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$NaHSO_4/SiO_2$: Solvent-Free 반응 조건에서 β-Enaminone들과 2-Methylquinolin-4(1*H*)-One들의 합성을 위한 효율적인 촉매

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$NaHSO_4/SiO_2$: An Efficient Catalyst for the Synthesis of β-Enaminones and 2-Methylquinolin-4(1*H*)-Ones under Solvent-Free Condition

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요약. 마이크로 반응을 이용하여 $NaHSO_4/SiO_2$ 을 촉매로 하는 solvent-free 합성을 통하여 β-enaminone 과 2-methylquinolin-4(1H)-one 및 그 유도체를 합성하는 효율적인 방법을 개발하였다. 반응 시간이 짧고, 수율이 좋았으며, 마이크로웨이브를 사용하지 않는 반응보다는 높은 선택성, 간단성, 무용매 반응 및 친환경적인 반응이다.

주제어: $NaHSO_4/SiO_2$ Catalyst, β-Enaminones, Quinoline-4-Ones, 축합반응

ABSTRACT. An efficient and simplified protocol for $NaHSO_4/SiO_2$ catalyzed solvent-free synthesis of β-enaminone and 2-methylquinolin-4(1H)-one derivatives under microwave irradiation is described. A series of functionalized derivatives have been synthesized in shorter reaction times with moderate to good yields. The use of milder catalyst in non-conventional method offers significant advantages over conventional methods, such as higher selectivities, simplicity, solvent-free reaction and non-environmental polluting conditions.

Keywords: $NaHSO_4/SiO_2$ Catalyst, β-enaminones, Quinoline-4-Ones, Condensation

INTRODUCTION

Nitrogen containing organic compounds are of special interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. Among those compounds, β-enaminones have been employed as synthetic building block of a wide veriety of heterocycles,[1] key intermediate in synthesis of different heterocycles and naturally occouring alkaloids[2] and in pharmaceuticles.[3] Despite the importance of β-enaminones as valuable biologically active compounds, their synthesis has received great attention of chemists and hence several routes have been recently reported in literature using Lewis acids,[4] P_2O_5/SiO_2,[5] Cu-nanoparticles,[6] and heteropoly acid.[7] In addition, β-enaminone have also been synthesized by using non-traditional methods.[8]

Another nitrogen containing heterocyclic compound is quinoline moiety. Quinolines possess diverse biological as well as physiological activities such as, anti-malerial, anti-tuberculosis, antagonists and anti-cancer activity.[9] Realizing the importance of quinoline molecule, several methods have been reported in literature such as, by the condensation of *o*-amino aldehyde/ketones,[10] Skraup,[11] Knorr,[12] Conard-Limpach,[13] Dober-Vonmiller,[14] Combs,[15] Friedlander[16] etc. Moreover, H_2SO_4,[17] $AcOH/CaSO_4$ in Ph_2O at 250 ^oC[17] and *P*-TsOH in EtOH/xylene at 250 ^oC[19] has been recently reported.

Unfortunately many of these methods for the synthesis of β-enaminones and quinolines suffers from relevant limitations such as, drastic condition, low product yield, tedious work-up procedure, low selectivity, and required chromatographic isolation technique. Therefore, search of new simple, clean and one-pot method for the synthesis of desired organic compounds is of prime interest. In search of better alternatives, we have paid attention to find convenient and efficient method based on green approach for the synthesis of β-enaminones and quinoline-4-one derivatives.

Solvent-free reactions have attracted much attention in

organic synthesis in recent years,[20] not only because solvent-free reactions offers practical advantages over reactions in organic solvents from economical, environmental and safety standpoints, but also because solvent-free reactions usually need shorter reaction time, low costs, simplicity in process, handling and no need to use harmful organic solvents. These factors are beneficial to industry as well as to environment. Thus solvent-free reactions are one of the most important synthesis techniques in green chemistry. Various solvent-free reactions were found to occurs using microwave irradiation.[21] Microwave irradiation takes a particular place being an emerging technique that provides an alternative to conventional heating by introducing energy into chemical reaction. Hence microwave technique has been successfully applied because of some advantages such as, very fast heating, better homogeneity in reaction temperature, shorter reaction time, improved conversion and clean product formation. Therefore, we would like to report the solvent-free synthesis of β-enaminones and 4-quinolones under microwave irradiation.

EXPERIMENTAL

All starting materials and reagents were commercially available and used without further purification. All the melting points were taken in an open capillary and are uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC). IR spectra were recorded on Perkin-Elmer FT-IR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on mercury plus Varian spectrometer at 400 MHz in DMSO-d_6 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

GENERAL PROCEDURE

Synthesis of β-enaminones

A mixture of aromatic amines (1 mmol), dimedone (1 mmol) and $NaHSO_4/SiO_2$ (0.5 g) were taken in a beaker. The reaction mixture homogenized with the help of glass rod and irradiated in microwave oven (180 W) by the interval of 10 second. The progress of reaction was monitored on TLC. After completion of the reaction, mixture was cooled to room temperature and poured on crushed ice. Thus, solid obtained was filtered, dried and purified by crystallization in ethanol.

Synthesis of 2-methylquinolin-4(1*H*)-ones

A mixture of anilines (1 mmol), ethyl acetoacetate (1 mmol) and $NaHSO_4/SiO_2$ (0.5 g) were taken in beaker. The reaction mixture was homogenized with the help of glass rod and irradiated under microwave oven (360 W) by interval of 10 second. After completion of the reaction as indicated on TLC. The reaction mixture was cooled at room temperature and poured on crushed ice. Thus, solid obtained was filtered, dried and purified by crystallization in ethanol.

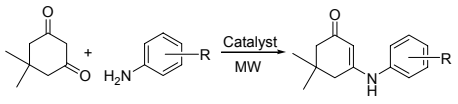
RESULTS AND DISCUSSION

In continuation of our research work on microwave assisted organic reactions for the synthesis of various bioactive compounds,[20a,22] herein an effective strategies catalyzed by $NaHSO_4/SiO_2$ under microwave irradiation have been discussed.

Initially we examined the efficiency of different catalysts for the condensation reactions of aniline with dimedone as representative reactants under microwave irradiation at 180 W (*Table* 1).

Our initial investigation focused on the use of acidic catalyst such as Lewis acids, acidic salts for the synthesis of β-enaminones by the condensation of the reactants. In search of an efficient catalyst and the best experimental condition, the preferred reactions in the presence of catalyst at 180 W have been considered. After successful screening of different catalysts shown in Table 1, it has been found that acidic salt $NaHSO_4$ in combination with SiO_2 as a solid support act as a best promoter for this reaction and gives 90% product yield within 4 min (*Table* 1, entry 7). This amazing result is may be due to $NaHSO_4$ act as Brønsted acid which protonate carbonyl oxygen of dimedone to enhance the electrophilicity of that carbonyl carbon preferably on the active solid support of SiO_2 to afford respective product yield. Such type of stepping-up performance about other catalysts was not ob-

***Table* 1.** Screening of different catalyst for the synthesis of β-enaminones



Entry	Catalyst	Time (min)	Yield (%)[a]
1	$MgSO_4$	15	30
2	$ZnCl_2$	20	25
3	Na_2SO_4	15	40
4	TiO_2	20	> 20
5	$NaHSO_4$	10	65
6	SiO_2	10	60
7	$NaHSO_4/SiO_2$	4	90

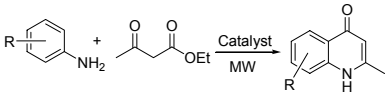
[a]Isolated yield

***Table* 2.** Synthesis of β-enaminone derivatives catalyzed by $NaHSO_4/SiO_2$

Products[a]	R	Time (min)	Yield (%)	mp °C
1	H	4	90	183 - 185
2	4-F	4	89	190 - 192
3	4-OMe	6	90	106 - 108
4	4-Br	5	88	164 - 166
5	4-Me	4	91	144 - 146
6	4-OEt	7	88	110 - 112
7	2,3-diCl	8	87	200 - 202
8	2-Me	5	89	133 - 135
9	3-Me	6	90	139 - 141
10	4-Cl	5	90	149 - 151

[a]Isolated product yield and all products were characterized from their spectroscopic (IR, ^{1}H NMR and MS) data and compared with authentic samples.

***Table* 3.** Screening of suitable catalyst for the synthesis of 4-quinolones



Entry	Catalyst	Time (min)	Yield (%)[a]
1	EPZ-10	30	> 20
2	EPZG	30	> 20
3	$MgSO_4$	20	35
4	Na_2SO_4	20	30
5	TiO_2	15	40
6	Al_2O_3	15	55
7	SiO_2	15	70
8	$NaHSO_4$	10	60
9	$NaHSO_4/SiO_2$	5	92

[a]Isolated yield

served (*Table* 1, entries 1-4).

Meanwhile, $MgSO_4$, Na_2SO_4, TiO_2, and $ZnCl_2$ have also been screened and required longer reaction time under microwave irradiation and conversion of reactant into corresponding products is less (> 20 - 40%). Even though use of $NaHSO_4$ or SiO_2 does not results into higher yield as it has given in combination of $NaHSO_4/SiO_2$ (*Table* 1, entry 5, 6). Herein we would like to report the combination of catalysts $NaHSO_4/SiO_2$ as a best catalyst for the synthesis of β-enaminone derivatives under microwave irradiation.

Our next attempt was to perform synthesis of 4-quinolone derivatives by the cyclocondensation of aromatic anilines with ethyl acetoacetate under solvent-free condition. The catalytic influence of various inorganic solid supports on the condensation of aniline with ethyl acetoacetate under microwave irradiation at 360 W has studied and the results are as shown in *Table* 3.

***Table* 4.** Synthesis of 4-quinolone derivatives catalyzed by $NaHSO_4/SiO_2$

Products[a]	R	Time (min)	Yield (%)	mp °C
1	H	5	92	132 - 134
2	4-F	4	93	141 - 143
3	4-OMe	5	90	129 - 131
4	4-Me	5	90	222 - 224
5	4-OEt	6	88	152 - 154
6	2,3-diCl	6	87	147 - 149
7	4-Br	5	92	126 - 128
8	2-Me	5	90	199 - 201
9	3-Me	6	90	195 - 197
10	3-OMe	6	90	112 - 114
11	3-Cl	6	89	208 - 210
12	2-Cl	5	87	214 - 216
13	4-Cl	5	90	202 - 204

[a]Isolated product yield and all products were characterized from their spectroscopic (IR, ^{1}H NMR and MS) data and compared with authentic samples.

In order to select an appropriate catalyst for the synthesis of 4-quinolones under solvent-free condition, initially we have screened the acidic clays such as, EPZ-10 and EPZG for the preferred reaction, it was observed that no significant product was formed even after 30 min (*Table* 3, entries 1,2). Moreover, starting materials were subjected with $MgSO_4$, Na_2SO_4 as compared to acidic clays; these gives more yield (*Table* 3, entries 3,4). In addition, we examined the TiO_2, Al_2O_3, and SiO_2 among these SiO_2 gives appreciable yield within 15 min (*Table* 3, entry 7). Fortunately, we think over acidic salt like $NaHSO_4$ and applied for the same reaction under microwave irradiation after 10 min 65% reactants were converted into corresponding product. Finally, we decided to use combination of catalyst $NaHSO_4/SiO_2$ amazingly, we obtained 92% product yield (*Table* 3, entry 9). As discussed in earlier results $NaHSO_4/SiO_2$ plays same mechanistic role to promote the rate of reaction furnishing better yield within shorter reaction time. When aromatic anilines and ethyl acetoacetate react with each other in the presence of $NaHSO_4/SiO_2$ under microwave irradiation, the cyclization of quinoline ring takes place through emine- enamine tautomerization eliminating water molecules we got appreciable yields of desired products within shorter reaction time as shown in *Table* 4.

Spectral Data for representative compounds

4-Br-enaminone: IR (KBr, cm^{-1}): 3264, 1592, 704; ^{1}H NMR (400, MHz, DMSO-d_6, δ ppm) 1.02 (6H, s), 2.14 (2H, s),

2.36 (2H, s), 5.13 (1H, s), 6.66 (1H, s broad peak), 6.96 (2H, d, J = 8.6 Hz), 7.39 (2H, d, J = 8.6 Hz); ^{13}C NMR (DMSO-d_6, TMS) δ = 26.8,28.5, 31.8, 44.1, 50.4, 100.2, 121.6, 129.8, 132.7, 140.3, 143.2, 198.7; ES-MS: *m*/*z* (m+): 393.

2,6-dimethyl-1*H*-quinolin-4-one: IR (KBr, cm^{-1}): 3255; 1628; ^{1}H NMR (400, MHz, DMSO-d_6, δ ppm): 2.05 (3H, s); 2.27 (3H, s); 5.99 (1H, s); 7.09 (1H, d, J = 7.5 Hz); 7.38 (1H, t,); 9.10 (1H, s); ^{13}C NMR (DMSO-d_6, TMS) δ = 20.87, 29.70, 98.51, 114.73, 120.26, 122.58, 126.43, 129.45, 134.20, 163.72, 205.03; ES-MS: *m*/*z* (m+): 173.

CONCLUSION

In conclusion, we have described simple, efficient and one-pot synthesis of some β-enaminones and quinoline-4-one derivatives under microwave irradiation in the presence of $NaHSO_4/SiO_2$ as a catalyst. The synthetic utility of the methodologies demonstrated in this work, whilst contributing the part of green and clean chemistry to sustain the human health and environment unaffected. The remarkable advantages offered by the methods presented are use of safer and ecofriendly catalysts, mild reaction conditions, simplicity of the reaction procedure and high yielding strategies.

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