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Sulfamic acid: an efficient, cost-effective and recyclable solid acid catalyst for the Friedlander quinoline synthesis

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Abstract—*o*-Aminoaryl ketones undergo smooth condensation with α-methylene ketones in the presence of sulfamic acid (NH_2SO_3H) (SA) under mild reaction conditions to afford the corresponding polysubstituted quinolines in excellent yields. The catalyst can be recovered by simple filtration and can be recycled in subsequent reactions. The method is simple, cost-effective and environmentally benign.

Quinolines are very important compounds due to their wide spectrum of biological activities behaving as anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-platelet activity and tyrokinase PDGF-RTK inhibiting agents.[1–3] In addition to medicinal applications, quinoline derivatives are found to undergo hierarchical self-assembly into a variety of nano-structures and meso-structures with enhanced electronic and photonic functions.[4] In addition quinolines have been employed in the study of bioorganic and bioorgano-metallic processes.[5] Considering the significant applications in the fields of medicinal, bio-organic, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinolines. Consequently, various procedures such as the Skraup, Doebner-Von Miller, Friedlander and Combes methods have been developed for the synthesis of quinoline derivatives.[6,7] Among them, the Friedlander annulation[7b] is still one of the most simple and straightforward approaches for the synthesis of polysubstituted quinolines. The Friedlander quinoline synthesis consists of the reaction between an aromatic *ortho*-amino aldehyde and an aldehyde or ketone and an alpha-methylene functionality. Friedlander reactions are generally carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of a base or by heating a mixture of the reactants at high temperatures ranging from 150 to 220 °C in the absence of a catalyst.[8] Under thermal or basic catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone, deoxybenzoin and β-keto esters.[8e] Subsequent work showed that acid catalysts are more effective than base catalysts for the Friedlander annulation.[8e] Acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid and polyphosphoric acids have been widely employed for this conversion.[8a,9] In addition, modified methods employing phosphoric acid, diphosgene, $AuCl_3$, NaF, $ZnCl_2$, microwaves and ionic liquids have been reported for the synthesis of quinolines.[9,10] More recently, $Y(OTf)_3$ has been employed for this conversion.[10f] However, most of the synthetic protocols reported so far suffer from high temperatures, prolonged reaction times, harsh reaction conditions, low yields of the products and the use of hazardous and often expensive acid and base 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, the development of simple, convenient and environmentally benign approaches for the synthesis of quinolines is still desirable.

In recent years, the use of solid acids as heterogeneous catalysts has received tremendous interest in different

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Keywords: Sulfamic acid (SA); *o*-Aminoaryl ketones; α-Methylene ketones; Quinolines.

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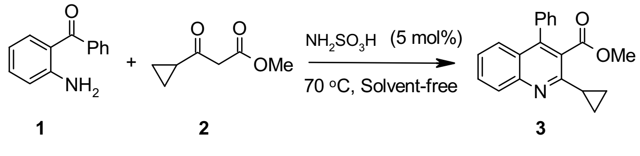
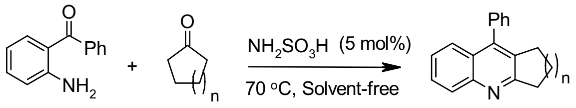
areas of organic synthesis.[11] Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be re-used after activation or without activation, thereby making the process economically more viable. During the last few years, sulfamic acid (NH_2SO_3H) (SA) has emerged as a substitute for conventional acidic catalysts. Sulfamic acid is a common inorganic acid with mild acidity, is non-volatile and non-corrosive, and is insoluble in common organic solvents. It is a white crystalline solid[12a] with outstanding physical and chemical properties and is a commercially available cheap chemical. It has already been determined by both X-ray and neutron diffraction techniques[12b,c] that SA is comprised not of an amino sulfonic acid, but rather of $H_3N^+SO_3^-$ zwitterionic units. In recent years, SA has been used as an efficient heterogeneous catalyst for acid catalyzed reactions, viz. acetalization,[13a] esterification,[13b,c] acetylation of alcohols and phenols,[13d] nitrile formation,[13e] tetrahydropyranylation of alcohols[13f] and transesterification of β-ketoesters.[13g] Moreover, some important organic transformations, including the Biginelli condensation,[13h] the Beckmann rearrangement,[13i] inter- and intramolecular imino Diels–Alder reactions[13j] and very recently Pechmann condensations,[13k] have been carried out in the presence of SA. The distinctive catalytic features and intrinsic zwitterionic property of SA are very different from conventional acidic catalysts. This has encouraged us to investigate further the applications of SA as an acidic catalysts in other carbon–carbon and carbon–heteroatom bond-forming reactions. However, there are no reports on the use of SA for the synthesis of quinolines via Friedlander annulation. The use of SA as a recyclable catalyst makes the process convenient, economic and environmentally benign.

In continuation of our efforts to develop new methods in the synthesis of quinolines,[14] herein, we wish to report a mild and efficient approach for the synthesis of polysubstituted quinolines via Friedlander annulation using a catalytic amount of SA under solvent-free conditions. Accordingly, treatment of 2-aminobenzophenone (**1**) with 3-cyclopropyl-3-oxopropionic acid methyl ester (**2**) in the presence of 5 mol % of SA resulted in the formation of quinoline **3a** in 95% yield[15] (Scheme 1).



Scheme 1.

To study the generality of this process, several examples were studied. Various 1,3-diketones such as 1,3-cyclohexanedione, 5,5-dimethylcyclohexandione (dimedone) and acyclic ketones including 2-butanone and 2-hexanone reacted efficiently with 2-aminobenzophenone to produce the corresponding substituted quinolines. Interestingly, cyclic ketones such as cyclopentanone and cyclohexanone also underwent smooth condensation with 2-aminoaryl ketones to afford the respective tricyclic quinolines (Scheme 2). In most cases, the products were isolated by simple filtration. The crude products were purified either by recrystallization from a mixture of diethyl ether/*n*-hexane or by silica gel column chromatography.



Scheme 2.

In addition, this method is equally effective for both cyclic and acyclic ketones (Table 1). Various substituted 2-aminoaryl ketones such as 2-aminoacetophenone, 2-aminobenzophenone, 2-amino-5-chlorobenzophenone and 2-amino-5-2′-dichlorobenzophenone reacted smoothly with α-methylene ketones to produce a range of quinoline derivatives. In order to optimize the reaction conditions, we conducted this reaction in different solvents. The results showed that the efficiency and the yield of the reaction in solution were much less than those obtained under solvent-free conditions (Table 2). The use of 5 mol % of the catalyst was sufficient to promote the reaction. Higher amounts of the catalyst did not improve the yields. The best result was obtained with 5 mol % of SA under solvent-free conditions at 70 °C. However, in the absence of SA, the reaction did not proceed even after long reaction times (12–24 h). The insolubility of the catalyst SA in different organic solvents provided an easy method for its separation from the product. The catalyst was separated by filtration and reused after activation with only a gradual decrease in its activity. For example, the reaction of 2-aminobenzophenone and ethyl acetoacetate afforded the corresponding quinoline **3a** in 92%, 89%, 85% and 80% yields over four runs. Furthermore, this method is clean and free from side-reactions. Unlike previous methods, the present protocol does not require either strong acids such as concd HCl, concd H_2SO_4, *p*-TSA and H_3PO_4 or high temperatures (190–250 °C) to afford quinoline derivatives. Thus, this method provides an easy access to the preparation of substituted quinolines with a wide range of substitution patterns. This method offers several advantages such as higher yields, shorter reaction times, cleaner reaction profiles and simple experimental and work up procedures. All the products were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy and also by comparison with authentic samples.[8a] The scope and generality of this process is illustrated with respect to various 2-aminoaryl ketones and α-methylene ketones and the results are summarized in Table 1.

In summary, we have described a mild and efficient protocol for the synthesis of quinolines and polycyclic quinolines via Friedlander condensation of 2-aminoarylketones with α-methylene ketones using sulfamic acid as a recyclable heterogeneous catalyst. The simple

Table 1. Sulfamic acid catalyzed synthesis of Friedlander quionlines[a]

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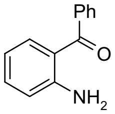
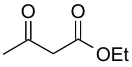
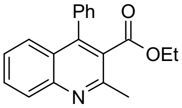
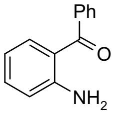
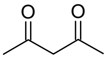
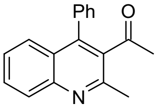
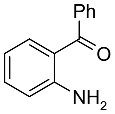
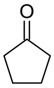
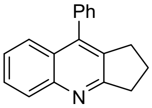
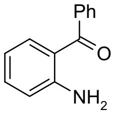
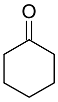
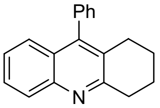
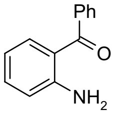
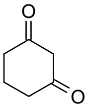
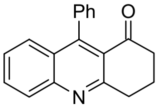
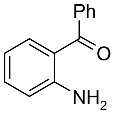
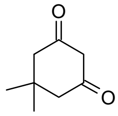
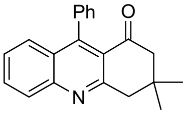
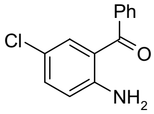
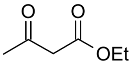
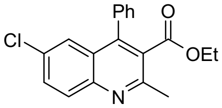
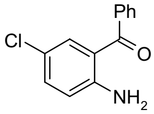
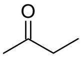
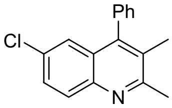
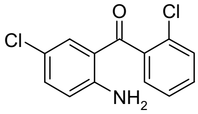
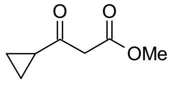
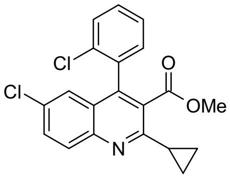
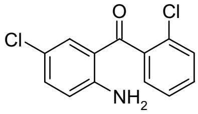
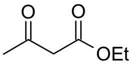
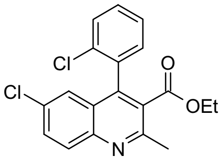
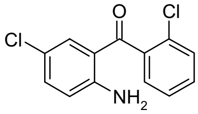
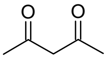
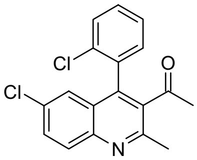
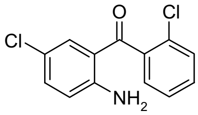
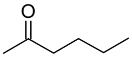
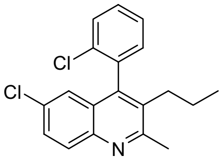
a				30	92
b				45	89
c				50	87
d				60	90
e				75	92
f				90	94
g				45	89
h				50	87
i				60	95
j				75	91
k				80	87
l				75	90

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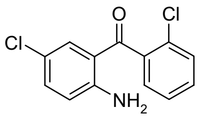
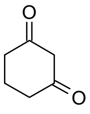
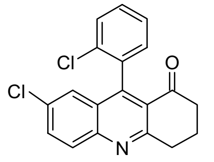
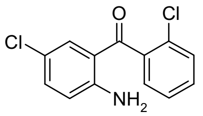
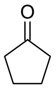
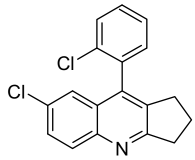
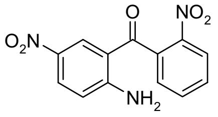
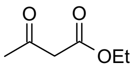
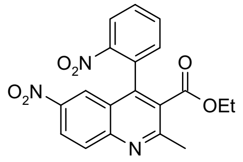
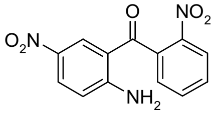
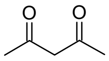
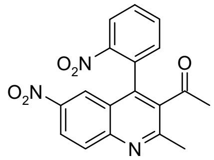
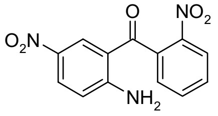
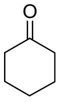
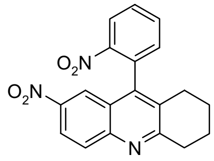
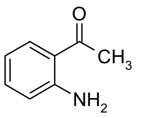
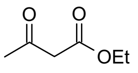
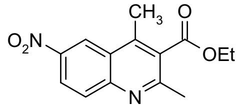
m				45	89
n				60	87
o				90	90
p				75	85
q				60	82
r				90	89

[a] Reaction conditions: 2-aminobenzophenone (1 mmol), ketone (1.5 mmol), sulfamic acid (5 mol %); 70 °C, solvent-free.

[b] All products were characterized by ^{1}H and ^{13}C NMR, IR and mass spectroscopy.

[c] Isolated and unoptimized yields.

Table 2. Friedlander quinoline **3i** synthesis catalyzed by SA in various solvents[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	Reflux	24	47
2	$CHCl_3$	Reflux	24	49
3	CH_3CN	Reflux	24	65
4	1,2-Dichloroethane	Reflux	24	73
5	MeOH	Reflux	24	74
6	EtOH	Reflux	24	76
7	Benzene	Reflux	24	77
8	Toluene	Reflux	24	79
9	Solvent-free	rt	24	43
10	Solvent-free	70	1.0	95

[a] Reaction conditions: 2-aminobenzophenone (1 mmol), ketone (1.5 mmol), SA (5 mol %), 70 °C, solvent-free conditions.

[b] Isolated and unoptimized yields.

experimental procedure combined with the ease of recovery and reuse of this novel catalyst makes this method quite simple, convenient and environmentally benign for the synthesis of highly functionalized quinolines.

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References and notes

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15. Experimental procedure: A mixture of *o*-aminobenzophenone (1 mmol), ketone (1.5 mmol) and sulfamic acid (5 mol %) was stirred at 70 °C under solvent-free conditions for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 1:9) to afford pure quinoline. The recovered catalyst was washed with diethyl ether and activated at 70 °C prior to reuse. Spectral data for selected products: Compound **3a**: pale yellow solid, mp 97 °C. IR (KBr): 3060, 2979, 2932, 1725, 1567, 1485, 1443, 1402, 1295, 1227, 1065, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 0.95 (t, $J = 6.9$ Hz, 3H), 2.78 (s, 3H), 4.00–4.05 (q, $J = 6.9$ Hz, 2H), 7.38–7.48 (m, 6H), 7.55 (d, $J = 8.1$ Hz, 1H), 7.70 (t, $J = 8.0$ Hz, 1H), 8.05 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 13.3, 23.5, 60.8, 96.0, 125.2, 126.0, 126.2, 127.8, 128.2, 129.0, 129.3, 129.7, 135.7, 145.7, 147.7, 154.2, 167.7. EI-MS: m/z (%): 291 (M^+, 80), 246 (100), 218 (46), 177 (10), 176 (20), 75 (27), 43 (25). Compound **3i**: Pale yellow solid, mp 162 °C. IR (KBr): 3006, 2921, 2850, 1732, 1576, 1501, 1471, 1435, 1310, 1224, 1042, 755 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.05 (m, 1H), 1.25 (m, 1H), 1.38–1.48 (m, 2H), 2.20 (m, 1H), 3.55 (s, 3H), 7.15–7.25 (m, 2H), 7.35–7.50 (m, 3H), 7.55–7.60 (m, 1H), 7.90 (d, $J = 8.0$ Hz, 1H). FAB-MS: m/z (%): 373 (M^{+1}, 15), 340 (6), 312 (3), 281 (4), 207 (6), 147 (29), 109 (18), 95 (37), 55 (100). Compound **3n**: Pale yellow solid, mp 142 °C. IR (KBr): 3059, 2960, 1607, 1475, 1385, 1210, 955, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.10–2.30 (m, 2H), 2.70–2.80 (m, 1H), 2.85–2.95 (m, 1H), 3.20–3.30 (m, 2H), 7.20–7.28 (m, 2H), 7.38–7.48 (m, 2H), 7.55–7.60 (m, 2H), 7.98 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 23.2, 29.9, 34.8, 124.0, 126.7, 127.0, 129.2, 129.8, 130.0, 130.4, 131.4, 133.0, 134.8, 135.5, 139.1, 146.2, 167.8. FAB-MS: m/z (%): 315 (M^{+1}, 100), 278 (14), 251 (5), 241 (7), 207 (8), 191 (6), 147 (21), 133 (17), 115 (8), 105 (8).