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Phosphonium-mediated cyclization of *N*-(2-aminophenyl)thioureas: efficient synthesis of 2-aminobenzimidazoles

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ABSTRACT

BOP efficiently promoted the phosphonium-mediated cyclization of thioureas, leading to a convenient synthesis of 2-aminobenzimidazoles. Compared to conventional methods, the reactions were complete at room temperature with times ranging from a few minutes to 1 h in near quantitative yields. This method is also applicable to the synthesis of more challenging structures such as 2-akylaminobenzimidazoles and 2-(*N*-acyl)-aminobenzimidazoles. The methodology described herein represents a mild and efficient route to a variety of 2-aminobenzimidazoles.

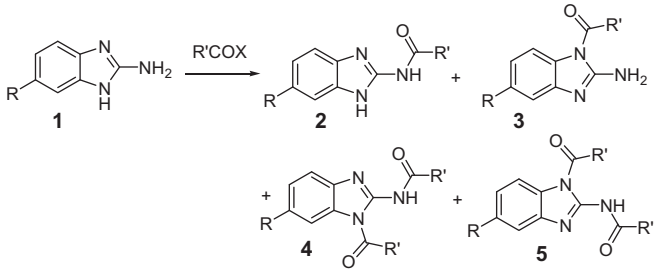
Introduction

2-Aminobenzimidazoles are interesting heterocycles that are found both in natural products as well as in drugs and drug candidates.[1] Despite the prevalence of the 2-aminobenzimidazole motif in drugs and natural products, the synthesis of 2-aminobenzimidazoles remains challenging. The conventional syntheses typically involve the mediation of a metal salt, alkylating agent or acylating agent.[2] While these methods are valuable, they also suffer from various limitations. A typical method for the cyclization of thioureas involves using stoichiometric amounts of metal salts of mercury[2–4] and copper,[5,6] as well as oxidants such as $PhI(OAc)_2$.[7] Another method relies on nonselective alkylating and acylating agents such as methyl iodide[8] and sulfonyl chloride.[9] Recent advances in this area using carbodiimide based reagents, such as DCC and EDC,[10] represent a milder method, but frequently require heating and long reaction times. Furthermore, formation of urea side-products can pose significant challenges during purification.

The direct synthesis of 2-(*N*-acyl)aminobenzimidazoles, through thiourea intermediates, is also challenging and has been sporadically reported with limited success.[11] This subclass of benzimidazoles possesses unique properties and has been exploited in the development of compounds such as Mebendazole **2** (Scheme 1, R = PhC(=O), R′ = OMe). Conventional acylation of 2-aminobenzimidazoles often lacks regio-selectivity and thus, leads to the formation of complex mixtures (Scheme 1).[2] For instance, Mebendazole was obtained as a minor product (a 1: 5 mixture with its *N*-1 isomer), when 2-amino-5-phenylacylbenzimidazole was treated with methyl chloroformate.[12]

We previously disclosed an efficient phosphonium-mediated bond formation[13] and applied this method to the synthesis of heterocycles such as 2-amino-3,4-oxadiazoles in an intermolecular fashion.[13d] While this methodology works well in various heterocyclic systems, formation of 2-aminobenzimidazoles from the corresponding benzimidazol-2-ones or benzimidazol-2-thiones was not successful. To circumvent this problem, we envisioned that an intramolecular amination would facilitate the formation of the desired products.

To our satisfaction, treatment of thiourea **6a** with BOP (1.5 equiv) in the presence of DBU (2.0 equiv) in MeCN provided the desired product **7a** at room temperature in near quantitative conversion, without the formation of side products, in just 10 min (Scheme 2). A solvent screen using the cyclization of thiourea **6a** as a model reaction (Scheme 2, Table 1) revealed that



Scheme 1. Nonselective synthesis of 2-(*N*-acyl)amino-benzimidazoles in literature.

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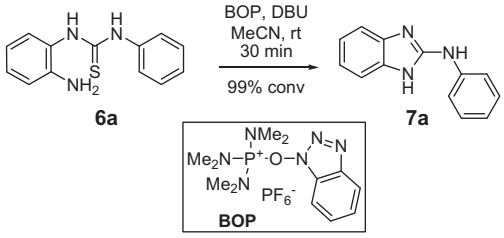


Scheme 2. BOP-mediated synthesis of **7a**.

Table 1
Base effect on the formation of **7a** from **6a**[a]

Entry	Base	Conv (%)
1	—	Trace
2	DBU	99
3	DBN	95
4	DIPEA	86
5	TEA	25
6	DMAP	9
7	Pyridine	5
58	Cs_2CO_3	23

[a] Reaction was run at rt (BOP: 1.5 equiv; base: 2.0 equiv); reaction was monitored by LC–MS at 30 min.

solvents, such as acetonitrile and dimethylformamide (DMF) were optimal amongst the solvents screened (DCM, THF, EtOAc, acetone, MeCN, DMF and DMSO). Furthermore, a base screen showed that stronger organic bases, such as DBU, DBN and diisopropylethylamine (DIPEA) are preferred (entries 2–4, respectively) and that the reaction does not proceed in the absence of a base. Reaction with inorganic bases such as Cs_2CO_3 was observed albeit with low conversion (23%).[14]

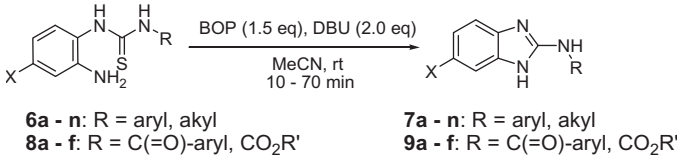
After completing the solvent and base studies, we turned our attention to evaluating a variety of commercially available phosphonium reagents. We chose to include EDC in this evaluation as we were eager to compare our method with the literature methods. We began as before with **6a** and employed our previously optimized conditions (DBU, acetonitrile and activating agent). The reactions were monitored at 10 and 30 min, respectively, by LC–MS (Table 2). The reaction with BOP proceeded to near completion in just 10 min (entry 1) and was found to be the optimal reagent of the ones evaluated (PyBOP, PyAOP, BroP, PyBroP, Ph_3PI_2 and EDC). Interestingly, in a head-to-head comparison, the BOP mediated reaction was complete in 10 min. while the EDC promoted reaction was at 16% conversion after 10 min (entry 7).

With the reaction conditions tuned, we set out to evaluate the substrate scope of our method (Scheme 3, Tables 3 and 4). As disclosed in Table 3, most reactions were complete within 1 h at room temperature. The desired products were isolated in good to

Table 2
Activation agent effect on the formation of **7a** from **6a**[a]

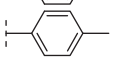
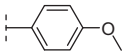
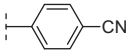
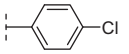
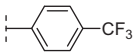
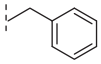
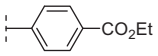
Entry	Base	Conv (10, 30 min)
1	BOP	98, 99+
2	PyBOP	26, 58
3	PyAOP	50, 60
4	Ph_3PI_2	~50, ~50[b]
5	BroP	<5, ~5
6	PyBroP	<5, ~5
7	EDC	16, 28[c]

[a] Reaction (BOP: 1.5 equiv; base: 2.0 equiv) was monitored by LC–MS.
[b] Reaction was messier than others.
[c] No DBU used.



Scheme 3. Synthesis of 2-aryl- and 2-alkyl-amino-benzimidazoles and 2-*N*-(acyl)amino-benzimidazoles.

Table 3
Phosphonium mediated synthesis of 2-aryl- and 2-alkyl-amino-benzimidazoles[16]

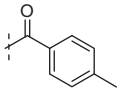
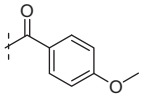
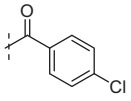
Entry	Substrate	X	R	Product	Yield[a] (%)
1	**6a**	H		**7a**	94
2	**6b**	H		**7b**	97
3	**6c**	H		**7c**	96
4	**6d**	H		**7d**	76
5	**6e**	H		**7e**	98
6	**6f**	H		**7f**	91
7	**6g**	H		**7g**	73[b,c]
8	**6h**	H		**7h**	91
9	**6i**	H		**7i**	99
10	**6j**	F		**7j**	94
11	**6k**	CN		**7k**	97
12	**6l**	NO_2		**7l**	99
13	**6m**	CO_2Et		**7m**	95
14	**6n**			**7n**	95

[a] Isolated yield by SiO_2 column chromatography.
[b] Precipitation observed during column purification.
[c] Quantitative conversion observed by LC–MS.

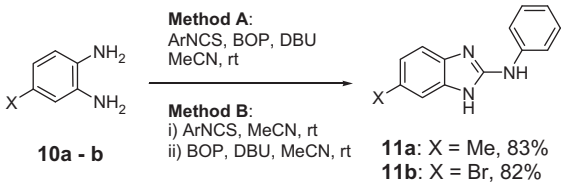
excellent yields with no obvious electronic effect observed. Neither electron rich (entries 2 and 3) nor electron deficient substituents (entries 4–7; 10–14) affected the reaction efficiencies or the reaction times. A steric effect was also briefly explored. Compared with cyclization of **6f,** which was complete in 10 min at room temperature, the cyclization of ortho-substituted thiourea **6g** was complete within 1 h. Furthermore, this method is useful for the construction of 2-alkylaminobenzimidazoles, which tends to be more challenging. The treatment of alkyl thioureas **6h** and **6i** with BOP under the standard conditions provided the desired 2-alkylaminobenzimidazoles **6h** and **6i** within 30 min in excellent yields (91% and 99%, respectively, entries 8 and 9). Overall, the assembly of compounds found in Table 3 is efficient under the BOP-mediated cyclization conditions and is complementary to other methods.

With our substrate scope studies complete, we were curious to see if our method could be applied to the direct synthesis of 2-(*N*-acyl)-aminobenzimidazoles. Direct and selective synthesis of these compounds has been rarely reported in the literature.[12] We found that treatment of a variety of acylthioureas **8a**–**f** with BOP under

Table 4
Synthesis of 2-(*N*-acyl)aminobenzimidazoles

Entry	Substrate	X	R	Product	Yield[a] (%)
1	**8a**	H		**9a**	77
2	**8b**	H		**9b**	95
3	**8c**	H		**9c**	87 (94[b])
4	**8d**	H		**9d**	76
5	**8e**	H		**9e**	94
6	**8f**			**9f**	98

[a] Product collected by direct filtration of the crude reaction mixture.
[b] Isolated yield by SiO_2 column chromatography.

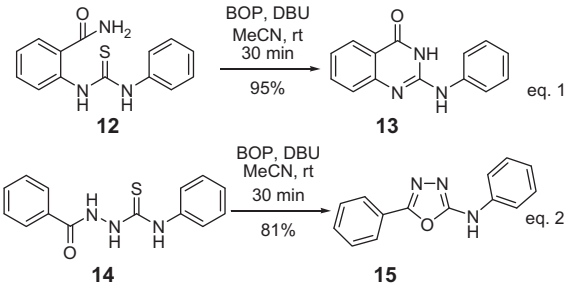


Scheme 4. Synthesis of **11a** and **11b** in one-pot fashion.

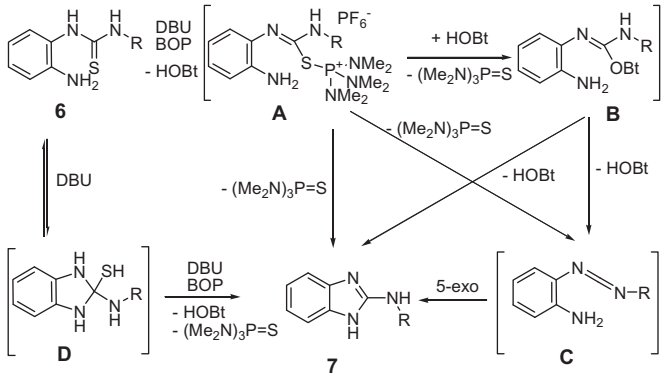
the optimized conditions afforded the desired products **9a**–**f** in excellent yields and as single regioisomers (Scheme 3, Table 4). As an illustration of this method, a close analogue of Mebendazole was synthesized (Table 4, entry 6, **9f**, 98%) in near quantitative yield. Furthermore, we found that a number of products directly precipitated out of the reaction mixtures and could be collected by filtration. As in our previous studies, no electronic effect was observed. In order to increase the utility of our method, we decided to explore whether the two step sequence (thiourea formation and cyclization) could be executed in a one-pot synthesis. We were surprised to find that while the method A (without pre-formation of thioureas) provided the desired product, a two-step, one-pot protocol in method B offered a cleaner reaction. As an example, treatment of diamine **10a** and **10b** with phenylthioisocyanate in MeCN followed by the reaction with BOP reagent in the presence of DBU provided the desired products **11a** and **11b** in 83% and 82% isolated yields, respectively (Scheme 4).

This BOP-mediated methodology was also briefly tested in other heterocyclic systems. When thiourea **12** was treated with BOP reagent, the desired 2-(phenylamino)quinazolin-4(3*H*)-one **13** was isolated in 95% yield (Scheme 5, eq. 1). Similarly, acyl-thiosemicarbazide **14** was converted to the desired 2-phenylamino-5-phenyl-1,3,4-oxadiazole **15** in 81% yield (Scheme 5, eq. 2).[15]

Although the detailed reaction pathway is not known, involvement of one or more of intermediates A, B, C and D might be possible. We propose that the intermediate **A** is formed upon nucleophlic attack of **6** to BOP after elimination of 1 equiv 1-hydroxybenzotriazole (HOBt). Once formed, a number of possible pathways become viable (Scheme 6). Intramolecular cyclization of **A** would lead to the desired product **7** upon the loss of 1 equiv of



Scheme 5. Synthesis of 2-(phenylamino)quinazolin-4(3*H*)-one **13** and 2-Phenylamino-5-phenyl-1,3,4-oxadiazole **15**.



Scheme 6. Proposed mechanism.

hexamethylthio-phosphonamide [$(Me_2N)_3P{=}S$]. Intermediate **A** could also be subject to nucleophilic attack by HOBt and lead to the formation of the second intermediate **B**. In addition, intramolecular cyclization of **B** could lead to product **9** upon expulsion of HOBt. Alternatively, both intermediates **A** and **B** could be transformed into intermediate **C** upon loss of 1 equiv $(Me_2N)_3P{=}S$ or HOBt, respectively. Intramolecular cyclization of **C** would provide the same product **7**. Compound **6** may be in equilibrium with intermediate **D**[10b], which could also lead to the desired product **7,** upon activation by BOP.

Conclusion

A facile and efficient, phosphonium-mediated synthesis of 2-aryl and 2-alkyl-amino-benzimidazoles has been discovered, thus providing a highly efficient and complementary route to these biologically interesting heterocycles. Selective formation of 2-(*N*-acyl)aminobenzimidazoles was also possible under similar conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.146.

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14. It is worth mentioning that the reaction with Cs_2CO_3 was also complete with prolonged reaction time at room temperature (~30 h).
15. A small amount of 1,3,4-thiooxadiazole was also detected by LC–MS. Detailed work on the synthesis of 2-amino-1,3,4-oxadiazole and 2-amino-quinazolin-4(3*H*)-one will be reported in the future.
16. For non-C2 symmetrical compounds, such as **7k–n**: one drop of DCl in D_2O was added to ^{13}C NMR samples to ensure observation of a single set of ^{13}C resonances.