2-MORPHOLINOETHANESULFONIC ACID CATALYZED ONE POT SYNTHESIS OF ISOINDOLO [2,1-a]QUINAZOLINE AT ROOM TEMPERATURE UNDER ULTRASONICATION

D. S. Bhagat[a], M. V. Katariya[a], R. D. Ingle[a], V. M. Joshi[b], M. R. Bachhav[b], R. N. Udavant[c] and R. P. Pawar [a]*

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An efficient and greener one pot method has been developed for the synthesis of isoindolo[2,1-*a*]quinazolines using 2-morpholinoethane sulfonic acid as a water soluble green catalyst at ambient temperature and excellent yield of product. The synergetic effect of 2-morpholineethane sulfonic acid and ultrasound irradiation process has been also discussed.

* Corresponding Authors
Fax: +91 0240 2334430
Tel.: +91 0240 2334577
E-Mail: rppawar@yahoo.com
[a] Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, India
[b] Department of Chemistry, K.R.A. Arts, Science and Commerce College, Deola, Nasik, India
[c] Department of Chemistry, Dnyanopasak College, Parbhani 431 401, India

Introduction

Construction of complex molecules through multicomponent reactions (MCRs) under ultrasonication constitutes a very attractive strategy in organic synthesis. Sonochemistry is widely used in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Ultrasound is the part of the sonic spectrum, which ranges about 20 to 100 MHz and can be roughly subdivided in three main regions: low frequency high power ultrasound (20–100 kHz), high frequency medium power ultrasound (100 kHz–1 MHz), and high frequency low power ultrasound (1– 10 MHz). Sonochemistry involves the use of ultrasound technique to promote the chemical reactions.[1] Ultrasonic irradiation has been introduced as an eco-environmental technology in green chemistry.[2] Ultrasonic energy provides an unusual mechanism to generate high-energy chemistry owing to the extraordinary temperature and pressure generated by the cavitations bubble collapse.[3]

Some compounds synthesized by using ultrasonication are pyrimidine,[4] 5-(pyrazol-4-yl)-4,5-dihydropyrazoles,[5] benzimidazoles, benzoxazoles and benzothiazoles,[6] amine-*N*-Oxides,[7] polyhydroquinolines[8] and Schiff's bases.[9] In MCRs three or more reactants are involved in a cascade of bond-forming individual steps to provide a complex molecule without isolation of intermediates or modification of the reaction conditions. Attractive features of MCRs are simplicity of operation, reduction in isolation and purification steps, and minimization of costs, time, energy, solvents, and waste production. 2-Morpholinoethanesulfonic acid (2-MESA) mediated reactions at room temperature in ultrasonication have been explored as a green approach for this purpose.

The quinazolinone moiety is a building block for approximately 150-200 natural important sub-structure of various biologically active natural products such as bhimamycin C, and bhimamycin D,[10] potent inhibitors of TNF-aw,[11] antifungal,[12] anti-tumour activity,[13,14] antibacterial,[15] anti-inflammatory,[16,17] anticonvulsant,[18] analgesic[19] and antitubercular.[20] Drugs containing quinazolinone moirty showed significant therapeutic efficiency against solid tumors,[21] antimalarial,[22] antivirals,[23] antimicrobial activities,[24,25] ovarian cancer cell lines and are also EP4 receptor agonists in the treatment of pain,[26] anticancer,[27] cytotoxicity and anti-HIV.[28]

The title synthesis has been carried out under different reactions conditions viz., without catalyst and solvent[29] and catalyzed by Pt-multi-walled carbon nanotubes (Pt-MWCNTs),[30] *Saccharomyces cerevisiae*,[31] montmorillonite K10 and (+)-camphor-10-sulfonic acid (CSA)[11] and DEAD[32], etc. A comparison of the yields is given in Table 1.

Experimental

General procedure for synthesis of 6-phenyl-6,6a-dihydroiso-indolo[2,1-a]quinazoline-5,11-dione (1)

To a mixture of isotonic anhydride (1 mmol), 2-formylbenzoic acid (1.1 mmol) and aniline (1.2 mmol) in ethanol (2.0 mL), 2-MESA (15 mol %) was added. The reaction vessel was irradiated in sonication bath for a period ranging from 1.8 to 2.8 h. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature the reaction mixture was poured onto ice cold water and the crude product was recrystallized from ethanol. Some derivatives were purified by column chromatography technique. The general reaction is depicted in Scheme 1.

Structures of the synthesized products were confirmed by comparison of their melting points with authentic values reported in literature and spectral data like ^{1}H NMR, IR, and LRMS.

Table 1. Comparison of catalyst and solvent on yields under different reaction conditions.

S. No.	Catalysts	Time	Yield (%)	Temp. (°C)	Solvent	Ref.
1	Pt-MWCNTs	15	95	600	EtOH	[30]
2	S. cerevisiae	2 h	84	RT	THF	[31]
3	CSA	6 min	72	80–850	EtOH	[11]
4	DEAD	10-12 h	40	RT	EtOH	[32]
5	No catalyst	3 h	80	1500	-	[29]
6	2-MESA	2h	90-98	RT	EtOH	Present work

Spectral data of representative compounds

6,6a-Dihydro-6-m-tolylisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 95 %. M.p. 162-163 °C. IR (KBr) 3028, 2926, 1662, 1584, 1489, 1332, 1138 cm^{-1}. ^1H NMR 1.63 (s, 3H), 7.37-7.41 (t, 1H), 7.48-7.52 (t, 3H), 7.65-7.67 (d, 3H), 7.75-7.88 (m, 4H), 8.30 (s, 1H), 8.51-8.53 (d, 1H). LRMS m/z 333 $(M)^+$.

6-(2,4-Dichlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 75 %. M.p. 223-225 °C. IR (KBr) 3052, 1661, 1585, 1489, 1327, 1135 , 734 cm^{-1}. ^1H NMR 7.38-7.52 (m, 4H), 7.65-7.88 (m, 6H), 8.30 (s, 1H), 8.51-8.53 (d, 1H). LRMS m/z 413, 416$(M)^+$.

6,6a-Dihydro-6-phenylisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 78 %. M.p. 184-185 °C. IR (KBr) 3038, 2926, 1660, 1592, 1489, 1332, 1137 cm^{-1}. ^1H NMR 7.38-7.41 (t, 1H), 7.49-7.52 (m, 3H), 7.66-7.67 (m, 3H), 7.75-7.86 (m, 5H), 8.30 (s, 1H), 8.51-8.52 (d, 1H),). LRMS m/z 351$(M)^+$.

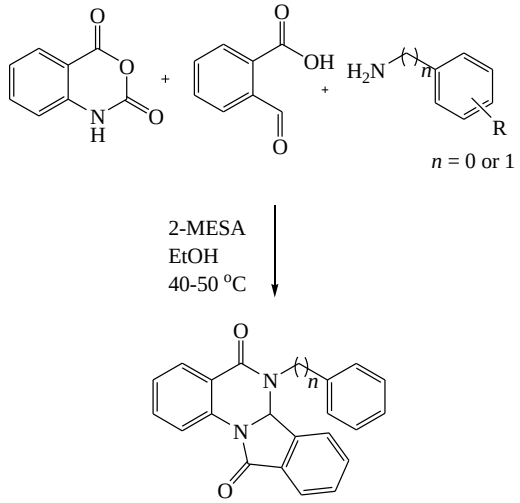
6-(4-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 85 %. M.p. 207-209 ^{0}C. IR (KBr) 3063, 2924, 1662, 1584, 1489, 1332, 1138, 767 $cm^{-1.}$ ^1H NMR 7.24-7.44 (m, 1H), 7.51-7.55 (m, 3H), 7.67-7.70 (m, 3H), 7.82-7.84 (m, 1H), 7.87-7.90 (m, 3H), 8.33 (s, 1H), 8.53-8.55 (d, 1H). LRMS m/z 385,386 $(M+Na)^+$.

Result and Discussion

In search of the best experimental reaction conditions, the reaction of isatoic anhydride, 2-formylbenzoic acid and aromatic amines or benzylamine in the presence of 2-MESA as a catalyst in ethanol was considered as a standard model reaction (Scheme l). To evaluate the exact concentration of 2-MESA required for the reaction, we investigated the model reaction of aniline using different concentrations. The result revealed (Table 2) that when the reaction was carried out in the absence of catalyst, the product formed in a very trace amount (entry 1).

When the reaction was carried out in presence of 2, 5 and 8 mol % of catalyst, yields were lower even after prolonged duration. The reaction in the presence of 10, 12 and 15 mol % of catalyst gave excellent yields in shorter time. The optimal results were obtained with 15 mol % of catalyst and this concentration was ideal of carry out reaction smoothly (entry 7).



Scheme 1. Synthesis of title compounds.

Table 2. Effect of concentration of catalyst.

S. No.	2-MESA, mol %	Time, h	Yield, %
1	0	a	10
2	2	8	40
3	5	6	50
4	8	2	60
5	10	2	80
6	12	1.5	85
7	15	1	90
8	20	1	90

In order to evaluate the effect of solvent, reactions were carried out in various solvents. Dichloromethane, acetonitrile, THF and DMSO afforded moderate yield 50, 65, 55 and 40 %, respectively. Methanol and DMF resulted in good yields of 80 and 70 %, respectively. However, ethanol furnished the product in 90 % yield making it the most suitable solvent. To investigate the role of substituents on

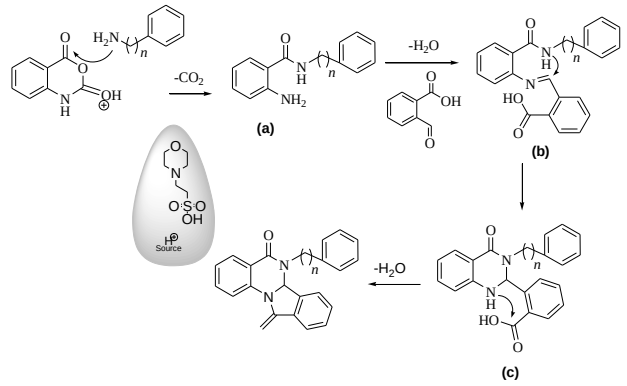
aniline on the reaction (*n*=0, Scheme 1) differently substituted anilines were treated with 2-formylbenzoic acid, isatoic anhydride in presence of 2-MESA using ethanol as a solvent to get desired product. The results found for benzylamine (entry h, *n*=1) is also mentioned in the Table 3. It was noticed that all the substrates are well tolerated under optimized conditions furnishing the product in good to excellent yields. The results are summarized in Table 3. Formation of the desired product was confirmed by comparing their physical constant, IR, 1H NMR and mass spectroscopic data with reported compounds.

Table 3. Synthesis of isoindolo[2,1-*a*]quinazolines derivatives

Entry	Amine moiety	Time, h	Yield, %	M.p. °C
a	3-Methylaniline	2	95	162-163
b	2,4-Dichloro-aniline	2.2	75	223-225
c	Aniline	2.8	78	184-185
d	4-Chloroaniline	2.4	85	207-209
e	4-Bromoaniline	2.2	82	111-112
f	4-Acetylaniline	2.6	77	158-161
g	3-Nitroaniline	2.8	83	235-237
h	Benzylamine	2	88	149-150
i	4-Methylaniline	2	82	195-196
j	4-Cyanoaniline	1.8	90	202-203
k	4-Hydroxyaniline	1.9	88	215-217

Reaction Mechanism

The nucleophic attack of the aromatic amine on isatoic anhydride gives an intermediate (**a**), the amino group of intermediate (**a**) attack on 2-formylbenzoic acid gives another intermediate (**b**), which on cyclization is converted to another intermediate (**c**). Finally intermediate (**c**) on dehydration gives isoindolo [2,1-*a*]quinazoline (Scheme 2).



Scheme 2. A probable mechanism of the sysnthesis.

Conclusion

Here we have demonstrated the use of 2-MESA as greener catalyst to accelerate the synthesis of isoindolo [2,1-*a*] quinazoline derivatives in ethanol. The role of ultrasonication in the use of greener organic acid catalyzed reaction has been highlighted. The methodology may prove useful for this transformation is high yield at room temperature under mild reaction conditions with fast, and easy isolation of the product under ultrasonic irradiation.

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