (not shown in Table I) is that of *p*-nitrobenzamide, where the lack of detected product formation is probably due to the strongly electron-withdrawing nature of the nitro substituent which disfavours the rearrangement. (Note, however, that this characteristic also makes the corresponding aniline more resistant against oxidative decomposition, and in fact *p*-nitroaniline is more easily prepared from *p*-nitrobenzamide through a Hofmann rearrangement catalyzed by stronger oxidative reagents such as lead tetraacetate.[3])

Table I. Conversion of Primary Carboxamides **1** to Methyl Carbamates **2** with NBS/NaOMe

$RCONH_2$ **1**	Yield of $RNHCO_2Me$ **2** (%)[a]	Observed m.p. (°C)	Literature m.p.(°C)
a *p*-$MeOC_6H_4$–	87[b]	88-89	88-89[7]
b *p*-MeC_6H_4–	85[b]	98-99	99-101[8]
c C_6H_5–	95	46-47	47-48.5[8]
d *p*-ClC_6H_4–	98	114-115	115-117[8]
e *p*-$CF_3C_6H_4$–	100	129-130	123-125[9]
f $C_6H_5CH_2$–	100	64-65	65[10]
g $CH_3(CH_2)_{14}$–	85[b]	61-62	61-62[1]
h $CH_3(CH_2)_8$–	93	< r.t.	-

[a] Yields are after final purification.

[b] Yield after final purification including recrystallization.

Recently it has been shown by Senanayake and co-workers[11] that at -5 °C in an aqueous potassium hydroxide solution, NBS forms the active brominating species $KOCOCH_2CH_2CONKBr$, which was found to decompose at 20 °C. In our case, using NaOMe in boiling methanol, the true brominating species is probably $MeOCOCH_2CH_2CONNaBr$. At 64 °C, prior to its decomposition, this species is apparently able to effectively convert a carboxamide to the corresponding N-bromocarboxamide, which subsequently undergoes rearrangement to form the product carbamate. Because of the instability of NBS in NaOMe at reflux, however, NBS was used in excess (molar ratio 2:1) and added in three portions to ensure complete conversion of the carboxamide.

The modified Hofmann rearrangement reported herein is rapid, economical and simple. As demonstrated by the number of different carbamates thereby prepared in milligram to gram quantities, this

method is both effective and practical. We have found it to be extremely useful in the preparation of a series of ^{15}N-labelled *p*-substituted anilines, especially for the synthesis of anisidine.

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