

Facile Synthesis of *N*-Bromoamides Using Benzyltrimethylammonium Tribromide in Alkaline Solution

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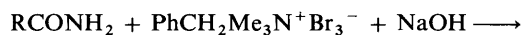
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Aliphatic and aromatic amides reacted with a stoichiometric amount of benzyltrimethylammonium tribromide in ice-cold aqueous sodium hydroxide to give *N*-bromoamides in good yields.

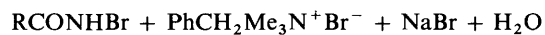
Although *N*-bromination of amides (1) with bromine and alkali has been widely investigated as the first step of the Hofmann degradation,¹ it is difficult to isolate the *N*-bromoamides (2) so formed since their subsequent reaction to give amines proceeds very readily under the prevailing alkaline conditions. *N*-Bromoamides (2) have however been prepared with special techniques.²⁻⁴ In addition, we have reported that amides can be *N*-brominated by the use of commercial sodium bromite (NaBrO₂) in acetic acid.⁵

During the course of our recent investigations on the synthetic utility of benzyltrimethylammonium tribromide (BTMA·Br₃) as an oxidizing agent, we found that it was a useful reagent for the Hofmann degradation of amides (1).⁶ Here, we report the facile *N*-bromination of amides using BTMA·Br₃.

The reaction of (1) with a stoichiometric amount of BTMA·Br₃ and sodium hydroxide in ice-water gave *N*-bromoamides (2) in good yields (see Scheme 1 and Table 1).



(1)



(2)

Scheme.

Our method can be applied to various types of aliphatic, aromatic, and heterocyclic amides.

A typical procedure was as follows. Finely powdered BTMA·Br₃ (5 mmol) was added to a stirred solution of sodium hydroxide (5 mmol) in ice-cooled water (20 ml), over 30 min. To the aqueous suspension was added (1) (5 mmol) and the mixture was stirred for 4 h under the same chilled conditions. The precipitate which formed was filtered off, washed successively with cold dilute aqueous acetic acid, and dried to give (2) as white crystals.

The described procedure compares well with other methods

Table. *N*-Bromination of amides (1) by BTMA·Br₃ in aqueous NaOH

Product (2)	M.p./°C (lit. value)	Yield (%) ^a	Active bromine (%)	
			Calc.	Found
CH ₃ (CH ₂) ₆ CONHBr	61—62 (63—65) ⁵	77	36.0	33.5
CH ₃ (CH ₂) ₈ CONHBr	72—74 (74—76) ⁵	66	31.9	29.7
CH ₃ (CH ₂) ₁₂ CONHBr	84—87 (86—88) ⁵	76	26.1	23.8
PhCONHBr	124—127 (129—131) ³	53	39.9	37.9
<i>p</i> -ClC ₆ H ₄ CONHBr	169—172 (170—174) ³	86	34.1	33.6
<i>m</i> -ClC ₆ H ₄ CONHBr	107—109 (102—105) ³	74	34.1	32.7
<i>p</i> -BrC ₆ H ₄ CONHBr	172—175	86	28.7	26.2
<i>m</i> -BrC ₆ H ₄ CONHBr	122—125 (122—126) ³	73	28.7	27.0
<i>p</i> -NO ₂ C ₆ H ₄ CONHBr	196—199 (198—202) ³	82	32.6	31.1
<i>m</i> -NO ₂ C ₆ H ₄ CONHBr	168—170 (173—176) ³	83	32.6	32.5
<i>p</i> -MeC ₆ H ₄ CONHBr	127—130 (131—133) ³	68	37.3	35.6
PhCH ₂ CONHBr	128—130 (126—129) ⁵	63	37.3	34.6
(3-pyridyl)CONHBr	210—213	47	39.8	38.2

^a Yield of isolated product.

in terms of the handling of the brominating agent. Benzyltrimethylammonium tribromide can be easily used stoichiometrically owing to its stable solid character. The simplicity of the operation and the availability of the substrates should also make it synthetically useful. One limitation of this method is that attempted *N*-bromination of lower aliphatic amides such as acetamide or propionamide were unsuccessful, because the desired products are soluble in water and decompose to the amides and bromine.

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Received 6th April 1989; Paper 9/02360G