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An efficient electrophilic N-amination utilizing in situ generated chloramine under phase transfer conditions

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Abstract—An efficient, one-pot, phase transfer N-amination technology was developed. The protocol utilizes chloramine, an inexpensive and safe electrophilic aminating agent potentially viable for commercial manufacturing.

As part of our ongoing industry-university collaborative research program established between Texas A&M University-Kingsville and Bristol-Myers Squibb Co., we needed an expeditious entry into a diverse spectrum of N-aminated pyrroles.[1] Although a number of electrophilic amination methodologies are well known, their utility is often limited by poor yields, prohibitive costs, and serious safety issues, making them unsuitable for large scale application.[2] An alternative N-amination of pyrroles and indoles utilizing chloramine (NH_2Cl) was recently reported by researchers at Bristol-Myers Squibb.[3] This N-amination protocol involves initial generation of NH_2Cl from aqueous NH_4OH, NH_4Cl and bleach, followed by extraction of NH_2Cl with methyl *tert*-butyl ether (MTBE) from the aqueous mixture. The chloramine solution is dried with anhydrous $CaCl_2$ and then reacted in a separate vessel with the pyrrole anion generated from NaH in DMF, to produce the corresponding N-aminated pyrroles. While this technology was invaluable during our early development efforts and provided us with multi-gram supplies of N-aminopyrroles, we sought improvements that would allow for greater safety, efficiency and operational simplicity. In the above procedure, because of the high solubility of chloramine in water and its limited solubility in MTBE (0.09 M), large solvent volumes are required for efficient, extractive removal of chloramine from the aqueous reaction mixture.[4] This reduces the overall reaction throughput. In addition, chloramine is not sufficiently stable for storage. On standing, chloramine disproportionates to $NHCl_2$ and NCl_3, a shock-sensitive compound constituting a potential safety concern.[5] Devising a technology where chloramine would be instantaneously consumed as soon as it is generated could potentially circumvent these problems by avoiding any undesirable accumulation during the process. Based on this premise, we devised a cost effective and practical one-pot, two phase (H_2O–MTBE) N-amination protocol. The process can be accomplished in good yields and efficiency and offers significant advantages over the existing technologies in terms of throughput, safety, and operational simplicity.

In the optimal procedure, chloramine is generated in the aqueous layer through oxidation of ammonia by NaOCl. At the same time, the substrate is deprotonated in the organic phase with the aid of a small amount of Aliquat-336 (methyltrioctylammonium chloride) and promptly reacts with the small portion of chloramine present in the organic layer, affording the desired N–NH_2 derivative in high yield. An excess of base (aq NaOH) is necessary to efficiently achieve the pyrrole deprotonation. After reaction completion, the organic layer is separated and can be utilized directly in the next step without further purification (Scheme 1).

This process avoids accumulation of unreacted chloramine at any given time, thereby rendering this approach

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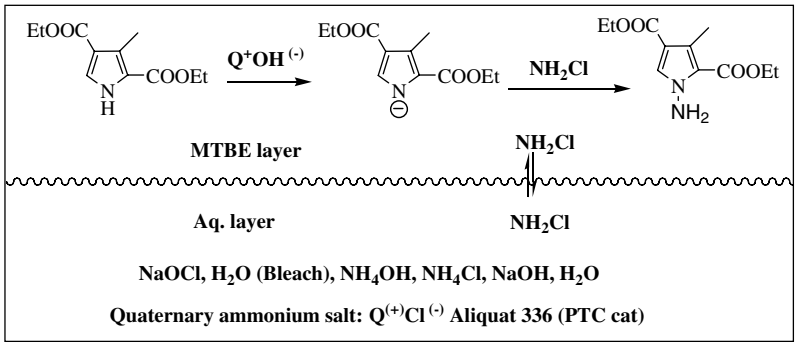
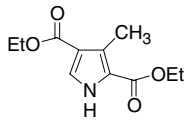
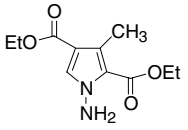
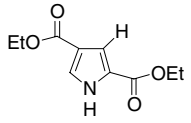
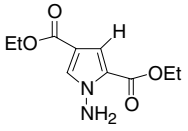
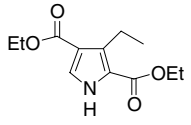
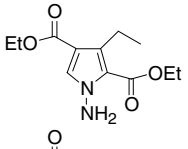
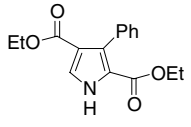
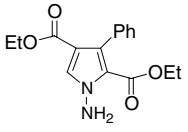
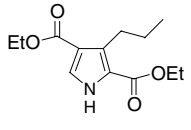
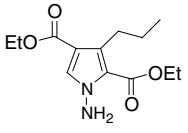
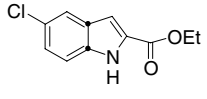
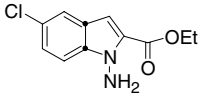
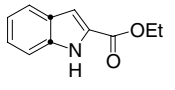
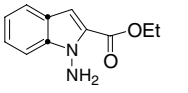


Scheme 1. One-pot, phase transfer N-amination of pyrrole with chloramine.

safe and viable for on-scale implementation. As opposed to the previously published chloramine N-amination protocol, this new procedure does not require the preparation of the pyrrole anion under anhydrous conditions in a separate vessel or the drying of the diluted organic chloramine solution after the extractions. The low solubility of chloramine in organic solvents is no longer a limiting factor to the reaction throughput. The presence of the quaternary ammonium salt, Aliquat-336, is imperative; reactions conducted without Aliquat-336 showed only trace amounts of the desired N-aminated product under otherwise identical conditions. Attempts to replace Aliquat-336 with several other surface active polyethylene glycol (PEG) type phase transfer agents such as Triton-X, were unsuccessful.[6] These conditions were also successfully applied to prepare a series of N-aminated heterocycles (pyrroles and indoles) in consistently high yield (Table 1). A typical experimental procedure is as follows: aqueous sodium hypochlorite (58.76 ml of ca. 9% solution) was added over a period of 20 min, at room temperature, to a vigorously stirred mixture of 3-methyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (2 g, 8.9 mmol) in MTBE (24 ml, ammonium chloride (2.9 g, 53.2 mmol), Aliquat-336 (0.1 g), aqueous NaOH (25.6 ml of 28.4% solution) and aqueous NH_4OH (8.28 ml of 28% solution). The resulting reaction mixture was stirred at room temperature for an additional 2–4 h at the end of which time the complete disappearance of starting material and formation of product is observed by capillary GC and HPLC. The upper product-rich organic layer was separated from the spent aqueous layer and washed with aqueous $Na_2S_2O_3$ (40 ml). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated in vacuo to produce 2.01 g of 1-amino-3-methyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (94% yield).

Table 1. Phase transfer catalyzed electrophilic N-amination of heterocycles with chloramine[7]

Entry	Substrate	N-Aminated substrate	Yield (%)
1			94
2			92
3			96
4			94
5			90
6			93
7			91

In summary, we have demonstrated an efficient, one-pot, phase transfer catalyzed N-amination process utilizing chloramine as an inexpensive electrophilic aminating agent which proved to be superior to the existing technologies. This protocol is practical and safe and is potentially viable for on-scale manufacturing. Studies aimed at extending the scope of this technology are in progress in our laboratories.

Acknowledgements

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References and notes

1. The program was aimed at giving BS/MS level students exposure to pharmaceutical process R&D in an academic setting. *Chem. Eng. News* **2001**, 41.

2. For *O*-(2,4-dinitrophenyl)hydroxylamine see: (a) Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833; A detonation has been reported while using this reagent. See: Radhakrishna, A. S.; Loudon, G. M.; Miller, M. J. *J. Org. Chem.* **1979**, *44*, 4836; For safety studies of substituted (nitrophenyl)hydroxylamines see: Boyles, D. C.; Curran, T. T.; Parlett, R. V. *Org. Proc. Res. Dev.* **2002**, *6*, 230; (b) Sheradsky, T. *Tetrahedron Lett.* **1968**, *16*, 1909; For a review on electrophilic amination see: (c) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
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4. The concentration of NH_2Cl was determined by iodometric titration.
5. Goehring, R. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 2, pp 1052–1053.
6. Bhattacharya, A.; Purohit, V.; Rinaldi, F. *Org. Proc. Res. Dev.* **2003**, *7*, 254.
7. NMR data for all the compounds synthesized are consistent with their expected structures, as for instance: 1-Amino-3-methyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 1): ^{1}H NMR (400-MHz, DMSO-d_6): δ 1.26 (t, $J = 7.3$, 3H), 1.32 (t, $J = 7.3$, 3H), 2.47 (s, 3H), 4.18 (q, $J = 7.3$, 2H), 4.28 (q, $J = 7.3$, 2H), 6.41 (s, 2H, NH_2), 7.43 (s, 1H); ^{13}C NMR (100-MHz, DMSO-d_6): δ 11.9, 14.4, 14.5, 59.4, 60.2, 110.4, 119.9, 128.4, 130.9, 161.5, 163.7; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{11}H_{17}N_2O_4$ 241.1188, found 241.1189. 1-Amino-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 2): ^{1}H NMR (400-MHz, DMSO-d_6): δ 1.24 (t, $J = 7.3$, 3H), 1.27 (t, $J = 7.3$, 3H), 4.16 (q, $J = 7.3$, 2H), 4.22 (q, $J = 7.3$, 2H), 6.50 (s, 2H, NH_2), 7.01 (s, 1H), 7.50 (s, 1H); ^{13}C NMR (100-MHz, DMSO-d_6): δ 15.0, 15.1, 60.4, 60.9, 112.4, 115.8, 122.1, 131.5, 161.0, 163.7; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{10}H_{15}N_2O_4$ 227.1032, found 227.1034. 1-Amino-3-ethyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 3): ^{1}H NMR (400-MHz, DMSO-d_6): δ 1.06 (t, $J = 7.3$, 3H), 1.23 (t, $J = 7.3$, 3H), 1.29 (t, $J = 7.3$, 3H), 2.96 (q, $J = 7.3$, 2H), 4.15 (q, $J = 7.3$, 2H), 4.25 (q, $J = 7.3$, 2H), 6.39 (s, 2H, NH_2), 7.40 (s, 1H); ^{13}C NMR (100-MHz, DMSO-d_6): δ 14.9, 15.1, 16.4, 19.3, 59.9, 60.8, 110.2, 119.9, 131.5, 135.6, 161.8, 164.0; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{12}H_{19}N_2O_4$ 255.1345, found 255.1336.
1-Amino-3-phenyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 4):): ^{1}H NMR (400-MHz, DMSO-d_6): δ 0.85 (t, $J = 7.3$, 3H), 1.03 (t, $J = 7.3$, 3H), 3.95 (q, $J = 7.3$, 2H), 3.99 (q, $J = 7.3$, 2H), 6.50 (s, 2H, NH_2), 7.29 (m, 5H), 7.55 (s, 1H); ^{13}C NMR (100-MHz, DMSO-d_6): δ 11.8, 12.3, 57.5, 58.2, 108.3, 124.9, 125.2, 128.4, 128.9, 133.0, 159.1, 161.7; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{16}H_{19}N_2O_4$ 303.1331, found 303.1345. 1-Amino-3-propyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 5): ^{1}H NMR (400-MHz, DMSO-d_6): δ 0.89 (t, $J = 7.3$, 3H), 1.25 (t, $J = 7.1$, 3H), 1.31 (t, $J = 7.1$, 3H), 1.48 (m, 2H), 2.95 (t, $J = 7.8$, 2H), 4.16 (q, $J = 7.1$, 2H), 4.26 (q, $J = 7.1$, 2H), 6.43 (s, 2H, NH_2), 7.43 (s, 1H); ^{13}C NMR (100-MHz, DMSO-d_6): δ 14.2, 14.3, 14.5, 24.5, 27.4, 59.4, 60.2, 109.9, 119.6, 131.0, 132.3, 161.4, 163.6; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{13}H_{21}N_2O_4$ 269.1501, found 269.1488. 1-Amino-5-chloro-1*H*-indole-2-carboxylic acid ethyl ester (entry 6): ^{1}H NMR (400-MHz, DMSO-d_6): δ 1.35 (t, $J = 7.3$, 3H), 4.36 (q, $J = 7.3$, 2H), 6.09 (s, 2H, NH_2), 7.11, (s, 1H) 7.32 (dd, $J = 9.2$, 2.2, 1H), 7.60 (d, $J = 9.2$, 1H), 7.71 (d, $J = 2.2$, 1H); ^{13}C NMR (100-MHz, DMSO-d_6): δ 14.5, 60.8, 106.3, 113.0, 121.3, 123.7, 125.1, 125.2, 128.2, 137.7, 161.2; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{11}H_{12}ClN_2O_2$ 239.0587, found 239.0581. 1-Amino-1*H*-indole-2-carboxylic acid ethyl ester (entry 7): ^{1}H NMR (400-MHz, CD_3OD): δ 1.41 (t, $J = 7.3$, 3H), 4.39 (q, $J = 7.3$, 2H), 7.09 (apparent t, $J = 8.1$, 1H), 7.14 (s, 1H), 7.30 (apparent t, $J = 8.1$, 1H), 7.60 (two overlapping d, $J = 9.9$, 2H); ^{13}C NMR (100-MHz, CD_3OD): δ 15.1, 62.1, 108.9, 112.2, 122.0, 123.6, 124.9, 126.5, 128.3, 141.1, 163.9; HRMS (ESI$^+$) calcd for (M+H$^+$) $C_{11}H_{13}N_2O_2$ 205.0977, found 205.0974.