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An Efficient Direct Amination of Cyclic Amides and Cyclic Ureas†

Zhao-Kui Wan,*,§ Sumrit Wacharasindhu,‡ Eva Binnun,§ and Tarek Mansour‡

Chemical and Screening Sciences, Wyeth Research, 200 Cambridge Park Drive, Cambridge, Massachusetts 02140, and Chemical and Screening Sciences, Wyeth Research, 401 Middletown Road, Pearl River, New York 10965

zwan@wyeth.com

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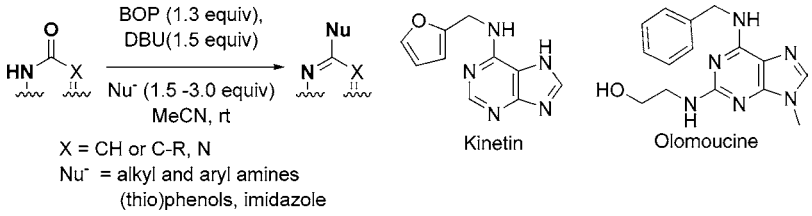
ABSTRACT

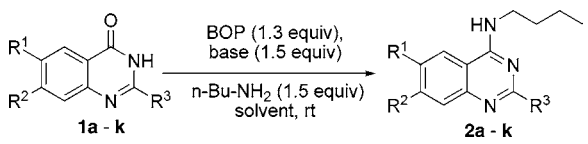


An efficient one-step amination of cyclic amides and ureas has been developed. Treatment of cyclic amides and cyclic ureas with BOP in the presence of DBU in various solvents led to the formation of cyclic amidines and cyclic guanidines in good to excellent yields. Concise syntheses of biologically intriguing kinetin and potent kinase inhibitor olomoucin were thus achieved in just one and two steps, respectively.

Amino heterocycles are ubiquitous and have great biological and pharmaceutical interest.[1] The synthesis of such compounds, however, remains challenging. Multiple steps are routinely required, including protection of functional groups if present, activation of corresponding cyclic amide or urea moieties often under harsh acidic conditions, followed by an S_NAr displacement, and finally deprotection of the functional groups to generate the desired products. The overall efficiency of these multistep syntheses is frequently unsatisfactory. Destruction of acid-labile functional groups and loss of protecting groups are common problems encountered in these transformations. Recently, the Buchwald−Hartwig amination[2] has gained enormous attention, allowing numerous amino heterocycles to be synthesized, all of which, however, also require preformation of a heteroaromatic halide. We have recently developed a one-step synthesis of N^6-adenosine and N^6-deoxyadenosine derivatives promoted by a phosphonium salt intermediate without protection of free hydroxyl groups.[3] The generality and applicability to many heterocyclic systems, including acceptability of various types of nucleophiles, as well as its application to concise syntheses of the biologically interesting kinetin and a potent and a selective kinase inhibitor olomoucin are reported herein.

Our studies began with the synthesis of 4-aminoquinazolines, a class of compounds which has drawn considerable attention due to its various pharmaceutical interests,[4] typically prepared from aniline derivatives.[5] Our BOP promoted amination conditions are first examined in the reactions with 4-hydroxyquinazoline (Scheme 1, Table 1).[6] DBU was found to be the most effective base (entry 1, Table 1) in comparison

Scheme 1



† Dedicated to Professor Yoshito Kishi on the occasion of his upcoming 70th birthday.

§ Wyeth Research, Cambridge.

‡ Wyeth Research, Pearl River.

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(3) (a) Wan, Z.-K.; Binnun, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877. For the syntheses under optimized Opeal conditions, see: (b) Lin, X.; Robins, M. J. *Org. Lett.* **2000**, *2*, 3497. (c) Véliz, E. A.; Beal, P. A. *J. Org. Chem.* **2001**, *66*, 8592.

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Table 1. Solvent and Base Effect on Direct Amination of 4-Hydroxyquinazoline **1a** ($R^1 = R^2 = R^3 = H$) with *n*-$BuNH_2$

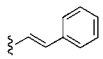
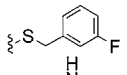
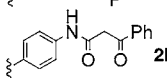
entry	base	solvent	product **2a** (%)[a] ($R^1 = R^2 = R^3 = H$)
1	DBU	NMP	95
2	TEA	NMP	87
3	DIPEA	NMP	78
4	colidine	NMP	74
5	proton sponge	NMP	54
6	NaO*t*-Bu	NMP	68
7	DBU	DMF	95
8	DBU	THF	99
9	DBU	DCM	93
10	DBU	MeCN	quant

[a] The percentage of yield was determined by LCMS analysis calibrated by an internal standard.

with others, although DIPEA and TEA were also satisfactory. The solvent effect was found to be minimal in our studies (entries 1 and 7−10, Table 1); however, MeCN was slightly favored. Near-quantitative conversion was achieved in MeCN within minutes at room temperature as judged by LCMS analysis (entry 10, Table 1).[7] Since heterocycles generally have a broad spectrum of solubility, it is believed that this solvent-independent amination could be beneficial to many systems.

It was of great significance in this new methodology development to demonstrate high compatibility of various functional groups, especially acid-labile ones. All reactions with 4-hydroxyquinazolines carrying various functionalities (Scheme 1, Table 2) gave desired products in excellent

Table 2. Compatibility of BOP Mediated Direct Amination of 4-Hydroxyquinazolines in the Presence of DBU in MeCN

entry	reactant	R^1	R^2	R^3	product (%)[8]
1	**1b**	H	CCl_3	H	**2b** (99)
2	**1c**	H	Br	H	**2c** (95)
3	**1d**	Cl	H	H	**2d** (87)
4	**1e**	H	H		**2e** (99)
5	**1f**	H	H		**2f** (99)
6	**1g**	H	H		**2g** (99)
7	**1h**	H	H		**2h** (86)
8	**1i**				**2i** (96)
9	**1j**	H	H		**2j** (92)
10	**1k**	H	H		**2k** (90)
11	**1l**	H	H		**2l** (85)

isolated yields (85−99%)[8] at room temperature under optimized conditions (base = DBU; solvent = MeCN). These functional groups include CCl_3 (entry 1), halide (entries 2 and 3), amine (entry 5), ester (entries 7 and 8), ketal (entry 8), olefin (entry 9), sulfide (entry 10), and acyclic amide and ketone (entry 11). There were no complications or side reactions observed in these transformations.

A panel of nucleophiles was subsequently examined in reaction with 4-hydroxyquinazoline **1a** (Scheme 2, Table 3).

Scheme 2

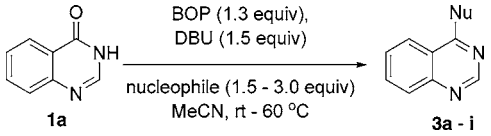
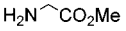
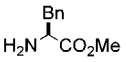


Table 3. Various Nucleophiles in Direct Amination with 4-Hydroxyquinazoline

entry	nucleophile	conditions[a]	product (%)[8]
1	-	A	**3a** (86)
2		B	**3b** (64)
3		A	**3c** (88)
4		A	**3d** (84)
5		B	**3e** (75)
6		B	**3f** (78)
7		B	**3g** (92)
8		A	**3h** (93)
9		A	**3i** (84)

[a] Conditions A: BOP (1.3 equiv), DBU (1.5 equiv), nucleophile (1.5 equiv), MeCN, rt. Conditions B: BOP (1.3 equiv), DBU (1.5 equiv), nucleophile (1.5−3.0 equiv), MeCN, rt to 60 °C.

Without an external nucleophile, **3a** (entry 1, Table 3, Figure 1) was isolated in 87% yield as the sole product. Primary and secondary amines (entries 3 and 4, Table 3) reacted with **1a** smoothly to give the desired products in good isolated

(4) For representative recent reviews, see: (a) Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994**, *265*, 1093. (b) Bridges, A. J. *Chem. Rev.* **2001**, *101*, 2541.

(5) For a recent synthesis, see: Yoon, D. S.; Han, Y.; Stark, T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775.

(6) PyBOP and PyBrOP were found to be less efficient (data not shown).

(7) The lower isolated yield (86%, entry 10, Table 1) was likely due to low solubility of the product and subsequent incomplete elusion from the SiO_2 column.

(8) Yields given after purification, unless otherwise noted.

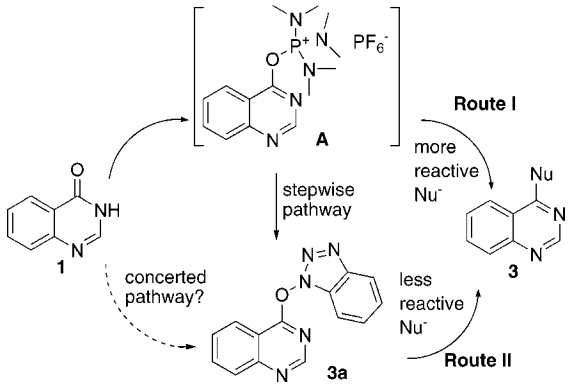


Figure 1. Proposed reaction pathways

yields. Sterically hindered *tert*-butylamine reacted more slowly, but also gave the desired product **3b** in 64% isolated yield (entry 2, Table 3). Similarly, more hindered phenylalanine methyl ester (entry 5) and less nucleophilic aniline and imidazole (entries 6 and 7) also required heating to drive the reactions to completion.

It was also observed that reactions with non-nitrogen-containing nucleophiles such as phenol and thiophenol also proceeded at room temperature to give the desired products in excellent isolated yields (entries 8 and 9, Table 3), thus representing a facile formation of C−S and C−O bonds in cyclic amide systems.

Although the desired products were observed generally within minutes by LCMS analysis, HOBt adducts, i.e., **3a**, were found to be the major products in cases with less reactive nucleophilies (i.e., aniline) at room temperature. Mechanistically, the formation of intermediate **A** (Figure 1) might be a fast process upon treatment with DBU followed by elimination of 1 equiv of HMPA.[9] Subsequent substitution would be largely dependent upon the nucleophilicity of the substituents. A likely ranking of nucleophiles in order of decreasing reactivity is as follows: alkylamine > HOBt > arylamine. This could thus explain the absence of HOBt adducts in reactions with alkylamines while they (e.g., **3a**) were found to be the major products with less reactive nucleophiles at room temperature. **3a** is presumably formed from **A** via a stepwise pathway, although a concerted pathway could not be ruled out at this point.[10] When **3a** was subjected to similar reaction conditions, it gave the desired product **3f**. It is thus reasonable to believe that reactions with more reactive nucleophiles go through Route I while those with less reactive nucleophiles mainly follow Route II.[11]

With these encouraging results in hand, a panel of heterocycles was then examined to demonstrate the generality of this direct and facile amination reaction (Scheme 3). Some of these results, all from commerically available starting materials, are summerized in Table 4.

Scheme 3

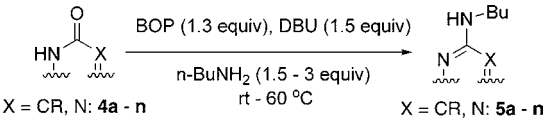
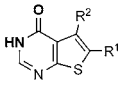
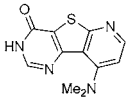
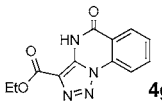
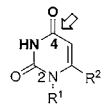
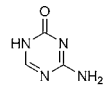
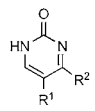


Table 4. BOP Promoted Direct Amidinylation and Guanidinylation on Various Heterocyclic Systems

entry	substrate		method[a]	product (%)[8]
1		**4a**	A	**5a** (79[b])
2		**4b**	A	**5b** (86[b])
3		**4c**: $R^1 = R^2 = H$ **4d**: $R^1 = CO_2Me$, $R^2 = Me$	B	**5c** (94) **5d** (81)
4		**4e**	B	**5e** (94)
5		**4f**	B	**5f** (95)
6		**4g**	B	**5g** (94)
7		**4h**:R^1 = Bn, R^2 = H **4i**: R^1 = Ph, R^2 = Me	B	**5h** (73) **5i** (81)
8		**4j**	A	**5j** (82[b])
9		**4k**	C	**5k** (75[b])
10		**4l**: R^1 = Br, R^2 = H **4m**: R^1 = H, R^2 = Me	B	**5l** (95[b]) **5m** (68)

[a] Conditions A: BOP (1.3 equiv), DBU (1.5 equiv), *n*-$BuNH_2$ (3−5 equiv), DMF, rt then 60 °C. Conditions B: BOP (1.3 equiv), DBU (1.5 equiv), *n*-$BuNH_2$ (1.5 equiv), MeCN, rt. Conditions C: BOP (1.2 equiv), DIPEA (1.2 equiv), *n*-$BuNH_2$ (3 equiv), CH_2Cl_2, rt. [b] LCMS yield calibrated with an internal standard

It was shown that this new C−N bond forming reaction is suitable for various heterocyclic amides ranging from monocyclic to tricyclic systems in good efficiency. To our

(9) Formation of HMPA was confirmed by ^{31}P NMR studies. The phosphoninum salt **A** could also be detected occasionally.

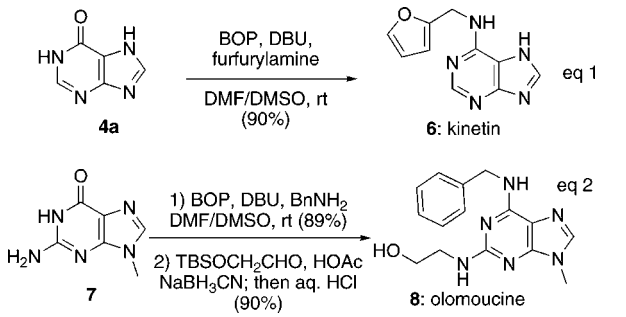
(10) Mechanistic studies and applications of these synthetic intermediates are underway. For work on BtH, see: Katritzky, R. A.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555.

(11) At room temperature, reactions of **5a** with anilline did not proceed while a small amount of **5f** was observed within a few minutes by LCMS analysis in the reaction conditions listed in entry 6, Table 3.

pleasant surprise, excellent chemoselectivity (C4 over C2−Cl) was achieved in the reaction with 6-chloropyrimidin-4(*3H*)-one (entry 9, Table 4), clearly demonstrating an advantage over conventional C−N bond formation from an aryl halide. Regioselectivity was also achieved with uracil systems (entry 7, Table 4) due to higher reactivity of the C4 position.[12] It was also discovered that guanidinylation of cyclic ureas proceeded smoothly to produce the desired cyclic guanidines **5*l*** and **5m**, in good yields (entry 10, Table 4).

The success of these direct aminations turned our attention to the syntheses of kinetin and olomoucine. Kinetin, a well-known plant growth factor that was first isolated from plant DNA[13] and recently from human urine,[14] has a wide variety of biological effects, including those on gene expression, inhibition of auxin action, stimulation of calcium flux, and human DNA-repair reactions.[15] Olomoucine has been shown to be a potent and selective cyclin dependent kinase inhibitor.[16] In our hands, kinetin **6** was synthesized in just one step from hypoxanthine **4a** in 90% yield (eq 1, Scheme 4). Meanwhile, direct amination of 1-methylguanine **7**, followed by one-pot reductive amination and desilylation, provided olomoucine **8** in 80% overall yield in just 2 steps (eq 2, Scheme 4).

Scheme 4



In summary, an efficient one-step amination of cyclic amides and cyclic ureas has been developed. This mild, metal-free amination of cyclic amides and cyclic ureas has demonstrated a clear advantage over existing procedures. It facilitated efficient and concise syntheses of biologically intriguing kinetin and olomoucine in just one and two steps, respectively. Direct amidinylation and guanidinylation of more challenging acyclic systems as well as the application to the syntheses of important heterocyclic products are underway. The results will be reported in future publications.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Peng, Z.-H.; Journet, M.; Humphrey, G. *Org. Lett.* **2006**, *8*, 395.

(13) Isolation: (a) Miller, C. O.; Skoog, F.; Von Saltza, M. H.; Strong, F. M. *J. Am. Chem. Soc*. **1955**, *77*, 1392. (b) Miller, C. O.; Skoog, F.; Okumura, F. S.; Von Saltza, M. H.; Strong, F. M. *J. Am. Chem. Soc*. **1956**, *78*, 1375. For syntheses see ref 13b and: (c) Villar, J. D. F.; Motta, M. A. *Nucleosides, Nucleotides & Nucleic Acids* **2000**, *19*, 1005.

(14) Barciszewski, J.; Mielcarek, M.; Stobiecki, M.; Siboska, G.; Clark, B. F. C. *Biochem. Biophys. Res. Commun*. **2000**, *279*, 69.

(15) For a recent review on kinetin see: Barciszewski, J.; Rattan, S. I. S.; Siboska, G.; Clark, B. F. C. *Plant Sci.* **1999**, *148*, 37.

(16) For representative biological activities see: (a) Vesely, J.; Havlicek, L.; Strnad, M.; Blow, J.; Donella-Deana, A.; Pinna, L.; Letham, D.; Kato, J.; Detivaud, L.; Leclerc, S.; Meijer, L. *Eur. J. Biochem.* **1994**, *224*, 771. (b) Mistelli, T.; Warren, G. *J. Cell Sci*. **1995**, *108*, 2715. (c) Hartwell, L. H.; Kastan, M. B. *Science* **1994**, *266*, 1821. For recent 6−9 step syntheses see: (d) Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem*. **1997**, *62*, 201. (e) Dorff, P. H.; Garigipati, R. S. *Tetrahedron Lett*. **2001**, *42*, 2771. (f) Hammarström, L. G. J.; Smith, D. B.; Talamás, F. X.; Labadie, S. S.; Krauss, N. E. *Tetrahedron Lett.* **2002**, *43*, 8071.