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COMMUNICATION

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A Tf_2O-Promoted Synthesis of Functionalized Quinolines from Ketoximes and Alkynes

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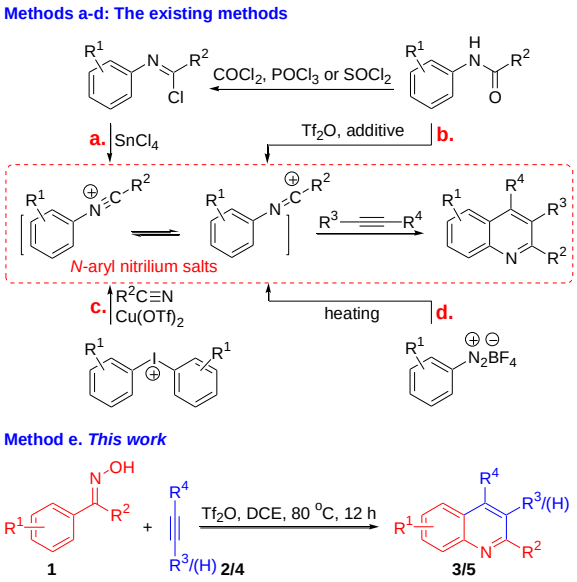
Abstract. A new general synthesis of quinolines was developed from ketoximes and alkynes in the presence of Tf_2O. It offered the first direct synthesis of quinolines by using the nitrilium salts generated *in situ* from a Tf_2O-promoted Beckmann rearrangement of ketoximes under very easy conditions.

Keywords: Beckmann rearrangement; ketoximes; alkynes; quinolines; nitrogen heterocycles; triflic anhydride.

Due to the unique structure of quinoline, functionalized quinolines have been widely used as starting materials, intermediates and target products in organic synthesis.[1,2] They have also found significant applications in biology[3] and material sciences.[4] Therefore, many strategies for the synthesis of quinolines have been developed.

Among the strategies for the synthesis of quinolines, the cyclization of *N*-aryl nitrilium salts with alkynes was reported as early as 1964[5] (Scheme 1a). Unfortunately, this strategy was rarely used for its first forty years[6] because the difficult generation of *N*-aryl nitrilium salts was incompatible with alkynes. In recent years, rapid progress has been made to achieve the generation of *N*-aryl nitrilium salt and its cyclization with alkyne in one-pot. As we know,[7] the nitrilium salts can be generated mainly from four types of substrates: amides, nitriles, ketoximes and isocyanides. The first two of them thus far have been successfully used for the direct synthesis of quinolines. The desired *N*-aryl nitrilium salts could be generated *in situ* by Tf_2O-promoted dehydration of *N*-aryl amides[8] (Scheme 1b) or by nucleophilic *N*-arylations of nitriles using aryliodonium salts[9] or aryl diazo salts[10] (Scheme 1c and 1d).

Although these pioneering works have their own advantages, they also suffered from some unavoidable drawbacks. For example, low efficiency usually was observed when using terminal alkynes as substrates in method-b, which caused by pyridine

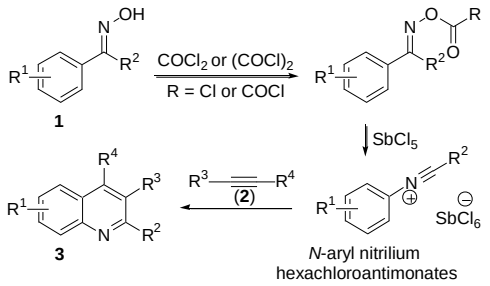


Scheme 1. The existing methods and this method.

additives.[8a] For method-c and method-d, the preparations of aryliodonium salts or aryl diazo salts usually are inconvenient or expensive. Therefore, development of methods for more efficient synthesis of quinolines from different substrates is still highly desirable. Herein, we report a direct method for the synthesis of quinolines **3**/**5** from aryl ketoximes **1** and alkynes **2**/**4** in the presence of Tf_2O (method-e). In this method, the *N*-aryl nitrilium salts were generated *in situ* by a Tf_2O-promoted Beckmann rearrangement of ketoximes under simple conditions. The method is characterized by using readily available substrates under additive-free conditions.

It is well known that nitrilium salts are the key intermediates in Beckmann rearrangement and their reactivity varies with different reagents.[11] But thus far, only one method has been reported to convert ketoximes to quinoline,[6, 12] where *N*-aryl nitrilium hexachloroantimonates needed to be premade from a

Beckmann rearrangement using toxic reagents and multi-step syntheses were used (Scheme 2).

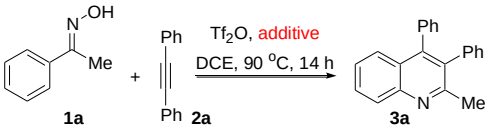


Scheme 2. Early synthesis of quinolines from ketoximes.

We assumed that these phenomena may be resulted from unsuitable reactivity and compatibility between the reagents in Beckmann rearrangement and alkynes. Therefore, solving these problems may achieve a novel and general method for the synthesis of functionalized quinolines from ketoximes. Thus, acetophenone oxime (**1a**) and 1,2-diphenyl ethyne (**2a**) were used as model substrates to be tested with different reagents of Beckmann rearrangement, such as $Ga(OTf)_3$,[13a] [Rh]/TfOH/PPh_3,[13b] ^{t}BuCOCl/DMF,[14a] TsCl,[14b] TfCl/py,[14c] BAC/HFIP,[15a] TFA,[15b] $ClSO_3H$,[15c] H_2NSO_3H,[15d] $PhI(OAc)_2/BF_3{\cdot}OEt_2$,[16a] NCS/$PPh_3$,[16b] TCT/$ZnCl_2$,[17a] TCT/DMF,[17b] and Tf_2O.[18] To our delight, the desired 2-methyl-3,4-diphenylquinoline (**3a**) was obtained as a single product in 50% yield by using Tf_2O[18] (entry 1, Table 1), even though the complicated mixtures were obtained by using all other reagents. To the best of our knowledge, no such transformation has been reported in literature to date.

Encouraged by our initial findings, we decided to optimize further this transformation. As shown in Table 1, the different additives were tested initially. Surprisingly, the product **3a** was obtained in only 18% yield when one equivalent of 2,6-Cl_2-pyridine was used as an additive[8] (entry 2). Similar low yields were obtained when other pyridine derivatives were used as additives (entries 3-5). These results suggested that both Tf_2O and the *in situ* formed TfOH may play important roles in the Beckmann rearrangement of **1a**.[19] These results also reminded us that the product **3a** may form a salt with TfOH at the end of the reaction, which may cause the low yield of **3a**. Therefore, the work-up step was tested by using different bases for different times. As was expected, **3a** was obtained in 71% yield when the reaction mixture was treated by Et_3N for 15 minutes (entry 6). The highest yield of **3a** was obtained when the treatment time was prolonged to 30 minutes (entry 7). Although similar results were obtained by using inorganic bases (entries 8-10), the conditions in entry 7 were chosen for further tests.

Table 1. The effects of additives and the bases.[a)]

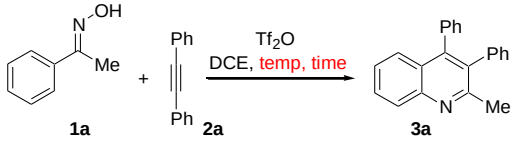


entry	additive	base in work-up (time)[b)]	**3a** (%)[c)]
1	---	Et_3N (< 3 min)	50
2	2,6-Cl_2-Py	Et_3N (< 3 min)	18
3	2,6-F_2-Py	Et_3N (< 3 min)	24
4	2-Cl-Py	Et_3N (< 3 min)	trace
5	2-F-Py	Et_3N (< 3 min)	9
6	---	Et_3N (15 min)	71
7	---	Et_3N (0.5 h)	80
8	---	10% aq. $NaHCO_3$ (0.5 h)	79
9	---	10% aq. Na_2CO_3 (0.5 h)	76
10	---	10% aq. NaOH (0.5 h)	71

[a)] After the mixture of **1a** (0.5 mmol), **2a** (0.5 mmol), Tf_2O (0.75 mmol) and an additive (0.75 mmol) in DCE (2 mL) was stirred at 90 °C for 14 h, the reaction was quenched by Et_3N (0.5 mL). [b)] The time for the treatment of reaction with a base. [c)] Isolated yields.

Further conditional tests (Table 2) indicated that the reaction in fact could be finished within 12 h at 80 °C (entries 1-3). The yield of **3a** was not improved by increasing the amounts of **2a** (entries 4), but it was increased by increasing the amounts of **1a** (entries 5-6). The best results were obtained when two equivalents of Tf_2O were used (entries 7-8). Finally, the entry 7 was assigned as our standard conditions.

Table 2. The effects of reaction conditions.[a)]



entry	temp (°C)	time (h)	**1a**/**2a** (mmol)	yield of **3a** (%)[b)]
1	80	14	0.5/0.5	84
2	80	12	0.5/0.5	84
3	70	12	0.5/0.5	74
4	80	12	0.5/0.6	83
5	80	12	0.55/0.5	87
6	80	12	0.6/0.5	90
7[c)]	80	12	0.6/0.5	93
8[d)]	80	12	0.6/0.5	93

[a)] After the mixture of **1a**, **2a** and Tf_2O (0.75 mmol) in DCE (2 mL) was stirred at the given temperature and time, the reaction was quenched by Et_3N. [b)] Isolated yields. [c)] 1 mmol of Tf_2O were used. [d)] 1.25 mmol of Tf_2O were used.

To generalize this method, the scopes of the substrates and products were tested under standard conditions. As shown in Scheme 3, by fixing 1,2-diphenyl ethyne (**2a**), different 3,4-diphenyl substituted quinolines **3a-3r** were synthesized from aryl alkyl ketoximes (**1a-1m**) or diaryl ketoximes (**1n-1r**) in moderate to excellent yields. The products **3m** and **3p** were obtained in relatively low yields because they were synthesized from two structurally

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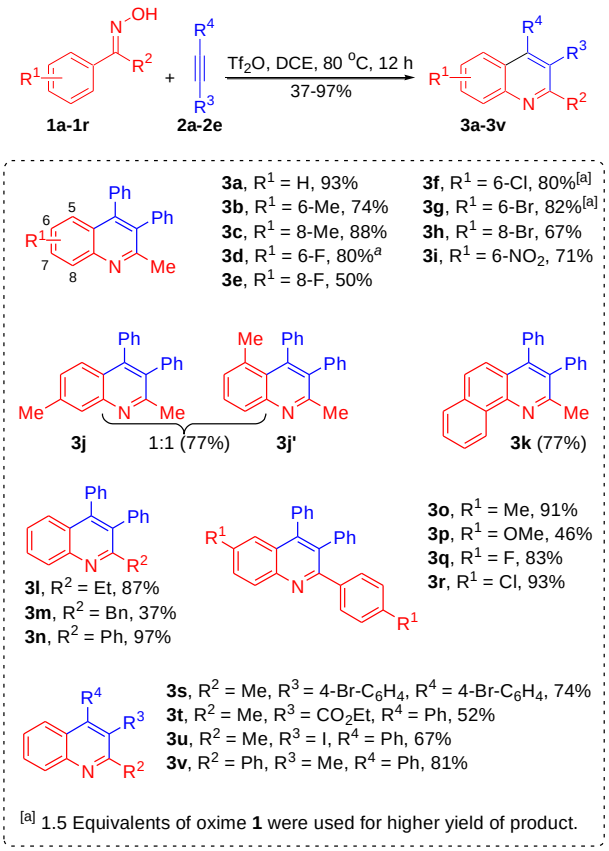
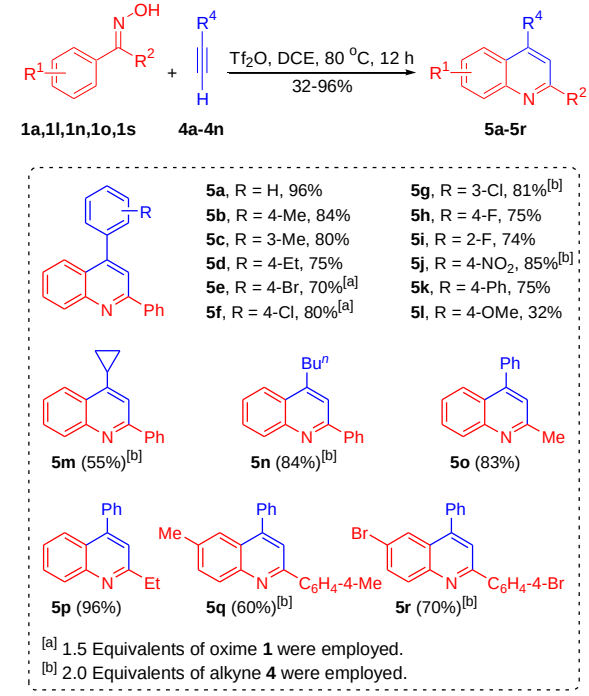
special oximes.[20] The synthesis of **3s-3v** indicated that this method has a wide product diversity and 3-iodoquinolin **3u** provided an important example.



Scheme 3. The synthesis of products **3a-3v**.

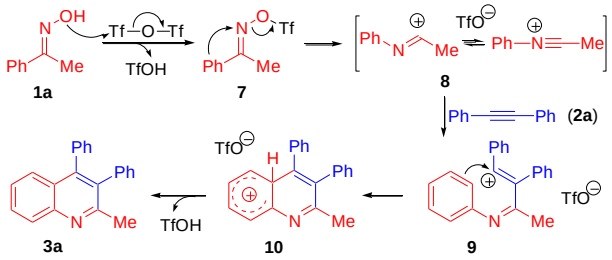
As shown in Scheme 4, the desired products **5a-5r** were obtained smoothly from the corresponding terminal alkynes **4a-4n** under the standard conditions. Since no pyridine additive was used, no byproduct



Scheme 4. The synthesis of products **5a-5r**.

alkynyl imines were formed completely. For similar reasons to **3p**,[20] the product **5l** was obtained in relatively low yield. Under standard conditions, the products **3a** and **5a** were prepared on 2-gram scales in 90% and 92% yields, respectively.

Based on the experimental results, a possible pathway for the synthesis of **3a** was proposed as shown in Scheme 5. Initially, the oxime **1a** carried out a Tf_2O-promoted Beckmann rearrangement to generate the reactive intermediate nitrilium salt **8**.[18] When the salt **8** was captured by alkyne **2a**, phenyl-substituted alkenyl cation intermediate **9** formed.[8-11] Finally, product **3a** was obtained by an intramolecular electrophilic substitution of **9**. Based on the proposed alkenyl cation intermediate **9**, the regioselectivity of products can be well explained. Thus, the stronger electron-donating group in the alkynes bearing two different groups regioselectively locates at 4-position on quinoline ring in the products **3t-3v** and **5a-5r**, because such group can stabilize the corresponding alkenyl cation intermediates (the analogues of **9**).



Scheme 5. Proposed pathway for the synthesis of **3a**.

In summary, a new synthesis of quinolines was developed from ketoximes and alkynes in the presence of Tf_2O. This method offers the first direct synthesis of quinolines by using the nitrilium salts generated *in situ* from a Tf_2O-promoted Beckmann rearrangement of ketoximes. Since the method was operated under simple conditions and the ketoximes are a huge family of substrates, we may expect that this method will have widespread applications in organic synthesis.

Experimental Section

A typical procedure for synthesis of 2-methyl-3,4-diphenylquinoline (3a). To a solution of *(E)*-aceto-phenone oxime (**1a**, 81 mg, 0.6 mmol) and 1,2-diphenyl ethyne (**2a**, 89 mg, 0.5 mmol) in dry DCE (2 mL) was added Tf_2O (282 mg, 168 µL, 1.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and then at 80 °C for 12 h. After the mixture was cooled to room temperature, Et_3N (0.5 mL) was added to quench the reaction and the mixture was stirred at room temperature for another 30 min. The reaction mixture was purified by a flash chromato-graphy [silica gel, 10% EtOAc in petroleum ether (60–90 °C)] to give 137 mg (93%) of product **3a** as a yellowish solid, mp 160−161 °C (lit.[8b] 171–172 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 8.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.26–7.13 (m, 6H), 7.13–6.99 (m, 4H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 147.0, 146.5, 138.6, 136.7, 134.0, 130.01 (2C), 129.96 (2C), 129.0, 128.6,

127.8 (2C), 127.6 (2C), 127.1, 126.7, 126.5, 126.2, 125.8, 25.4.

The products **3b-3v** and **5a-5r** were prepared by the similar procedure.

Acknowledgements

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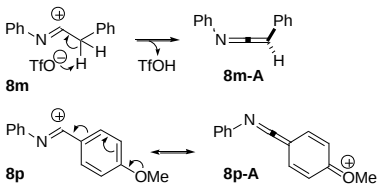
[19] No product **3a** was obtained from the same reaction by complete replacement of Tf_2O with TfOH.

[20] The lower yields of **3m** and **3p** may be caused by the facts that their nitrilium salts **8m** and **8p** are partially converted into the isomer **8m-A** and the resonance contributor **8p-A**, respectively, by which the positive charges on **8m** and **8p** are dispersed.



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