Ultrasonicated synthesis of 1-(2-hydroxyaryl)-3-(pyrrolidin-1-yl)-prop-2-en-1-ones and their antimicrobial screening

Sharad N. Shelke[a]*, Mahendra P. Sonawane[a], Bhausaheb K. Karale[a] and Charnshing H. Gill[b]

[a] P.G. Department of Chemistry, S.S.G.M. College, Kopargaon (M.H.), 423 601, India. E-mail: snshelke@yahoo.co.in

[b] Department of chemistry, Dr. B. A. M. University, Aurangabad, India.

Abstract: A facile synthesis of title compounds has been carried out under ultrasound irradiation. The main advantages of the present procedure are shorter reaction time and higher yield. Products have been characterized by IR, PMR, CMR, GCMS study and screened for their antimicrobial activity.

Keywords: Ultrasonication, 3-formylchromone, enaminiketone, bioactivity.

Among the different functionalized chromones, 3-formylchromones occupy a unique position because they can be transformed into various heterocycles by interesting reactions with different nucleophiles.[1] 3-Formylchromone when treated with phenyl hydrazine gives 1-phenyl-4-(2-hydroxy benzoyl) pyrazoles,[2] whereas substituted 3-formylchromone when treated with pyrrolidine[3] under reflux gives 1-(2-hydroxyaryl)-3-(pyrrolidin-1-yl)-prop-2-en-1-one. The enaminoketones[4] constitute an important class of synthon, which can be elaborated to a wide variety of heterocyclic compounds. The titled compound 1-(2-hydroxyaryl)-3-(pyrrolidin-1-yl)-prop-2-en-1-ones was utilized for the synthesis of pyrazoles[3].

Pyrrolidine containing compounds are versatile antidiabetic, antiobesity,[5] anticonvulsant[6] and antibacterial agents.[7]

The chemical applications of ultrasound, now called sonochemistry, have become an exciting new field of research during the last few decades.[8] The use of ultrasound irradiation technique for activating various reactions is well documented in the literature such as synthesis of azoles and diazines,[9] Reformatsky reaction,[10] oxidation of substrates like hydroquinones,[11] conversion of nitro compounds to carbamates,[12] Pinacol coupling,[13] Ullmann condensation,[14] Suzuki cross-coupling[15] and various other transformations in synthetic organic chemistry.16]

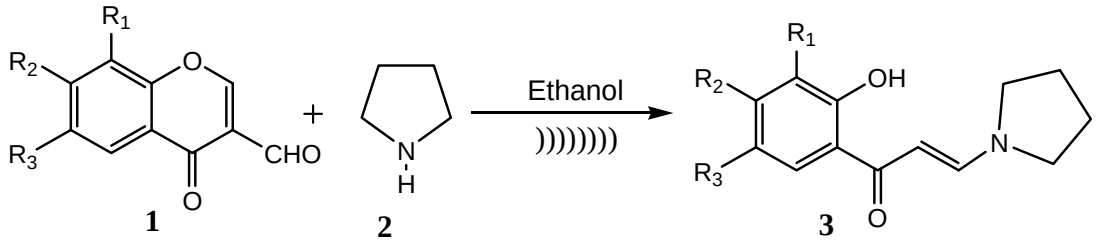
Result and Discussion

In view of advantages of ultrasound irradiation in organic synthesis and utility of the titled compound, we aimed the synthesis of 1-(2-hydroxyaryl)-3-(pyrrolidin-1-yl)-prop-2-en-1-ones **3** by the reaction of pyrrolidine **2** on 3-formylchromones **1** under the influence of ultrasound irradiation. In earlier report[3] 2-hydroxyaryl)-3-(pyrrolidin-1-yl)-prop-2-en-1-ones have been prepared by time consuming conventional method require 5 hours and yield obtained was pour.

In this communication, a number of 3-formylchromone **1** are treated with pyrrolidine **2** in dry ethanol under influence of ultrasound irradiation. By this method, the time required for completion of the reaction is less and yields are better at room temperature, hence no vigorous heating is required. In general, the reactions using ultrasonication technique is very clean and required shorter time for completion.

Compounds **3c** and **3i** were obtained in good yield within 30-35 min under ultrasonication Each experiment using ultrasonication technique was repeated three times to confirm the consistency of the results. Comparative results obtained are tabulated in the ***Table-I***.

Scheme:



Pyrrolidine reacts with 3-formylchromones by attacking the electron-deficient center of the C_2 carbon, and the probable mechanism may be as follows.

The required 4-oxo-4*H*-chromone-3-carbaldehydes **1** was prepared by Vilsmeir-Haack reaction from variously substituted o-hydroxyacetophenones.

Experimental:

All experiments under ultrasonication were carried out in bath type ultrasonicator model EN-20U-S manufactured by Enertech Electronica Pvt., Ltd., Mumbai, India having maximum power output of 100W and 33 KHz operating frequency.

All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. The ^{1}H NMR and ^{13}C NMR spectra were scanned on Bruker 300 MHz and 400 MHz FT

spectrophotometer respectively using *DMSO-d6 or* $CDCl_3$ as a solvent and TMS as an internal standard, while mass spectra were recorded on Finnigan mass spectrometer.

General procedure:

1-(2-Hydroxy-phenyl)-3-pyrrolidin-1-yl-propenone 3a

To a 100 mL RBF was added 6-chloro-4-oxo-4*H*-chromone-3-carbaldehyde **1a** (2.08 gm, 0.01 mol) and pyrrolidine **2** (1.42 gm, 0.02 mol) and dry ethanol (10 mL). The reaction vessel was then lowered into a sonication bath and sonicated for 25-40 minutes till a clear solution was obtained. Progress of the reaction was monitored with the help of TLC. After completion of the reaction the contents were poured into crushed ice and the product obtained was separated by filtration. The product was crystallized from alcohol. This typical experimental procedure was followed to prepare the compounds **3 b-i**. The compounds synthesized by above procedures are listed in ***Table-I*** with their characterization data. IR, PMR, CMR and GC-MS data have confirmed their structures and agreement with those obtained for the products synthesized by earlier method.[3]

Table-I**:** Characterization data of synthesized compounds **3 a-i**.

Comp. No.	R^1	R^2	R^3	Time (min)	Yield (%)	Melting Points (^oC)	Lit. Yield[3] (%)
3a	H	H	Cl	25	82	148	79
3b	H	H	F	28	82	170	80
3c	H	H	Me	30	87	174	75
3d	H	Me	Cl	40	80	172	70
3e	H	Me	H	28	79	140	65
3f	Cl	H	Cl	35	81	166	76
3g	Me	H	Me	30	80	158	75
3h	H	H	H	25	82	142	74
3i	H	H	Et	35	84	100	80

Spectral data of representative example 3c:

Entry **3c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.99 (m, 4H), 2.30 (s, 3H), 3.34 (t, 2H), 3.59 (t, 2H), 5.70 (d, 1H, J=18 Hz), 6.82 to 7.47 (m, 3H), 8.05 (d, 1H, J=18 Hz), 13.83 (s, 1H); ^{13}H NMR (DMSO, 400 MHz) δ: 189.85, 160.05, 150.21, 117.02-134.10, 90.03, 52.49, 46.58, 24.59, 24.49, 20.05; IR (KBr) cm^{-1}: 3122, 1623, 1585 & 1544; GC-MS (70 eV) *m/z*: 231 (M^+), 161, 70.

Antimicrobial Screening:

Compounds listed in **Table-II** were screened (doses of 100 μg) for their antibacterial activity against gram-ve bacteria *E. coli* and gram+ve bacteria *S. albus* using filter paper disc method. Plates inoculated with *E. coli* were incubated for 48 hr and plates inoculated with *S. albus* for 24 hr respectively at RT. Streptomycin sulphate were used as a standard. Inhibition zones were measured in mm and results obtained are shown in ***Table-II***.

All these compounds were also screened (doses of 100 μg) for their antifungal activity against *A. niger* using greseofulvin as a standard. The results are shown in ***Table-II***.

***Table-II*:** Antimicrobial Activities of 1-(2-hydroxy-phenyl)-3-pyrrolidin-1-yl-propenones **3**.

Compound	Inhibition zone in mm (diameter)		
	E. coli	*S. albus*	*A.niger*
3a	08	12	04
3b	08	06	04
3c	08	06	-
3d	06	10	-
3f	08	10	4
Streptomycin sulphate	18	22	Not tested
Griseofulvin	Not tested	Not tested	12

Acknowledgement:

Authors are thankful to the Principal G. T. Sangle, S.S.G.M. College, Kopargaon, Ahmednagar for providing necessary facilities and constant encouragement. One of the authors (SNS) thanks UGC, New Delhi for the award of Teacher Fellowship.

References:

1. Ghosh, C. K. CHEMISTRY of 4-oxo-4*H*-[1]benopyran-3-carboxaldehyde. *J. Heterocycl. Chem.*, **20**, 1437 (1983).
2. Ghosh, C. K.; Mukhopadhyay, K. K. REACTION of 4-oxo-4*H*-[1]benzopyran-3-carboxaldehyde with phenyl hydrazine and formation of 1-phenyl-4-(2-hydroxybenzoyl) pyrazoles. *J. Indian Chem. Soc.*, **LV**, 52 (1978).
3. Shelke, S. N.; Dalvi, N. R.; Shingare, M. S., Gill, C. H.; Karale, B. K. SYNTHESIS of 2-(1*H*-pyrazol-3-yl)-phenols, *Indian J. Heterocycl. Chem.*, **15**, 403 (2006).
4. Mousawi, S. A.; John, E.; Kandery, N. A. SYNTHESIS and chemical reactivity of 2-(4-dimethylamino-2-oxobut-3-enyl)-isoindole-1,3-dione and of 4-(4-dimethylamino-2-oxobut-3-enyloxy)-2*H*-phthalazin-1-one. *J. Heterocycl. Chem.*, **41 (3)**, 381 (2004).
5. Cheng, T. W.; Chen, S.; Devasthale, P.; Ding, C. Z.; Herpin, T. F.; Wu, S.; Zhang, H.; Wang, W; Ye, X. PREPARATION of substituted heterocyclic derivatives as antidiabetic and antiobesity. *PCT Int. Appl. WO 2004004665 A2*, 543 (2004).
6. Kwon, T.; Kwon, P.; Song, S.; Park, M.; Choi, J. SYNTHESIS and anticonvulsant evalution of 5-vinyl-pyrrolidin-2-ones:a potential GABA-AT inhibitor. *Bull. Korean. Chem. Soc.*, **23(6)**, 917 (2002).
7. Hattori, K.; Yamada, A.; Kuroda, S.; Chiba, T.; Murata, M.; Sakane, K. SYNTHESIS and antibacterial evalution of noval 2[N-lmidoylpyrrolidinyl] carbapenems. , *Bioorg. Med. Chem. Lett.*, **12(3)**, 383 (2003).
8. Salvatare, D. L.; Yuanjun, H. USE of Sonication for the coupling of Sterically Hindered Substrates in the phenolic Mitsunobu Reaction. *J. Org. Chem*, 68, 8261 (2003).
9. Kidwai, M.; Venkataramanan, R.; Dave, B. POTASSIUM carbonate, a support for the green synthesis of azoles and diazines. *J. Heterocycl. Chem.*, **39**, 1045 (2002).

10. Singh, V.; Sapehiyia, V.; Kad, G. L. ULTRASONICALLY activated oxidation of hydroquinones to quinones catalysed by ceric ammonium nitrate doped on metal exchange K-10 clay. *Synthesis*, **2**, 198 (2003).
11. Ross, N. A.; Bartsch, R. A. SONOCHEMICAL Reformatsky reactions of a-bromoester with sym-(keto)dibenzo-16-crown-5. *J. Heterocycl. Chem.*, **38**, 1255 (2001).
12. Chandrashekhar, S.; Narsihmulu, C.; Jagadeshwar, V. ULTRASOUND promoted "onepot" conversion of nitro compounds to carbamates. *Synlett.*, **5**, 771 (2002).
13. Li, J.-T.; Bian, Y.-J.; Zang, H.-J.; Li, T.-S. Pinacol coupling of aromatic aldehydes and ketones using magnesium in aq. ammonium chloride under ultrasound. *Synth. Commun.*, **32 (4)**, 542 (2002).
14. Robin, M.; Pique, V.; Faure, R.; Glay, J. ULTRASONIC irradiation of the Ullmann condensation: Application to the preparation of dioxolo, dioxino, cyclopent, and imidazolo anthranilic acid derivatives. *J. Heterocycl. Chem*., **39**, 1083 (2002).
15. Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. ULTRASOUND-promoted Suzuki cross-coupling reactions in ionic liquid at ambient conditions. *Chem. Commun*., **61**, 616 (2002).
16. Shelke, S. N.; Dalvi, N. R.; Kale, S. B.; More, M. S.; Gill, C.H. and Karale, B. K. ENVIRONMENTALLY benign synthesis of fluorinated pyrazolone derivatives and their antimicrobial activity. *Indian J. Chem.*, **46B**, 1174 (2007).

Graphical abstract:

Ultrasonicated synthesis of 1-(2-hydroxyaryl)-3-(pyrrolidin-1-yl)-prop-2-en-1-ones and their antimicrobial screening

Sharad N. Shelke*, Mahendra P. Sonawane, Bhausaheb K. Karale and Charnshing H. Gill.