Silica Supported Phosphomolybdic Acid: An Efficient Heterogeneous Catalyst for Friedlander Synthesis of Quinolines[1)]

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Silica supported phosphomolybdic acid, an eco-friendly heterogeneous catalyst, has been found to be highly efficient for Friedlander synthesis of quinolines in excellent yields. A variety of ketones afford the quinolines smoothly. The catalyst can be easily recovered and reused.

Key words Friedlander synthesis; quinoline; silica supported phosphomolybdic acid; heterogeneous catalyst

Quinoline moiety is frequently found in natural products and bioactive compounds.[2—4)] Various quinolines are known to possess different important medicinal properties such as antimalarial, antibacterial and tyrosine kinase inhibiting activities.[3—5)] Quinolines are also employed for the synthesis of nano- and meso-structures having enhanced electronic and photonic properties.[6,7)] A straight-forward method for the synthesis of quinolines is the Friedlander annulation.[8)] This reaction involves the base or acid catalyzed or thermal condensation between a 2-aminoaryl ketone and an another carbonyl compound having a reactive α-methylene group followed by cyclodehydration. However, under thermal or base catalysis conditions 2-aminobenzophenone could not react with cyclohexanone and β-keto esters while under acid catalysis conditions side products were formed. Lewis acids such as $ZnCl_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, $AuCl_3$ and ionic liquids have also recently been employed for the synthesis of quinolines.[9—12)] However most of the methods suffer from harsh reaction conditions, prolonged reaction times, unsatisfactory yields and tedious experimental procedure. In several cases the recovery of the catalyst is also a problem. Here we report a convenient and efficient method for the preparation of quinolines using silica supported phosphomolybdic acid ($PMA \cdot SiO_2$) as a heterogeneous catalyst.

In recent years, heterogeneous catalysts have gained much importance in organic synthesis due to eco-economic benefits. In connection with our work[13—16)] on the applications of heterogeneous catalysts for the development of useful synthetic methodologies we have discovered that $PMA \cdot SiO_2$[17)] is highly effective to catalyze the Friedlander synthesis of quinolines (Chart 1).

A series of quinolines were prepared from various 2-aminoaryl ketones (**1**) and α-methylene carbonyl compound (**2**) (Table 1). The 2-aminoaryl ketones used for the preparation of quinolines included both 2-amino acetophenone and 2-aminobenzophenone while α-methylene carbonyl compounds included 1,3- and 1,4-diketones, β-ketoesters and cycloalkanones. The products were formed in high yields (81—95%) within 45—100 min. A cyclic 1,3-diketone such as dimedone (entry **3d**, **3o**) also underwent the conversion smoothly. The reaction is free of side products, which are generally formed by self-condensation of ketones under basic conditions. The structures of the quinolines were established from their spectral (^{1}H-NMR and MS) data.

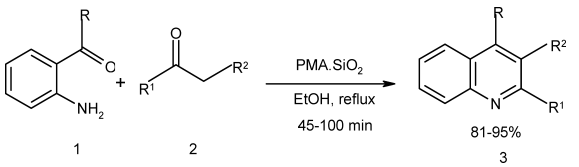

Chart 1

The catalyst, $PMA \cdot SiO_2$ is important from an environmental point of view as it works under heterogeneous conditions and possesses low toxicity and high stability.[17)] Its catalytic activity towards the synthesis of quinolines is impressive. It was recovered from the reaction mixture and reused. In absence of the catalyst or in the presence of only silica gel the reaction could not proceed while in the presence of only PMA the yields were low.

In conclusion, we have developed an efficient general route for the synthesis of quinolines *via* Friedlander annulation using $PMA \cdot SiO_2$ as a novel catalyst. The simple experimental procedure, mild reaction conditions, excellent yields, rapid conversion and recovery of the catalyst are the notable advantages of the present protocol. The catalyst is highly suitable for the preparation of diverse types of quinoline derivatives.

Experimental

To a mixture of 2-aminoaryl ketone (1 mmol) and α-methylene carbonyl compound (1.1 mmol) in EtOH (5 ml) $PMA \cdot SiO_2$ (10%, 100 mg) was added. The mixture was heated under reflux and the reaction was monitored by TLC. After the completion the mixture was filtered and the catalyst was recovered. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (silica gel, 5% EtOAc in hexane) to obtain pure quinoline derivative.

The recovered catalyst was used consecutively three times to afford the product without hampering its yield. As for an example, the reaction of 2-aminoacetophenone with ethyl acetoacetate in the presence of the catalyst ($PMA \cdot SiO_2$) afforded the corresponding quinoline (**3a**, Table 1, entry a) in an yield of 88% while the same reaction using the recovered catalyst in consecutive three cycles furnished the products in the yields of 88, 87 and 87%.

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

Product **3b** (Table 1): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.98 (2H, t, J=8.0 Hz), 7.68 (1H, t, J=8.0 Hz), 7.50 (1H, t, J=8.0 Hz), 3.98 (3H, s), 2.65 (3H, s), 2.61 (3H, s); FAB-MS: m/z 238 $[M+Na]^+$.

Product **3g** (Table 1): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.75 (1H, d, J=8.0 Hz), 7.57 (1H, t, J=8.0 Hz), 7.49 (1H, t, J=8.0 Hz), 7.21 (1H, d, J=8.0 Hz), 5.88 (2H, s), 1.97 (6H, s), 1.72 (3H, s); FAB-MS: m/z 236 $[M+Na]^+$.

Product **3h** (Table 1): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.02 (1H, d, J=8.0 Hz), 7.71 (1H, t, J=8.0 Hz), 7.60—7.42 (5H, m), 7.40—7.29 (2H, m), 4.02 (2H, q, J=7.0 Hz), 2.71 (3H, s), 0.94 (3H, t, J=7.0 Hz), FAB-MS: m/z 314 $[M+Na]^+$.

Product **3l** (Table 1): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.05 (1H, d, J=8.0 Hz), 7.66—7.29 (8H, m), 3.22 (2H, t, J=7.0 Hz), 2.90 (2H, t, J=7.0 Hz),

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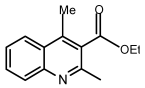
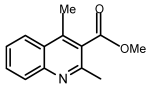
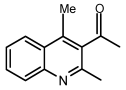
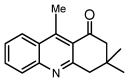
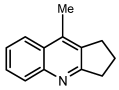
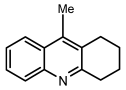
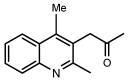
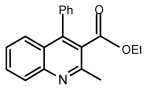
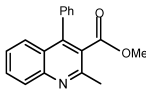
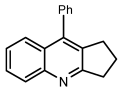
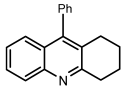
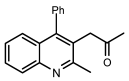
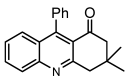
Table 1. PMA·SiO_2 Catalyzed Friedlander Annulation of Quinolines[a)]

Entry	2-Aminoaryl ketone **1**	α-Methylene carbonyl compound **2**	Quinoline **3**	Time (min)	Yield (%)[b)]	mp (°C) Observed (Reported)
a				75	88	Oil[18)]
b				65	86	77—78
c				60	91	Oil[19)]
d				100	81	104—105 (105—106)[19)]
e				85	93	57—59 (58—60)[19)]
f				50	95	76—78 (75—77)[19)]
g				65	90	72
h				60	94	95 (96)[20)]
i				45	90	68—69
l				75	89	131 (132)[20)]
m				70	82	139 (139)[20)]
n				55	90	115
o				90	80	190 (190—192)[20)]

a) The structures of the products were established from their spectral (^{1}H-NMR and MS) data. *b*) Isolated yield.

2.23—2.08 (2H, m); FAB-MS: *m*/*z* 268 $[M+Na]^+$.

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