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Synthesis of quinolines and their *In vitro* antioxidant activities under solvent free conditions by using the SiO_2–Zn–MgO as a novel and reusable catalyst

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ABSTRACT

The present study was aimed to determine a novel route of synthesis of quinolines and their *in vitro* antioxidant activities. Synthesis of quinolines is simple, economic, effective and an easy way process has been developed by using the SiO_2–Zn-MgO as a novel catalyst. The quinolines antioxidative potential was evaluated using 1,1-Diphenyi-2-Picrylhydrazyl (DPPH), superoxide radical, hydroxyl radical, and hydrogen peroxide radical assay by *in vitro* methods. Quinolines exhibited highest level of antioxidant activities, and therefore it could be used as antioxidant that may have potential benefits in health and disease management.

INTRODUCTION

Quinolines are the naturally occurring alkaloids containing a hetero atom (Nitrogen) in the skeleton. Friedlander annulation is the well known named reaction for the preparation of quinolines from the past 100 years (Wu *et al*., 2005; Narasimhulu *et al*., 2007). For the condensation of quinolines so much acid catalysts were applied in friedlander reactions, which were most effective in such conditions like sulfamic acid (Yadav *et al*., 2005), phosphoric acid (Das *et al*., 2007), HCl (Wang *et al*., 2006) and other more catalysts like triflates (Atechian *et al*., 2007), ionic liquids (Palimkar *et al*., 2003). Somehow, these all above mentioned catalysts undergo from poor yields, relatively expensive, lengthy times, difficulties to work-up, and tedious procedures (Ghassamipour and Sardarian, 2009).

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To handle this particular condensation in smooth way, we have developed a neutral, heterogeneous solid catalyst under solvent free conditions with effect of inexpensive and the yields were at 98%. The increasing yields were due to the large surface area, surface activity of the catalyst with effect of reduced time to get the products. Quinolines are having wide applicability towards pharmacological, antihypertensive, antimalarial, antibacterial and insecticidal agents (Kalluraya and Sreenivas, 1998; Doube *et al*., 1998; Chen *et al*., 2001; Rajanarendar *et al*., 2012). However, the role of reactive oxygen species (ROS) has been implicated in several diseases including cancer, diabetes, and cardiovascular diseases (Valko *et al*., 2007). Antioxidants are vital substances which possess the ability to protect the body from damage caused by free radical induced oxidative stress (Sherwin, 1990). There is an increasing interest in antioxidants which are might help in preventing oxidative damage. Therefore, the purpose of this present study was to investigate quinolines synthesis by an eco-friendly, effective, inexpensive and smooth rea ction handlings in the

presence of SiO_2-Zn-MgO as a reversible catalyst under solvent free conditions and antioxidant activity by using different *in vitro* methods.

MATERIALS AND METHODS

Catalyst Preparation

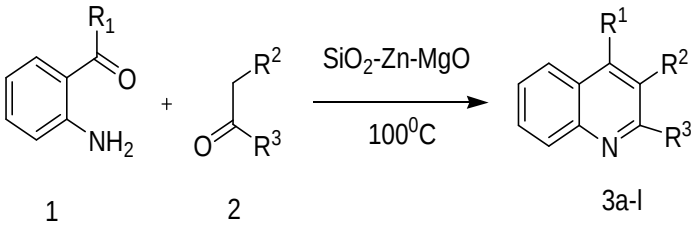
Chemicals like SiO_2, Zn (powder), MgO were purchased from Merck, Darmstadt, Germany. In the experiment, three components SiO_2 (0.5 gm), Zn (powder) (0.5gm), MgO (0.5gm) were dissolved in 100 ml of deionized water at room temperature to form a homogeneous mixture. Then it was refluxed for 8 hours and cooled.

It was centrifuged and washed with deionized water and absolute ethanol and dried at 75°C for 6 hours. The coordinated SiO_2---Zn---MgO catalyst was obtained by calcining the precursor in a furnace in air at 400°C for 1hour.

General procedure synthesis of quinoline derivatives

To a mixture of α-methylen carbonyl compound (1.8 mmol) and 2-amino aryl ketone (1.2 mmol), SiO_2–Zn–MgO (0.006 gm, 10 mol%) was added. This reaction mixture was heated at 100°C and the reaction was monitored by TLC, G.C. After the completion of the reaction, Ethylacetate (EtOAc) was added to the reaction mixture and centrifuge to decant the catalyst.

The organic layer was evaporated under reduced pressure. It was purified by chromatography on silica gel (70:30 n-Hexane: Ethylacetate), the light yellow solid and was recrystallized by ethanol was obtained. All the products were characterized by ^{1}HNMR, FTIR, Mass spectra. The selected compounds 3d, 3e, 3j were given as spectral data. In the view of fluoro and non-fluoro examples 3e and 3j were examined for their biological activities given at table number 3.



1 2 3a-l

R^1 = -CH_3 , Ph. **R^2** = COMe , CO_2Me , $COCF_3$, CO_2Et, CH_3

R^3 = CH_3 , CF_3

SCHEME-1

Spectral Data

Compound 3d: (light yellowish solid) (m.p 153-158°C), ^{1}HNMR ($CDCl_3$) : δ 7. 89 – 7.94 (2m, 2H/Ar-H) 7.40 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 2.45 (3H, S, -CH_3), 2.35 (3H, S, - CH_3) Mass (M/Z) : 253 (M^+), 221.

Compound (3e) **:** light yellowish solid (m.p 84-88°C), ^{1}HNMR ($CDCl_3$) δ 7.3 – 7.4 (m, 4H, ArH), 3.81 – 4.1 (m, 2H, -OCH_2), 2.41(s, 3H, $ArCH_3$), 1.2 (t, 3H, J = 7.2 Hz, OCH_2 (CH_3), Mass (m/z) : 283 (M^+), 251.

Compound (3i) : light Yellow solid (m.p 163-166°C) ^{1}HNMR (($CDCl_3$) ; δ 7.2 – 8.1 (9H, m, ArH), 5.0 (m, 2H, -OCH_2), 2.0 (t, 3H, J = 7.0 Hz, - OCH_2 (CH_3) : Mass (m/z) : 345 (M^+), 313.

In vitro antioxidant studies

The DPPH free radical scavenging activity of 3e and 3j was determined by the method of Bilos, (1958). The superoxide radical scavenging activity was determined using NBT (nitroblue tetrazolium reagent) method as described by Nishikimi *et al*., (1972). The hydroxyl radical scavenging activity was determined using modified method of Halliwell *et al*., (1987). The ability of the 3e and 3j to hydrogen peroxide scavenging activity was assayed according to the method of Ruch *et al*., (1989).

RESULTS AND DISCUSSION

In the view of the good results, the catalyst acquired additional surface area with the support of SiO_2 (Silica gel-GF 254) along with Zn powder, as well as commercially available MgO towards the synthesis of biologically active quinolines and their derivatives, we have shown a lot of continued effort. In this way, α-amino acetophenone (1a) was reacted with ethylacetoacetate (2a) in the presence of metal oxide as shown in the scheme-1 (Table-1). Two kinds of metal oxides SiO_2-Zn-MgO, SiO_2-MgO were used. We examined the reaction under organic solvents and water which requires longer reaction times and afford low yields of the product (entries -2,4), while the reaction was failed in water (entry 8)

Table. 1: Optimization of the Synthesis of quinolines (3a[a]).

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	SiO_2 – Zn – MgO (2mol%)	None	20	60
2	SiO_2 – Zn – MgO(5mol %)	None	10	90
3	SiO_2 – Zn – MgO (10mol %)	None	3	98
4	SiO_2 – Zn – MgO (20mol%)	None	3	96
5	SiO_2 – Zn – MgO (10mol%)	Tolune	20	Trace
6	SiO_2 – Zn – MgO (10mol %)	THF	20	Trace
7	SiO_2 – Zn – MgO (10mol %)	CH_3CN	20	Trace
8	SiO_2 – Zn – MgO (10mol %)	H_2O	20	0

[a]Conditions: A mixture of 1a (1.2 mmol) and 2a (1.8mmol) and catalyst were heated at 100°C . [b]Isolated yield

The reaction was explored under solvent free conditions, affords the best results, shown in table (1), table (2), and applied the same reaction procedures to obtain 3a-3l series **(3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l)** under solvent free conditions (Scheme-1). We had not found any other isomeric products other than 3a-3l series in our experiment with ^{1}HNMR of the crude product mixture. All the compounds were well characterized by

Table. 2: Synthesis of substituted quinolines (3a-l) under solvent free conditions.

Entry	R^1	R^2	R^3	Catalyst	Time (h)	Yields (%)[a]
3a	CH_3	COMe	CH_3	SiO_2-Zn-MgO	9	98
3b	CH_3	CO_2Me	CH_3	SiO_2-Zn-MgO	4	95
3c	CH_3	CO_2Et	CH_3	SiO_2-Zn-MgO	6	97
3d	CH_3	$COCF_3$	CH_3	SiO_2-Zn-MgO	5	94
3e	CH_3	CO_2Et	CF_3	SiO_2-Zn-MgO	6	97
3f	CH_3	CH_3	CH_3	SiO_2-Zn-MgO	3	98
3g	CH_3	CH_3	CF_3	SiO_2-Zn-MgO	4	96
3h	CH_3	$COCF_3$	CF_3	SiO_2-Zn-MgO	4	94
3i	Ph	CO_2Et	CF_3	SiO_2-Zn-MgO	6	94
3j	Ph	CO_2Me	CH_3	SiO_2-Zn-MgO	8	98
3k	Ph	COMe	CH_3	SiO_2-Zn-MgO	7	97
3l	Ph	$COCF_3$	CH_3	SiO_2-Zn-MgO	5	93

[a] Yields were isolated

Table. 3: *In vitro* antioxidant activities of quinolines (3e, 3j).

Concentration (µg/ml)		1	2	5	10	20	IC_{50}
DPPH radical Scavenging activity (%)	**3e**	38.57 ± 0.13	43.62 ± 0.19	59.89 ± 0.11	73.42 ± 0.12	88.43 ± 0.14	**3.39 ± 0.08**
	3j	39.54 ± 0.16	46.63 ± 0.11	61.92 ± 0.22	77.23 ± 0.15	91.69 ± 0.12	**2.54 ± 0.06**
Super oxide scavenging activity (%)	**3e**	29.36 ± 0.11	34.39 ± 0.09	46.39 ± 0.12	59.13 ± 0.09	73.55 ± 0.08	**8.22 ± 0.04**
	3j	31.45 ± 0.07	39.23 ± 0.07	48.32 ± 0.09	65.14 ± 0.11	78.52 ± 0.17	**6.54 ± 0.07**
Hydroxyl radical scavenging activity	**3e**	31.67 ± 0.05	39.23 ± 0.05	57.78 ± 0.07	64.41 ± 0.09	79.24 ± 0.08	**5.67 ± 0.05**
	3j	34.29 ± 0.07	43.52 ± 0.11	58.23 ± 0.09	72.45 ± 0.12	88.14 ± 0.08	**4.11 ± 0.05**
Hydrogen peroxide scavenging	**3e**	34.62 ± 0.08	42.24 ± 0.09	59.71 ± 0.11	72.33 ± 0.12	86.44 ± 0.11	**4.10 ± 0.04**
	3j	35.47 ± 0.11	46.35 ± 0.09	64.35 ± 0.11	75.24 ± 0.14	89.76 ± 0.12	**2.93 ± 0.03**

melting point, ^{1}HNMR, Mass spectroscopy and elemental analysis with high regiospecificity. The catalytic activity of the SiO_2-Zn-MgO had shown high regioselectivity for the yields compared to SiO_2-MgO which was examined and neglected due to low yields (20 %). The Lewis base sites (O^{2-}) and Lewis acid sites (Mg^+) Si^+, Zn^+ from the source of the catalyst was one of the major reason for the good yields.

The *in vitro* antioxidant activity of 3e and 3j was shown in table 3. The IC_{50} value of 3e and 3j of DPPH was calculated to be 3.39 µg/ml, 2.54 µg/ml. While for the standard Vitamin C it was 35.13µg/ml respectively. The IC_{50} value of the 3e and 3j of the superoxide radical was found to be 8.22 µg/ml, 6.54 µg/ml and it was lower than that of the standard drug Vitamin C (27.34 µg/ml). The IC_{50} value of the 3e and 3j of the hydroxyl radical scavenging activity was 5.67 µg/ml, 4.11 µg/ml and the IC_{50} value of 3e and 3j was lower than the standard, Vitamin E (41.82 µg/ml). The Hydrogen Peroxide scavenging activity IC_{50} values for 3e, 3j were found to be 4.10 µg/ml and 2.93 µg/ml respectively, and it was lower than that of the standard drug Vitamin C (23.34 µg/ml). In the present study 3e (example of fluoro-compound) and 3j (example non-fluoro compound) was able to show the antioxidant properties like DPPH radical scavenging activity, superoxide radical scavenging activity, hydroxyl radical scavenging activity, hydrogen peroxide scavenging activity. The 3e and 3j was found to be efficacy against free radicals due to the presence of different substituents {3e = CH_3 [R_1], COOEt [R_2], CF_3 [R_3], 3j = Ph [R_1], $COOCH_3$ [R_2], CH_3 [R_3] } which are different from the rest of the synthesized compounds and might be useful in preventing free radical induced disorders like cardiovascular disease, diabetes and cancer etc (Ghinet *et al*., 2012).

CONCLUSION

The following conclusions are drawn from the above experimental observations. By supporting Zn (powder) on SiO_2, MgO a considerable amount of Lewis acid sites and Lewis base sites could be generated due to the formation of coordinating interaction between metal oxides, due to the reaction the selectivity of the products were increased. Quinolines are act like antioxidants and prevent oxidative stress induced disorders.

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