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A Facile Synthesis of Substituted 2-Alkylquinolines through [3 + 3] Annulation between 3-Ethoxycyclobutanones and Aromatic Amines at Room Temperature

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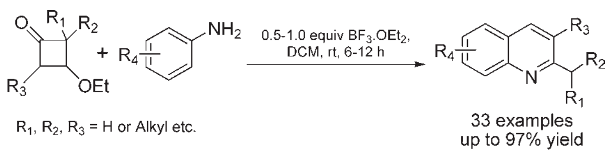
ABSTRACT



An efficient single-step approach toward the synthesis of 2-alkylquinolines is described. Through a Lewis acid mediated [3 + 3] annulation reaction between 3-ethoxycyclobutanones and aromatic amines, a variety of multisubstituted 2-alkylquinoline derivatives were prepared regioselectively at room temperature.

Quinoline derivatives represent a major class of heterocycles that find extensive utility in the pharmaceutical industry.[1] Compounds containing quinoline scaffolds are being developed in a wide range of therapeutic areas including infectious diseases, CNS, inflammation, and oncology.[2] To date, a number of quinoline-containing compounds have been successfully commercialized, such as Singulair, Tafenoquine, Aldara, and Hydroxychloroquine.[3] Substituted quinoline derivatives have also been employed as ligands for the preparation of OLED phosphorescent complexes[4] and organocatalysts for enantioselective synthesis of chiral molecules.[5]

(1) For reviews: (a) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 5, p 245. (b) Wagman, A. S.; Wentland, M. P. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, D. J., Eds.; Elsevier Ltd.: Oxford, U.K., 2006; Vol. 7, pp 567–596. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187. (d) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246. (e) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627–646.

(2) For examples: (a) Charris, J. E.; Dominguez, J. N.; Gamboa, N.; Rodrigues, J. R.; Angel, J. E. *Eur. J. Med. Chem.* **2005**, *40*, 875–881. (b) Dayam, R.; Al-Mawsawi, L. Q.; Zawahir, Z.; Witvrouw, M.; Debyser, Z.; Neamati, N. *J. Med. Chem.* **2008**, *51*, 1136–1144. (c) Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. *Bioorg. Med. Chem.* **2006**, *14*, 4600–4609. (d) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H. H.; Keith, J. C., Jr.; Nickerson-Nutter, C.; Shilling, A.; Young-Sciame, R.; Wang., Q. *J. Med. Chem.* **2007**, *50*, 21–39. (e) Klingenstein, R.; Melnyk, P.; Leliveld, S. R.; Ryckebusch, A.; Korth., C. *J. Med. Chem.* **2006**, *49*, 5300–5308.

(3) (a) Elslager, E.; Tendick, F.; Werbel, L. *J. Med. Chem.* **1969**, *12*, 600–607. (b) Czarniecki, M. *J. Med. Chem.* **2008**, *51*, 6621–6626. (c) Halama, A.; Jirman, J.; Boušková, O.; Gibala, P.; Jarrah, K. *Org. Process Res. Dev.* **2010**, *14*, 425–431. (d) Shanks, G.; Oloo, A.; Aleman, G.; Ohrt, C.; Klotz, F.; Braitman, D.; Horton, J.; Brueckner, R. *Clin. Infect. Dis.* **2001**, *33*, 1968–1974.

(4) (a) Cheng, C. H.; Chen, R. M.; Huang, C. W.; Yang, C. C. U.S. Patent 20050025995A1, 2005. (b) Thompson, M. E.; Ma, B.; Djurovich, P. U.S. Patent 20050164031A1, 2005. (c) Knowles, D. B.; Kwong, R. U.S. Patent 20050164030A1, 2005. (e) Kim, J. L.; Shin, I. S.; Kim, H. *J. Am. Chem. Soc.* **2005**, *127*, 1614.

(5) (a) Abrunhosa, I.; Delain-Bioton, L.; Gaumont, A. C.; Gulea, M.; Masson, S. *Tetrahedron* **2004**, *60*, 9263. (b) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076. (c) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831. (d) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425–3428.

(6) For reviews: (a) Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 77–277. (b) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116–1183. (c) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141–161. (d) Arisawa, M.; Terada, Y.; Theeraladanon, C.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Organomet. Chem.* **2005**, *690*, 5398–5406. (e) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593. (f) Yamashkin, S. A.; Oreshkina, E. A. *J. Heterocycl. Chem.* **2006**, *42*, 701–718.

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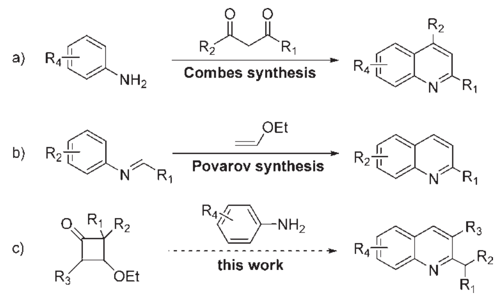
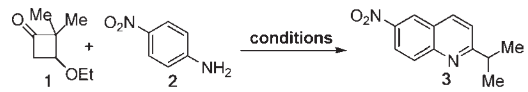
Scheme 1. General Strategies for Construction of Quinoline Rings



Owing to the important applications of quinolines, their synthesis had been extensively studied for more than 100 years since the discovery of quinoline.[6,7] By far the most prevalent strategies for constructing quinoline rings are the classic annulation reactions such as Friedländer,[8] Combes,[9] Povarov,[10] Doebner–Miller,[11] and Skraup[12] syntheses, etc. (Scheme 1a,b). However, these methods usually suffer from one or more limitations which include poor regioselectivity, low yield, high temperature, long reaction time, harsh reaction conditions, and tedious reaction procedures. Therefore, the development of mild, simple, and complementary approaches to quinoline derivatives is still highly desired because of their extreme significance.

Serving as a versatile intermediate, 3-ethoxycyclobutanones have been used to prepare various types of compounds such as bicyclobutanes, silyloxy dienes, and six-membered cyclic compounds.[13] In those studies, 3-ethoxycyclobutanones were involved as a formal 1, 4-dipole.[14] Recently our group reported the synthesis of pyrazoles through a '3 + 2' annulation reaction between 3-ethoxycyclobutanones and substituted hydrazines.[15] Our studies demonstrated, for the first time, 3-ethoxycyclobutanones can be employed as a 1,3-dicarbonyl synthon for useful chemical transformations. Based on these findings, we therefore envisioned that if aromatic amines were adopted as substrates instead of substituted hydrazines in the reaction, theoretically a '3 + 3' annulation between 3-ethoxycyclobutanones and aromatic amines would be possible. In contrast to forming pyrazoles with substituted hydrazines, a formal cycloaddition between 3-ethoxycyclobutanones and substituted aromatic amines could furnish corresponding 2-alkylquinoline derivatives as products (Scheme 1c). Herein we report the development of a new efficient one-step approach toward regioselective synthesis of quinolines through Lewis acid promoted annulation reactions between 3-ethoxycyclobutanones and substituted aromatic amines.

Table 1. Optimization of the Reaction Conditions



entry	catalyst	condition	yield[a]
1	$SeCl_4$	0.3 equiv, DCM, rt, 12 h	25%
2	BF_3OEt_2	0.3 equiv, DCM, rt, 12 h	28%
3	$TiCl_4$	0.3 equiv, DCM, rt, 12 h	9%
4	$Sc(OTf)_3$	0.3 equiv, DCM, rt, 12 h	15%
5	$SnCl_4$	0.5 equiv, DCM, rt, 12 h	65%
6	BF_3OEt_2	0.5 equiv, DCM, rt, 12 h	74% (50%[b])
7	BF_3OEt_2	0.5 equiv, DCE, rt, 12 h	33%
8	BF_3OEt_2	0.5 equiv, THF, rt, 12 h	26%
9	BF_3OEt_2	0.5 equiv, MeCN, rt, 12 h	20%
10	BF_3OEt_2	0.1 equiv, DCM, rt, 12 h	15%
11	BF_3OEt_2	1.0 equiv, MeOH, rt, 12 h	39%[b]
18	BF_3OEt_2	1.0 equiv, EtOH, rt, 12 h	29%[b]
19	BF_3OEt_2	1.0 equiv, EtOAc, rt, 12 h	49%
14	BF_3OEt_2	1.0 equiv, 1,4-dioxane, rt, 12 h	59%

[a] Conversion ratio. [b] Isolated yield.

To test our hypothesis, a model study was initiated with 2,2-dimethyl 3-ethoxycyclobutanone and 4-nitroaniline (Table 1). As a Lewis acid promoter, 0.3 equiv of $SnCl_4$ was added to the reaction mixture. Delightfully the reaction afforded the desired product **3** (entry 1) with complete regioselectivity after overnight stirring at room temperature. Encouraged by this preliminary result, we started to

(7) For recent examples: (a) Venkatesan, H.; Hocutt, F.; Jones, T.; Rabinowitz, M. *J. Org. Chem.* **2010**, *75*, 3488–3491. (b) Huo, Z.; Ilya D. Gridnev, I.; Yoshinori Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266–1270. (c) Gao, G.; Niu, Y.; Yan, Z.; Wang, H.; Wang, G.; Shaukat, A.; Liang, Y. *J. Org. Chem.* **2010**, *75*, 1305–1308. (d) Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4886–4888. (e) Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* **2008**, *10*, 173–175. (f) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707–10713. (g) Austin, M.; Egan, O. J.; Tully, R.; Pratt, A. C. *Org. Biomol. Chem.* **2007**, *5*, 3778–3786. (h) Atechian, S.; Nock, R.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811–2823.

(8) (a) Friedlander, P. *Chem. Ber.* **1882**, *15*, 2572. (b) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652. (c) Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menéndez, J. C. *J. Org. Chem.* **2009**, *74*, 5715. (d) Miller, B. L.; Mcnaughton, B. R. *Org. Lett.* **2003**, *5*, 4257. (e) Hu, Y.-Z.; Zhang, G.; Thummel, R. P. *Org. Lett.* **2003**, *5*, 2251.

(9) (a) Combes, A. *Bull. Soc. Chim. Fr.* **1888**, *49*, 89. (b) Jerry L. Born, J. *J. Org. Chem.* **1972**, *37*, 3952–3953.

(10) (a) Vicente-García, E.; Catti, F.; Ramón, R.; Lavilla, R. *Org. Lett.* **2010**, *12*, 860–863. (b) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451–7456. (c) Zhao, Y.; Zhang, W.; Wang, S.; Qun Liu, Q. *J. Org. Chem.* **2007**, *72*, 4985–4988.

(11) (a) Mackenzie, A. R.; Moody, C. J.; Rees, C. W. *Tetrahedron* **1986**, *42*, 3259. (b) Boger, D. L.; Chen, J. H. *J. Org. Chem.* **1995**, *60*, 7369. (c) Tanaka, S.-Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800. (d) Denmark, S. E.; Venkatraman, S. *J. Org. Chem.* **2006**, *71*, 1668.

(12) (a) Manske, R. H. F.; Kulka, M. *Org. React.* **1953**, *7*, 59–98. (b) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813.

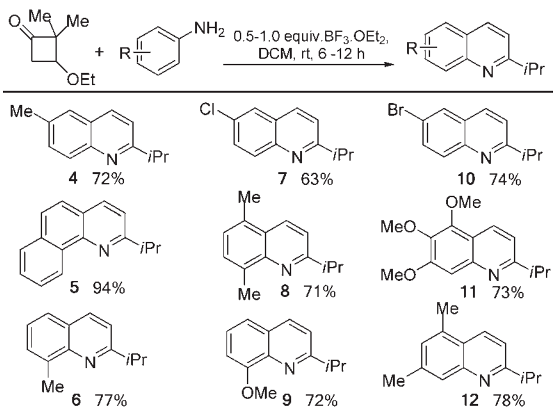
(13) (a) Aben, R. W.; Scheeren, H. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3132. (b) Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 130. (c) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600. (d) Matsuo, J.; Okado, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3266. (e) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822. (f) Matsuo, J.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831. (g) Intramolecular reaction: Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Chem. Commun* **2010**, *46*, 934.

(14) For examples about formation of zwitterionic intermediates from cyclobutane derivatives: (a) Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. J. *Chem. Commun.* **2009**, 7339. (b) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202.

(15) Shan, G.; Liu, P.; Rao, Y. *Org. Lett.* **2011**, *13*, 1746.

optimize the reaction conditions. After a comprehensive screening, we found that $BF_3 \cdot OEt_2$ was superior over other Lewis acids, such as $SnCl_4$, $TiCl_4$, and $Sc(OTf)_3$, etc., with a high level of efficiency.[16] Generally, a 0.50 to 1.0 equiv amount of $BF_3 \cdot OEt_2$ was necessary to effectively promote the reaction. Smaller Lewis acid loadings slow reaction rates and give rise to low conversion ratios. It was observed that, besides DCM, the reaction also proceeded smoothly in other solvents, such as DCE, EtOAc, MeOH, and 1,4-dioxane, and gave product **3** in fair yields. Typically the reaction will proceed to completion within 12 h, in a clean manner, at ambient temperature.

Scheme 2. Reaction Scope with Respect to Different Aromatic Amines



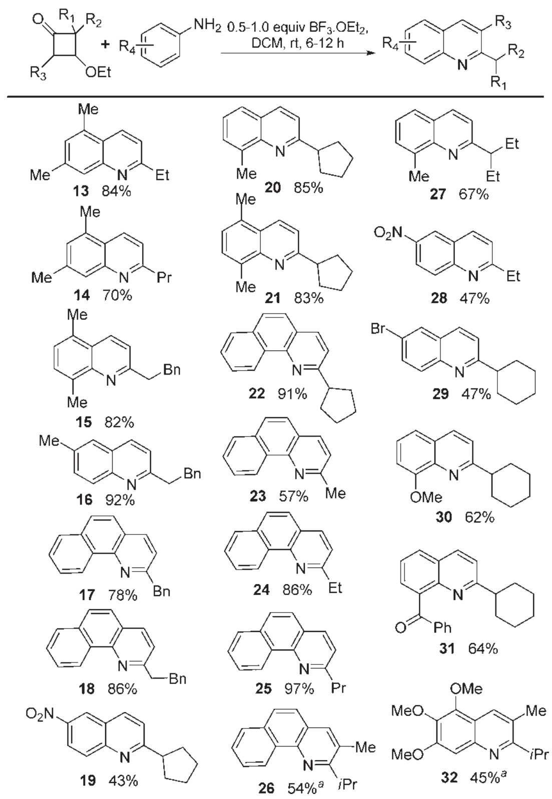
Having identified these optimal conditions, we set out to explore the scope for this new reaction. As shown in Scheme 2, a variety of aromatic amines were reacted with 2,2-dimethyl 3-ethoxycyclobutanone in the presence of $BF_3 \cdot OEt_2$. The scope of the aniline substituents was found to be very broad. The *ortho*-, *meta*-, and *para*-substituted aryl groups, as well as the electron-rich and -deficient aryl groups, were well tolerated. Different aryl amines produced the corresponding quinoline products smoothly in good to excellent yields (compounds **4**–**12**, Scheme 2).[17] Notably, only one single product was isolated in all cases; no other regioisomer was obtained.

As illustrated in Scheme 3, the optimum reaction conditions also proved to be compatible with a variety of 3-ethoxycyclobutanones which reacted with aromatic amines to readily provide different novel multisubstituted quinoline derivatives (compounds **13**–**32**). In comparison with other substrates, *para*-nitro aniline gave relatively lower yields (compounds **19** and **28**), which may reflect its strong electon-withdrawing nature. Especially noteworthy is the synthesis of quinolines containing 2, 3-substituents (Scheme 3, compounds **26** and **32**), since it is difficult to access those compounds by conventional methods. In general, these reactions showed great reactivity, broad functional group tolerance, and satisfactory yields as well. In particular, consistent complete regioselectivity of the reaction was observed. Only single isomers were obtained in all examples.

(16) Some other Lewis acids such as TMSOTf, TfOH, $Cu(OTf)_2$, $CuBr_2$, $CuCl_2$,$FeCl_2$, $FeBr_3$ etc. were also tested but were not able to effectively promote these reactions.

(17) In the case of meta monosubstituted anilines, usually two unisolatable regioisomers were observed, which would arise from two potential reactive sites of meta-substituted anilines. More details can be found in the Supporting Information.

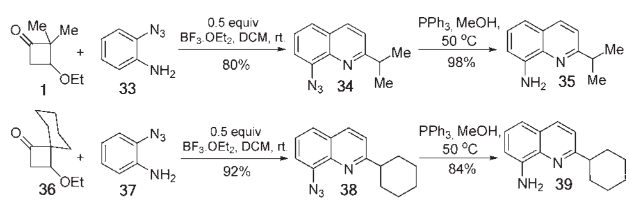
Scheme 3. Reaction Scope with Respect to 3-Ethoxycyclobutanones and Aromatic Amines[a]



[a] The yield was based on recovered materials.

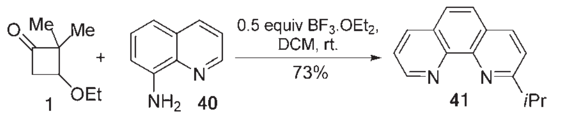
This new method provides new opportunities for the construction of some biologically important molecules, which was exemplified in Scheme 4. Two 2-substituted 8-amino quinolines (**35** and **39**) were smoothly prepared via a sequential chemical transformation including annulation and Staudinger reduction in excellent yields.

Scheme 4. Synthesis of 2-Substituted 8-Aminoquinolines



As shown in Scheme 5 a further application of our method is in the synthesis of a phenanthroline which is a widely used ligand in coordination chemistry. 2-Isopropyl 1,10-phenanthroline **41** was prepared readily from **1** and **40** in one step.

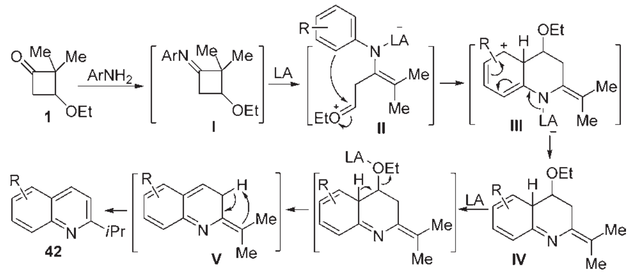
Scheme 5. Synthesis of 2-Substituted 1,10-Phenanthroline



A plausible mechanism for this new reaction is demonstrated in Scheme 6. Upon activation of the possible *in situ* generated imine intermediate **I** from 2,2-dimethyl 3-ethoxycyclobutanone (**1**), with Lewis acids, the more substituted C2−C3 bond of the hydrazone intermediate is broken down preferentially to form a zwitterionic intermediate **II**. Subsequently the intermediate **II** ring-closes to form the less strained six-membered ring intermediate **III**. Following this intramolecular cyclization, an electron transfer provides intermediate **IV**. Finally, elimination of one molecue of EtOH from **IV** and a proton transfer furnishes the quinoline product **42**.

In summary, a concise, one-pot method has been developed for the facile synthesis of functionalized quinolines from easily accessible starting materials at ambient temperature. This method has been found to be generally useful for the preparation of a variety of substituted quinolines some of which are difficult to make via conventional approaches. The reaction demonstrates excellent reactivity, good functional group tolerance, complete regioselectivity, and high yields. The synthetic utilities were further displayed in convenient syntheses of 8-amino quinoline derivatives and 2-isopropyl 1,10-phenanthroline. By employing 3-ethoxycyclobutanones as synthons for a Lewis acid promoted union with aromatic amines, we have shown that this masked 1,3-dicarbonyl synthon efficiently acts as a three-carbon synthon of 3-ethoxycyclobutanones in the preparation of multisubstituted 2-alkylquinolines which could be useful intermediates for making biologically active molecules as well as optoelectronic materials. Further studies using 3-ethoxycyclobutanones as a three-carbon component in other useful chemical transformations are currently in progress

Scheme 6. Plausible Mechanism



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