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An Efficient Method for the Hofmann Degradation of Amides by Use of Benzyltrimethylammonium Tribromide[1)]

Shoji KAJIGAESHI,* Kohichi ASANO, Shizuo FUJISAKI,
Takaaki KAKINAMI,† and Tsuyoshi OKAMOTO†
Department of Industrial Chemistry, Faculty of Engineering,
Yamaguchi University, Tokiwadai, Ube 755
†Department of Industrial Chemistry, Ube Technical College, Tokiwadai, Ube 755

The reaction of amides with a calculated amount of benzyltrimethylammonium tribromide in aqueous sodium hydroxide under mild conditions gave corresponding amines in fairly good yields.

Although amines (**2**) are obtained from the Hofmann degradation of amides (**1**) with alkaline solution of bromine or chlorine,[2)] these methods are occasionally accompanied by difficulties in terms of satisfactory, reliable results. Methyl hypobromite generated in situ from bromine and sodium methoxide in methanol,[3)] lead tetraacetate in t-butyl alcohol in the presence of catalyst such as triethylamine or tin(IV) chloride,[4)] and iodobenzene bis(trifluoroacetate) in aqueous acetonitrile[5)] have been used for the degradation of **1** instead of alkaline solution of halogen. We have reported that amides **1** can be converted into **2** by the use of commercial sodium bromite ($NaBrO_2$) in place of bromine in aqueous sodium hydroxide.[6)]

During the course of our investigation on the utility of benzyltrimethyl ammonium tribromide (BTMA Br_3) as a brominating agent,[7)] we now find that BTMA Br_3 is also an effective oxidating agent. In this paper, we wish to report on a facile synthesis of **2** from **1** using BTMA Br_3.

The reaction of **1** with a calculated amount of BTMA Br_3 and aqueous sodium hydroxide at room temperature or at 70 °C gave **2** in fairly good yields. The reaction scheme can be presented in the following equation:

$$\underset{\mathbf{1}}{R\text{-}CONH_2} + PhCH_2(CH_3)_3N^+Br_3^- + 4\ NaOH$$

$$\longrightarrow \underset{\mathbf{2}}{R\text{-}NH_2} + PhCH_2(CH_3)_3N^+Br^- + 2\ NaBr + Na_2CO_3 + 2\ H_2O.$$

The results are summarized in Table 1. Our method can be applied to **1** of various types; aliphatic, aromatic, and heterocyclic amides. However, in the case of the reaction of higher aliphatic amides ($CH_3(CH_2)_nCONH_2$; n>6) with BTMA Br_3/NaOH aq, the corresponding acylureas ($CH_3(CH_2)_nNHCONHCO\text{-}(CH_2)_nCH_3$) were obtained as major products. The procedure for the Hofmann degradation of **1** using BTMA Br_3 has a large merit in that this reagent can be treated safely and quantitatively compared with toxic gaseous chlorine or liquid bromine owing to its stable solid character.

The following is a typical procedure for the synthesis of aniline (**2f**) from benzamide (**1f**): To a solution of sodium hydroxide (0.8g, 20 mmol) in water (30 ml) were added **1f** (0.61g, 5 mmol) and BTMA Br_3 (1.95g, 5 mmol), and the mixture was stirred for 2 h at room temperature. During the period of stirring, BTMA Br_3 (orange red) soon dissolved in the alkaline solution and the mixture became yellow suspension, and then the mixture changed to homogeneous orange solution, and finally to brown solution. The resultant solution was steam distilled and the distillate was extracted with dichloromethane (40 ml x 4). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give **2f** as colorless liquid; yield 0.34g (72%); bp 183 °C/760 mmHg.

Table 1. Hofmann Degradation of Amides with BTMA Br_3/NaOHaq

Run	Product[a] (2)	Reaction conditions		Yield[b]	Mp/°C or
		temp/°C	time/h	%	Bp/°C (mmHg)
a	Methylamine	70	2	85[c]	221-222[d]
b	Propylamine	70	2	90[c]	154-156[d]
c	Pentylamine	70	2	80	101(760)
d	Nonylamine	rt	2	trace[e]	-
e	Pentadecylamine	rt	2	-[f]	-
f	Aniline	rt	2	72	183(760)
g	o-Chloroaniline	rt	2	86	208(760)
h	m-Chloroaniline	rt	2	79	223(760)
i	p-Chloroaniline	rt	3	68	69-70
j	m-Bromoaniline	rt	1	76	248(760)
k	o-Nitroaniline	70	1	76	50-52
l	p-Nitroaniline	70	1	75	147-148
m	m-Toluidine	rt	2	93	201(760)
n	Benzylamine	70	3	75	180(760)
o	1-Naphthylmethylamine	rt	5	51	267-269
p	3-Aminopyridine	70	5	44	62-63

a) Products were characterized by comparing ^1H NMR spectra and bp or mp with those of authentic samples or reported data. b) Yield of isolated product. c) Yield of HCl-salt.

d) Mp of HCl-salt. e) Major product: $CH_3(CH_2)_8NHCONHCO(CH_2)_8CH_3$ (mp 83-85 °C).

f) Only $CH_3(CH_2)_{14}NHCONHCO(CH_2)_{14}CH_3$ (mp 109-111 °C) was obtained.

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