A Rapid, High-yielding, and Efficient Friedlander Synthesis of Quinolines Catalyzed by 2,4,6-Trichloro-1,3,5-triazine#

Biswanath Das,* Kongara Damodar, Nikhil Chowdhury, and Kanaparthy Suneel
Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad–500 007, India

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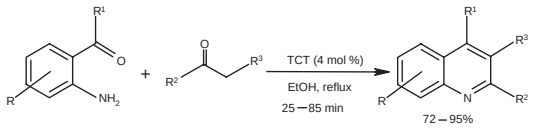
A general procedure for the synthesis of quinolines via the Friedlander annulation using 2,4,6-trichloro-1,3,5-triazine (TCT) (4 mol %) as a novel catalyst is described. The method is simple, efficient, and rapid to afford quinolines in high yields.

Quinolines occur widely in natural products[1] and biologically active compounds.[2] They are important in medicinal chemistry as antiasthmatic, antibacterial, antihypertensive, anti-inflammatory, antimalarial, and tyrosine kinase inhibiting agents.[2,3] They are also useful synthons for preparation of nano- and meso-structures with enhanced electronic and photonic properties.[4] Thus, considering the useful applications in the fields of medicine, industry, and synthetic organic chemistry, the development of efficient methods for the synthesis of quinolines is highly desirable. The Friedlander annulation is the most simple and straightforward method for the synthesis of these compounds.[5] This method involves the acid- or base-catalyzed or thermal condensation between a 2-aminoaryl ketone and a second carbonyl compound having a reactive α-methylene group followed by cyclodehydration. Various Brønsted acids have been used[6] as catalysts but the methods using these catalysts are associated with harsh reaction conditions and side reactions. Under thermal or base catalysis conditions 2-aminobenzophenone could not react with cyclohexanone and β-keto esters. Some Lewis acids such as $ZnCl_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, and $AuCl_3$ and ionic liquids have recently been utilized for the synthesis of quinolines.[7] However, most of the methods suffered from certain drawbacks such as drastic conditions, long reaction times, unsatisfactory yields, difficulties in work up, and the use of stoichiometric quantities of the reagents. So although different methods are available for the synthesis of quinolines, development of an efficient and high-yielding preparation is still of great importance. In continuation of our work[8] on the development of useful synthetic methodologies, we have observed that 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) acts as an efficient catalyst for the synthesis of quinolines via the Friedlander annulation (Scheme 1). Among the solvents used (EtOH, THF, MeCN, $CHCl_3$, and CH_2Cl_2) EtOH was found to be the best.

Various 2-aminoaryl ketones were condensed with different carbonyl compounds having an active methylene group to form a series of substituted quinolines (Table 1). TCT with a loading



1 2 3

Scheme 1.

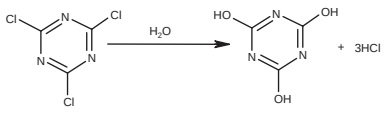
Table 1. TCT-catalysed Friedlander synthesis of quinolines[a]

Entry	2-Aminoaryl ketone **1**	α-Methylene carbonyl compound **2**	Quinoline **3**	Time /min	Isolated yield/%
1				35	89
2				40	84
3				40	89
4				85	72
5				30	92
6				30	90
7				25	92
8				35	90
9				45	85
10				40	93
11				85	74
12				35	91
13				35	90
14				30	95
15				55	86
16				40	88
17				50	82
18				40	86

[a]All the products were characterized from their spectral (^{1}H NMR and MS) and analytical data.

of only 4 mol % was effective to catalyze this condensation. The quinolines were formed in high yields within 25–85 min. The α-methylene carbonyl compounds used for the preparation of these quinolines include cycloalkanones, 1,3-diketones (cyclic and acyclic), and 1,4-diketones. 2-Aminobenzophenone underwent the conversion smoothly with cyclohexanone and a β-ketoester to afford the corresponding quinolines in high yields (Table 1, Entries 9, 12, and 13). The reaction is clean and free from side reactions such as self-condensation of ketones which normally occurs under basic conditions. In the present synthesis, alkyl, ketone, halogen, and ester remained uneffected.

TCT has recently been utilized in different organic transformations due to its excellent catalytic activity.[9] It is a safe and inexpensive reagent. It has been applied here for the first time to the synthesis of quinolines.[10] TCT is known to react with "incipient" moisture to form HCl (Scheme 2) which possibly catalyzes the condensation.[8a] However, with HCl a reaction temperature as high as 200 °C is required for the condensation.[6] Thus, TCT is more effective catalyst to carry out the synthesis of quinolines.



Scheme 2.

In conclusion, we have developed a simple, rapid, and efficient general synthesis of quinolines catalyzed by TCT with low load (4 mol %) to form the products in high yields via the Friedlander annulation. The method is an easy access to different substituted quinolines.

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10 General experimental procedure: To a mixture of 2-aminoaryl ketone (1 mmol) and α-methylene carbonyl compound (1.1 mmol) in EtOH (6 mL) TCT (4 mol %) was added. The mixture was heated under reflex and the reaction was monitered by TLC. After completion, the solvent was evaporated and H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL) and the extract was concentrated. The residue was purified by column chromatography (silica gel, 8% EtOAc in hexane) to obtain pure quinoline.

The spectral (^{1}H NMR and MS) and analytical data of some representive products are given below.

Methyl 2,4-dimethylquinoline-3-carboxylate (**3e**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (1H, d, $J = 8.0$ Hz), 7.96 (1H, d, $J = 8.0$ Hz), 7.69 (1H, t, $J = 8.0$ Hz), 7.01 (1H, t, $J = 8.0$ Hz), 3.98 (3H, s), 2.67 (3H, s), 2.62 (3H, s); FAB-MS: m/z 216 $[M + H]^{+\cdot}$ Anal. Calcd for $C_{13}H_{13}NO_2$ C, 72.56; H, 6.05; N, 6.98%. Found: C, 72.48; H, 6.12; N, 6.87%.

1-(2,4-Dimethylquinoline-3-yl)propan-2-one (**3g**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.75 (1H, d, $J = 8.0$ Hz), 7.59 (1H, t, $J = 8.0$ Hz), 7.48 (1H, t, $J = 8.0$ Hz), 7.22 (1H, d, $J = 8.0$ Hz), 5.88 (2H, s), 1.95 (6H, s), 1.72 (3H, s); FAB-MS: m/z 214 $[M + H]^{+\cdot}$; Anal. Calcd for $C_{14}H_{15}NO$: C, 78.87; H, 7.04; N, 7.04%. Found: C, 78.81; H, 7.11; N, 7.12%.

Methyl 2-methyl-4-phenylquinoline-3-carboxylate (**3l**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.08 (1H, d, $J = 8.0$ Hz), 7.80–7.23 (8H, m), 3.55 (3H, s), 2.72 (3H, s); FAB-MS: m/z 278 $[M + H]^{+\cdot}$ Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.42%. Found: C, 77.87; H, 5.48; N, 5.47%.

1-(2-Methyl-4-phenylquinoline-3-yl)propan-2-one (**3n**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.62–7.06 (9H, m), 5.57 (2H, s), 1.92 (6H, s); FAB-MS: m/z 276 $[M + H]^{+\cdot}$; Anal. Calcd for $C_{19}H_{17}NO$: C, 82.91; H, 6.18; N, 5.45%. Found: C, 82.87; H, 6.27, N, 5.38%.

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