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Short communication

Silica supported perchloric acid: A mild and highly efficient heterogeneous catalyst for the synthesis of poly-substituted quinolines *via* Friedländer hetero-annulation☆

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Abstract

Silica supported perchloric acid ($HClO_4$-SiO_2) is found to be a heterogeneous recyclable catalyst for the rapid and efficient synthesis of various poly-substituted quinolines in the Friedländer condensation of 2-aminoarylketones with carbonyl compounds and β-keto esters at ambient temperature. The catalyst can be reused at least three times.
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Keywords: Quinolines; Friedländer reaction; Silica supported perchloric acid; Heterogeneous catalyst

Quinoline is a well-known structural unit in alkaloids, therapeutics and synthetic analogues with interesting biological activities such as antimalarial, antibacterial, antiasthmatic, antihypertensive, anti-inflammatory and tyrokinase PDGF-RTK inhibiting agents [1,2]. In addition, poly-substituted quinolines have been found to undergo hierarchical self-assembly into a variety of nano- and meso-structures with enhanced electronic and photonic functions [3]. Because of their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed into the development of new quinoline based structures [4] and new methods for their construction [5]. Various methods such as Skraup, Doebner von Miller, Friedländer and Combes methods have been developed for the preparation of quinoline derivatives [6–8].

Among these methods, Friedländer annulation [8c,d], an acid- or base-catalyzed condensation followed by a cycolde-hydration between an aromatic 2-aminoaldehyde or ketone and a carbonyl compound containing a reactive α-methylene group, is one of the most simple and straightforward approaches for the synthesis of poly-substituted quinolines.

Brønsted acids catalysts, such as sulfamic acid, hydrochloric acid, sulfuric acid, *p*-toluene sulfonic acid, phosphoric acid and trifluoro acetic acid were widely used [9] for Friedländer annulation. However, many of these methods require high temperature and extended reaction times, which lead to several side reactions. Under thermal and basic conditions, *o*-amino benzophenone fails to react with cyclohexanone, deoxybenzoin and β-ketoesters [10]. Recently, Lewis acids such as $FeCl_3$, $Mg(ClO_4)_2$, $CuSO_4{\cdot}5H_2O$, $FeSO_4{\cdot}7H_2O$, $SnCl_2$, $AlCl_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, $CeCl_3{\cdot}7H_2O$, silver phosphotungstate, molecular iodine, sodium fluoride and $NaAuCl_4{\cdot}2H_2O$ are found to be effective for this conversion [9e,11]. Even some of these methods also suffer form harsh reaction conditions, low yields, high temperature, tedious work-up and the use of stoichiometric and relatively expensive reagents. Since, quinoline derivatives are useful in drugs and pharmaceuticals, the development of simple, convenient and high yielding protocols is desirable.

Silica supported perchloric acid ($HClO_4$-SiO_2) has received considerable attention as an inexpensive, non-toxic and recyclable catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity [12]. However, to the best of our knowledge there has been no report on the use of $HClO_4$-SiO_2 for Friedländer quinoline synthesis. We observed that $HClO_4$-SiO_2 is an efficient catalyst for the synthesis of poly-substituted quinolines through

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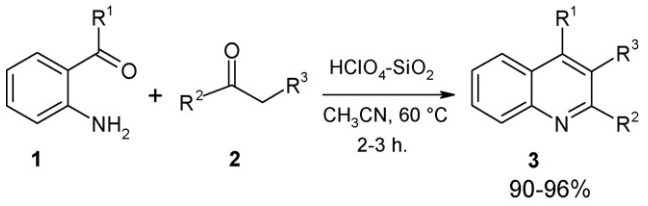


Scheme 1.

condensation/annulation reaction of 2-aminoaryl ketones and carbonyl compounds (Scheme 1).

In a typical example we have reacted 2-amino acetophenone with ethyl acetoacetate in the presence of silica supported perchloric acid in acetonitrile at reflux temperature (60 °C) to afford the corresponding ethyl 2,4-dimetyl quinoline-3-carboxylate (entry 1) in 96% yield without any side products. This two component coupling reaction proceeded efficiently at reflux temperature with high selectivity. Both ketones and β-keto esters afforded excellent yields of products in a short reaction time. Indeed, the reaction proceeds at room temperature with 50% completion. The scope and generality of this process is illustrated by reacting various 2-amino aryl ketones with ketones and β-keto esters. The results are presented in Table 1.

The catalyst $HClO_4$-SiO_2 was prepared following the reported procedure [12d] in which 1 g of silica gel contains 0.37 mmol $HClO_4$. After the completion of the reaction, the cat-

Table 1
$HClO_4$·SiO_2 catalyzed Friedländer synthesis of quinolines

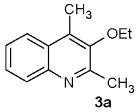
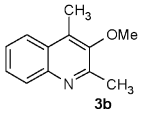
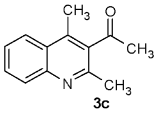
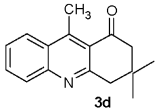
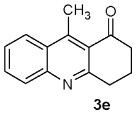
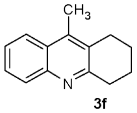
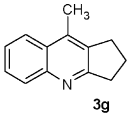
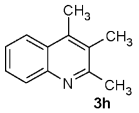
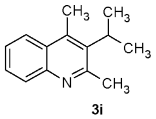
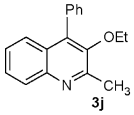
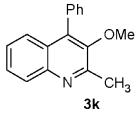
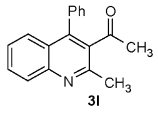
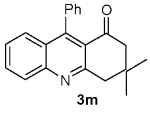
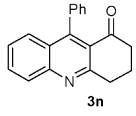
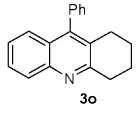
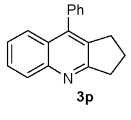
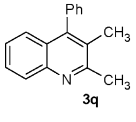
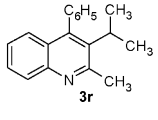
Entry	R^1	R^2	R^3	Time (h)	Product[a]	Yield (%)
1	CH_3	CH_3	OEt	2	 3a	96 [9e]
2	CH_3	CH_3	OMe	2	 3b	96
3	CH_3	CH_3	$COCH_3$	2.5	 3c	92 [11g]
4	CH_3	$CH_2C(CH_3)_2CH_2CO$		2.5	 3d	96 [9d]
5	CH_3	$CH_2CH_2CH_2CO$		2.5	 3e	92 [9d]
6	CH_3	$CH_2(CH_2)_2CH_2$		3	 3f	90 [11e]
7	CH_3	$CH_2CH_2CH_2$		3	 3g	90 [9d]
8	CH_3	CH_3	CH_3	2	 3h	92
9	CH_3	CH_3	$(CH_3)_2CH$	2.5	 3i	93

Table 1 (*Continued*)

Entry	R^1	R^2	R^3	Time (h)	Product[a]	Yield (%)
10	C_6H_5	CH_3	OEt	2	 **3j**	94 [11e]
11	C_6H_5	CH_3	OMe	2	 **3k**	94
12	C_6H_5	CH_3	$COCH_3$	2	 **3l**	94 [11g]
13	C_6H_5	$CH_2C(CH_3)_2CH_2CO$		2	 **3m**	96 [11e]
14	C_6H_5	$CH_2CH_2CH_2CO$		2	 **3n**	92 [11e]
15	C_6H_5	$CH_2(CH_2)_2CH_2$		3	 **3o**	92 [11e]
16	C_6H_5	$CH_2CH_2CH_2$		3	 **3p**	92 [11e]
17	C_6H_5	CH_3	CH_3	3	 **3q**	92 [11e]
18	C_6H_5	CH_3	$(CH_3)_2CH$	2.5	 **3r**	94

[a] All products were characterized by ^1H NMR and mass spectroscopy.

alyst was recovered by filtration, washed with acetonitrile and recycled (after activation at 120 °C for 4–5 h) for three times in subsequent reactions without substantial loss of its catalytic activity. The recyclability of the catalyst was verified on the reaction of 2-amino acetophenone and ethyl acetoacetate (entry 1, Table 1) to afford quinolines in 96, 92, and 89% yields over three cycles. In conclusion, we described a simple, efficient and practical method for the synthesis of quinolines and polycyclic quinolines through a one-pot two component coupling of 2-amino aryl ketones and β-keto esters or ketones by using heterogeneous solid, silica supported perchloric acid. This simple experimental [13] and product isolation procedure combined with easy recovery and reusability of the catalyst is expected to contribute to the development of clean and environmentally benign strategy for the synthesis of quinolines.

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[13] **General procedure**: A mixture of 2-amino acetophenone (1 mmol), ethyl acetoacetate (1.2 mmol) and silica supported perchloric acid (200 mg) in acetonitrile (5 mL) was stirred at reflux temperature (60 °C) for an appropriate time (Table 1). After completion of the reaction, as monitored by TLC, the reaction mixture was filtered and washed with acetonitrile (2× 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford pure quinolines. The spectral (^{1}H NMR and MS) data and melting points of some the representative compounds are given below: **3b: Methyl 2,4-dimethyl quinoline-3-carboxylate**: Solid; mp 97–99 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.22$ (d, $J = 8.3$ Hz, 1H); 7.92–8.32 (m, 3H); 3.58 (s, 3H); 3.08 (s, 3H); 2.92 (s, 3H). EIMS: *m/z* 215 (M^+). **3d: 3,3,9-Trimethyl-1,2,3,4-tetrahydro-1-acridinone:** Solid; mp 186–188 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.42$ (m, 2H); 8.06 (m, 2H); 3.24 (s, 2H); 3.06 (s, 3H); 2.54 (s, 2H); 1.16 (s, 6H). EIMS: *m/z* 239 (M^+). **3h: 2,3,4-Trimethyl quinoline:** Solid; mp 137–139 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.98$ (d, 8.4 Hz); 7.32–7.38 (m, 3H); 2.92 (s, 3H); 2.72 (s, 3H); 2.18 (s, 3H). EIMS: *m/z*: 271 (M^+). **3i: 3-Isopropyl 2,4-dimethyl quinoline:** Solid; mp 73–77 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.18$ (m, 1H); 7.98–8.20 (m, 3H); 2.98 (s, 3H) 2.82 (s, 3H) 2.30 (m, 1H), 1.08 (d, 6H). EIMS: *m/z* 299 (M^+). **3k: Methyl-2-methyl-4-phenyl quinoline-3-carboxylate:** Solid; mp 96–98 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.06$ (d, 8.4 Hz, 1H); 7.32–7.72 (m, 8H); 3.54 (s, 3H) 2.75 (s, 3H). EIMS: *m/z*: 277 (M^+). **3m: 3,3-Dimethyl-9-phenyl-1,2,3,4-tetrahydro-1-acridinone:** Solid, mp 189–192 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.04$ (d, $J = 8.48$ Hz, 1H); 7.52–7.58 (m, 4H); 7.18–7.7.26 (m, 4H); 3.22 (s, 2H); 2.52 (s, 2H); 1.18 (s, 6H). EIMS: *m/z* 301 (M^+). **3n: 9-Phenyl-1,2,3,4-tetrahydroacridine:** Solid; mp 139–141 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.96$ (d, $J = 8.3$ Hz, 1H); 7.48–7.58 (m, 4H) 7.22–7.28 (m, 4H); 3.21 (t, $J = 6.8$ Hz, 2H); 2.62 (t, $J = 6.6$ Hz, 2H); 1.92 (m, 2H); 1.84 (m, 2H). EIMS: *m/z* 259 (M^+). **3q: 4-Phenyl-2,3-dimethyl quinoline:** Solid; mp 112–115 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.98$ (d, $J = 8.31$ Hz); 7.48–7.54 (m, 4H); 7.22–7.28 (m, 4H); 2.74 (s, 3H); 2.16 (s, 3H). EIMS: *m/z* 233 (M^+). **3r: 3-Isopropyl-2-methyl-4-phenyl-quinoline:** Solid; mp134-136 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.22$ (d, 8.3 Hz); 7.42–7.98 (m, 8H); 2.92 (s, 3H); 2.32 (m, 1H); 1.06 (d, 6H). EIMS: *m/z*: 261 (M^+).