

Practical Synthesis of N-Bromoamides with Benzyltrimethylammonium Tribromide in the Presence of Aqueous Disodium Hydrogenphosphate¹⁾

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Abstract

The reaction of aliphatic and aromatic amides with a calculated amount of benzyltrimethylammonium tribromide in aqueous disodium hydrogenphosphate at room temperature gave N-bromoamides in good yields.

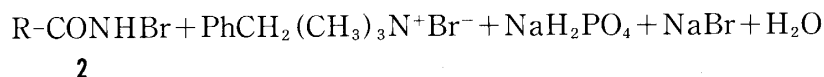
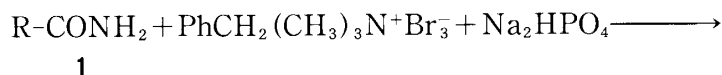
Introduction

N-bromination of amides **1** with bromine and alkali has been well investigated as the first step of Hofmann degradation.²⁾ However, the isolation of N-bromoamides **2** is not so easy because the subsequent reaction of **2** to amines should proceed more readily under the alkaline conditions. A few reports for the preparation of **2** by the use of special techniques³⁻⁵⁾ have been presented. We have also shown that **1** can be converted into **2** by the use of sodium bromite (NaBrO₂) in acetic acid⁶⁾.

During the course of our investigation on the synthetic utility of benzyltrimethylammonium tribromide (BTMA Br₃) as an oxidizing agent, we recently found that BTMA Br₃ in aqueous sodium hydroxide was a useful reagent for the Hofmann degradation⁷⁾ and N-bromination of **1**⁸⁾. In this paper, we wish to report on a more practical synthetic procedure of **2** from **1** using BTMA Br₃ in aqueous disodium hydrogenphosphate (Na₂HPO₄) in stead of aqueous NaOH.

Results and Discussion

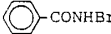
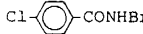
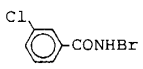
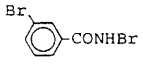
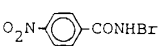
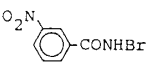
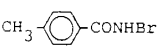
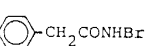
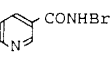
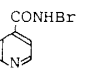
The reaction of **1** with a stoichiometric amount of BTMA Br₃ in aqueous Na₂HPO₄ at room temperature for several hours gave **2** in good yields. The results are summarized in Table 1. Our method can be applied to **1** of various types; aliphatic, aromatic, and heterocyclic amides.



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Table 1 N-Bromoamides **2** from Amides **1** with BTMA Br₃/aq Na₂HPO₄

Run	Product 2	Yield ^{a)} %	Mp(°C)		Active bromine(%)	
			Found	Reported	Found	Calcd
a	CH ₃ (CH ₂) ₆ CONHBr	66	62-63	63-65 ⁶⁾	34.4	36.0
b	CH ₃ (CH ₂) ₈ CONHBr	83	72-74	74-76 ⁶⁾	30.3	31.9
c	CH ₃ (CH ₂) ₁₀ CONHBr	75	82-84	85-87 ⁶⁾	26.8	28.7
d	CH ₃ (CH ₂) ₁₂ CONHBr	84	85-88	89-92 ⁶⁾	24.4	26.1
e	CH ₃ (CH ₂) ₁₄ CONHBr	75	96-99	93-96 ⁶⁾	22.6	23.9
f	 -CONHBr	55	124-127	129-131 ⁴⁾	39.0	39.9
g	 -CONHBr	98	168-170	170-174 ⁴⁾	33.2	34.1
h	 -CONHBr	96	108-110	102-105 ⁴⁾	32.1	34.1
i	 -CONHBr	81	125-127	122-126 ⁴⁾	27.9	28.6
j	 -CONHBr	95	198-203	198-202 ⁴⁾	30.2	32.6
k	 -CONHBr	78	170-172	173-176 ⁴⁾	31.2	32.6
l	CH ₃ -  -CONHBr	61	130-134	131-133 ⁴⁾	37.0	37.3
m	 -CONHBr	64	120-124	126-129 ⁶⁾	36.1	37.3
n	 CONHBr	45	114-117	-	37.6	39.7
o	 CONHBr	95	148-150	-	37.4	39.7

a) Yield of isolated product.

In the case of using aq Na₂HPO₄ (pH=9.5), the N-bromination of **1** with BTMA Br₃ proceeds smoothly at room temperature. Furthermore, the treatment of Na₂HPO₄ is more easy than that of NaOH because Na₂HPO₄ is stable and not hygroscopic. Thus, we noticed that the BTMA Br₃-Na₂HPO₄ system gave a more excellent procedure for the oxidation of **1** to **2** than the BTMA Br₃-NaOH system. The simplicity of the operation and the availability of substrates should also make it synthetically useful.

As limitation of this method, attempts for the N-bromination of lower aliphatic amides such as acetamide or propionamide were unsuccessful because the desired products were soluble in water and decompose to amides and bromine. Furthermore, N-brominations of ortho-substituted benzamides were also unsuccessful.

Experimental

N-Bromo-p-nitrobenzamide (2j) ; **Typical Procedure** : A finely powdered BTMA Br₃ (1.95g, 5 mmol) was added to a stirred mixture of p-nitrobenzamide (**1j**) (0.83 g, 5 mmol) and Na₂HPO₄ 12H₂O (2.69g, 7.5 mmol) in water (20 ml), and the mixture was stirred for 4 h at room temperature. The obtained precipitate was filtered, washed with dichloromethane (5 ml), and dried in vacuo to give **2j** as colorless crystals ; yield 1.17g (95%) ; mp 198-203°C (dec.) (lit,⁴) mp 198-202°C). Active bromine measurement : Found ; Br, 30.2%. Calcd for C₇H₅N₂O₃Br ; Br, 32.6%.

References

- 1) Oxidation using quaternary ammonium polyhalides VI.
- 2) E. S. Wallis and J. F. Lane, "Organic Reactions," ed R. Adams, John Wiley & Sons, Inc., New York, 1946, vol, 3, p. 267.
- 3) E. P. Oliveto and C. Gerold, *Org. Synth.*, Coll. Vol. IV, 104 (1963).
- 4) C. R. Hauser and W. B. Renfrow, Jr., *J. Am. Chem. Soc.*, **59**, 121 (1937).
- 5) T. D. Waugh and R. C. Waugh, *U. S. Pat.* 61/2971959, *Chem. Abstr.*, **55**, 14483 (1961).
- 6) S. Kajigaeshi, T. Nakagawa, and S. Fujisaki, *Chem. Lett.*, **1984**, 2045.
- 7) S. Kajigaeshi, K. Asano, S. Fujisaki, T. Kakinami, and T. Okamoto, *Chem. Lett.*, **1989**, 463.
- 8) S. Kajigaeshi, K. Murakawa, K. Asano, S. Fujisaki, and T. Kakinami, *J. Chem. Soc., Perkin Trans.1*, **1989**, 1702.