

An Efficient Method for the Hofmann Degradation of Amides by Use of
Benzyltrimethylammonium Tribromide¹⁾

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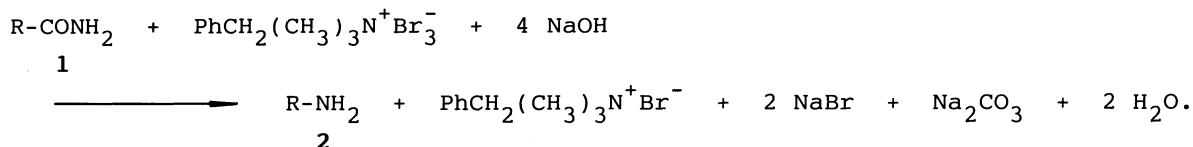
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The reaction of amides with a calculated amount of benzyltri-
methylammonium tribromide in aqueous sodium hydroxide under mild
conditions gave corresponding amines in fairly good yields.

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 acetonitrile⁵⁾ 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 (NaBrO₂) in place of bromine in aqueous sodium hydroxide.⁶⁾

During the course of our investigation on the utility of benzyltrimethyl ammonium tribromide (BTMA Br₃) as a brominating agent,⁷⁾ we now find that BTMA Br₃ is also an effective oxidating agent. In this paper, we wish to report on a facile synthesis of 2 from 1 using BTMA Br₃.

The reaction of 1 with a calculated amount of BTMA Br₃ 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:



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 (CH₃(CH₂)_nCONH₂; n>6) with BTMA Br₃/NaOH aq, the corresponding acylureas (CH₃(CH₂)_nNHCONHCO-(CH₂)_nCH₃) were obtained as major products. The procedure for the Hofmann degradation of 1 using BTMA Br₃ 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 Br₃ (1.95g, 5 mmol), and the mixture was stirred for 2 h at room temperature. During the period of stirring, BTMA Br₃ (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 MgSO₄ 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 Br₃/NaOHaq

Run	Product ^{a)} (2)	Reaction conditions		Yield ^{b)} %	Mp/°C or Bp/°C (mmHg)
		temp/°C	time/h		
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: CH₃(CH₂)₈NHCONHCO(CH₂)₈CH₃ (mp 83-85 °C).

f) Only CH₃(CH₂)₁₄NHCONHCO(CH₂)₁₄CH₃ (mp 109-111 °C) was obtained.

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