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LHMDS mediated tandem acylation–cyclization of 2-aminobenzenecarbonitriles with 2-benzymidazol-2-yl acetates: a short and efficient route to the synthesis of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones

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Abstract—We herein describe the discovery of a mild, one-pot tandem acylation–cyclization for the synthesis of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones from 2-aminobenzenecarbonitriles and ethyl 2-benzimidazol-2-yl acetates.

1. Introduction

Receptor tyrosine kinases (RTK) and their ligands are involved in important signal transduction pathways within the cell. In particular, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF) and their receptors play a fundamental role in cell proliferation, differentiation (i.e., vasculogenesis and angiogenesis) and cell death.[1–4] These kinases are overexpressed in several malignancies in vivo and their pathways are deregulated.[5,6] Inhibition of growth factor receptor tyrosine kinases represents an attractive therapeutic modality in oncology, and several RTK inhibitors are currently being evaluated preclinically or in clinical trials.[7–9]

4-Amino-3-benzimidazol-2-ylhydroquinolin-2-ones (e.g., **4**) are a class of potent RTK inhibitors with attractive physicochemical and pharmacokinetic properties and significant efficacy in murine and human xenograft tumor models.[10] In the course of our RTK inhibitor program, we encountered the need for an efficient and scalable synthetic route to 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones.

Two main approaches to 3-substituted-4-*amino*hydroquinolin-2-ones are described in the literature. The most widely used is based on nucleophilic substitution on 4-chlorohydroquinolin-2-ones with ammonia, ammonia equivalents or amines.[11–14] More direct transformations begin with a 2-aminobenzenecarbonitrile and an active methylene compound and are promoted with either Lewis acids[15–18] or bases.[14,19–21] These two methods incorporate esters, nitriles or aryl groups at the C-3 position of the hydroquinolin-2-one. The only reported method incorporating a benzimidazole in the C-3 position of a 4-*hydroxy*hydroquinolin-2-one involves high temperatures (130–140 °C).[22–24]

In the course of our work, these synthetic routes were examined for the synthesis of 4-*amino*-3-benzimidazol-2-ylhydroquinolin-2-ones but were not optimal due to lengthy reaction sequences, harsh reaction conditions, or inability to accommodate various functionalities. This paper describes a one pot, tandem acylation–cyclization

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sequence to obtain 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones with mild conditions and in good yields.

2. Results and discussion

The reported synthesis of the 3-ethyl ester 4-*amino*hydroquinolin-2-one used NaOEt in EtOH (1 equiv at 80 °C).[14,25,26] Our attempts to reproduce this work for the 3-benzimidazole analog, starting from ethyl 2-benzimidazol-2-ylacetate **1**[32] and 2-aminobenzenecarbonitrile **2** (Scheme 1), gave a very low conversion (Table 1). Moreover, the reaction afforded a mixture of the desired cyclized product **4** together with the uncyclized 2-benzimidazol-2-yl-*N*-(2-cyanophenyl)acetamide **3**.

Changing the base from NaOEt to LHMDS (1 equiv) led exclusively to the formation of the uncyclized amide **3**.[27] Earlier literature reports[28–31] suggest that similar amide intermediates containing an acidic methylene group can be cyclized to hydroquinolinones in the presence of bases such as NaH in DMF or NaOEt in EtOH, albeit in poor yields. When the crude amide **3** was treated with NaOEt in EtOH, the desired product **4** could be obtained in very low yields and was contaminated by numerous impurities.

The deprotonation of the benzimidazole NH in compound **3** may in fact deactivate the α methylene, slowing down the cyclization step and favoring undesired side reactions. These preliminary results, however, prompted us to optimize the reaction conditions to obtain **4** exclusively and in one step.

A number of inorganic and organometallic bases were surveyed. In general, when a mixture of ethyl 2-benzimidazol-2-ylacetate **1**[32] and 2-aminobenzenecarbonitrile **2** was treated with 3 equiv of base, the formation of the desired cyclized **4** together with variable amounts of uncyclized **3** was observed (Table 1). Alkoxides gave low conversion of starting material to products and an unfavorable ratio of **3** and **4**. The main side product was 2-methyl benzimidazole, derived from hydrolysis and decarboxylation of the ethyl ester. The use of NaH at room temperature gave mostly cyclized product **4**, but the conversion was also very low. Attempts to improve the reaction conversion by heating to reflux led to decomposition. *s*-BuLi and LHMDS gave better results, with the conversion of starting material to **3** and **4** being superior with LHMDS. LDA gave very poor conversion of starting material to products with the undesired **3** being the predominant product. Commercially available and freshly prepared LDA gave similarly disappointing and unexplainable results.

Table 1.

Base (3 equiv)[a]	Temp. (°C)	% Conversion[b]	Ratio **3**:**4**[b]
KO*t*Bu[c]	80	20	50:50
NaOEt[d]	80	10	70:30
NaH	25	10	10:90
s-BuLi	−78 to 25	50	30:70
LDA	−78 to 25	4	95:5
LHMDS	−78 to 25	100	45:55

[a] In THF unless otherwise indicated.
[b] % Conversions and ratios determined by HPLC.
[c] In PhMe.
[d] NaOEt in EtOH.

Having found LHMDS to be the optimal base for obtaining the desired product **4**, the effect of temperature on the reaction was then assessed (Table 2). At low temperature, cyclized product **4** did not form at all. Warming to room temperature gave approximately a 1:1 ratio of **3**:**4**, while heating to 40 °C for 2–4 h resulted in complete conversion to **4**.

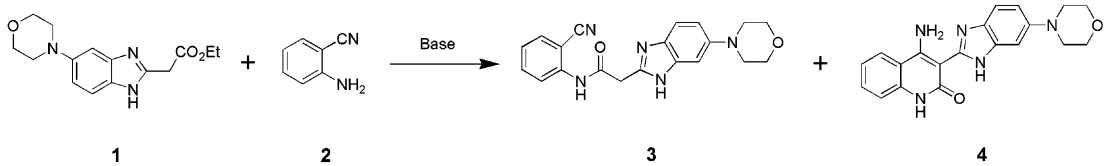
For compound **4**, the optimal reaction conditions employed 3 equiv of LHMDS at 40 °C resulting in a 61% yield (Table 3).[33] However, most 2-benzimidazol-2-ylacetates were sensitive to temperatures above 25 °C, and extensive decarboxylation to 2-methylbenzimidazole occurred prior to reaction with the 2-aminobenzonitriles. Lowering the temperature and increasing the equivalents of LHMDS led to better yields, and the most general reaction conditions are 5 equiv of LHMDS at room temperature for 2–3 h. Under these conditions, yields typically range from 30% to 80%. Table 3 highlights several examples synthesized by this method.

A variety of functional groups, including halo, nitrile, ester, aniline, and ether substituents, on either the hydroquinolinone or the benzimidazole, are tolerated using the optimized reaction conditions, and several hundred 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones have been synthesized by this method.

Table 2.

Temperature (°C)[a]	Ratio **3**:**4**[b]
−78	100:0
−78 to 25	45:55
40	0:100

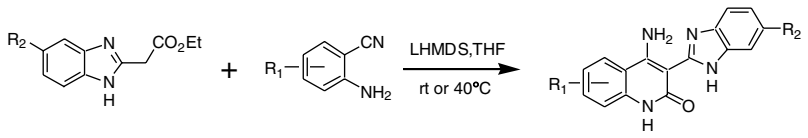
[a] 3 equiv LHMDS in THF.
[b] Ratios determined by HPLC.



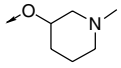
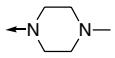
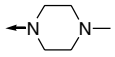
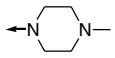
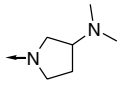
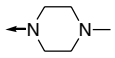
1 **2** **3** **4**

Scheme 1.

Table 3.



5

Compound	R_1	R_2	Yield
5a	5-F	$-CO_2Me$	45[a]
5b	H	–CN	63[a]
5c	H		34[b]
4	H		61[c]
5d	5-NH_2		49[a]
5e	5-OMe		87[a]
5f	5-F		60[a]
5g	6-Cl		63[a]
5h	7-F		80[a]

[a] Yield after sonication in a solution of 94.5:5:0.5 Et_2O/acetone/MeOH and filtration.
[b] Yield after reverse phase HPLC.
[c] Yield after column chromatography.

3. Conclusions

In conclusion, LHMDS promotes a one-pot tandem acylation–cyclization of 2-aminobenzene carbonitriles and 2-benzimidazolyl acetates under very mild conditions and in moderate to good yields.

Supplementary data

Supplementary data (^1H and ^{13}C NMR) are available for compound **4**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.113.

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33. 4-Amino-3-(6-morpholin-4-ylbenzimidazol-2-yl)hydroquinolin-2-one **4**. To a flame dried 500 mL round-bottomed flask were added ethyl 2-(5-morpholin-4-ylbenzimidazol-2-yl)acetate **1** (5.0 g, 17 mmol), anthranilonitrile **2** (2.0 g, 17 mmol), and anhydrous THF (50 mL). To the resulting solution was added LHMDS (1.0 M solution in THF, 50 mL, 50 mmol), via a syringe, over 10 min. The reaction mixture was heated at 40 °C for 2 h, cooled to room temperature, and then poured into a vigorously stirred mixture of satd aq NH_4Cl (30 mL) and EtOAc (200 mL). The two phases were separated, and the aqueous phase was extracted with EtOAc (3×100 mL). The organic extracts were collected, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was triturated with Et_2O, and the resulting greenish-brown powder was purified by chromatography on silica gel (10% MeOH in CH_2Cl_2), to afford the desired product **4** (3.7 g, 61% yield) as a light yellow solid.