

# Hofmann Rearrangement of $\alpha$ -Hydroxy Amides

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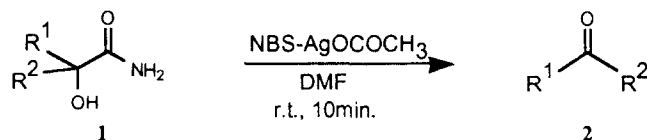
It has been reported that Hofmann rearrangement of *N,N'*-unsubstituted  $\alpha$ -hydroxy amides by treating with NaOCl gave the corresponding aldehydes that have one carbon fewer than the starting  $\alpha$ -hydroxy-amides (Wallis *et al.*, 1946; March 1992). The rearrangement has been believed to be a very important reaction in organic synthesis.

The process was applied to the amides of mandelic acid and polyhydroxy acids which possess a hydroxy group in the  $\alpha$ -position i.e., *d*-gluconic, *d*-galactonic, *l*-mannonic and *l*-arabonic amide long ago, but the desired aldehydes were obtained in low yields (Weerman, 1917; Haworth *et al.*, 1938). It has not been entirely utilized in organic synthesis thereafter. Since, we believe, there was few successful methods for the Hofmann rearrangement of the  $\alpha$ -hydroxy amides, it would be important to develop the facile and efficient synthetic method under mild conditions.

Recently we reported the practical methods for Hofmann rearrangement using *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin in the presence of Hg(OCOCH<sub>3</sub>)<sub>2</sub>, AgOCOCH<sub>3</sub> or Ag<sub>2</sub>O in MeOH-DMF or MeOH-CH<sub>3</sub>CN (Jew *et al.*, 1990; Jew *et al.*, 1992).

Since we felt that those methods would allow the Hofmann rearrangement for the  $\alpha$ -hydroxy amides to be carried out under a neutral and very mild condition, it was applied to a series of  $\alpha,\alpha$ -disubstituted  $\alpha$ -hydroxy amides (Scheme 1).

A typical procedure is as follows: To a white suspension of AgOCOCH<sub>3</sub> (83 mg, 0.50 mmol) in 1 ml of DMF, a solution of 2-hydroxy-2-methyltridecanamide **1a** (61 mg, 0.25 mol) in 1 ml of DMF, which



Scheme 1

**Table I.** The Hofmann rearrangement of  $\alpha,\alpha$ -disubstituted  $\alpha$ -hydroxy amides<sup>a,b</sup>

	R <sup>1</sup>	R <sup>2</sup>	Yield (%)
a	CH <sub>3</sub>	n-C <sub>11</sub> H <sub>23</sub>	100
b		CH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> CH	100
c		CH <sub>2</sub> CH <sub>2</sub> (C <sub>6</sub> H <sub>5</sub> )CH(CH <sub>2</sub> ) <sub>2</sub> CH	100
d	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	57
e	CH <sub>3</sub>	p-C <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub>	72
f	CH <sub>3</sub>	$\alpha$ -naphthyl	100
g	n-C <sub>4</sub> H <sub>9</sub>	C <sub>6</sub> H <sub>5</sub>	100
h	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	84
i	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	100

<sup>a</sup>All new compounds (**1a**, **1c**, **1e-1h**) were fully characterized spectrally and purity was established by combustion analysis ( $\pm 0.3\%$ ).

<sup>b</sup>The products (**2a-2i**) were identical to a commercially available (Aldrich) sample by <sup>1</sup>H NMR.

was obtained by the treatment of the ketone **2a** with (CH<sub>3</sub>)<sub>3</sub>SiCN-ZnI, followed by hydrolysis with HCl (Gruenwald *et al.*, 1981) was added, followed by addition of a solution of NBS (102 mg, 0.57 mmol) in 2 ml of DMF at the room temperature under argon atmosphere. The initial white suspension was vigorously stirred for 10 minutes to become gray colored, and then it was diluted with 200 ml of EtOAc and filtered. The filtrate was washed with H<sub>2</sub>O (5  $\times$  20 ml), 5% aq. HCl solution (5  $\times$  20 ml), H<sub>2</sub>O (5  $\times$  20 ml), and brine (2  $\times$  20 ml); dried over anhyd. MgSO<sub>4</sub>; filtered; and the solution was evaporated under reduced pressure to give yellow residues. It was purified by flash column chromatography (hexane:EtOAc = 5:1) to afford 49 mg of colorless solid, 2-tridecanone (**2a**) (yield 100%). The rearrangement for the other  $\alpha$ -hydroxy amides (Grundwald *et al.*, 1981) were performed in the same manner as **1a** and the results are summarized in Table I.

As shown in Table I, the treatment of the  $\alpha$ -hydroxy amides (**1**) with NBS-AgOCOCH<sub>3</sub>-DMF at room temperature for 10 minutes gave the corresponding ketones (**2**) in 84-100% yields, except for **2d** and **2e**. The presenting result is the first example of the Hofmann rearrangement of a series of  $\alpha$ -hydroxy amides, exclu-

sive of 1i. (Rahman *et al.*, 1954). It deserves special emphasis that the rearrangement under neutral mild condition could be carried out fast and efficiently.

Further works are underway to utilize this rearrangement as a highly chemoselective protecting method for ketones and an efficient synthetic method for the preparation of biologically very important unnatural sugars.

#### ACKNOWLEDGEMENT

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