

Synthesis of Poly-Substituted Quinolines via Friedländer Hetero-Annulation Reaction Using Silica-Supported P_2O_5 under Solvent-Free Conditions

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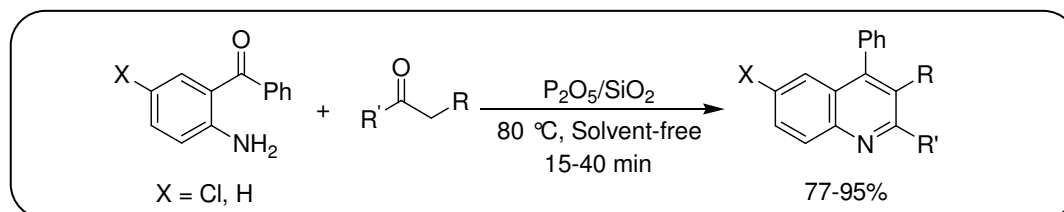
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ABSTRACT: A highly efficient, simple and green solvent-free protocol for the preparation of poly-substituted quinolines via Friedländer hetero-annulation reaction between 2-aminoaryl ketones and carbonyl compounds in the presence of silica-supported P_2O_5 (P_2O_5 / SiO_2) is described. In this method, the title compounds are obtained in high to excellent yields and in short reaction times.



KEY WORDS: Quinoline, Friedländer hetero-annulation, P_2O_5/SiO_2 , Solvent-free, Green chemistry.

INTRODUCTION

Quinoline derivatives are of importance as they have various biological and pharmaceutical activities such as antimalarial, antibacterial, anti-inflammatory, anti-asthmatic,

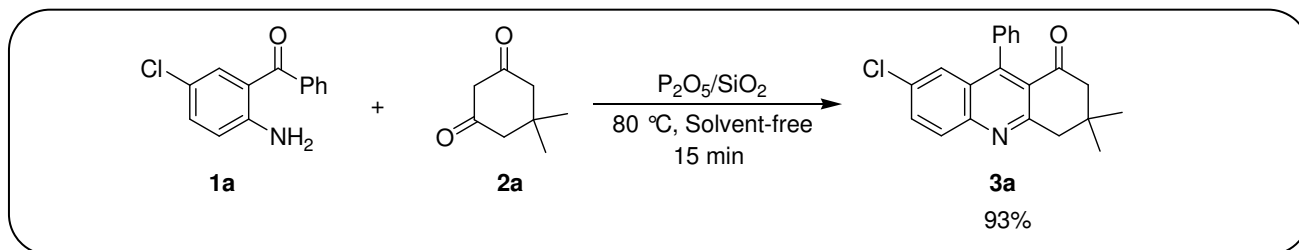
anti-hypertensive, and tyrosine kinase inhibiting properties [1-4]. In addition, poly-substituted quinolines can achieve hierarchical self-assembly into a variety of

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Scheme 1: Friedländer synthesis of poly-substituted quinolines.

meso and nano structures with enhanced photonic and electronic properties [5-7]. Therefore, development of new efficient protocols for the synthesis of quinoline derivatives is of interest in both medicinal chemistry and synthetic organic chemistry. Some methods such as Skraup, Doebner-Von Miller, Pfitzinger, Conrad-Limpach and Combes procedures have been reported for the preparation of quinolines [1,3,8-12]; nevertheless, Friedländer hetero-annulation is still one of the most simple and straightforward approaches for the preparation of poly-substituted quinolines [13]. Friedländer reaction is acid or base-catalyzed condensation of 2-aminoaryl ketones with carbonyl compounds containing a reactive α -methylene group followed by cyclodehydration [14 - 32]. This reaction is generally carried out by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base at high temperature [14,15]. Other catalysts which have been reported for the synthesis of quinolines via Friedländer reaction include protic and Lewis acids such as $HClO_4/SiO_2$ [16], $NaHSO_4/SiO_2$ [17], amberlyst-15 [18], trifluoroacetic acid [19], concentrated HCl [20], cellulose sulfuric acid [21], sulfamic acid [22], $Zr(HSO_4)_4$ [23], $Y(OTf)_3$ [24], zirconium tetrakis(dodecyl sulfate) [25], $NaAuCl_4$ [26,27], $Ag_3POW_{12}O_{40}$ [28], $Bi(OTf)_3$ [29], $CeCl_3 \cdot 7H_2O$ [30], I_2 [31], and neodymium nitrate [32]. However, most of the reported protocols for synthesis of quinolines have some disadvantages including long reaction times, low product yields and use of hazardous and expensive catalysts. Moreover, this reaction is usually carried out in harmful organic solvents such as acetonitrile, THF, DMF and DMSO; therefore, workup of the reaction mixture is not only cumbersome but also the green aspect of the reaction is annihilated by using these solvents specially DMF. Consequently, search for finding a simple, green, rapid, inexpensive and efficient procedure for the preparation of these important heterocycles is in demand.

Reactions on solid-supports under solvent-free conditions are currently the subject of considerable attention for synthetic chemists to develop eco-friendly techniques because these heterogeneous organic reactions have many advantages, such as ease of handling, low corrosion, minimum execution time, environmentally safe disposal and waste minimization by developing cleaner synthetic routes [33-51]. Consequently, it is important to note that the combination of heterogeneous catalysis with the use of solvent-free conditions represent a suitable way toward the so-called ideal synthesis.

Phosphorus pentoxide supported on silica gel (P_2O_5/SiO_2) is an inexpensive, green, and heterogeneous catalytic system which has been used in several organic transformations, such as the synthesis of bis(indolyl)methanes [50], synthesis of *N*-sulfonyl imines [51], oxime preparation [52], conversion of aldehydes to acylals [53], selective deprotection of acylals [54], oxidation of sulfides to sulfoxides [55], acetalization of carbonylic compounds [56], nitration of aromatic compounds [57], esterification [58], Fries rearrangement [59], Schmidt reaction [60], direct sulfonylation of aromatic rings [61], and conversion of aldehydes to nitriles [62]. In this paper, we report an efficient one-pot synthesis of various substituted quinolines via Friedländer hetero-annulation between 2-aminoaryl ketones and different carbonyl compounds in the presence of catalytic amounts of P_2O_5/SiO_2 under solvent free conditions at 80°C (Scheme 1).

EXPERIMENTAL SECTION

All chemicals were purchased from Merck or Fluka chemical companies. Silica gel 60, 0.063-0.200 mm (70-230 mesh ASTM) was used as the support. 1H and ^{13}C NMR spectra were recorded at 90 and 22.5 MHz, respectively (δ in ppm). Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Stuart Scientific apparatus SMP3 (UK) in open capillary tubes.

Table 1: Effect of amount of P_2O_5/SiO_2 and temperature on the reaction of 2-amino-5-chlorobenzophenone (2 mmol) with dimedone (3 mmol).

Entry	Amount of catalyst (g)	Temperature (°C)	Time (min)	Yield (%) ^a
1	0.2	80	50	71
2	0.4	80	15	93
3	0.6	80	15	93
4	0.4	40	150	47
5	0.4	60	50	85
6	0.4	70	35	90
7	0.4	90	15	93

a) Isolated yield

Table 2: Comparative the hetero-annulation reaction between 2-amino-5-chlorobenzophenone and dimedone using P_2O_5/SiO_2 in solution conditions versus the solvent-free method.

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%) ^a
1	Solvent-free	80	15	93
2	EtOH	Reflux	300	81
3	CH_2Cl_2	Reflux	480	40
4	$CHCl_3$	Reflux	300	52
5	CH_3CN	Reflux	300	76
6	THF	Reflux	300	64

a) Isolated yield.

Preparation of P_2O_5/SiO_2 Catalytic System

A mixture of SiO_2 (1.4 g) and P_2O_5 (0.6 g) was ground vigorously to give P_2O_5/SiO_2 catalytic system (30% w/w) as a white powder (2 g) [50,51].

General Procedure for the Preparation of Quinoline Derivatives

To a mixture of 2-aminoaryl ketone (2 mmol) and carbonyl compound (3 mmol) in a 10 mL round-bottomed flask connected to a reflux condenser was added P_2O_5/SiO_2 (0.4 g). The resulting mixture was stirred in an oil-bath (80 °C) for the appropriate time (Table 3). After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature and EtOAc (40 mL) was added to it, stirred for 3 min and filtered. The solvent was evaporated and the crude product was purified by column chromatography on silica gel eluted with EtOAc-*n*-hexane (1:9).

Some Selected Physical and Spectral Data of the Products

7-Chloro -3,3- dimethyl -9- phenyl -3,4- dihydroacridin-1(2H)-one (3a)

Yellow solid, m.p. 211-212 °C (Lit. [19] m.p. 208-210 °C). 1H NMR ($CDCl_3$): δ 1.15 (s, 6H), 2.56 (s, 2H), 3.25 (s, 2H), 7.21-7.95 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 28.3, 32.2, 48.3, 54.2, 123.3, 126.7, 127.9, 128.1, 128.3, 130.3, 132.4, 136.8, 147.4, 150.0, 161.4, 197.5. Anal. calcd. for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.36; H, 5.26; N, 4.35.

(6- Chloro -2- methyl -4- phenylquinolin -3-yl) (phenyl) methanone (3d)

White solid, m.p. 217-218 °C (Lit. [31] m.p. 217 °C). 1H NMR ($CDCl_3$): δ 2.62 (s, 3H), 7.25-8.03 (m, 13H). ^{13}C NMR ($CDCl_3$): δ 23.9, 124.9, 126.1, 128.2, 128.5, 129.2, 129.9, 130.6, 130.9, 132.4, 133.6, 134.2, 136.9, 144.7,

Table 3: The solvent-free synthesis of poly-substituted quinolines via Friedländer hetero-annulation between 2-aminoaryl ketones and carbonyl compounds using P_2O_5/SiO_2 at 80 °C.

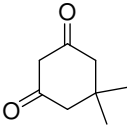
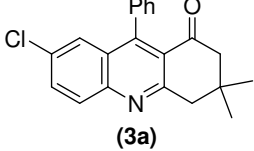
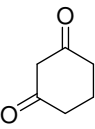
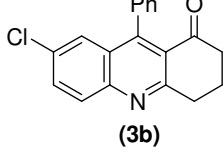
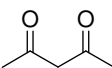
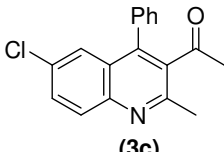
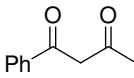
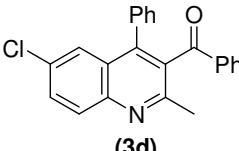
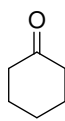
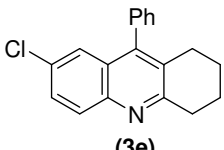
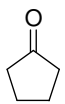
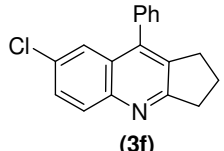
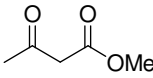
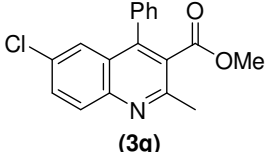
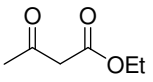
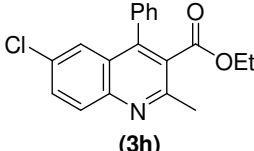
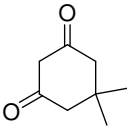
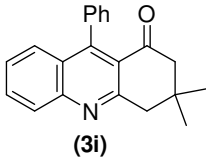
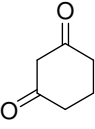
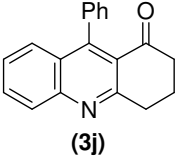
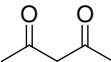
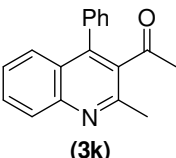
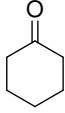
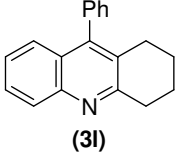
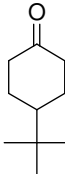
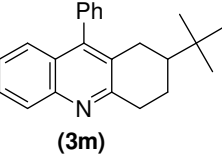
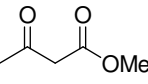
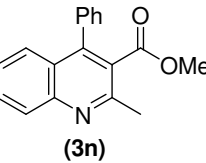
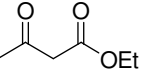
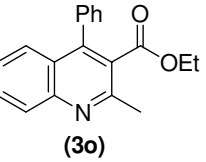
Entry	Carbonyl Compound	Product ^a	Time (min)	Yield (%) ^b	M.p. °C (Lit.)
1		 (3a)	15	93	211-212 (208-210) [19]
2		 (3b)	15	95	187-189 (185-189) [19]
3		 (3c)	15	93	156-157 (152-153) [21]
4		 (3d)	40	77	217-218 (217) [31]
5		 (3e)	20	87	165-166 (165) [31]
6		 (3f)	20	86	99-101 (104-105) [21]
7		 (3g)	20	93	136-137 (135) [31]
8		 (3h)	20	91	101-102 (101) [31]

Table 3: Continued

Entry	Carbonyl Compound	Product ^a	Time (min)	Yield (%) ^b	M.p. °C (Lit.)
9		 (3i)	35	94	192-193 (191-192) [19]
10		 (3j)	30	91	158-159 (156-158) [19]
11		 (3k)	15	88	109-110 (112-113) [21]
12		 (3l)	20	85	143-145 (139) [17]
13		 (3m)	25	87	134-136 (132-133) [30]
14		 (3n)	30	91	106-107 (107) [25]
15		 (3o)	30	88	100-102 (96) [17]

148.3, 155.1, 197.2. Anal. calcd. for $C_{23}H_{16}ClNO$: C, 77.20; H, 4.51; N, 3.97. Found: C, 77.41; H, 4.39; N, 4.11.

Ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3o)

Yellow solid, m.p. 100-102 °C (Lit. [17] m.p. 96 °C). 1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $J = 7.7$ Hz), 2.71 (s, 3H), 3.93 (q, 2H, $J = 7.7$ Hz), 7.35-7.95 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 13.5, 23.4, 61.2, 125.1, 126.4, 127.4, 128.4, 129.2, 130.3, 135.5, 146.6, 147.1, 154.4, 168.0. Anal. calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.16; H, 5.97; N, 4.69.

RESULTS AND DISCUSSION

We have previously used solid-supported catalysts in several organic transformations [35-40,50,51,63,64]. One of these green catalytic systems is P_2O_5/SiO_2 that it is easily prepared by mixing of P_2O_5 and SiO_2 , and grounding them. We have successfully applied this catalyst for the preparation of bis(indolyl)methanes [50], and N-sulfonyl imines [51]. Considering these subjects and also the unique properties of P_2O_5/SiO_2 , we decided to extend application of this catalyst in organic synthesis. Herein, we found that P_2O_5/SiO_2 can efficiently catalyze Friedländer hetero-annulation between 2-aminoaryl ketones and carbonyl compounds to give quinoline derivatives. At first, the condensation of 2-amino-5-chlorobenzophenone (1a) (2 mmol) with dimedone (2a) (3 mmol) was examined in the presence of different amounts of P_2O_5/SiO_2 (30% w/w) at range of 40-90 °C under solvent-free conditions in order to optimize the reaction conditions with respect to the amount of the catalyst and temperature (Scheme 1). As Table 1 indicates, reasonable results were obtained when the reaction was performed using 0.4 g of the catalyst at 80 °C.

In another set of experiments, efficiency and capacity of the solvent-free procedure in comparison with solution conditions were studied. For this purpose, a mixture of 2-amino-5-chlorobenzophenone (2 mmol), dimedone (3 mmol) and P_2O_5/SiO_2 (0.4 g) was stirred in some solvents (10 mL) at 80 °C or under reflux conditions (Table 2). As it can be seen in Table 2, the solvent-free method is more efficient.

To assess the generality and scope of the method, the reaction was examined with different carbonyl compounds and 2-aminoaryl ketones. As it is shown in table 3, reactions of 2-amino-5-chlorobenzophenone or

2-aminobenzophenone with various kinds of carbonyl compounds including cyclic and acyclic β -diketones, aliphatic and aromatic β -diketones, ketones and β -ketoesters proceeded efficiently and the desired products were obtained in high to excellent yields and in short reaction times. Thus, the method is highly efficient and general. Moreover, in most of the entries, 2-amino-5-chlorobenzophenone in comparison with 2-aminobenzophenone afforded the corresponding quinolines in shorter reaction times.

CONCLUSIONS

In summary, we have developed a new method for the synthesis of poly-substituted quinolines via Friedländer hetero-annulation reaction between 2-aminoaryl ketones and carbonyl compounds. The advantages of this method are the efficiency, generality, high yields, short reaction times, low cost, cleaner reaction profile, simplicity, ease of preparation of the catalyst, ease of product isolation, and compliance with the green chemistry protocols.

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