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Mukaiyama's reagent promoted C–N bond formation: a new method to synthesize 3-alkylquinazolin-4-ones

Puminun Punthasee, Avassaya Vanitcha, Sumrit Wacharasindhu *

Organic Synthesis Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

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ABSTRACT

A new approach to synthesize 3-alkylquinazolin-4-ones is developed. Treatment of quinazolin-4-ones with Mukaiyama's reagent, a base and a primary amine nucleophile results in the formation of 3-alkylquinazolin-4-ones in moderate to good yields under mild conditions. Using this methodology, a one-step synthesis of the natural alkaloid, echinozolinone, is accomplished.

Quinazolinones **1** and related quinazolines **2** are nitrogen-containing heterocycles that are common in nature. They possess a wide range of biological properties including antimalarial, anti-inflammatory, anti-cancer, and anticonvulsant amongst others.[1] For example, febrifugine (**3**), a quinazolinone isolated from the Chinese herb *Dichroa febrifuga*, is used as an antimalarial drug[2] while erlotinib (**4**), a quinazoline, has stimulated intense interest as a potent kinase inhibitor (Fig. 1).[3] In this Letter, we report a new method to synthesize 3-alkylquinazolin-4-ones via a coupling reaction between quinazolin-4-one and a primary amine in the presence of Mukaiyama's reagent.

Retrosynthetically, the most common procedure to 3-alkylquinazolin-4-ones is N-alkylation at the 3 position of quinazolin-4-one with appropriate alkyl halides in the presence of a strong base.[4] These methods, however, require harsh conditions and produce unavoidable elimination products from the alkyl halide in addition to non-selective O-alkylation. In the case of aminoquinazoline **2**, strong and acidic reagents such as $SOCl_2$, $POCl_3$, and PCl_5 were used to activate the carbonyl of quinazolin-4-one prior to the addition of the corresponding amine.[5]

In continuing attempts to develop robust synthetic methods for aminoquinazolines **2**, we recently demonstrated an efficient 'one-step' synthesis of cyclic amidines using the phosphonium reagent, benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP **6**); this amination was accomplished in high yield.[6] Nevertheless, this method is inconvenient for scale-up because the phosphonium reagent is expensive and has a high molecular weight resulting in atom inefficiency. Moreover, the by-product of the reaction is HMPA which is considered to be a carcinogenic substance.[7] In search of new activators, we reasoned that there was a possibility of using another amide-coupling agent.[8] Mukaiyama's reagent, 2-chloro-1-methyl-pyridinium iodide **7** would appear to be appropriate for the activation due to its high stability and low cost.[9] Surprisingly, the use of this activator under our previous conditions led to the isolation of 3-butylquinazolin-4-one **9** as the sole product in 60% yield with 20% recovery of starting material and without detection of the expected amidine **8** (Scheme 1). The ^{1}H NMR data of **8** and **9** are clearly distinguishable since the 2-H signal of **8** appears at 8.60 ppm while the same proton in **9** resonates at higher field (8.03 ppm) due to the aromaticity of the quinazoline ring. Moreover, the HMBC spectrum of **9** confirmed the regioselectivity of this coupling reaction which occurred at N-3 instead of N-1.[10]

To explore the scope of this new procedure, a panel of low cost amide bond-coupling agents was screened (Table 1). DCC gave a lower yield compared to Mukaiyama's reagent while cyanuric chloride and 2,4-dichloro-6-methoxy[1,3,5]triazine (DCMT) resulted in decomposition and only trace amounts of the desired quinazolinones **9** were detected. This short survey revealed that Mukaiyama's reagent was well-suited for this transformation.[11]

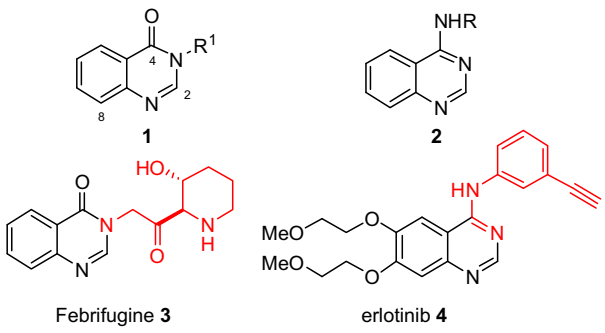

Figure 1. Representative 3-substituted-quinazolin-4-ones and a related quinazoline.

* Corresponding author. Tel.: +66 2 218 7634; fax:+66 2 218 7598.
E-mail address: sumrit.w@chula.ac.th (S. Wacharasindhu).

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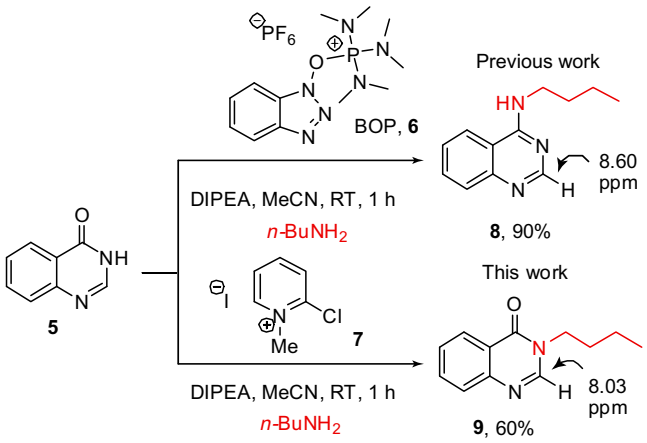


Scheme 1. Reaction of **5** with BOP and Mukaiyama's reagent.

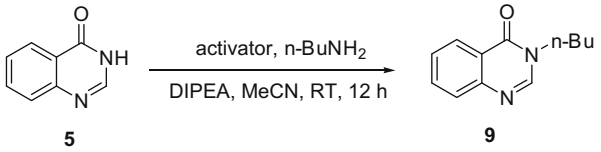
Consequently, the optimization study was performed on quinazolin-4-one **5** with *n*-butylamine and Mukaiyama's reagent by evaluating various bases, solvents and temperatures (Table 2). Screening the base indicated that diisopropylethylamine was the most effective base in comparison with others, although triethylamine gave a satisfactory result (entries 1–4). With DIPEA as the base of choice, CH_2Cl_2 and DCE proved to be the best solvents (entries 8 and 9).

Having identified optimum reaction conditions, various quinazolin-4-ones were subjected to the reaction conditions to examine the scope of the reaction.[12] The expected product of each substrate was obtained in fair to good yield, as presented in Table 3. The investigated quinazolin-4-ones ranged from bicyclic to tricyclic ring systems carrying a variety of substituents. These include nitro, dimethoxy, dichloro, and a benzo analog. Electronic effects were also observed. In the case of electron-withdrawing groups such as nitro and chloro, the product yields were excellent and the reaction was carried out at ambient temperature. However, coupling 7,8-dimethoxy-4-hydroxyquinazoline with *n*-butylamine required heating to drive the reaction to completion to give the desired product **12** in only 43% yield.

To further demonstrate the scope of this reaction, a panel of primary amine nucleophiles were tested in the reaction with quinazolin-4-one (**5**) and the products are shown in Scheme 2. Unhindered primary amines such as *n*-butylamine, benzylamine and 2-phenylethanamine, reacted smoothly at room temperature to provide the target compounds (**9**, **14** and **15**) in good isolated yields. Coupling of a sterically hindered nucleophile such as cyclohexylamine was facilitated by increasing the temperature to generate **16** in 68% yield. In the case of the weak nucleophile aniline, only a trace amount of the desired product was detected. Next, the reaction was extended to nucleophiles with various acid-labile functional groups. Reaction of **5** with glycine methyl ester using Mukaiyama's reagent gave **18** in moderate yield. Moreover, primary amines with an acetal moiety reacted with **5** to afford products **19** and **20** in 87% and 57% yield, respectively.

With the success of this coupling reaction, our attention turned to the synthesis of echinozolinone (**22**) which was first isolated from *Echinops echinatus* in 1987.[13] The reported preparation involved the reaction of 4(3*H*)-quinazoline **5** with 2-chloroethanol in the presence of a large excess of a phase-transfer catalyst (PTC), in only 49% yield.[14] With our methodology, echinozolinone was synthesized in a single step from **5** and ethanolamine in 81% yield (Scheme 3). This methodology clearly provides an alternative route to the conventional alkylation reaction.

Table 1
Results of activator screening[a]



Entry	Activator	Yield[b] (%)
1	DCC	20%
2	DCMT	Trace
3	Cyanuric chloride	Trace
4	Mukaiyama's reagent	60%[c]

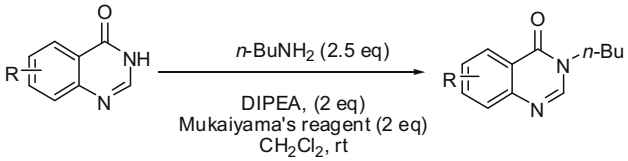
[a] The reaction was performed by treatment of **5** (1 equiv) in MeCN at room temperature with *n*-$BuNH_2$ (2 equiv), DIPEA (2 equiv), and activator (2 equiv).
[b] Yield of pure, isolated product (characterized by ^1H and ^{13}C NMR spectroscopy).
[c] Starting material was recovered in 20% yield.

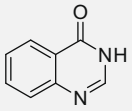
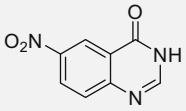
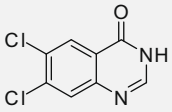
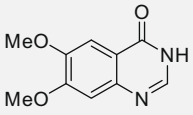
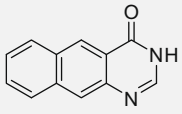
Table 2
Results of the optimization study

Entry	Solvent/base/temp	Yield[a] (%)
1	MeCN/DBU/rt	20
2	MeCN/Et_3N/rt	60
3	MeCN/NaO*t*-Bu/70 °C	15
4	MeCN/DIPEA/rt	70
5	DMSO/DIPEA/rt	23
6	DMF/DIPEA/rt	40
7	Benzene/DIPEA/rt	50
8	CH_2Cl_2/DIPEA/rt	78
9	DCE/DIPEA/80 °C	79

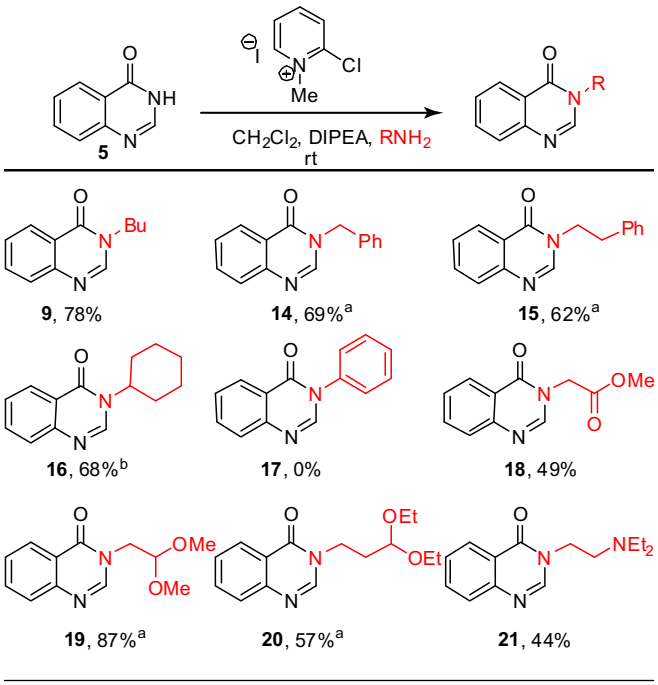
[a] Yield of pure, isolated product (characterized by ^1H and ^{13}C NMR spectroscopy).

Table 3
Functional group tolerance



Entry	Substrate	Product	Yield[a] (%)
1		**9**	78
2		**10**	86
3		**11**	76
4		**12**	43[b]
5		**13**	37[b]

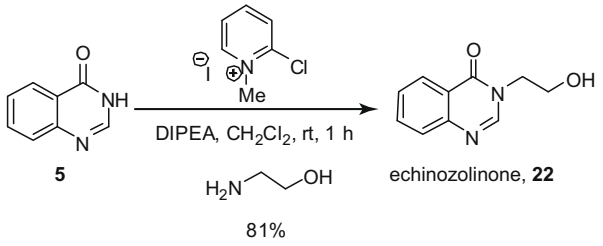
[a] Yield of pure, isolated product (characterized by ^1H and ^{13}C NMR spectroscopy).
[b] The reaction was carried out at 80 °C and DCE was used as the solvent.



[a]The reaction was carried out at 45 °C

[b]The reaction was carried out at 80 °C and DCE was used as the solvent.

Scheme 2. Nucleophile scope.



Scheme 3. Synthesis of echinozolinone.

Mechanistically, we hypothesize that the Mukaiyama reagent first activates the N atom of the quinazolinone at the 3 position leading to the formation of a pyridinium-quinazolinone intermediate **23** (Scheme 4). Attack of the primary amine on the amide moiety results in the ring opening product, enamine **24**. Cyclization followed by elimination of an aminopyridinium generates the observed product **9**.

In conclusion, a new synthetic method to 3-alkylquinazolin-4-ones has been developed employing Mukaiyama's reagent as a coupling agent. This reaction offers several advantages including mild conditions, less by-product formation, high compatibility as well as the use of an inexpensive, commercially available activator. Further studies on the scope of the Mukaiyama reagent promoted C–N bond formation as well as mechanistic investigations are under study and will be reported in due course.

Acknowledgements

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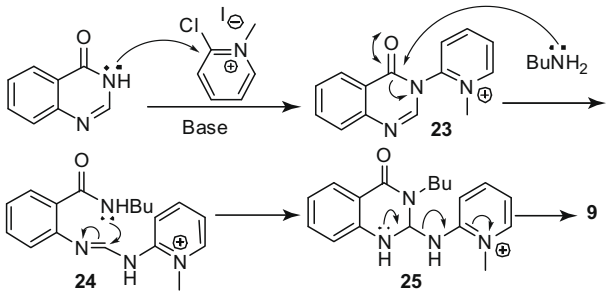

Scheme 4. A plausible mechanistic pathway.

We also thank Dr. Paitoon Rashatasakhon, of the Chemistry Department, Chulalongkorn University and Dr. Zhou-Kui Wan of Pfizer INc., Cambridge, MA, USA, for useful and interesting discussions.

Supplementary data

Supplementary data (experimental details and characterization of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.087.

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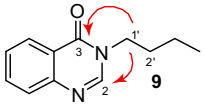
10. The HMBC spectrum of **9** showed correlations between H-1′ and C-2 and C-3. For additional details, please see the Supplementary data.



11. Upon completion of our studies, Yang and co-workers reported an analogous synthesis using HATU: Xiao, Z.; Yang, M. G.; Li, P.; Carter, P. H. *Org. Lett.* **2009**, *6*, 1421.

12. *General procedure*: To a solution of quinazolin-4-one (73.1 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at room temperature was added 2-chloro-1-methylpyridinium iodide (255.49 mg, 1.0 mmol) followed by diisopropylethylamine (435.48 μl, 2.5 mmol). The solution was stirred at room temperature for 1 h after which was added *n*-butylamine (248 μl, 2.5 mmol). The mixture was stirred at room temperature overnight and then concentrated and purified by column chromatography on silica gel (eluent: EtOAc/hexanes, 50%) to give 3-butylquinazolin-4(3*H*)-one (**9**). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32 (1H, d, J = 7.96 Hz), 8.03 (1H, s), 7.81–7.65 (2H, m), 7.51 (1H, t, J = 7.42 Hz), 4.01 (2H, t, J = 7.31 Hz), 1.87–1.70 (2H, m), 1.51–1.32 (2H, m), 0.97 (3H, t, J = 7.34 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.4, 147.6, 146.2, 133.5, 126.8, 126.6, 126.1, 121.6, 46.2, 30.9, 19.4, 13.2. HRMS [M+H$^+$]: calcd for $C_{12}H_{13}N_2O$ 203.1184, found 203.1007.
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