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# Amination of Heterocyclic Compounds with *O*-Benzoylhydroxylamine Derivatives

**Luca Parlanti, Robert P. Discordia, John Hynes, Jr.,[†] Michael M. Miller,[†]
Harold R. O'Grady,[†] and Zhongping Shi***

*Departments of Process Research and Development and Drug Discovery Chemistry,
Bristol-Myers Squibb Research & Development, P.O. Box 4000,
Princeton, New Jersey 08543*

*zhongping.shi@bms.com*

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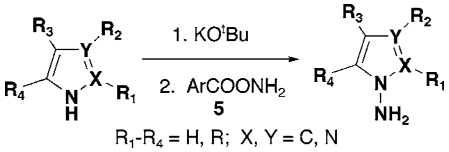
## ABSTRACT



**The N-amination of heterocyclic compounds 1a–k with *O*-benzoylhydroxylamine derivatives 5 was developed and demonstrated to be a superior alternative to existing N-amination methods. A structure–reactivity relationship study was performed on variously substituted *O*-benzoylhydroxylamine derivatives, leading to the discovery of the novel and more efficient aminating reagents 5h and 5i.**

The amination of nitrogen and carbon nucleophiles is an attractive tool for synthetic and medicinal chemists and can provide easy access to a variety of useful substances. Numerous NH$_2$-transfer agents have been previously described in the literature,[1] including a variety of hydroxylamine-based compounds, such as the *O*-acyl,[2] *O*-alkyl,[3] *O*-sulfonyl,[1a,4] *O*-nitrophenyl,[5] and *O*-diarylphosphinyl[6] derivatives. However, due to their limited availability,[1,6a,7] stability,[1,2c,4a] as well as the safety concerns around their handling,[5a,7] the latter class of compounds has seen limited utility in large scale processes. Therefore, seeking and developing safe, convenient, and efficient reagents and processes for the direct amination of carbon and nitrogen nucleophiles continues to be an area of interest in organic synthesis.[2a,5a,6a,7]

A general N-amination methodology for pyrroles and indoles was recently developed by researchers at Bristol-Myers Squibb using an in situ prepared ethereal monochloramine (NH$_2$Cl) solution to produce the corresponding amino pyrroles and indoles in high yield.[7] This method was successfully applied on a multigram scale and provided an easy entry to 11 *N*-amino heterocycles. Nevertheless, despite its high efficiency for NH$_2^+$ transfer and operational simplic-

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[†] Department of Drug Discovery Chemistry.

(1) (a) Tamura, Y.; Minamikaw, J.; Ikeda, M. *Synthesis* **1977**, 1. (b) Erdik, E. *Tetrahedron* **2004**, *60*, 8747.

(2) (a) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236. (b) Carpino, L.; Giza, C.; Carpino, B. *J. Am. Chem. Soc.* **1959**, *81*, 955. (c) Marmer, W.; Maerker, G. *J. Org. Chem.* **1972**, *37*, 3520. (d) Boche, G. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, New York, 1995; Vol. 5, pp 3270. (e) Carpino, L. A. *J. Org. Chem.* **1965**, *30*, 736. (f) Carpino, L. A. *J. Org. Chem.* **1965**, *30*, 321. (g) Johnson, J. S.; Berman, A. M. *J. Org. Chem.* **2005**, *70*, 364.

(3) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 173.

(4) (a) Carpino, L. *J. Am. Chem. Soc.* **1960**, *82*, 3133. (b) Taylor, E.; Sun, J.-H. *Synthesis* **1980**, 801.

(5) (a) Boyles, D. C.; Curran, T. T.; Partlett, R. V.; Partlett, T. T. *Org. Process Res. Dev.* **2002**, *6*, 230. (b) Radhakrishna, A. S.; Loudon, G. M.; Miller, M. *J. Org. Chem.* **1979**, *44*, 4836. (c) Bellettini, J. R.; Olson, E. R.; Teng, M.; Miller, M. J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 3, pp 2189−2190. (d) Mavunkel, B.; Perumattam, J. J.; Tester, R. W.; Dugar, S. Int. Pat. Appl. Publ., 2004, 36 pp, Cont.-in-part of U.S. Ser. No. 36,293. PTC/US2003/021888 WO 2004/007462 A1.

(6) (a) Smulik, J.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187. (b) Boche, G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 4, pp 2240−2242. (c) Boche, G.; BernHeim, M.; Schott, W. *Tetrahedron Lett.* **1982**, *23*, 5399. (d) Colvin, E.; Kirby, G.; Wilson, A. *Tetrahedron Lett.* **1982**, *23*, 3835.

(7) Hynes, J.; Doubleday, W.; Dyckman, A.; Godfrey, J.; Grosso, J.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368.

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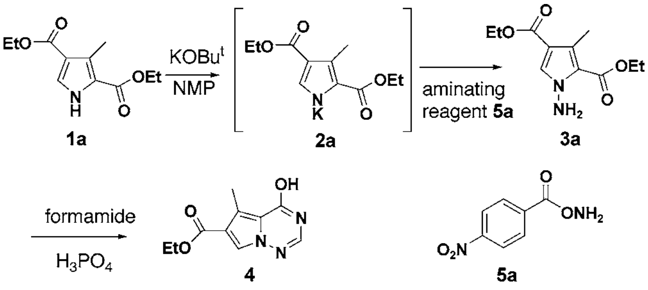
ity on a laboratory scale, the above procedure had limited potential on a multikilo scale due to a significantly lower conversion (70%) observed upon scale-up. In addition, the low solubility of $NH_2Cl$ in organic solvents resulted in elevated reaction volumes and poor efficiency.

The pyrrolotriazine derivative **4** is a key intermediate in the synthesis of several biologically active compounds under investigation at Bristol-Myers Squibb.[8] The compound is obtained from the amino pyrrole **3a**, prepared from pyrrole **1a** through N-amination (Scheme 1). The need for high volumes of **4**, along with the previously discussed limitations of the available amination protocols, led us to focus our efforts on seeking new reagents with improved physical and chemical properties, to enable large scale access to the above compounds.

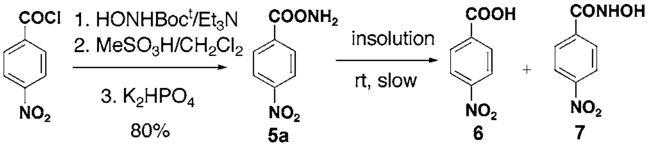
**Scheme 1.** Preparation of Pyrrolotriazine **4**



Friestad and co-workers reported the $NH_2^+$ transfer to the nitrogen of a cyclic carbamate through the use of *O*-(4-nitrobenzoyl)hydroxylamine **5a** (Scheme 1).[2a] To the best of our knowledge, the application of *O*-benzoylhydroxylamines to the N-amination of pyrrole, indole, imidazole, or pyrazole substrates has not been previously disclosed, although *O*-mesitoylhydroxylamine is known to react with pyrroles[2e] and carbazoles[2f] to afford the related amino compounds in low yields, 37% and 60%, respectively. Because **5a** appeared to be an accessible compound fairly easy to synthesize from common starting materials,[2b,c] we decided to evaluate its reactivity toward pyrrole **1a**.

After a brief optimization of the literature methods,[2b,9] we developed a process capable of providing **5a** in a single step from *p*-nitrobenzoyl chloride and *N*-Boc-hydroxylamine in 80% yield and 99% purity by HPLC (Scheme 2). During our work, we also observed that **5a** is relatively unstable in NMP solutions. After 16 h, ~2% hydrolysis to benzoic acid **6** was observed at ambient conditions. The half-life of **5a** was estimated to be ~5 days (0.28 M) with partial conversion (~3%) to *p*-nitrobenzohydroxamic acid **7** also occurring (Scheme 2). Addition of water (10% in NMP) did not impact the hydrolysis/isomerization significantly. However, the presence of hydroxylamine did accelerate the hydrolysis/isomerization process reducing the half-life of **5a** to 3 h and significantly increasing the level of **7** (~15%). It is interesting to point out that **5a** is more stable in acetonitrile with <1% hydrolysis in 40 h. In such conditions, the observed half-life was ~6 days with **7** being the major degradation product (~40%). On the other hand, the pure crystalline form of **5a** is stable at room temperature for up to 6 months or at 0 °C for more than 2 years. This provides a reasonable shelf life for storage and use in manufacturing. Furthermore, the thermal stability analysis of **5a** displayed exothermic behavior with activity at 100.2 °C (641.2 J/g) and 161.9 °C (656.5 J/g), which offers a reasonable safety window when operating at room temperature.

**Scheme 2.** Preparation of **5a** and Its Hydrolysis/Isomerization to **6** and **7**



When treated with potassium *t*-butoxide in NMP, **1a** converted to anion **2a**, which reacted with **5a** to provide the desired *N*-amino pyrrole **3a**. The reaction was complete in 15 min at room temperature using optimized conditions (1.05−1.10 equiv of base and 1.1−1.2 equiv of **5a**). The highest conversion (92%) was achieved in anhydrous NMP, and data clearly indicated a negative effect of moisture. After further fine-tuning, the above procedure was then progressively scaled-up to eventually produce multihundred kilogram lots of amino pyrrole **3a** and subsequently pyrrolotriazine **4** in 70% overall yield.

As this new methodology was proven efficient for **1a**, its scope was then extended to various heterocyclic compounds including pyrroles **1b**−**1c**, indoles **1d**−**1g**, imidazoles **1h** and **1i**, pyrazole **1j**, and carbazole **1k** (see Table 1 for results). Amination of **1a**,**b**,**d**,**e** with **5a** gave results similar to those obtained with monochloramine, including the same chemoselective amination of the pyrrole ring in the case of substrate **1b** containing an amide substituent.[7] It was noted that pyrroles with more electron-withdrawing groups, such as **1a**, gave higher conversion (92%) than those with more electron-donating groups, such as **1c** (84%). All four indole substrates examined, **1d**−**1g**, gave excellent conversions (82−92%). It was found that the aminated product **3g** from formylindole **1g** was not stable during isolation, ostensibly due to the reaction of the aldehyde and the amino group polymerizing through the Schiff base. The present amination method also worked well for pyrazole **1j** and carbazole **1k** with conversions of 95% and 80%, respectively. However, amination of imidazole **1h** and **1i** only provided moderate conversions of 59% and 61%, respectively. The conversion was improved to 75% and 76% when potassium *t*-butoxide was replaced with potassium bis(bistrimethylsilyl)-amide.

Having demonstrated the generality of this amination reaction on a series of heterocyclic compounds with various

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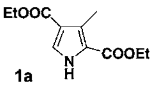
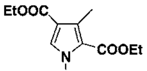
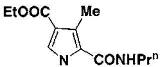
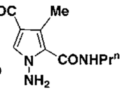
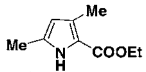
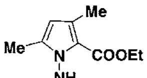
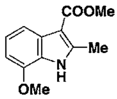
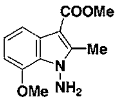
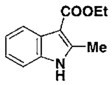
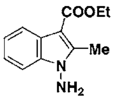
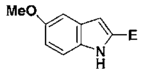
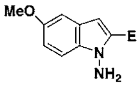
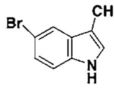
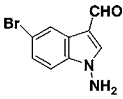
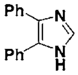
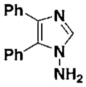
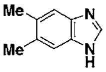
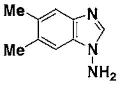
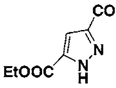
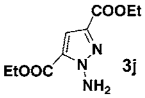
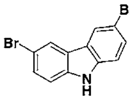
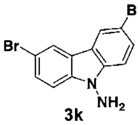
(8) Godfrey, J. D.; Hynes, J.; Dyckman, A. J.; Leftheris, K.; Shi, Z.; Wrobleski, S. T.; Doubleday, W. W.; Grosso, J. A. U. S. Pat. Appl. Publ., 2003, 36 pp, Cont.-in-part of U.S. Ser. No. 36,293. US 2003186982 A1 20031002 CAN 139:292275 AN 2003:777390.

(9) (a) Jencks, W. P. *J. Am. Chem. Soc.* **1958**, *80*, 4581. (b) Jencks, W. P. *J. Am. Chem. Soc.* **1958**, *80*, 4585.

**Table 1.** Results and Comparison of the Amination Reactions with **5a**, **5h**, and **5i**

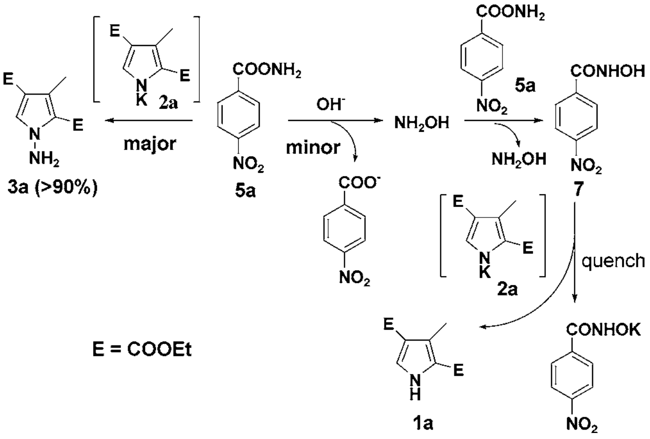
| substrate | product | 5a | 5h | 5i |
|---|---|---|---|---|
| | | conversion[a] (% yield[b]) | | |
|  1a |  3a | 92%<br>(86%) | 97%<br>(92%) | 96% |
|  1b |  3b | 85% | 91%<br>(86%) | 94% |
|  1c |  3c | 84% | 91%<br>(84%) | 96% |
|  1d |  3d | 92% | 97%<br>(91%) | 95% |
|  1e |  3e | 82% | 92%<br>(88%) | 90% |
|  1f E = COOEt |  3f E = COOEt | 88% | 95%<br>(82%) | 95% |
|  1g |  3g | 86% | 94% | 92% |
|  1h |  3h | A. 59%<br>B. 75%[c] | 85%[c]<br>(80%) | 89%<br>87%[c] |
|  1i |  3i | A. 61%<br>B. 76%[c] | 89%[c]<br>(84%) | 86%<br>88%[c] |
|  1j |  3j | 95% | 99%<br>(95%) | 97% |
|  1k |  3k | 80% | 96%<br>(87%) | 91% |

[a] HPLC conversion after 0.5−3 h at room temperature (Waters XTerra RP-18, 3.5 μm, 4.6 × 50 mm, 1−100% 0.05% TFA water/acetonitrile (95:5); 0.05% TFA water/acetonitrile (5:95), 2.5 mL/min, 8 min gradient, 256 nm). [b] Isolated. [c] KHMDS was used as base.

functional groups, we then tried to further improve the reaction to maximize conversions. However, efforts to improve the conversion of **1a** to **3a** under various conditions (including using excess base and/or reagent **5a**) were unsuccessful. The reaction always suffered from incomplete conversion, leaving 7−10% of residual **1a**. Vedejs and coworkers also reported low yields for amination of nonstabilized enolates using phosphine-based hydroxylamine derivatives. This was rationalized assuming a proton transfer from the aminating agents ($pK_a$ 20−24) quenching the enolates ($pK_a$ 22−24).[6a] However, pyrrole **1a** has a much lower $pK_a$ (8.7),[7] which should exclude the possibility of proton transfer from **5a** to the preformed anion **2a**.

We surmised that the incomplete conversion of **1a** is likely due to the presence of residual moisture, which can compete with the pyrrole to react with **5a**. As noted above, amination in anhydrous solvents provided the highest conversions. In line with this hypothesis, addition of water (1 equiv) to the reaction mixture led to a significantly lower conversion (78%). Also, we had demonstrated that hydroxylamine catalyzes the conversion of *O*-*p*-nitrobenzoylhydroxylamine (**5a**) to *p*-nitrobenzohydroxamic acid **7**.[9] Under the reaction conditions and in the presence of residual moisture, hydroxylamine could be generated from hydrolysis of **5a**, initiating the transformation to **7** (Scheme 3). Quenching of the reactive anion **2a** to **1a** by proton transfer from **7** (Scheme 3) is then the most likely cause for the incomplete reaction.[10] As expected, addition of excess **5a** (>2 equiv) did not improve the conversion.

**Scheme 3.** Rate-Controlled Reactions of **5a** with Pyrrole Anion **2a** and Water



Because our experimental results indicate that amination of **1a** with **5a** (>90%) was inherently faster than the reaction of **5a** with water, we hypothesized that we might favorably tune the reactivity and therefore the selectivity of *O*-benzoylhydroxylamine derivatives in amino-transfer reactions by replacing the nitro group with less electronegative substituents. To evaluate this hypothesis, a series of substituted *O*-benzoylhydroxylamine analogues were prepared from the corresponding benzoyl chloride, using a method similar to that described for **5a** (Table 2). Compounds **5b**, **5d**, **5e**, and **5g** are novel, whereas **5h**[11] has been reported as an unisolated intermediate converted in situ to an oxime with acetone. Compounds **5c**[2c] and **5f**[2b,9a] are known. The crystal-

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(10) Hydroxamic acid **6** was reported to have a $pK_a$ of 8.9. Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 5754.

(11) King, F. D.; Walton, D. R. M. *Synthesis* **1975**, 788.

**Table 2.** Amination of **1a** with *O*-Benzoylhydroxylamine Analogues **5a**−**5i**

| compound **5** R = (yield)[a] | substituent constant (*s*) | p$K_a$ of BzOH | conversion[b] |
|---|---|---|---|
| **a**, 4-$NO_2$ (85%) | 0.81 | 3.45 | 92 |
| **b**, 4-F (84%) | 0.15 | 4.15 | 93 |
| **c**, 3-Cl (77%) | 0.37 | 3.84 | 95 |
| **d**, 4-Cl (89%) | 0.24 | 3.99 | 95 |
| **e**, 4-Br (82%) | 0.26 | 3.97 | 96 |
| **f**, 4-H[c] | 0 | 4.19 | 91[d] |
| **g**, 4-Me[c] | −0.14 | 4.37 | 94[d] |
| **h**, 4-OMe (89%) | −0.12 | 4.50 | 97 |
| **i**, 2,4-dimethoxy (84%) | − | 4.36 | 96 |

[a] Yield for preparation of reagent **5**. [b] HPLC % conversion after 0.5−3.0 h at room temperature (Waters XTerra RP-18, 3.5 μm, 4.6 × 50 mm, 10% water/acetonitrile to 0.2% $H_3PO_4$/water, 2.5 mL/min, 8 min gradient, 256 nm). [c] Oil, not stable. [d] Because pure **5f** and **5g** were not stable, a solution of **5f** or **5g** in NMP was prepared in situ from its related methanesulfonate salt and used for the amination.

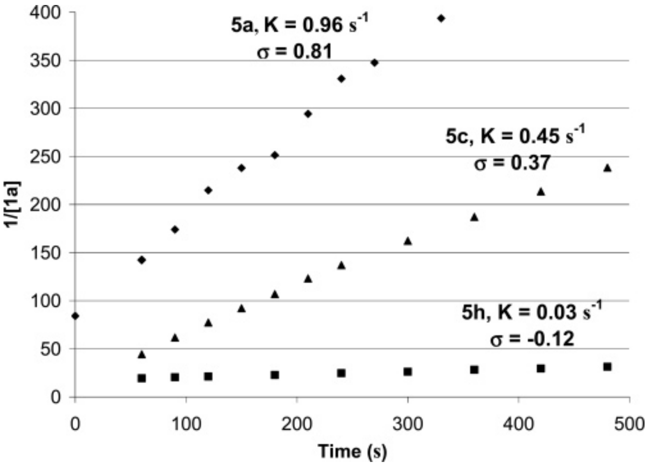

**Figure 1.** Kinetic constants for amination of **1a** with **5a**, **5c**, and **5h**.

line analogues **5b**−**e** and **5h** are stable at room temperature. However, **5f** and **5g** are oils and unstable at room temperature with significant degradation in 1 h.[2b,11]

The results from the reactions of pyrrole **1a** with **5a**−**h** are summarized in Table 2. As expected, **5h**, bearing the strongest electron-donating group, was the least reactive reagent and provided the highest conversion (97%). The reaction of **5h** was significantly slower than **5a**, requiring more than 2 h (at 20 °C) to reach the end point, as compared to 15 min with **5a**. Similarly, hydrolysis of **5h** in DMSO−water was also much slower, with a half-life of 26 h, as compared to 1.8 h for **5a**. Significant rate differences were observed across the different reagents. Kinetic constants for the N-amination reactions with the *p*-nitro (**5a**), *m*-chloro (**5c**), and *p*-methoxy (**5h**) benzoylhydroxylamines were calculated as shown in Figure 1. A conversion of 92%, 95%, and 97% was obtained with **5a**, **5c**, and **5h** in 15, 60, and 120 min, respectively, which confirmed our rate control assumption.

As **5h** was demonstrated to be a superior $NH_2^+$ transfer agent for pyrrole **1a**, its application was then extended to other heterocyclic compounds **1b**−**1k**. As expected, the conversion for all substrates was significantly improved, from 59−95% (with **5a**) to 84−99% (with **5h**) (Table 1). Another novel compound **5i** (R = 2,4-dimethoxy) was also prepared similarly to **5h**. In most cases, this reagent provided results analogous to those with **5h**, and a higher conversion (96% vs 91%) was obtained for pyrrole **1c**. Furthermore, **5i** was a more convenient compound to handle due to its higher melting point (66.0−67.0 °C vs 34.0−35.0 °C for **5h**).

In summary, a general, efficient, and practical N-amination of heterocyclic compounds using *O*-benzoylhydroxylamine derivatives was developed, providing a superior alternative to other existing methods. To optimize the methodology, the structure−reactivity relationship of *O*-benzoylhydroxylamine analogues **5a**−**h** was explored, thereby leading to the discovery of the novel and more efficient reagents **5h** and **5i**.

**Acknowledgment.** The Authors would like to thank the Department of Discovery Analytical Sciences for HRMS and p$K_a$ determinations, Dr. Francis J. Okuniewicz (PR&D) for thermal evaluations of **5a**, and Professor G. K. Friestad (University of Vermont) for useful discussions regarding **5a**.

**Supporting Information Available:** Experimental procedures and $^1$H and $^{13}$C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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