Communication

Microwave-assisted Friedländer Synthesis of Polysubstituted Quinolines Based on Poly(ethylene glycol) Bound Acetoacetate

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Received September 2, 2010; Accepted December 2, 2010; Published Online January 12, 2011

Polysubstituted quinolines were efficiently prepared on the soluble polyethylene glycol (PEG) by microwave irradiation Friedländer condensation of PEG bound acetoacetate with 2-aminoarylketones promoted by catalytic amount of polyphosphoric acid, and subsequently cleavage from the PEG with MeONa in MeOH. The polymer-supported synthesis provided the target compounds in excellent yield and purity with a facile work-up procedure.

Keywords: Liquid-phase synthesis; PEG bound acetoacetate; 2-Aminoarylketone; Polysubstituted quinoline.

INTRODUCTION

Quinolines are very important compounds because of their wide occurrence in natural products[1] and their interesting biological activities such as antimalarial, anti-inflammatory agents, antiasthmatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[2] In addition, quinolines have been used for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic or non-linear optical properties with excellent mechanical properties.[3] As a result of their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed toward the development of new quinoline-based structures and new methods for their construction.[4] Among these methods, the Friedländer annulation,[5] an acid or base catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone and a carbonyl compound containing a reactive α-methylene group, is still one of the simplest and most straightforward procedure for the synthesis of polysubstituted quinolines. Brønsted acids catalysts, such as NH_2SO_3H, HCl, H_2SO_4, *p*-TSA, H_3PO_4, TFA, $NaHSO_4$-SiO_2 and $HClO_4$-SiO_2 were widely used[6] for the Friedländer annulation. However, many of these methods required high temperature (150-200 ^oC) and extended reaction times, which led to several side reactions. Under thermal and basic conditions, 2-aminobezophenone failed to react with cyclohexanone, deoxybenzoin and β-ketoesters.[7] Recently, iodine,[8] Lewis acids and inorganic salts[9] such as $FeCl_3$, $Mg(ClO_4)_2$, $CuSO_4·5H_2O$, $FeSO_4·7H_2O$, $SnCl_2$, $AlCl_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, $Y(OTf)_3$, $CeCl_3·7H_2O$, NaF, $NaAuCl_4·2H_2O$, $Nd(NO_3)_3·6H_2O$ and $Ag_3POW_{12}O_{40}$, and a combination of acidic catalysts and microwave irradiation,[10] ionic liquids,[11] chlorotrimethylsilane,[12] cyanuric chloride,[13] 1-methylimidazolium trifluoroacetate,[14] $[RuCl_2(p\text{-cymene})]_2$ [15] and dodecylphosphonic acid,[16] as well as poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide)[17] have been utilized for this synthesis. Although these methods are valuable for the preparation of quinoline derivatives, some of the reported protocols suffered form harsh reaction conditions, low yields, high temperatures, tedious work-up and the use of stoichiometric and relatively expensive reagents. Therefore, the development of simple, convenient and environmentally benign approaches for the preparation of quinolines is still desirable. In the past years, there has been a considerable growth in interest in the use of soluble polymer-supported catalysts and re-

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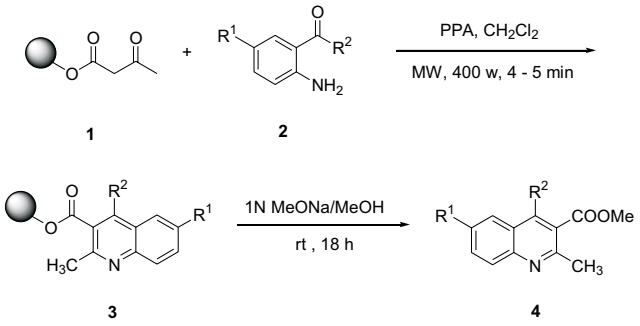
agents in organic synthesis because of their low cost, easy of preparation and simple workup.[18] As part of an ongoing research program focused on the use polyethylene glycol (PEG) as support in liquid-phase organic synthesis,[19] we report herein a novel method to the soluble polymer-supported synthesis of polysubstituted quinolines based on PEG bound acetoacetate with 2-aminoarylketones as shown in Scheme I.

Scheme I PEG support synthetic route to polysubstituted quinolines



RESULTS AND DISCUSSION

Our current methodology takes place from PEG 4000 bound acetoacetate **1**,[19a] simply prepared by acetoacetylation of dihydroxyl PEG 4000 with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (toluene, 111 °C, 5 h). The quantitative conversion of PEG to **1** was observed following the presence of the C=O absorptions at 1743 and 1718 cm^{-1} in FT-IR spectrum, which corresponded to ester and ketone carbonyl group, respectively. Apparently, the first step of Friedländer condensation of PEG-bound acetoacetate **1** with 2-aminoarylketones **2** in our present idea would be the key step for the success of this protocol. As a model study, the condensation of acetoacetate **1** and 2-aminoacetophenone (**2a**) was chosen for optimization. In view of a green chemistry, and on the basis of the previously reported protocols, some catalysts such as such as *p*-TSA, $NaHSO_4$, NaF, I_2, $FeSO_4 \cdot 7H_2O$ and TMSCl, as well as microwave irradiation (MW) technique were used, and the corresponding reaction conditions, for example, the different solvents such as CH_3OH, CH_3CN and CH_2Cl_2, the reaction time, and the amount of catalyst were varied for the present Friedländer reaction. After a series of experiments, the condensation reaction between **1** and **2a** was completed in CH_2Cl_2 in the presence of catalytic amount of non-volatile, high boiling point and non-oxidant polyphosphoric acid (PPA) in a MW domestic oven (400 W) adapted for the use of a reflux condenser only for 5 min.

The reaction transformation of the PEG support was feasible monitored directly using conventional microscopy FT-IR and ^1H NMR spectroscopy. After the cyclodehydration **1** with **2a**, the FT-IR spectrum of the PEG bound intermediate **3a** showed complete disappearance of the ketone carbonyl stretch at 1718 cm^{-1} corresponding to the ketone carbonyl group of PEG bound acetoacetate **1**, and the appearance of a new carbonyl stretch group in pyridine ring near 1730 cm^{-1}. Furthermore, this reaction process was further confirmed by ^1H NMR spectroscopy of the intermediate **3a** since the methyl proton (CH_3) of the PEG-bound acetoacetate **1** was shifted downfield from 2.27 to 2.55 ppm.

Upon completion of the optimal Friedländer reaction conditions, PEG immobilized quinoline-3-carboxylate **3a** was selectively precipitated out after the addition of diethyl ether to the reaction mixtures. The target compound **4a** was obtained in 93% yield and 96% (Entry 1) HPLC purity of crude product by cleavage from the PEG support under the treatment of the PEG bound intermediate **3a** with MeONa in MeOH with stirring for 18 h. Completed cleavage of the PEG support was also verified by observing an upfield shift of α-methylene protons in the polymer attachment site from 4.3 to 3.7 ppm.

It was worthy to note that, the same reaction of **1** and **2a** promoted only by PPA in refluxing CH_2Cl_2 took 6 h to achieve the completion, and the corresponding yield of compound **4a** cleaved from PEG was about 85%. It indicates that the MW-induced protocol could not only achieve significantly improved yield, but also decrease the reaction time over those under traditional Friedländer reaction conditions.

After finishing the cleavage reaction, the residual polymer was recovered with about 90% yield based on original PEG by addition of diethyl ether to the reaction mixtures. The recovered PEG was reacted again with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one to regenerate PEG-bound ester **1** cleanly.[19a] To show the reactivity of the regenerated PEG-bound ester **1**, the reaction of polymeric reagent **1** with 2-aminoacetophenone (**2a**) was repeated four times in the same reaction. As seen from Table 1 (entries **2** and **3**),

Table 1. The yields and purities of polysubstituted quinolines **4a-4k**

Entry	R^1	R^2	Product	Yield (%) [a]	Crude purity (%) [b]
1	H	CH_3	**4a**	93	96
2	H	CH_3	**4a**	89 [c]	93
3	H	CH_3	**4a**	84 [d]	90
4	H	C_6H_5	**4b**	90	95
5	H	2-ClC_6H_4	**4c**	88	95
6	Cl	CH_3	**4d**	93	96
7	Cl	C_6H_5	**4e**	92	94
8	Cl	2-ClC_6H_4	**4f**	90	95
9	NO_2	CH_3	**4g**	94	97
10	NO_2	C_6H_5	**4h**	93	96
11	H	$C_6H_5CH_2$	**4i**	91	93
12	Cl	$C_6H_5CH_2$	**4j**	92	96
13	NO_2	$C_6H_5CH_2$	**4k**	93	96

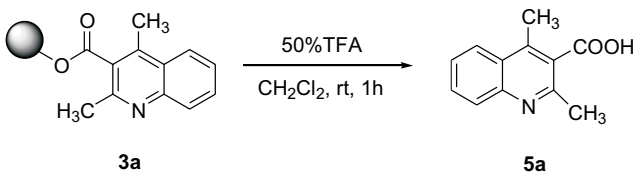
[a] Isolated yield based on loading of original HO-PEG-OH. [b] Determined on HPLC analysis of crude products before purification. [c] With the third regenerated reagent **1**. [d] With the fourth regenerated reagent **1**.

comparing with the result when the reagent **1** was first used, the yield and purity of **4a** decreased, which indicated that recycling 3-4 times led to a gradual deterioration of the reagent **1**.

Following the synthesis of **4a** on PEG, a set of related compounds (**4b-4k**) was prepared using an analogous synthetic protocol. As shown in Table 1, the yields (88-94%) were excellent and the purities were satisfactory (93-97%). Their ^{1}H NMR, ^{13}C NMR, and analytical data confirmed the structures of all final products.

On the other hand, the PEG-bound intermediate **3** cleaved *via* another process was further investigated as shown in Scheme II. For example, treatment of **3a** with 50% TFA in CH_2Cl_2 at room temperature for 1 h yielded 2,4-dimethylquinoline-3-carboxylic acid **5a** in 90% yield and 95% HPLC purity.

Scheme II Transformation of **3a** to the corresponding carboxylic acid **5a**



3a **5a**

In conclusion, a novel and efficient liquid-phase synthesis method for the construction of polysubstituted quinolines on soluble PEG support was developed, which used Friedländer condensation of PEG-bound acetoacetate with 2-aminoarylketones in the presence of catalytic amount of PPA under microwave promotion, followed by the cleavage from the PEG. The coupling of MW technology with liquid-phase synthetic strategy provided a new procedure for the rapid generation of polysubstituted quinolines in excellent yields with simple workup. This versatile method has potential applications in combinatorial synthesis of analogous heterocyclic compounds libraries for chemical biological screening and the drug discovery process.

EXPERIMENTAL SECTION

General Procedure

Melting points were determined on X_4 melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR (400 MHz) spectra were recorded on a Bruker AVANCE (400 MHz) spectrometer. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer. HPLC analysis was carried out on Agilent 1100 automated system having a PDA detector (λ_{max} = 254 nm) using a gradient from 100% of the aqueous 0.1% TFA (eluent A) to 60% eluent A-40% of 0.5% TFA in acetonitrile (eluent B) over 35 min (0.8 mL/min) on a RP-18e column (100 × 4.6 mm). MW experiments were performed on a Galaz WP 800J-823 microwave oven altered with a reflux condenser. Polyethylene glycol (PEG) 4000, 2-aminoarylketones and other reagents were obtained from commercial source and used without further purification.

General Procedure for the Preparation of Polysubstituted Quinolines (4a-4k)

To a solution of PEG 4000 bound acetoacetate acet **1**[19a] (2.0 g, 1.0 mmol) in CH_2Cl_2 (15 mL) was added 2-aminoarylketones **2** (3.0 mmol) and PPA (2-3 drops) at room temperature. The resulting mixture was subjected to microwave irradiation at 400 W for 5 min at a temperature of 110 ^{o}C, the mixture was then cooled to room temperature and the solvent was removed under reduced pressure and the PEG bound quinoline-3-carboxylate **3** was obtained by precipitating and washing with excess cold ether (5 × 10 mL). After drying in vacuo, the intermediate **3** was added to the MeONa (1N)/MeOH solution (15 mL) to cleave the

product at room temperature for 18 h (checked by TLC). After completion of the reaction, the residual PEG was precipitated by addition of Et_2O (100 mL) to the mixture. For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The white precipitate was collected and washed several times with Et_2O (2 × 5 mL), and dried in vacuo in 90% yield based on the original PEG. The crude product was obtained by extraction with Et_2O, dilution with H_2O (2 × 10 mL) and then removal of the solvent. All crude products with 93-97% purity determined by HPLC, were further purified by passing the crude product through silica gel chromatographic column (10-15% ethyl acetate in hexane) affording the pure products **4a**-**4k** for their structure analyses.

Methyl 2,4-dimethyl quinoline-3-carboxylate (4a)

Oil (lit.[8c] oil); ^{1}H NMR: δ = 8.04 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.60 (s, 3H), 2.71 (s, 3H), 2.64 (s, 3H); ^{13}C NMR: δ = 168.5, 154.4, 147.0, 141.3, 129.6, 128.8, 127.7, 126.2, 125.8, 123.6, 52.5, 23.9, 15.8; IR (neat): ν = 1730, 1613 cm^{-1}; Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.41; H, 6.18; N, 6.60.

Methyl 2-methyl-4-phenylquinoline-3-carboxylate (4b)

White solid, mp 115-117 °C; ^{1}H NMR: δ = 8.10 (d, *J* = 8.4 Hz, 1H), 8.07-7.35 (m, 8H), 3.58 (s, 3H), 2.79 (s, 3H); ^{13}C NMR: δ = 167.8, 154.1, 147.5, 145.4, 135.7, 135.5, 130.3, 129.2, 128.9, 128.5, 128.3, 127.3, 126.5, 125.1, 52.2, 23.9; IR (KBr): ν = 1730, 1584 cm^{-1}; Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.80; H, 5.57; N, 5.14.

Methyl 4-(2-chlorophenyl)-2-methylquinoline-3-carboxylate (4c)

Yellow solid, mp 123-125 °C; ^{1}H NMR: δ = 8.07-7.37 (m, 8H), 3.62 (s, 3H), 2.74 (s, 3H); ^{13}C NMR: δ = 168.7, 154.2, 146.8, 141.5, 133.2, 130.1, 129.8, 129.5, 128.8, 128.5, 128.2, 127.6, 127.1, 126.4, 126.2, 125.4, 52.5, 23.8; IR (KBr): ν = 1728, 1610 cm^{-1}; Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49. Found: C, 69.15; H, 4.68; N, 4.62.

Methyl 6-chloro-2,4-dimethylquinoline-3-carboxylate (4d)

White solid, mp 64-66 °C; ^{1}H NMR: δ = 8.10 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 3.60 (s, 3H), 2.75 (s, 3H), 2.65 (s, 3H); ^{13}C NMR: δ = 168.4, 154.3, 146.3, 135.6, 132.6, 130.2, 129.3, 128.3, 127.4, 124.8, 52.7, 24.2, 16.0; IR (KBr): ν = 1728, 1610 cm^{-1}; Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.38; H, 4.96; N, 5.70.

Methyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (4e)

Yellow solid, mp 131-133 °C (lit.[7] mp 135 °C); ^{1}H NMR: δ = 8.02 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 8.0 Hz, 1H), 7.52-7.44 (m, 4H), 7.37-7.31 (m, 2H), 3.59 (s, 3H), 2.75 (s, 3H); ^{13}C NMR: δ = 168.3, 154.8, 148.0, 145.4, 135.0, 132.3, 131.0, 130.4, 129.1, 128.7, 128.4, 127.5, 125.7, 125.1, 52.4, 24.1; IR (KBr): ν = 1734, 1586 cm^{-1}; Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49. Found: C, 69.22; H, 4.66; N, 4.60.

Methyl 6-chloro-4-(2-chlorophenyl)-2-methylquinoline-3-carboxylate (4f)

Yellow solid, mp 134-136 °C; ^{1}H NMR: δ = 8.05 (d, *J* = 9.2 Hz, 1H), 7.55-7.26 (m, 6H), 3.58 (s, 3H), 2.78 (s, 3H); ^{13}C NMR: δ = 168.3, 154.8, 139.6, 135.5, 134.7, 133.4, 132.3, 130.4, 129.8, 129.2, 128.7, 128.4, 128.0, 127.6, 126.5, 125.8, 52.6, 23.8; IR (KBr): ν = 1730, 1604 cm^{-1}; Anal. Calcd for $C_{18}H_{13}Cl_2NO_2$: C, 62.45; H, 3.78; N, 4.05. Found: C, 62.32; H, 3.90; N, 4.12.

Methyl 6-nitro-2,4-dimethylquinoline-3-carboxylate (4g)

Yellow solid, mp 78-80 °C; ^{1}H NMR: δ = 8.43 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 3.62 (s, 3H), 2.76 (s, 3H), 2.66 (s, 3H), ^{13}C NMR: δ = 168.5, 154.5, 148.3, 135.4, 132.8, 130.5, 129.4, 128.7, 127.5, 125.1, 52.8, 24.3, 16.2; IR (KBr): ν = 1730, 1618 cm^{-1}; Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.82; H, 4.81; N, 10.63.

Methyl 2-methyl-6-nitro-4-phenylquinoline-3-carboxylate (4h)

Yellow solid, mp 159-161 °C; ^{1}H NMR: δ = 8.50-7.40 (m, 8H), 3.68 (s, 3H), 2.73 (s, 3H); ^{13}C NMR: δ = 168.5, 155.1, 148.4, 145.6, 135.4, 132.6, 131.2, 130.5, 129.4, 128.8, 128.5, 127.8, 125.6, 124.6, 52.5, 24.4; IR (KBr): ν = 1731, 1620, 1526 cm^{-1}; Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.91; H, 5.55; N, 8.54.

Methyl 4-benzyl-2-methylquinoline-3-carboxylate (4i)

White solid, mp 103-105 °C; ^{1}H NMR: δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.36-7.20 (m, 5H), 3.95 (s, 2H), 3.58 (s, 3H), 2.62 (s, 3H); ^{13}C NMR: δ = 168.4, 154.5, 147.3, 141.6, 131.2, 129.8, 128.8, 128.5, 128.2, 127.9,

127.7, 126.5, 126.2, 124.2, 51.9, 37.3, 23.5; IR (KBr): ν = 1724, 1565 cm^{-1}; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.14; H, 6.02; N, 5.96.

Methyl 4-benzyl-6-chloro-2-methylquinoline-3-carboxylate (4j)

White solid, mp 117-119 °C; ^{1}H NMR: δ = 8.08 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.35-7.25 (m, 2H), 7.22-7.17 (m, 3H), 3.98 (s, 2H), 3.60 (s, 3H), 2.65 (s, 3H); ^{13}C NMR: δ = 168.5, 154.2, 146.6, 135.7, 132.5, 131.5, 130.4, 129.2, 128.9, 128.4, 128.2, 127.9, 127.6, 125.2, 52.0, 37.6, 24.0; IR (KBr): ν = 1722, 1580 cm^{-1}; Anal. Calcd for $C_{19}H_{16}ClNO_2$: C, 70.05; H, 4.95; N, 4.30. Found: C, 69.77; H, 5.12; N, 4.41.

Methyl 4-benzyl-2-methyl-6-nitroquinoline-3-carboxylate (4k)

Yellow solid, mp 164-166 °C; ^{1}H NMR: δ = 8.45 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.45-7.28 (m, 5H), 4.02 (s, 2H), 3.62 (s, 3H), 2.66 (s, 3H); ^{13}C NMR: δ = 168.8, 154.5, 148.5, 135.3, 133.1, 131.4, 130.8, 129.6, 129.2, 128.7, 128.3, 127.9, 127.8, 126.0, 52.6, 37.7, 24.5; IR (KBr): ν = 1730, 1618 cm^{-1}; Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.63; H, 4.95; N, 8.45.

2,4-Dimethylquinoline-3-carboxylic acid (5a)

Colorless solid, mp 270-272 °C (lit.[20] mp 270-272 °C); ^{1}H NMR (DMSO-d_6): δ = 11.98 (s, 1H), 7.82-7.21 (m, 4H), 2.45 (s, 3H), 2.32 (s, 3H); ^{13}C NMR: δ = 200.2, 160.1, 149.0, 142.5, 130.3, 129.4, 128.2, 127.7, 126.3, 123.6, 31.6, 19.2; IR (KBr): ν = 3466, 1690, 1656 cm^{-1}; Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.45; H, 5.75; N, 6.77.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (No. 21062007), NSF of Jiangxi Province (No. 2009GZH0016) and the Research Program of Jiangxi Province Department of Education (No. GJJ10385).

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