

## Nature of *N*-Bromosuccinimide in Basic Media: The True Oxidizing Species in the Hofmann Rearrangement

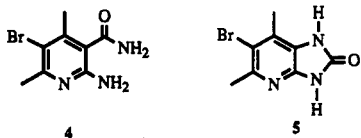
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The Hofmann rearrangement is among the oldest reactions in organic synthesis<sup>1</sup> and is often used for the introduction of the amine functionality.<sup>2</sup> Practical reagents for this transformation, however, are still lacking. For example, the classical means for converting a primary carboxamide to an amine using an alkaline solution of bromine can be unsatisfactory and unreliable.<sup>3</sup> Numerous modifications of this protocol have extended its utility to other oxidants, such as iodine(III) reagents<sup>4</sup> [PhI(OCOCF<sub>3</sub>)<sub>2</sub>, PhIO–HCO<sub>2</sub>H, PhI(OTf)OH, and PhI(OAc)<sub>2</sub>], lead tetraacetate,<sup>5</sup> benzyltrimethylammonium tribromide,<sup>3b</sup> *N*-bromosuccinimide (NBS)–Hg(OAc)<sub>2</sub>, and NBS–AgOAc.<sup>6</sup> The related elemental bromine or heavy-metal-mediated Hofmann rearrangement has much more limited applicability due to environmental hazards, and the iodine reagents can be chemically unstable.

Recently we reported a highly effective method for the synthesis of imidazopyridines which have become a prominent feature in the class of nonpeptide AII receptor antagonists, as exemplified by the potent antihypertensive MK-996.<sup>7</sup> The 2,3-diamino moiety of **2** was constructed via a Hofmann rearrangement of an aminonicotinamide to the corresponding urea with PhI(OAc)<sub>2</sub> in high yield (Scheme 1). Nevertheless, NBS would be a much more practical reagent for this conversion. Unfortunately, the Hofmann rearrangement of **1** with NBS–KOH in MeOH at –5 °C provided only a 60% yield of urea **2** along with a 30% recovery of the starting material and a mixture of the brominated byproducts **4** and **5**.<sup>8</sup> The potential benefits of NBS were overshadowed by its dual nature as a brominating and oxidizing agent and its failure to oxidize the substrate completely. Herein, we report the discovery of the true nature of NBS in basic media, which has led to a fuller understanding and, thereby, greater control and efficacy of the oxidizing agent.



Base completely alters the chemistry of NBS. In the absence of KOH in MeOH, **4** was obtained exclusively; no urea was observed. As the base was increased by 0.25-equiv increments,

(1) (a) Hofmann, A. W. *Ber. Dtsch. Chem.* **1881**, *14*, 2725. (b) Hofmann, A. W. *Ber. Dtsch. Chem.* **1885**, *18*, 2734.

(2) (a) Loudon, G. M.; Parham, M. E. *Tetrahedron Lett.* **1978**, 437. (b) Waki, M.; Kitajima, Y.; Zumiya, N. *Synthesis* **1981**, 266. (c) Pallai, P.; Goodman, M. *J. Chem. Soc., Chem. Commun.* **1982**, 280. (d) Squadriani, F.; Verdini, A. S.; Viscomi, G. C. *Gazz. Chim. Ital.* **1984**, *114*, 25. (e) Fuller, W. D.; Goodman, M.; Verlander, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 5821. (f) Shimihashi, Y.; Kodama, H.; Waki, M.; Costa, T. *Chem. Lett.* **1988**, 1821.

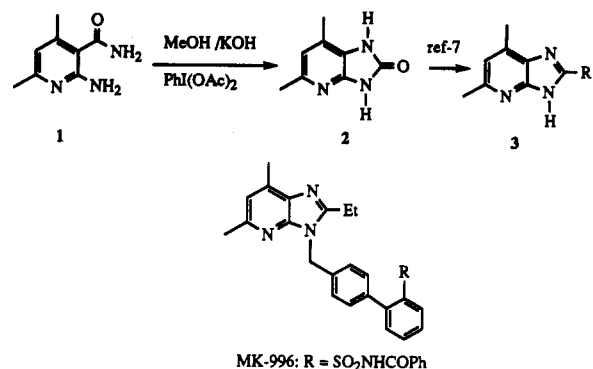
(3) (a) Wallis, E. S.; Lane, J. F. *Org. React. (N.Y.)* **1946**, *3*, 267. (b) Kajigaishi, S.; Asano, K.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *Chem. Lett.* **1989**, 463.

(4) Moriarty, M. R.; Chany, J. C., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2482 and references cited therein.

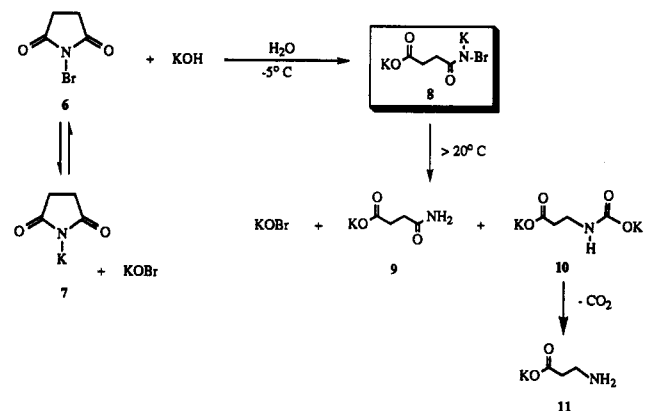
(5) Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554.

(6) Jew, S. S.; Park, H. G.; Park, H. J.; Park, M. S.; Cho, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1559.

### Scheme 1



### Scheme 2



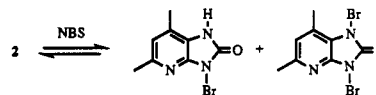
decreasing amounts of **4** and increasing amounts of the urea **2** were obtained. The maximum conversion reached 60% with 2.5 equiv of KOH and 1.0 equiv of **5** were also formed.<sup>8,9</sup> Apparently, under nonbasic conditions NBS acts solely as a brominating agent, whereas, with base, an oxidizing species is generated. Even so, in the presence of excess base, ring bromination still occurred and the reaction failed to complete, indicating that a more complex system was involved.

Low-temperature NMR studies of KOH and NBS in solution clarified this seemingly confusing reaction. KOH was dissolved in D<sub>2</sub>O, and the resulting solution was cooled to –5 °C. NBS was then added, and the solution was stirred at –5 °C until the NBS dissolved. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the resulting yellow solution were taken periodically at –5 °C. Immediately after dissolution no NBS remained; two new species, one major (85%) and one minor (15%), were generated (Scheme 2). The major and minor species were identified as *N*-bromosuccinamide dipotassium salt (**8**) and potassium succinimide (**7**), respectively.

(7) Senanayake, C. H.; Fredenburgh, L. E.; Reamer, R. A.; Liu, J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.*, in press. (b) Chakravarty, P. K.; Naylor, E. M.; Chen, A.; Chang, R. S. L.; Chen T.; Faust, K. A.; Lotti, V. J.; Kivlighn, S. D.; Gable, R. A.; Zingaro, G. J.; Schorn, T. W.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. Submitted to *J. Med. Chem.*

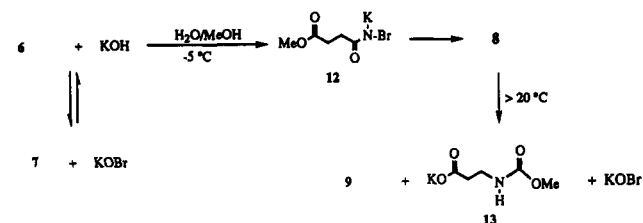
(8) In a control study the brominated urea **5** was only derived from **4** and not by bromination of **2**.

(9) Additional NBS, once the reaction had ceased, did not improve the product conversion. The urea nitrogens may interfere with generation of **8** by picking up the bromonium ions from NBS. Because of the insolubility of **2** in the NMR solvent, observation of this interaction was inconclusive. Interestingly, addition of iodobenzene diacetate to the incomplete reaction mixture consumed most of the nicotinamide. Since the oxidation still occurred with the iodine reagent, the formation of **8** presumably is prevented in the presence of **2**.



**Table 1.** Effect of Age at  $-5\text{ }^{\circ}\text{C}$  on Generation of Oxidizing Species 8

age	7 (%)	8 (%)	9 (%)	10 (%)
5 min	15	85		
5.5 h	4.5	95.5		
16 h	2.5	96.0		1.5
9 days	0.5	78	16.5	5

**Scheme 3**

Over time, NBS (**6**) in equilibrium with the succinimide salt **7** irreversibly converted to species **8** (Table 1): After 5.5 h, **8** had grown to 95.5% with only 4.5% of **7** remaining. After 16 h at  $-5\text{ }^{\circ}\text{C}$ , **8** had grown to 96.0%, the succinimide salt had decreased to 2.5%, and 1.5% of a new species, **10**, had been generated. Compound **10** was characterized as the  $\beta$ -alanine derivative, the Hofmann rearrangement product of the *N*-bromo species **8**.<sup>10</sup>

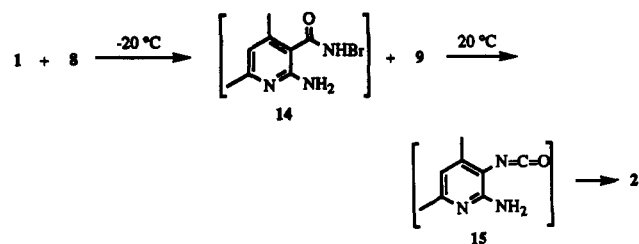
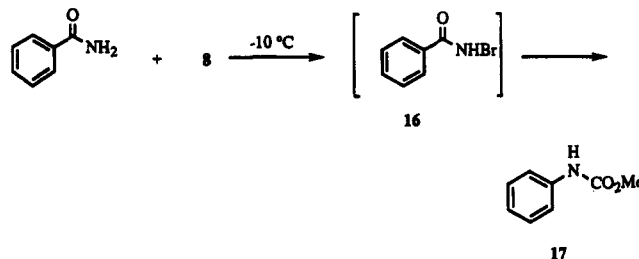
The true oxidizing agent in the Hofmann rearrangement with NBS is *N*-bromosuccinamic acid dipotassium salt (**8**). Further evidence was also gained by isolation of a compound from the filtrate of **2** which was identical by NMR with an authentic sample of succinamic acid potassium salt, the expected spent oxidizing agent. Attempts to independently synthesize *N*-bromosuccinamic acid by addition of KOH/ $\text{Br}_2$  to succinamic acid at  $-5$  or  $20\text{ }^{\circ}\text{C}$  failed. Evidently **8** is only derived from ring opening of NBS and not the reaction of succinamic acid with KOBBr.

NMR studies of the NBS–KOH reagent were also conducted in a  $\text{D}_2\text{O}$ – $\text{CD}_3\text{OD}$  medium (3:7) at  $-5\text{ }^{\circ}\text{C}$ . Immediately upon addition of NBS to the basic  $\text{D}_2\text{O}$ – $\text{CD}_3\text{OD}$  at  $-5\text{ }^{\circ}\text{C}$  the succinimide salt **7** and a new unsymmetric compound, identified as the methyl ester of *N*-bromosuccinamic acid **12** (Scheme 3), were generated. The latter species disappeared with time from hydrolysis to yield compound **8**. When only 1 equiv of KOH was used, thereby suppressing the saponification, the ester **12** remained the major compound.

These findings alleviated the bromination side reactions. Previously, the NBS–KOH solution was added to the substrate after 5 min; in this time frame only 85% of the desired reagent had been generated (Table 1), leaving unreacted NBS as the brominating agent. A longer age of the NBS–KOH solution effectively converted the succinimide salt **7**–NBS mixture to the oxidizing species **8** (Scheme 2): After 16 h at  $-5\text{ }^{\circ}\text{C}$ , 96% conversion to **8** was assayed by NMR. Addition of this mixture to the nicotinamide at  $-20\text{ }^{\circ}\text{C}$  increased the conversion of the amide **1** to the urea **2** from 60 to 95%.

In addition, this study revealed that the incomplete reactions were due to the instability of the NBS–KOH mixture at room temperature. As the reagent was being syringed into the reaction flask, decomposition had already occurred. The instability of the reagent at room temperature was demonstrated: after >95% conversion of **6** to **8** at  $-5\text{ }^{\circ}\text{C}$  the mixture was warmed at room

(10) Others have observed the tendency of NBS to degrade to  $\beta$ -alanine-derived intermediates; see: (a) Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett.* 1993, 34, 931. (b) Clarke, H. T.; Behr, L. D. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 19.

**Scheme 4****Scheme 5**

temperature for 2 h; the reagent had sufficiently degraded to give only a 17% yield of the urea **1** with 82.5% of the nicotinamide **1** recovered. This result is consistent with the decomposition observed by NMR. Compound **8** is quite stable at  $-5\text{ }^{\circ}\text{C}$ ; for example, after 9 days in  $\text{D}_2\text{O}$  78% remained with some decomposition to potassium succinamate **9** and rearrangement to the carbamate **10**. After the solution was warmed to room temperature, however, approximately half of the reagent had decomposed to **9** within 30 min. Over 2 h virtually all of **8** had decomposed to **9** (70%) and to four Hofmann-rearrangement products: **10**, **11**, and two unidentified species (30%). Similarly in MeOH at room temperature the oxidizing agent rapidly rearranged to the isocyanate, which was quenched by the solvent to yield 67% of the corresponding methyl carbamate **13**. The remaining 33% of the original reagent decomposed to **9**. To maintain the stability of **8** it is crucial to store the reagent mixture at  $<-5\text{ }^{\circ}\text{C}$  during the aging and addition.

The urea formation takes place through transfer of the bromonium ion from the oxidizing agent **8** to the nicotinamide; the intermediate *N*-Br amide **14** then rearranges to the isocyanate **15**, which is captured intramolecularly to yield the cyclic urea **2** (Scheme 4). An NMR study of the oxidation of the aminonicotinamide **1** was difficult because of the precipitation of the urea **2**. As an alternative, the reaction of benzamide with **8** at  $-10\text{ }^{\circ}\text{C}$  remains as a solution; the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of this mixture were markedly different from those of benzamide. The intermediate, assigned as *N*-bromobenzamide (**16**), slowly rearranged to the corresponding methyl carbamate **17** (Scheme 5).

By an understanding of the true nature of NBS in basic media the shortcomings of this reagent for the Hofmann rearrangement were overcome. A practical, highly effective method for introduction of amines from the corresponding primary carboxamides is now available. The scope of *N*-bromosuccinamic acid dipotassium salt (**8**) as an oxidizing agent is being explored.

**Supplementary Material Available:** Experimental details and NMR data of the intermediates **7**–**13** and **16** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.