Monatshefte für Chemie 138, 659–661 (2007)
DOI 10.1007/s00706-007-0678-2
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

An Efficient and Rapid Approach to Quinolines *via Friedländer* Synthesis Catalyzed by Silica Gel Supported Sodium Hydrogen Sulfate Under Solvent-Free Conditions

Minoo Dabiri, Seyyedeh Cobra Azimi, and **Ayoob Bazgir***

Department of Chemistry, Shahid Beheshti University, Tehran, Iran

Received February 14, 2007; accepted March 8, 2007; published online May 11, 2007

Summary. A simple and efficient method for the synthesis of quinolines and polycyclic quinolines using silica gel supported sodium hydrogen sulfate as reusable eco-friendly catalyst *via Friedländer* annulation under solvent-free conditions is described.

Keywords. *Friedländer*; Solvent-free; Silica gel supported sodium hydrogen sulfate; Quinoline; Reusable catalyst.

Introduction

Quinolines and their derivatives have recently received great attention because of their wide range of therapeutic and biological properties [1]. They have emerged as antimalarial, antiasthmatic, anti-inflamatory, antibacterial, antihypertensive, and tyrosine kinase PDGF-RTK inhibiting agents [2, 3]. Moreover, polyquinolines are found to undergo hierarchical self-assembly into a variety of nano- and meso-structures with enhanced electronic and photonic functions [4].

The simple and straightforward method for the synthesis of polysubstituted quinolines was reported by *Friedländer* in 1882 [5]. *Friedländer* reactions are generally carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of base or by heating a mixture of the reactants at high temperatures ranging from 150 to 220°C in the absence of catalyst [6]. Under thermal or base catalysts conditions, *o*-aminobenzophenone fails to react with simple ketones, such as cyclohexanone and β-keto esters [7]. Subsequent work showed that acid catalysts are more effective than base catalysts for the *Friedländer* annulation. Acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and polyphosphoric acid have been widely employed for this conversion [6a, 8]. In addition, modified methods employing phosphoric acid, diphosgene, $AuCl_3$, NaF, $ZnCl_2$, microwave, and ionic liquids have been reported for the synthesis of quinolines [8, 9]. Recently, $Y(OTf)_3$ has been employed for this conversion [10]. However, most of these methods have significant drawbacks such as low yields of the products, prolonged reaction times, harsh reaction conditions, and the use of hazardous and often expensive catalysts. Moreover, this reaction is usually carried out in polar solvents such as acetonitrile, *THF*, *DMF*, and *DMSO* leading to tedious work-up procedures. The main disadvantage of most of the existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or re-used.

Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, recyclability, and simple work-up for the preparation of quinoline derivatives under neutral and practical conditions is of prime interest. Due to the acidic properties of silica gel supported sodium hydrogen sulfate ($NaHSO_4$–SiO_2) in recent years, $NaHSO_4$–SiO_2 has been used as an efficient heterogeneous catalyst for many organic

* Corresponding author. E-mail: a_bazgir@sbu.ac.ir

transformations [11], because of its low cost, ease of preparation [11b], catalyst recycling, and ease of handling. Since the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration. However, there are no reports on the use of $NaHSO_4$–SiO_2 for the synthesis of quinolines *via Friedländer* annulation. The use of $NaHSO_4$–SiO_2 as a recyclable catalyst makes the process convenient, economic, and environmentally benign.

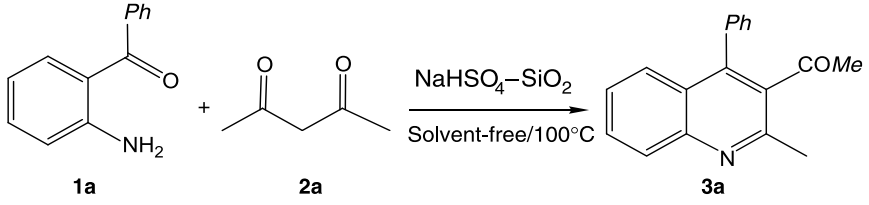
In continuation of our interest on the application of heterogeneous catalysts, especially $NaHSO_4$–SiO_2, for development of useful synthesis methodology [12], we wish to report a simple, convenient, and high-yielding method for the synthesis of polysubstituted quinolines *via Friedländer* annulation using silica gel supported sodium hydrogen sulfate as reusable eco-friendly catalyst under solvent-free conditions.

Results and Discussion

We started to study this condensation reaction by examining the amount of catalysts for the reaction involving 2-aminobenzophenone (**1a**, 1 mmol) with acetylacetone (**2a**, 1 mmol) to afford the product **3a** under solvent-free conditions at 100°C (Scheme 1). The best result was obtained with 0.2 g of catalyst. Higher amounts of catalyst did not improve the result to any greater extent.

Then, various cyclic 1,3-diketones, such as 1,3-cyclohexanedione, 5,5-dimethylcyclohexanedione (dimedone), and acyclic 1,3-diketones including acetylacetone and ethyl or methyl acetoacetate reacted with 2-aminobenzophenone or 2-amino-5-chloro-benzophenone (**1b**) in the presence of the optimized quantity of $NaHSO_4$–SiO_2 under solvent-free conditions at 100°C. In all cases corresponding substituted quinolines were obtained in excellent yields for reaction times of 1–1.5 h (Table 1).

Interestingly, cyclic ketones such as cyclopentanone, cyclohexanone, and cycloheptanone reacted with 2-aminoarylketones to afford the respective tricyclic quinolines in excellent yields for 1–1.5 h (Table 1). In general, the reaction is very clean, rapid, efficient, and free from side reactions, such as self-condensation of ketones which is normally observed under basic conditions.



Scheme 1

Table 1. $NaHSO_4$–SiO_2 catalyzed synthesis of quinoline derivatives

Entry	Compound **1**	Compound **2**	Quinoline **3**	Time/h	Yield[a]/%	Ref.
1	**1a**	acetylacetone (**2a**)	**3a**	1	87	[9e]
2	**1a**	ethyl acetoacetate (**2b**)	**3b**	1	92 (91, 90, 91)[b]	[9e]
3	**1a**	methyl acetoacetate (**2c**)	**3c**	1	94	This work
4	**1a**	cyclopentanone (**2d**)	**3d**	1	90	[9e]
5	**1a**	cyclohexanone (**2e**)	**3e**	1	91	[9e]
6	**1a**	cycloheptanone (**2f**)	**3f**	1.5	86	[9e]
7	**1a**	dimedone (**2g**)	**3g**	1.5	95	[13]
8	**1a**	1,3-cyclohexanedione (**2h**)	**3h**	1	85	[13]
9	**1b**	**2a**	**3i**	1	82	[9e]
10	**1b**	**2b**	**3j**	1	84	[9e]
11	**1b**	**2c**	**3k**	1	92	[14]
12	**1b**	**2d**	**3l**	1	85	[9e]
13	**1b**	**2e**	**3m**	1	83	[9e]
14	**1b**	**2f**	**3n**	1.5	94	[9e]
15	**1b**	**2g**	**3o**	1.5	96	[13]
16	**1b**	**2h**	**3p**	1	88	[13]

[a] Isolated yields. [b] Isolated yields after recycling of catalyst

In these experiments the product was isolated by filtration and the catalyst could be reloaded with fresh reagents for further runs. Thus, recyclization of catalyst is possible without significant loss of activity (Table 1, entry **2**). Finally, it should be mentioned that when reactions were carried out in the absence of catalyst for long period of time (4–5 h) and in solvent free condition at 100°C the yields of products were low (<30%).

In conclusion, we have developed a simple, efficient, and green methodology for the synthesis of quinolines using $NaHSO_4$–SiO_2 under solvent-free conditions. The simple experimental procedure, solvent-free reaction conditions, good yields, and utilization of an inexpensive and reusable catalyst are the advantages of the present method.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$ using *TMS*. All the products are known compounds and were characterized by IR, NMR, and mass spectroscopic data and their melting points were compared with reported values.

General Procedure

A mixture of 1 mmol 2-aminoarylketones (**1a**, **1b**), 1 mmol 1,3-diketones or ketones (**2a**–**2h**), and 0.2 g $NaHSO_4$–SiO_2 was heated at 100°C. The reaction was monitored by TLC. After completion, the reaction mixture was washed with 10 cm^3 *Et*OA*c* and filtered to recover the catalyst. Evaporation of the solvent followed by purification by column chromatography (silica gel, *Et*OA*c*:*n*-hexane, 1:8) afforded the corresponding pure quinoline derivative.

Methyl-2-methyl-4-phenylquinoline-3-carboxylate
(**3c**, $C_{18}H_{15}NO_2$)

White powder (0.26 g, 94%), mp 147–149°C; IR (KBr): $\bar{\nu} = 3030$, 2958, 1704, 1615 cm^{-1}; MS: m/z (%) = 277 (M^+, 100), 246 (89), 218 (76); ^{1}H NMR ($CDCl_3$): $\delta = 2.84$ (s, CH_3), 3.58 (s, OCH_3), 7.27–8.22 (m, H–*Ar*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.25$, 52.30, 125.19, 126.61, 126.87, 127.43, 128.10, 128.36, 128.71, 129.15, 130.93, 135.35, 146.64, 147.46, 154.57, 168.54 ppm.

Methyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylate
(**3k**, $C_{18}H_{14}ClNO_2$)

White powder (0.29 g, 92%), mp 131–133°C; IR (KBr): $\bar{\nu} = 3027$, 2964, 1701, 1617 cm^{-1}; MS: m/z (%) = 311 (M^+, 100), 281 (181), 252 (40); ^{1}H NMR ($CDCl_3$): $\delta = 2.81$ (s, CH_3), 3.59 (s, OCH_3), 7.26–8.13 (m, H–*Ar*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.34$, 52.40, 125.34, 126.02, 128.20, 128.57, 129.01, 129.08, 129.92, 131.69, 132.83, 134.70, 145.24, 146.42, 154.94, 168.27 ppm.

Acknowledgements

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

References

[1] (a) Larsen RD, Corley EG, King AO, Carrol JD, Davis P, Verhoeven TR, Reider PJ, Labelle M, Gauthier JY, Xiang YB, Zamboni RJ (1996) J Org Chem **61**: 3398; (b) Chen YL, Fang KC, Shen JY, Hsu SL, Tzeng CC (2001) J Med Chem **44**: 2374; (c) Roma G, Braccio MD, Grossi G, Mattioli F, Ghia M (2000) J Med Chem **35**: 1021

[2] (a) Kalluraya B, Sreenivasa S (1998) Farmaco **53**: 399; (b) Doube D, Blouin M, Brideau C, Chan C, Desmarais S, Eithier D, Falgueyret JP, Friesen RW, Girrard M, Girard Y, Guay J, Tagari P, Young RN (1998) Bioorg Med Chem Lett **8**: 1255

[3] Maguire MP, Sheets KR, McVety K, Spada AP, Zilberstein A (1994) J Med Chem **37**: 2129

[4] (a) Agrawal AK, Jenekhe SA (1991) Macromolecules **24**: 6806; (b) Zhang X, Shetty AS, Jenekhe SA (2000) Macromolecules **33**: 2064

[5] Friedländer P (1882) Chem Ber **15**: 2572

[6] (a) Cheng CC, Yan SJ (1982) Org React **28**: 37; (b) Thummel RP (1992) Synlett: 1; (c) Gladiali S, Chelucci G, Mudadu MS, Gastaut MA, Thummel RP (2001) J Org Chem **66**: 400

[7] Fehnel EA (1966) J Heterocycl Chem **31**: 2899

[8] (a) Sterkowski L, Czamy A (2000) J Fluorin Chem **104**: 281; (b) Hu YZ, Zang G, Thummel RP (2003) Org Lett **5**: 2251

[9] (a) Lee BS, Lee JH, Chi DY (2002) J Org Chem **67**: 7884; (b) Arcadi A, Chiarini M, Giuseppe SD, Marinelli F (2003) Synlett: 203; (c) Jiang B, Si YG (2002) J Org Chem **67**: 9449; (d) Song SJ, Cho SJ, Park DK, Kwan TW, Jenekhe SA (2003) Tetrahedron Lett **44**: 255; (e) Palimkar SA, Siddiqui SA, Daniel T, Lahoti RJ, Srinivasan KV (2003) J Org Chem **68**: 9371

[10] De SK, Gibbs RA (2005) Tetrahedron Lett **46**: 1647

[11] (a) Dos B, Venkataiah B (2000) Synthesis: 1671; (b) Barton GW (1997) J Org Chem **62**: 8952; (c) Dos B, Venkateswarlu K, Mehender G, Holla H (2004) J Chem Res (s): 836; (d) Ramesh C, Mahender G, Ravindranath N, Das B (2003) Tetrahedron Let **44**: 1465

[12] (a) Dabiri M, Arvin-Nezhad H, Khavasi HR, Bazgie A (2007) Tetrahedron **63**: 1770; (b) Shaabani A, Bazgir A (2004) Tetrahedron Lett **45**: 2575; (c) Shaabani A, Dabiri M, Bazgir A (2006) Dye and Pigments **71**: 68; (d) Bazgir A (2006) J Chem Res (s): 1

[13] Yadav JS, Rao PP, Sreenu D, Rao RS, Kumar VN, Nagaiah K, Prasad AR (2005) Tetrahedron Lett **46**: 7249

[14] Muscia GC, Bollini M, Carnevale JP, Bruno AM, Asis SE (2006) Tetrahedron Lett **47**: 8811