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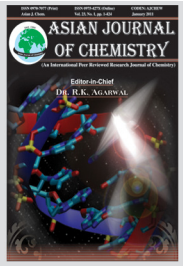

Solvent-Free Protocol for Stereo Selective Crossed Aldol Condensation Assisted by Solid Acid Catalyst

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A highly efficient, inexpensive, recyclable, green and solvent free protocol has been developed for crossed-aldol reaction. SiO_2-OSO_3H has been found to be an efficient catalyst for the synthesis of 4-hydroxy-3-(3-phenyl-acryloyl)-1*H*-quinoline-2-one derivatives **3(a-i)** from 4-hydroxy-3-acetyl-1*H*-quinoline-2-one (**1**) and substituted benzaldehydes **2(a-i)**. Reactions occurred smoothly with variations of the substituents. The reagent can be reused for five cycles with out sacrificing the yields and activity. This method is simple, convenient and the target compounds are produced in good to excellent yields. Compound **1** can be synthesized by the acylation of methyl anthranilate (**4**) with acetoacetic ester (**5**) in refluxing xylene and subsequent Dieckman cyclization of the intermediary 2-methoxycarbonyl anilide (**6**).

Key Words: Quinolones, Chalcones, Silica, Sulphuric acid, Crossed-aldol.

INTRODUCTION

Multistep organic syntheses can be substantially facilitated by conducting reactions on substrates that are covalently attached to insoluble supports[1]. The principles of "solid-phase synthesis" were introduced by Merrifield[1]. Since then, the concept of solid phase synthesis has been applied extensively in numerous areas[1] and there has been significant progress[1] in small molecules, especially heterocycles, due to several advantages like operational simplicity, easier work-up, better yield and eco-friendly nature. In recent years, chemists are paying more interest in the applicaton of solvent free methods. Among these reactions, aldol condensation is useful for the formation of carbon-carbon bond in many kinds of carbonyl compounds[2]. Condensation of ketones with aldehydes is of special interest and crossed aldol condensation is an effective pathway for those preparations[3]. But the traditional acid-base catalyzed reactions suffer from the reverse reaction and self condensation of starting molecules[4]. Solid-phase organic synthesis (SPOS) is a valuable tool for the generation of structurally diverse compounds for combinatorial libraries[5]. Recently, silica-sulfuric acid (SSA) has been widely used as a reusable, heterogeneous, inexpensive solid Brønsted acid catalyst[6]. This heterogeneous catalyst can be easily separated from the reaction media, has greater selectivity and is recyclable, easier to handle, more stable, nontoxic and insoluble in organic solvents.

The 2-quinolone moiety is greatly found in various alkaloids, many of which posses interesting biological activity[7]. There has been large interest in developing 2-quinolones as anticancer[8] and antihypertensive[9] agents. 2-Quinolones are also valuable intermediates since they can be easily converted into 2-chloro and then 2-aminoquinoline derivatives[10] which are very important synthons in organic synthesis. Most quinolones demonstrate their widespread use in clinical practice[11]. Recent reports[12] show that 4-hydroxy-2-quinolone[13] derivatives are selective for stroke, epilepsy, schizophrenia, parkinsons disease and alzheimers disease.

Chalcones are α,β-unsaturated ketones which constitute an important pharmacophore of natural products that serve as precursors for the synthesis[14] of various heterocyclic compounds like pyrimidines, imidazoles, pyrazoles. Chalcones either natural or synthetic, are known[15] to exhibit various biological activities such as antiinflammatory, antimalarial, antihuman immunodeficiency virus (HIV) and antitumor activities.

Keeping in view the great significance of 4-hydroxy-1*H*-2-quinolone derivatives and simple chalcones, it was considered sufficiently valuable that both moieties were synthesized in a single molecule. It may be mentioned here that Villemain and co-workers first reported the preparations of ferrocene chalcones[16], by condensing 3-acetyl ferrocene with various aromatic aldehydes. Earlier from this laboratory,the synthesis of benzimidazole chalcones was reported[17]. In continuation

of our research interest in the synthesis of N-heterocyclic chalcones, herein we report the synthesis of some new substituted quinolone chalcones by solid acid catalst.

EXPERIMENTAL

General information: Melting points were determined on a Buchi melting-point apparatus and were uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC) performed on silica gel G (Merck) and spots were exposed to iodine vapour or UV light. IR spectra were recorded by using KBr disc on a perkin-Elmer 240c analyzer. ^{1}H NMR spectra were recorded on Brucker DPX-400 at 400-MHz (chemical shifts in δ, ppm) and mass spectra on an Agilent LC-MS instrument giving only M^+ values in Q + 1 mode. All the solvents and acetoacetic ester were distilled before being used.

Preparation of 4-hydroxy-3-acetyl-1*H*-quinoline-2-one (1): A mixture of freshly distilled acetoacetic ester (**5**) (1.39 mL, 10 mmol) and xylene (5 mL) was heated to reflux. A solution of methyl anthranilate (**4**) (1.29 mL, 10 mmol) in xylene (5 mL) was added dropwise to the refluxing solution not allowing a marked fall in temperature. After addition of all of the methyl anthranilate (**4**), the refluxing was continued for 3 h. At the end of this period, the solution of 2-methoxycarbonyl anilide (**6**) in xylene was cooled and a solution of 10 % NaOH in water (10 mL) was added to it with stirring. Cyclization occurred with a marked evolution of heat and required much external cooling. Stirring was continued for 1 h. The precipitated acetylquinolone was filtered off, washed with cold water and dried. Yield 1.8 g (90 %), m.p. 248-250 ºC. (Lit. m.p. 252-254 ºC).

Preparation of target molecules 3(a-i) (general procedure): 4-Hydroxy-3-acetyl-1*H*-quinoline-2-one (**1**) (0.1 mmol), substituted benzaldehydes **2(a-i)** (0.1 mmol) and silica-sulphuric acid catalyst were mixed thoroughly. The mixture was heated at 60 ºC for 2.0-2.5 h. After completion of the reaction, monitered by TLC, the mixture was cooled to room temperature. Ethyl acetate was added to the mixture and catalyst removed by filtration. The filterate was concentrated and the obtained crude products were recrystallized with suitable solvent to obtain pure products as yellow flocculent solids. The catalyst was recovered by washing the solid reagent with methanol followed by drying at 100 ºC and reused for another reaction run.

3a: IR (KBr, ν_{max}, cm^{-1}): 1728 and 1674 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 6.95-7.59 (m, 11H, 9H aromatic + 2H styryl protons), δ 8.20 (s, NH); M/Z (M^+ + 1): 292; anal. calcd. (%) for ($C_{18}H_{13}NO_3$) requires C, 74.22; H, 4.5; N, 4.81; found (%) C, 74.21; H, 4.49; N, 4.79.

3b: IR (KBr, ν_{max}, cm^{-1}): 1748 and 1656 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.73 (s, -CH_3) δ 6.65-7.59 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.12 (s, -NH); M/Z (M^+ + 1): 322; anal. calcd. (%) for ($C_{19}H_{15}NO_4$) requires C, 71.02; H, 4.71; N, 4.36; found (%) C, 71.10; H, 4.70; N, 4.35.

3c: IR (KBr, ν_{max}, cm^{-1}): 1744 and 1660 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 6.97-7.62 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.22 (s, -NH); M/Z (M^+ + 1): 326; anal. calcd. (%) for ($C_{18}H_{12}NO_3Cl$) requires C, 66.37; H, 3.71; N, 4.30; found (%) C, 66.36; H, 3.70; N, 4.35.

3d: IR (KBr, ν_{max}, cm^{-1}): 1739 and 1647 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 6.89-7.55 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.20 (s, -NH); M/Z (M^+ + 1): 310; anal. calcd. (%) for ($C_{18}H_{12}NO_3F$) requires C, 69.90; H, 3.91; N,4.53; found (%) C, 69.89; H, 3.90; N, 4.52.

3e: IR (KBr, ν_{max}, cm^{-1}): 1758 and 1650 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 7.12-8.07 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.32 (s, -NH); M/Z (M^+ + 1): 337; anal. calcd. (%) for ($C_{18}H_{12}N_2O_5$) requires C, 64.29; H, 3.60; N, 8.33; found (%) C, 64.28; H, 3.59; N, 8.32.

3f: IR (KBr, ν_{max}., cm^{-1}): 1730 and 1660 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 5.2 (s, -OH) δ 6.61-7.7 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.05 (s, -NH); M/Z (M^+ + 1): 308; anal. calcd. (%) for ($C_{18}H_{13}NO_4$) requires C, 70.35; H, 4.26; N,4.56; found (%) C, 70.35; H, 4.26; N, 4.55.

3g: IR (KBr, ν_{max}, cm^{-1}): 1735 and 1655 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 4.9 (s, -OH) δ 6.61-7.7 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.05 (s, -NH); M/Z (M^+ + 1): 308; anal. calcd. (%) for ($C_{18}H_{13}NO_4$) requires C, 70.35; H, 4.26; N, 4.56; found (%) C, 70.35; H, 4.26; N, 4.55.

3h: IR (KBr, ν_{max}, cm^{-1}): 1710 and 1635 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 2.85 (s, 6H, $N(CH_3)_2$) δ 6.47-7.48 (m, 10H, 8H aromatic + 2H styryl protons), δ 8.0 (s, -NH); M/Z (M^+ + 1): 335; anal. calcd. for ($C_{20}H_{18}N_2O_3$) requires C, 71.84; H, 5.43; N, 8.38; found (%) C, 71.82; H, 5.42; N, 8.37.

3i: IR (KBr, ν_{max}, cm^{-1}): 1715 and 1640 (both s, sharp, two -C=O groups); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 3.73 (s, 3H, -OCH_3) δ 5.0 (s, -OH) δ 6.47-7.48 (m, 9H, 7H aromatic + 2H styryl protons), δ 8.0 (s, -NH); M/Z (M^+ + 1): 338; anal. calcd. (%) for ($C_{19}H_{15}NO_5$) requires C, 67.65; H, 4.48; N, 4.15; found (%) C, 67.66; H, 4.47; N, 4.13.

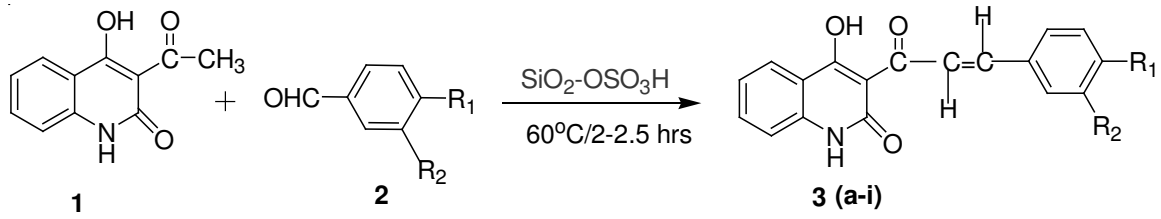
RESULTS AND DISCUSSION

Different types of aldehydes **2 (a-i)** were subjected to condensation with 4-hydroxy-3-acetyl-1*H*-quinoline-2-one (**1**), containing either electron-releasing or electron-withdrawing groups, in the presence of this reagent under solvent-free conditions (**Scheme-I**). The results are summarized in the Table-1. The reactions were completed within 2.0-2.5 h and high yields were obtained. Under these conditions, no self-condensation of the starting materials was observed.

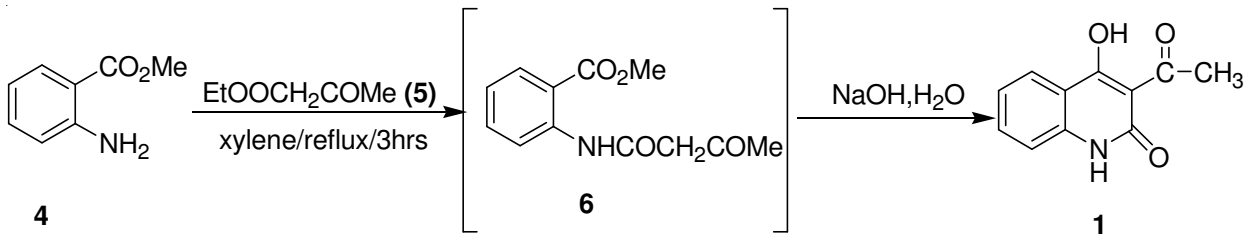
The catalyst was prepared by the reaction of silica gel (80-200 mesh) with chloro suphonic acid in methylene chloride (Fig. 1) and characterized by IR ν/cm^{-1}: 1282 (S=O), 886, 852 (S-O). The catalyst was found to be recyclable and the reaction condition can be scaled up. In order to test the reusability of the catalyst, a reaction of **1** with **2a** was carried out in the presence of SiO_2-OSO_3H at 60 ºC for 2.0-2.5 h and the catalyst was recovered after completion and activated by heating to 100 ºC under vacuum for 1 h. The recovered catalyst was reused

TABLE-1
CONDENSATION OF 4-HYDROXY-3-ACETYL-1*H*-QUINOLINE-2-ONE (**1**) WITH SUBSTITUTED BENZALDEHYDES **2(a-i)** TO OBTAIN 4-HYDROXY-3-(3-PHENYL-ACRYLOYL)-1*H*-QUINOLINE-2-ONE DERIVATIVES **3(a-i)**

Entry	Aldehyde used	Product obtained	m.p. (%)	Time (h)	Yield (%)
1	**2a** ($R^1 = R^2 = H$)	3a ($R^1 = R^2 = H$)	210-212	2	88
2	**2b** ($R^1 = OCH_3$, $R^2 = H$)	3b ($R^1 = OCH_3$, $R^2 = H$)	>250	2.2	80
3	**2c** ($R^1 = Cl$, $R^2 = H$)	3c ($R^1 = Cl$, $R^2 = H$)	>250	2.3	89
4	**2d** ($R^1 = F$, $R^2 = H$)	3d ($R^1 = F$, $R^2 = H$)	>250	2	85
5	**2e** ($R^1 = NO_2$, $R^2 = H$)	3e ($R^1 = NO_2$, $R^2 = H$)	198-202	2	90
6	**2f** ($R^1 = OH$, $R^2 = H$)	3f ($R^1 = OH$, $R^2 = H$)	>250	2.5	83
7	**2g** ($R^1 = H$, $R^2 = OH$)	3g ($R^1 = H$, $R^2 = OH$)	>250	2.5	82
8	**2h** ($R^1 = N(CH_3)_2$, $R^2 = H$)	**3h** ($R^1 = N(CH_3)_2$, $R^2 = H$)	220-222	2.5	80
9	**2i** ($R^1 = OCH_3$, $R^2 = OH$)	**3i** ($R^1 = OCH_3$, $R^2 = OH$)	230-234	2.3	86



Scheme-I



Scheme-II

for another batch of **1** with **2a** giving 90 % yield of the desired product after 2 h. Again, the catalyst was recovered, reactivated and reused repeatedly for three more consecutive times for the synthesis of chalcones with 85, 75 and 70 % yields, respectively. From this observation, it is clear that the reaction can be scaled up and the catalyst is reusable with a slight decrease in catalytic activity.

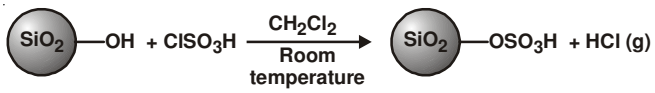


Fig. 1. Synthesis of silica-sulphuric acid catalyst

To compare the catalytic activity of SiO_2-OSO_3H with ordinary silica and chlorosulphonic acid, an identical experiment was performed by compound **1** (0.01 mmol) with compound **2a** (0.01 mmol) in the presence of silica (240-400 mesh, 100 mg) and chlorosulphonic acid at 60 ºC. No condensed product was formed even after 24 h, which indicated that the requirement of SiO_2-OSO_3H is key factor for the successful outcome of the reaction. Furthermore, using of SiO_2-OSO_3H reduces the cost of the crossed-aldol reactions and the reactions completed in less time.

Compound **1** itself was prepared by a slight modification of the literature method[18] suitable to our laboratory conditions. Thus, acylation of methyl anthranilate (**4**) using acetoacetic ester (**5**) with subsequent Dieckman intramolecular cyclization of the intermediary 2-methoxycarbonylanilide (**6**) led to compound **1** in convenient yield and as a clean product. The compounds **3(a-i)** obtained were assigned structures on the basis of analytical and spectral data. The results are shown in Table-1. All the above descriptions are summarized in the **Schemes I** and **II**.

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REFERENCES

1. R.B. Merrifield, *J. Am. Chem. Soc*., **85**, 2149 (1963).
2. J.P. Guthrie and X.-P. Wan, *Can. J. Chem*., **69**, 339 (1991).
3. D. Sung and P.A. Nadar, *Bull. Korean. Chem. Soc*., **20**, 1487 (1999).
4. T. Nakano, S. Irifune, S. Umano, A. Inada, Y. Ishii and M. Ogawa, *J. Org. Chem*., **52**, 2239 (1987).
5. K. Tanaka and F. Toda, *Chem. Rev*., **100**, 1025 (2000).
6. D.M. Pore, M.S. Soudagarn and U.V. Desai, *Tetrahedron Lett*., **47**, 9325 (2006).
7. F. Baur, D. Beattie, D. Beer, D. Bentley, M. Bradley, I. Bruce, S.J. Charlton, B. Cuenoud, R. Ernst, R.A. Fairhurst, B. Faller, D. Farr, T. Keller, J.R. Fozard, J. Fullerton, S. Garman, J. Hatto, C. Hayden, H. He, C. Howes, D. Janus, Z. Jiang, C. Lewis, F. Loeuillet-Ritzler, H. Moser, J. Reilly, A. Steward, D. Sykes, L. Tedaldi, A. Trifilieff, M. Tweed, S. Watson, E. Wissler and D. Wyss, *J. Med. Chem*., **53**, 3675 (2010).
8. S. Srivastava, A. Jha, K. Shiv, R. Mukherjeev and A. Burman, *Anticancer Agents Med. Chem.*, **7**, 685 (2007).
9. R.V. Davies and R.D. Green, Antihypertensive 3-tetrazoyl-4-quinolones, US Patent 4659718 (1987).
10. (a) M. Anzini, A. Cappelli and S. Vomero, *J. Heterocycl. Chem*., **28**, 1809 (1991); (b) A. Godard, J.M. Fourquez, R. Tamion, F. Marsais and G. Queguiner, *Synlett*, 235 (1994).
11. V.T. Andriole, *Drugs*., **58** (Suppl. 2) 1 (1999).
12. L.A. McQuaid, E.C. Smith, D. Lodge, E. Pralong, J.H. Wikel, D.O. Calligaro and P.J. Malley, *J. Med. Chem*., **35**, 3423 (1992).
13. L. Varga, T. Nagy, I. Kövesdi, J. Benet-Buchholz, G. Dormán, L. Ürge and F. Darvas, *Tetrahedron*, **59**, 655 (2003).
14. T. Narender, K.S. Tanvir, M.S. Rao, K. Srivastava and S.K. Puri, *Org. Letts*., **9**, 5369 (2007).
15. D. Villemin, B. Martin, M. Puciova and S.T. Toma, *J. Organomet. Chem*., **484**, 27 (1994).
16. P.K. Dubey, C. Ravikumar and B. Balaji, *Indian. J. Chem*., **42B**, 3128 (2003).
17. I.V. Ukrainets, A.A. Tkach and Y. Liu, *Chem. Heterocycl. Comp*., **45**, 169 (2009).
18. W. Stadlbaver and G. Hojas, *J. Heterocycl. Chem.*, **41**, 681 (2004).