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Synthesis of 3-Substituted-4(3*H*)-quinazolinones via HATU-Mediated Coupling of 4-Hydroxyquinazolines with Amines

Zili Xiao, Michael G. Yang,* Peng Li, and Percy H. Carter

Research & Development, Bristol-Myers Squibb Company,
Princeton, New Jersey 08543

michael.yang@bms.com

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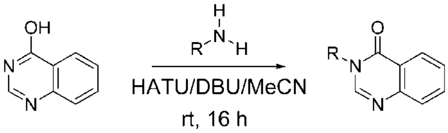
ABSTRACT



A novel synthesis of 3-substituted 4(3*H*)-quinazolinones via HATU-mediated coupling of 4-hydroxyquinazolines with primary amines has been developed. Under mild reaction conditions, the products were achieved in good yield from commercially available starting materials.

3-Substituted 4(3*H*)-quinazolinones are useful heterocyclic motifs found in many pharmaceutically active compounds. One of the most direct ways to access this class of compounds is N-alkylation of 4-hydroxyquinazolines.[1] However, issues still exist for the synthesis of sterically hindered 3-alkyl 4(3*H*)-quinazolinones,[2] and there are very few studies on the direct 3-arylation of 4-hydroxyquinazolines.[3] In this paper, we report a novel synthesis of 3-substituted 4(3*H*)-quinazolinones via HATU-mediated coupling of 4-hydroxyquinazolines with amines. The mechanism of this transformation is discussed in light of the recently reported phosphonium-mediated synthesis of 4-aminoquinazolines.[4]

In a medicinal discovery program directed toward CCR2 antagonism, we were interested in synthesizing quinazoline **2**.[5] Based on the procedure reported in the literature,[6] we envisioned that **2** could be made through the BOP-mediated coupling of amine **1** with the 4-hydroxyquinazoline (eq 1, Scheme 1). When the reaction failed to provide the desired product, we speculated that HATU could be used to improve the reaction conditions. To our surprise, the reaction gave quinazolinone **3** in 34% yield; compound **2** was not detected (eq 2, Scheme 1).

Following this initial observation, we surveyed a variety of coupling reagents under the original conditions (MeCN, DBU). As shown in Table 1, compound **7a** was the major

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[1] Some representative examples include: (a) Wee, G. H. A.; Fan, G. J. *Org. Lett.* **2008**, *10*, 386. (b) Michael, J. P.; Koning, C. B. de.; Pienaar, D. P. *Synlett* **2006**, *3*, 383. (c) Testard, A.; Loge, C.; Leger, B.; Robert, J.-M.; Lozach, O.; Blairvacq, M.; Meijer, L.; Thiery, V.; Besson, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3419. (d) For review articles on the synthesis of quinazolinones, see: Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153.

[2] Some representative examples include: (a) Review:Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757,and references cited therein. (b) Liu, H.; Ko, S. B.; Josien, H.; Curran, D. P. *Tetrahedron Lett.* **1995**, *36*, 8917. (c) Bavetsias, V.; Yafai, S. F.; Wilson, M. S. C.; Allan, W. B.; Jackman, A. L. *J. Med. Chem.* **2002**, *45*, 3692. (d) Bowman, W. R.; Bridge, C. F. *Synth. Commun.* **1999**, *29*, 4051. (e) Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2008**, *73*, 6425.

[3] (a) Russell, S. S.; Jahangir, *Synth. Commun.* **1994**, *24*, 123. (b) Filipski, K. J.; Kohrt, J. T.; Casimiro-Garcia, A.; Van Huis, C. A.; Dudley, D. A.; Cody, W. L.; Bigge, C. F.; Desiraju, S.; Sun, S.; Maiti, S. N.; Jaber, M. R.; Edmunds, J. J. *Tetrahedron Lett.* **2006**, *47*, 7677. (c) Tiwari, S. S.; Zaidi, S. M. M.; Rajesh, A.; Satsangi, R. K. *J. Indian Chem. Soc.* **1980**, *57*, 1039.

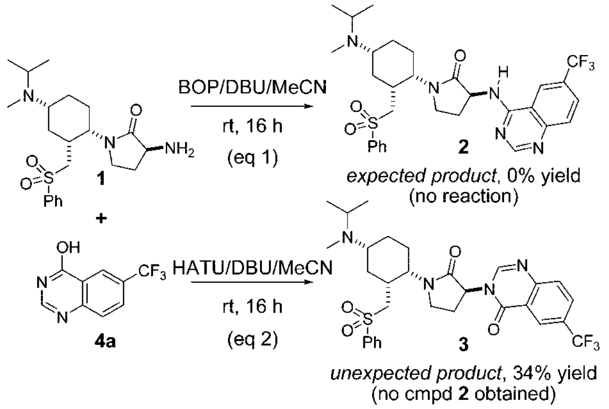
[4] Wan, Z.-K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194, and references cited therein.

[5] Carter, P. H.; Cherney, R. J.; Batt, D. G.; Brown, G. D.; Duncia, J. V.; Gardner, D. S.; Yang, M. G. WO Patent 05021500, 2005.

[6] Wan, Z.-K.; Wacharasindhu, S.; Binnun, E; Mansour, T. S. *Org. Lett.* **2006**, *8*, 2425.

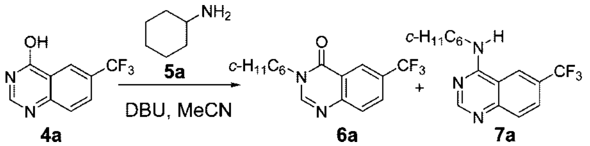
10.1021/ol802946p CCC: $40.75

Scheme 1. Initial Observations



product[7] when a phosphonium-based coupling reagent was used (entries 1−4), and the yield of **7a** was maximized via the use of pyrrolidinephosphoniums. In contrast, when a uronium-based coupling reagent was used, compound **6a** was the sole product (entries 5−7). HATU provided the highest yield. Consistent with these observations, the carbodiimide EDC, which also allows for the production of an acyluronium intermediate, provided **6a** as the sole product (entry 8).

Table 1. Effect of Coupling Reagent[a]

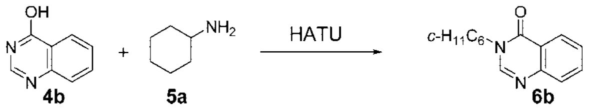


entry	coupling reagent[b]	yield (%) of **6a**[c]	yield (%) of **7a**[c]
1	BOP	28	40
2	BOP-Cl	26	38
3	PyBOP	0	60
4	PyAOP	0	57
5	HBTU	61	0
6	**HATU**	**77**	**0**
7	TBTU	70	0
8	EDC/HOBt	60	0

[a] Conditions: **5a** (1 equiv), **4a** (1.2 equiv), DBU (1.5 equiv), coupling reagents (1.3 equiv), rt, 16 h. [b] Full reagent names are listed in the Supporting Information (see Note 1). [c] Isolated yield after chromatographic purification.

A brief study on the effect of solvent and base is shown in Table 2. At room temperature in DMF, trialkylamines provided lower yields than the stronger bases tBuOK and DBU (entries 1−5). The effect of solvent appeared generally less important (entries 5−9). Based on this brief survey, MeCN and DBU appeared to be the optimal solvent and base combination, and these conditions were utilized throughout the remainder of the study.

Table 2. Effect of Solvent and Base[a]



entry	solvent	base	yield (%) of **6b**[b]
1	DMF	*t*-BuOK	61
2	DMF	DIEA	33
3	DMF	TEA	34
4	DMF	NMM	32
5	DMF	DBU	72
6	NMP	DBU	53
7	**MeCN**	**DBU**	**75**
8	THF	DBU	72
9	DCM	DBU	72

[a] Conditions: **5a** (1 equiv), **4b** (1.2 equiv), base (1.5 equiv), HATU (1.2 equiv), rt, 16 h. [b] Isolated yield after chromatographic purification.

The amination results of cyclohexylamine and a variety of 4-hydroxyquinazolines are summarized in Table 3. All of the 4-hydroxyquinazolines studied were suitable for this HATU-mediated coupling reaction (entries 1−3 and 5).[8] In addition, 6-(trifluoromethyl)pyrido[3,2-*d*]pyrimidin-4-ol **4f**, with a nitrogen incorporated in the distal aromatic ring, provided **6f** in 63% yield (entry 6) and 3,4-dihydrothieno[2,3-*d*]pyrimidin-4-ol **4g** provided **6g** in 56% yield (entry 7). Analogue **4d** was a reasonable substrate but provided a lower yield (entry 4).[9] A limitation of the reaction was noted when an imidazole derivative **4h** was used (entry 8).

A broad range of amines has been studied for this reaction. Some of the results are summarized in Table 4. Comparing the results from entries 1−3 reveals that sterically hindered nucleophiles have a negative impact on reaction yields.[10] In the case of the *tert*-butylamine, heating was necessary to obtain any product.[11] Good yields were observed for analogues of cyclohexanamine **5e** and **5f** as shown in entries 4 and 5. In the reaction of **5f**, the Boc protecting group was well tolerated. Even for some of the weaker nucleophiles, **5g** and **5h**, the reactions proceeded well and provided the excellent examples of 3-arylated-4(3*H*)-quinazolinones (entries 6 and 7). Although aminophenylacetic acid itself was

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(7) Compound **7a** was the only product observed under the following reaction conditions: in MeCN at rt with 3 equiv of **5a**, 1.3 equiv of BOP, 1 equiv of **4a**, and 1.5 equiv of DBU.

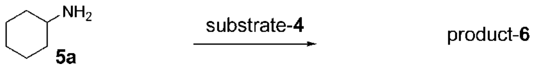
(8) A closely related analogue of 4-hydroxyquinazolines was also studied, and the experimental result is described in the Supporting Information (see Note 2).

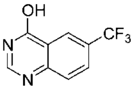
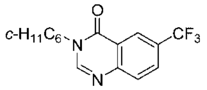
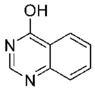
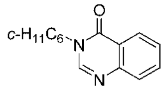
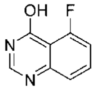
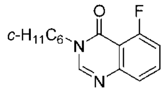
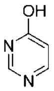
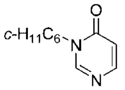
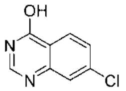
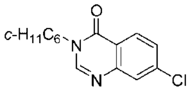
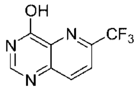
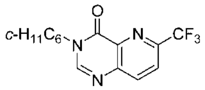
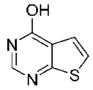
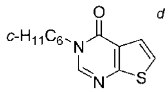
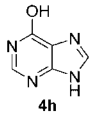
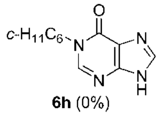
(9) An abundance of starting material **4d** remained even after heating for 20 h. See the Supporting Information (Note 3) for further description of the reaction yields.

(10) To optimize reaction yield, the reaction of **4b** with **5c** (entry 2, Table 4) was heated at 50 °C for 16 h, but the yield was not improved.

(11) The reaction was conducted at room temperature for 16 h with 20 equiv of tButyl amine and no desired product was observed by LC/MS analysis. The reaction mixture was then heated at 75 °C for 60 h. After work-up and chromatographic purification, the product **9d** was isolated in 11% yield.

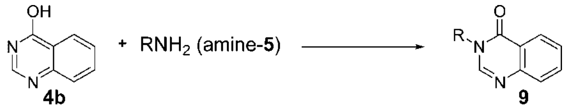
Table 3. Reactions with 4-Hydroxyquinazoline Derivatives[a]

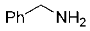
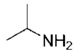
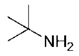
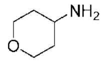
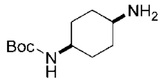
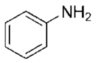
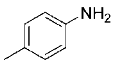
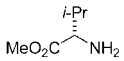
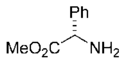
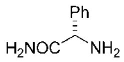


entry	substrate-4	product-6 (yield %)[b]
1	 **4a**	 **6a** (77%)
2	 **4b**	 **6b** (75%)
3	 **4c**	 **6c** (55%)
4	 **4d**	 **6d** (28%) [c]
5	 **4e**	 **6e** (56%)
6	 **4f**	 **6f** (63%)
7	 **4g**	 **6g** (56%) [d]
8	 [e] **4h**	 **6h** (0%)

[a] Conditions: **5a** (1 equiv), substrate-**4** (1.2 equiv), DBU (1.3 equiv), HATU (1.3 equiv), MeCN, rt, 16 h. [b] Isolated yield after chromatographic purification. [c] 45 °C for 20 h. [d] 75 °C for 4 h. [e] It was purchased as hypoxanthine, monosodium salt.

Table 4. Reactions with Different Amines[a]



entry	amine-5		9 (yield %)[b]
1	**5b**		**9b** (45)
2	**5c**		**9c** (43)
3	**5d**		**9d** (11)[c]
4	**5e**		**9e** (59)
5	**5f**		**9f** (70)
6	**5g**		**9g** (37)[d]
7	**5h**		**9h** (41)[e]
8	**5i**		**9i** (50)
9	**5j**		**9j** (41)[f] racemic mixture
10	**5k**		**9k** (45) racemic mixture

[a] Conditions: **4b** (1 equiv), **5** (1.2−3 equiv), DBU (1.5 equiv), HATU (1.3 equiv), MeCN, rt, 16 h. [b] Isolated yield after chromatographic purification. [c] See ref 11. [d] 75 °C for 16 h. [e] 70 °C for 30 h. [f] rt for 60 h.

not suitable for this reaction,[12] its derivatives were excellent substrates (entries 9 and 10). Both **9j** and **9k** were obtained in racemic forms, as revealed by chiral HPLC analysis (entries 9 and 10), which suggests that the 2-phenylglycine motif is prone to isomerization under the current reaction conditions. On the other hand, the valine analogue **5i** did not epimerize; quinazolinone **9i** was obtained as a single isomer based on the chiral HPLC analysis (entry 8).

We conducted some preliminary experiments to probe the reaction mechanism, as shown in Scheme 2. Since mixtures of products were obtained in our early conditions (Table 1), we wanted to rule out the possibility that the quinazoline was an intermediate en route to the quinazolinone. As shown in eq 3 (Scheme 2), treatment of quinazoline **7a** under the normal reaction conditions (plus 1 equiv of H_2O, which would normally be present in the reaction from the dehydration of the quinazolinol) did not provide product **6a**, even at elevated temperatures. This result suggests that the two reaction types (e.g., PyAOP vs HATU) are proceeding along different mechanistic pathways. We next addressed the question of the origin of the substituted nitrogen in the reaction product. As expected, an ^{15}N experiment confirmed that the 3-substituted nitrogen in product **9a** was derived from the starting amine **8** (eq 4, Scheme 2). Note that this hypothesis was further confirmed by a single-crystal structure analysis of related compound **9f**, which showed that no stereochemical inversion occurred during the reaction.[13] Finally, we demonstrated that the secondary amine **10** was

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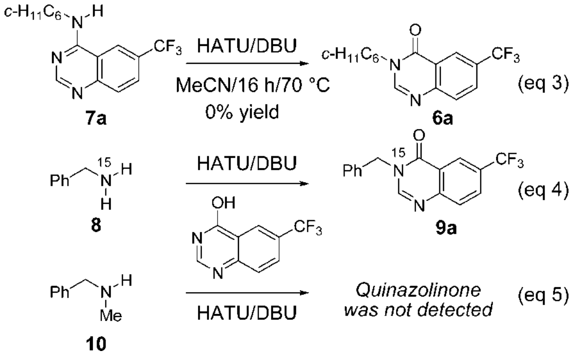
(12) Amino phenylacetic acid was used for the reaction of 4-hydroxyquinazoline **4b** under the reaction conditions of 75 °C for 16 h. No desired product was observed by LC/MS analysis except the remaining starting material.

(13) A single crystal structure was obtained from a mixture of Et_2O and EtOAc solution. The crystal structure analysis of **9f** can be found in the Supporting Information section.

unable to provide the desired quinazolinone under the reaction conditions (eq 5, Scheme 2).[14]

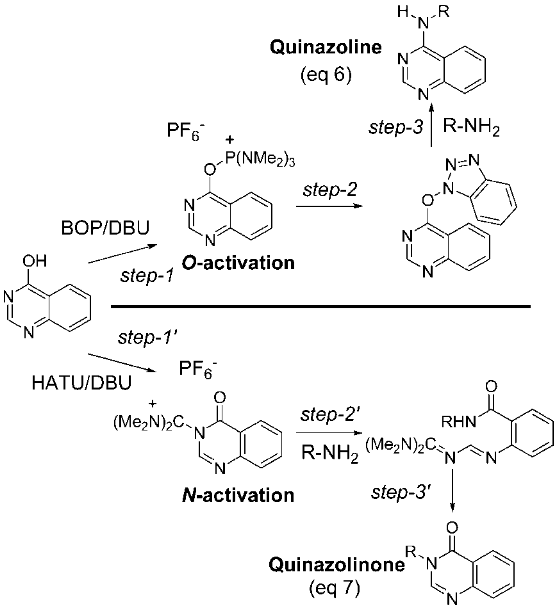
Scheme 2. Study of the Reaction Mechanism



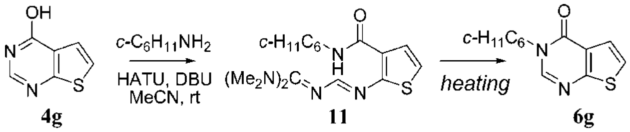
Collectively, the observations in Scheme 2 are in accord with the reaction mechanisms proposed in Scheme 3. Wan and co-workers have already demonstrated that the use of phosphonium reagents results in *O*-activation of the quinazolinol,[15] eventually producing the HOBT intermediate. Further reaction of this intermediate with an amine provides the product 4-aminoquinazoline (eq 6, Scheme 3). Since our data suggest that the 4-aminoquinazoline is not involved in the reaction mechanism with HATU, we propose that the uronium-based reactions proceed via *N*-activation, followed by amide formation. Closure then provides the observed quinazolinone (eq 7, Scheme 3).[16]

In support of the hypothesis shown above (eq 7, Scheme 3), we noted that it was possible to isolate an intermediate from one of the more sluggish couplings. Thus, subjection of **4g** to cyclohexylamine in the presence of HATU and DBU *at room temperature* provided compound **11**, our putative reaction intermediate (Scheme 4). Heating of the reaction mixture provided quinazolinone **6g**. Of note, intermediate **11** was stable enough that it could be isolated by flash chromatography after the initial step.

Scheme 3. Proposed Major Reaction Pathways



Scheme 4. Isolation of Putative Reaction Intermediate **11** in the Synthesis of **6g**



In summary, we have developed a novel method for the synthesis of 3-substituted 4(3*H*)-quinazolinones from unsubstituted quinazolinones via a uronium-mediated coupling with amines. The reaction mechanism appears to be completely complementary to that engaged by phosphonium reagents such as PyAOP. The combination of mild reaction conditions, substrate scope, and commercial availability of all reagents makes this protocol both useful and practical.

Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802946P

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[14] Detailed results are provided in the Supporting Information section (see Note 4).

[15] A plausible explanation of this observation is discussed in the Supporting Information section (see Note 5).

[16] For related reaction mechanisms, see: (a) Leonard, N. J.; Ruyle, W. V.; Bannister, L. C. *J. Org. Chem.* **1948**, *13*, 617. (b) Dai, X.; Virgil, S. *Tetrahedron: Asymmetry* **1999**, *40*, 1245. (c) Dandia, A.; Singh, R.; Sarawgi, P. *J. Fluorine Chem.* **2004**, *125*, 1835.