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Application of heterogeneous solid acid catalysts for Friedlander synthesis of quinolines☆

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Abstract

The catalytic activity of various heterogeneous solid acid catalysts including $NaHSO_4$-SiO_2, H_2SO_4-SiO_2, Amberlyst-15 and $HClO_4$-SiO_2 on the Friedlander synthesis of quinolines has been studied. Amberlyst-15 has been found to be most effective in terms of the reaction times, yields and reusability of the catalyst. A series of quinolines have been prepared using this catalyst.

Keywords: Friedlander synthesis; Quinoline; Heterogeneous solid acid catalyst; Amberlyst-15

Quinolines are well known for a wide range of medicinal properties being used as antimalarial, antiasthmatic, antihypertensive, antibacterial and tyrosine kinase inhibiting agents [1]. They are also applied for the preparation of nano- and mesostructures having enhanced electronic and photonic properties [2]. Thus, the synthesis of quinolines is an important and useful task in organic chemistry. The Friedlander annulation is a straightforward synthesis of these compounds [3]. This method involves the acid or base catalyzed or thermal condensation between a 2-aminoaryl ketone and an another carbonyl compound possessing a reactive α-methylene group followed by cyclodehydration. Lewis acids such as $ZnCl_2$, $SnCl_2$, $Bi(OTf)_3$, $AuCl_3$, $CeCl_3.7H_2O$ and ionic liquids have also recently been utilized for this synthesis [4]. However, most of the earlier methods are associated with different disadvantages such as harsh conditions, long reaction times, poor yields and tedious experimental work. The recovery of the catalyst is also a problem. Although different methods are available for the synthesis of quinolines, development of an efficient and practically applicable preparation is still of great importance. As a part of our continuing effort towards the development of useful synthetic methodologies [5] here we report our work on the application of heterogeneous solid acid catalysts for Friedlander synthesis of quinolines.

We attempted the Friedlander annulation initially using 2-amino benzophenone and ethylacetoacetate in the presence of heterogeneous solid acid catalysts including $NaHSO_4$-SiO_2, H_2SO_4-SiO_2, Amberlyst-15 and $HClO_4$-SiO_2 in ethanol under reflux (Table 1). Considering the reaction time and yield Amberlyst-15 was found to be most effective. Subsequently a series of substituted quinolines were prepared following the same method using this catalyst (Scheme 1, Table 2).

Substituted quinolines were prepared from different 2-aminoaryl ketones and various α-methylene carbonyl compounds. 2-Aminoaryl ketones included both 2-amino acetophenone and benzophenone derivatives while the α-methylene carbonyl compounds included cycloalkanones, 1,3-diketones (cyclic and acyclic) and β-keto esters. The quinolines were formed in high yields (69–93%) within 2.0–3.5 h. The method showed the compatibility with different functional groups such as alkyl, ketone, halogen and ester. The structures of the products were settled from their spectral (^{1}H NMR and MS) data.

The catalyst, Amberlyst-15 is commercially available, inexpensive and non-hazardous. It works under heterogeneous conditions and conveniently be handled and removed from the reaction mixture by simple filtration. The recovered catalyst was reused three times consecutively showing almost equal catalytic activity.

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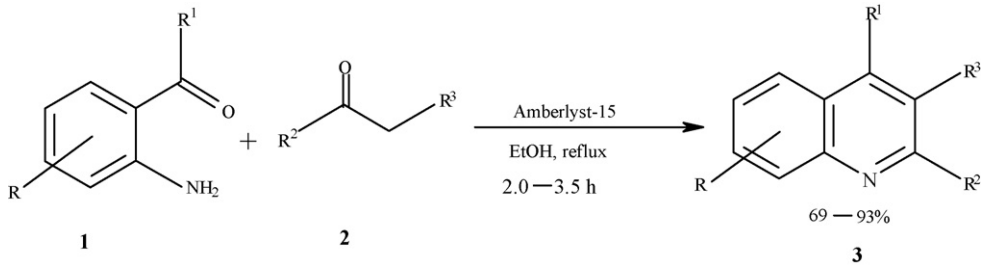
Table 1
Effect of different heterogeneous solid acid catalysts on Friedlander reaction of 2-aminobenzophenone and ethyl acetoacetate[a]

Entry	Catalyst	Amount (%, w/w)	Time (h)	Temperature[b]	Isolated yield (%)
1	None	–	12	Reflux	Trace
2	$NaHSO_4$-SiO_2	15	6	r.t	40
3	$NaHSO_4$-SiO_2	15	3	Reflux	59
4	H_2SO_4-SiO_2	10	6	r.t	47
5	H_2SO_4-SiO_2	10	3	Reflux	71
6	$HClO_4$-SiO_2	10	6	r.t	50
7	$HClO_4$-SiO_2	10	3	Reflux	73
8	Amberlyst-15	10	6	r.t	53
9	Amberlyst-15	10	2.5	Reflux	89, 87, 85, 79[c]

[a] Reaction conditions: 2-amino benzophenone (1 mmol), ethyl acetoacetate (1.2 mmol) and ethanol (6 ml).
[b] r.t: room temperature.
[c] Catalyst was used over four times.



Scheme 1.

In conclusion, the application of various heterogeneous solid acid catalysts for the preparation of quinolines via Friedlander annulation has been studied. Amberlyst-15 has been demonstrated here as the most effective catalyst for this synthesis. The simple experimental procedure and impressive yields by applying this inexpensive reusable catalyst have made this protocol practically useful for the synthesis of quinolines.

1. Experimental

1.1. Typical experimental procedure

To a mixture of 2-aminoaryl ketone (1 mmol) and α-methylene carbonyl compound (1.2 mmol) in ethanol (6 ml) Amberlyst-15 (10%, w/w) was added. The mixture was heated under reflux and the reaction was monitored by TLC. After completion, the solvent was removed under vacuum and a mixture of water (10 ml) and EtOAc (20 ml) was added. The total material was shaken and filtered to recover the catalyst. The organic portion from filtrate was separated and concentrated under reduced pressure. The residue was subjected to column chromatography over silica gel using EtOAc (8%) in hexane to obtain pure quinoline.

The recovered catalyst was used consecutively three times to afford the products with minimum variation of the yields.

The above experimental procedure was repeated using other heterogeneous solid acid catalysts such as $NaHSO_4$-SiO_2, H_2SO_4-SiO_2 and $HClO_4$-SiO_2.

The spectral (^{1}H NMR and MS) and analytical data of some representative products are given below.

1.1.1. Product 3a

^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 8.02 (1H, d, J = 8.0 Hz), 7.71 (1H, t, J = 8.0 Hz), 7.62–7.41 (5H, m), 7.40–7.30 (2H, s), 4.01 (2H, q, J = 7.0 Hz), 2.71 (3H, s), 0.90 (3H, t, J = 7.0 Hz); FABMS; m/z 292 $[M+H]^+$; Anal. Calcd. for: $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81%; Found: C, 78.28; H, 5.92; N, 4.75%.

1.1.2. Product 3b

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.08 (1H, d, J = 8.0 Hz), 7.80–7.23 (8H, m), 3.55 (3H, s), 2.72 (3H, s); FABMS: m/z 278 $[M+H]^{+\cdot}$; Anal. Calcd. for: $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05%; Found: C, 77.88; H, 5.46; N, 5.12%.

1.1.3. Product 3e

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.04 (1H, d, J = 8.0 Hz), 7.67–7.29 (8H, m), 3.21 (2H, t, J = 7.0 Hz), 2.88 (2H, t, J = 7.0 Hz), 2.22–2.10 (2H, m), FABMS; m/z 246 $[M+H]^+$; Anal. Calcd. for: $C_{18}H_{15}N$: C, 88.16; H, 6.12; N, 5.71%; Found: C, 88.25; H, 6.21; N, 5.78%.

1.1.4. Product 3g

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.99 (1H, d, J = 8.0 Hz), 7.97 (1H, d, J = 8.0 Hz), 7.69 (1H, t, J = 8.0 Hz), 7.51 (1H, t, J = 8.0 Hz), 4.46 (2H, q, J = 7.0 Hz), 2.70 (3H, s), 2.62 (3H, s), 1.46 (3H, t, J = 7.0 Hz); FABMS; m/z 230 $[M+H]^+$; Anal. Calcd.

Table 2
Amberlyst-15 catalyzed Friedlander annulation of quinolines[a]

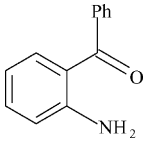
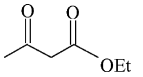
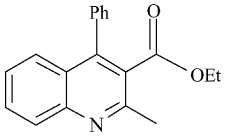
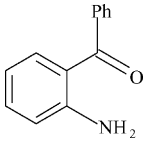
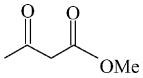
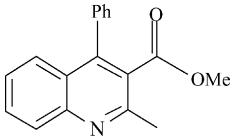
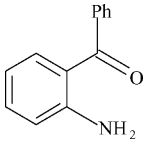
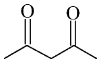
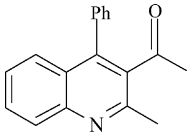
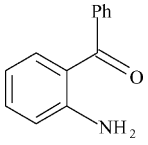
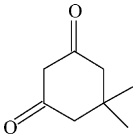
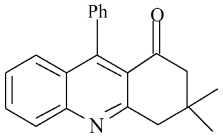
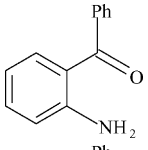
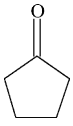
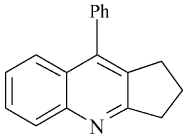
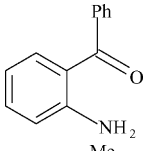
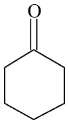
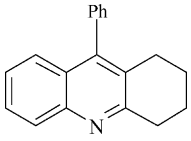
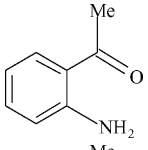
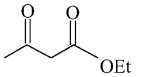
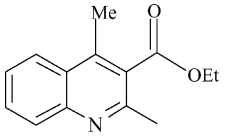
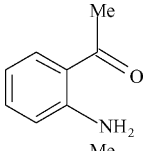
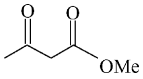
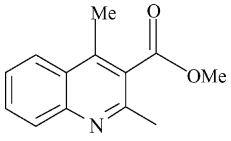
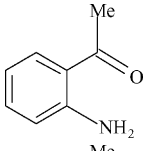
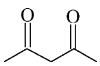
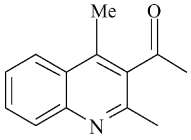
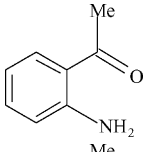
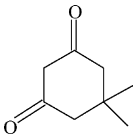
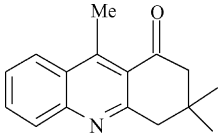
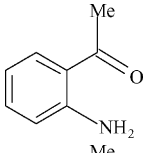
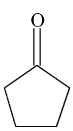
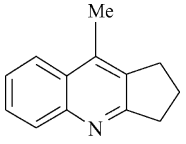
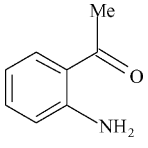
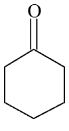
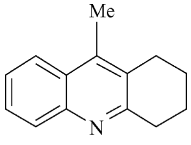
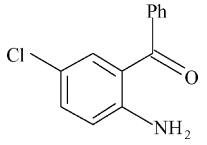
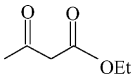
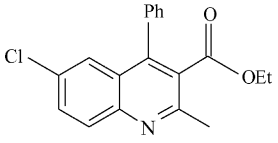
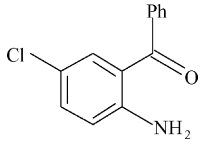
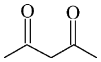
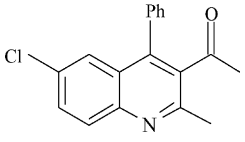
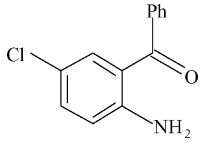
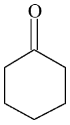
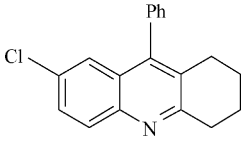
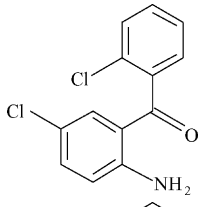
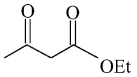
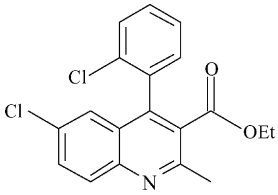
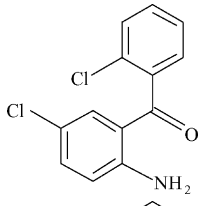
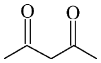
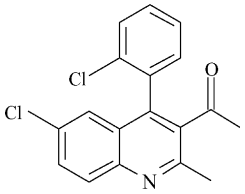
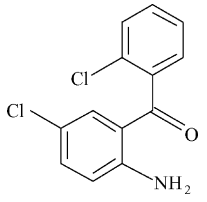
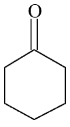
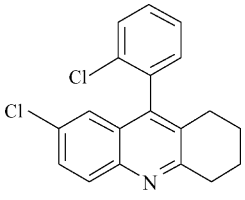
Entry	2-Aminoaryl ketone **1**	α-Methylene carbonyl compound **2**	Quinoline **3**	Time (h)	Isolated yield (%)
a				2.5	89
b				2.5	90
c				2.0	93
d				3.5	72
e				2.0	90
f				2.0	88
g				2.5	87
h				2.5	88
i				2.0	91
j				3.5	69
k				2.0	89
l				2.0	86

Table 2 (*Continued*)

Entry	2-Aminoaryl ketone **1**	α-Methylene carbonyl compound **2**	Quinoline **3**	Time (h)	Isolated yield (%)
m				2.5	87
n				2.0	90
o				2.0	85
p				2.5	75
q				2.0	82
r				3.0	76

[a] The structures of the products were settled from their spectral (^{1}H NMR and MS) and analytical data.

for: $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.11%; Found: C, 73.12; H, 6.67; N, 6.05%.

1.1.5. Product 3h

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 8.0 Hz), 7.69 (1H, t, J = 8.0 Hz), 7.01 (1H, t, J = 8.0 Hz), 3.98 (3H, s), 2.67 (3H, s), 2.62 (3H, s); FABMS: m/z 216 $[M+H]^+$; Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.05; N, 6.51%; Found: C, 72.59; H, 6.12; N, 6.59%.

1.1.6. Product 3k

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.98 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.59 (1H, t, J = 8.0 Hz), 7.43 (1H, t, J = 8.0 Hz), 3.18 (2H, t, J = 7.0 Hz), 3.07 (2H, t, J = 7.0 Hz), 2.61 (3H, s), 2.25–2.16 (2H, m); FABMS; m/z 184 $[M+H]^+$; Anal. Calcd. for: $C_{13}H_{13}N$: C, 85.25; H, 7.10; N, 7.65%; Found: C, 85.16; H, 7.17; N, 7.71%.

Acknowledgements

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