A Versatile Modification of the Hofmann Rearrangement

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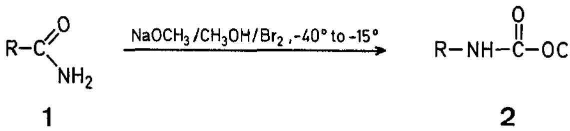
A survey of the literature regarding the Hofmann rearrangement reveals that this classic reaction is fraught with difficulties in terms of satisfactory, reliable results. Magnien and Baltzly examined the problem and made several good recommendations for improvement of the procedure[1]. There were still many cases where insolubility of the substrate in aqueous or partially aqueous media, thermal lability of the substrate or product, and extreme reactivity of the substrate to the halogen, i.e. bromine or chlorine, precluded the use of the available published procedures. What was still needed was a non-aqueous, low-temperature procedure which did not involve side reactions of the halogen.

The restraints that we have placed upon the reaction conditions require preformation of a positive-halogen source which must be soluble in organic solvent. We chose methyl hypobromite. To our knowledge it has not been isolated or characterized. However, there was reason to believe that it should be a stable substance at low temperatures. Treatment of a solution of sodium methoxide in methanol at −40° with bromine causes rapid decolorization and results in a pale yellow solution. This solution upon warming results in the rapid development of a precipitate[2] at ~ −20° with concurrent loss in activity as far as usefulness in the Hofmann rearrangement is concerned. We have not characterized the substance that is formed in this reaction as methyl hypobromite but we believe that it is present

$$NaOCH_3 + Br_2 \longrightarrow [H_3COBr] + NaBr$$

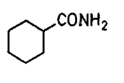
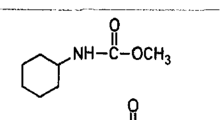
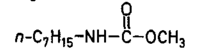
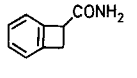
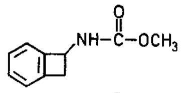
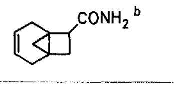
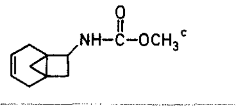
and that it functions as the source of positive bromine for the Hofmann rearrangement, since addition of an amide (**1**) to this cold, basic solution, followed by gentle heating to ~50°, results in high yields of the expected carbamates (**2**).



1 **2**

The Table shows the typical results obtained upon application of this reaction to a few amides. The most remarkable is that of the **1d**→**2d** transformation. We have found, in agreement with Warner[3], that the 1,6 bond in this ring system is extremely reactive[4]. In fact, the modification described in this paper is a result of many attempts to effect transformations of the tricyclo[4.2.1.0^{1,6}]nonane skeleton not involving the 1,6 bond. That we have been successful in performing the Hoffman rearrangement upon **1d** is evidence for the applicability of this procedure to compounds which are highly reactive to electrophilic addition reactions.

Table. Hofmann Rearrangement with Methyl Hypobromite *in situ*

	1		**2**	Yield[a] (%)	m.p. (Lit. m.p.)
a		→		87	72–75°
b	n-C_7H_{15}–$CONH_2$	→	 $n\text{-}C_7H_{15}\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3$	85	b.p. 85–88°/0.5 torr
c		→		89	92–94°
d		→		68	80–81.5°

[a] Yields are after final purification.

[b] Details of preparation for **1d** have been submitted to *J. Org. Chem.*

[c] New Compound: $C_{11}H_{15}NO_2$ (193.2) calc. C 68.37 H 7.82; found 68.4 7.8

2d:

^{1}H-N.M.R. (CCl_4): $\delta = 5.48$ (s, 2H), 4.93 (1H), 4.13 (m, 1H), 3.66 (s, 3H), 2.43 (m, 1H), 2.35 (s, 4H), 1.55 (m, 1H), 0.9 (d, 1H), 0.6 ppm (m, 1H).

The following Procedure is typical.

1-Methoxycarbonylamino-benzocyclobutene (2c):

A solution of sodium methoxide in methanol (232 ml) was prepared from sodium (10.55 g, 0.459 g-atom) in a three-necked 1000-ml flask equipped with mechanical stirrer, reflux condenser, and addition funnel. The solution was cooled to −45° with a Dry Ice/acetone bath. Bromine (25.7 g, 0.1607 mol) was added dropwise with vigorous stirring until all the bromine color was discharged. A solution of benzocyclobuten-1-carboxamide[5] (22.5 g, 0.153 mol) in dioxane (100 ml) and methanol (68 ml) was added slowly while maintaining the temperature at ~ −40°. At this temperature, a considerable amount of amide crystallized out of solution; stirring became rather inefficient and additional methanol (75 ml) was added. The temperature was then raised using a water bath. At −20° to −15°, all the amide quite suddenly went back into solution. The clear solution was further heated to 55°, at which temperature the reaction proceeded vigorously enough to raise the temperature spontaneously to 61°. After 15 min, the flask was cooled to 25°, and the solution was made acidic with acetic acid. All solvent was removed under reduced pressure. The white residue was mixed with water and extracted with ether (3 × 100 ml). The combined organic fractions were washed with water (2 × 100 ml), saturated sodium chloride solution, dried with magnesium sulfate, and filtered. The solvent was removed and the solid residue recrystallized from cyclohexane to give colorless crystals; yield: 25.45 g (94%); m.p. 87°–91.5°. Recrystallization from methanol/water gave very fluffy, colorless crystals; yield: 24.25 g (89%); m.p. 92–94°.

$C_{10}H_{11}NO_2$	calc.	C 67.78	H 6.26
(177.2)	found	67.6	6.2

^{1}H-N.M.R. (CCl_4): $\delta = 7.3$–7.0 (4H), 5.7–5.3 (1H), 5.3–5.2 (q, 1H), 3.6 (3H), 3.8–3.5 ppm (2H).

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[1] E. Magnien, R. Baltzly, *J. Org. Chem.* **23**, 2029 (1958).

[2] The precipitate was not characterized but is probably a mixture of sodium bromates and other various oxidation states of BrO$^{\ominus}_{x}$.

[3] P. Warner, R. LaRose, *Tetrahedron Lett.* **1972**, 2141.

[4] Our results indicate that the cyclopropane ring in **1d** reacts faster than the double bond in electrophilic addition with bromine at −78°.

[5] This amide was prepared from the corresponding nitrile by standard procedures. 1-Cyanobenzocyclobutene: P. Radlick, L. Brown, *J. Org. Chem.* **38**, 3412 (1973).