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Gallium (III) Chloride Catalyzed Synthesis of Polyhydroquinoline at Ambient Temperature and Photoluminance Study of Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate

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ABSTRACT

A general and convenient practical approach for the synthesis of polyhydroquinoline derivatives has been achieved via one-pot four-component Hantzsch condensation of aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of a catalytic amount of gallium (III) chloride, in ethanol solvent at ambient temperature. The UV-Visible and photo-luminescence (PL) spectra of Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5(6H)-oxoquinolin-3-carboxylate is also reported. The interaction of synthesized compound and salicylic acid was studied by using steady state emission spectroscopy. The fluorescence quenching of salicylic acid showed red shift with increasing concentration of polyhydroquinolines (acceptor) is in accordance with Stern–Volmer relation. The quenching rate constant $3.8x10^{-6}M^{-1}S^{-1}$ was obtained from the fluorescence lifetime of salicylic acid measured on time resolved fluorimeter (TRF) in absence of polyhydroquinolines.

Keywords: Gallium (III) chloride, Polyhydroquinoline, Hantzsch condensation, Fluorescence quenching, Stern-Volmer relation.

INTRODUCTION

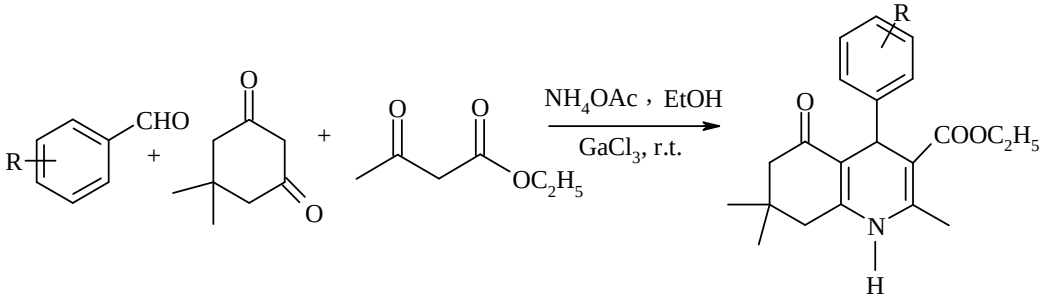
1,4-Dihydropyridine (1, 4-DHP) scaffold have been received strong attention because of their several biological activities [1-6]. Some reports in the literature describe the application of these substrates for the treatment of cardiovascular diseases [7]. In addition this, these compounds have been shown to possess diverse medicinal utility such as neuroprotectant, platelet anti-aggregatory activity, and cerebral antischaemic activity in the treatment of Alzheimer's disease and chemosensitiser behavior in tumor therapy [8]. Most of the synthesized polyhydroquinolines have reported for their biological activity but yet no one has reported the photophysical study. As

the research into and development of organic electroluminescent diodes (OLEDs) has advanced, more and more international companies, for example: Philips, Siemens, Pioneer, Toyota, NEC, Kodak, HP, IBM, DuPont, Dow Chemical, Samsung, Sanyo and so on, have paid considerable attention to this topic. Luminescent materials include small organic molecules, organometallic compounds and polymers. Most of them are heterocyclic compounds and polymers containing heterocycles. Quinoline, isoquinoline and their derivatives are among the most important heterocyclic precursors [9].

In most of the methods, multi-component synthesis has been carried out. The development of multi-component reactions (MCRs) has attracted much attention from the advantage point of combinatorial and medicinal chemistry [10]. Owing to the great importance of polyhydroquinoline in various drug frameworks, there have been some reports on its synthesis [11-15]. However, many of these events have significant drawbacks such as use of relatively expensive reagents and drastic reaction conditions.

As the applications of the gallium chloride have increases day by day in organic synthesis due to its ability to tolerate variety of functional groups. In recent years gallium mediated transformations have received considerable attention [16]. As a result of their unique catalytic properties, gallium halides have been used widely for a variety of organic transformations [17].

As part of our on going research in synthesis of biodynamic heterocycles through multi-component synthesis [18] and photo physical study [19] we wish to report highly efficient Hantzsch four-component condensation reaction by using gallium (III) chloride as efficient catalyst at ambient temperature (**Scheme 1**). Along with the synthesis photophysical study of Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate as a representative compound is also reported.



Scheme 1

MATERIALS AND METHODS

Reagents. All chemicals were reagent grade and were used as purchased without further purification. Solvents were used after double distillation.

Apparatus. Analytical thin-layer chromatography was performed on percolated silica gel 60-F 254 plates. The IR spectra were recorded with KBr disks on a Schimazdu IR-470 FT-IR spectrophotometer. The Routine nuclear magnetic resonance spectra (^{1}H NMR) were taken in $CDCl_3$ using a Bruker Spectrospin Avance II- 200 and 300 MHz spectrophotometer with TMS as an internal standard. Melting points were determined in open capillary tube and are uncorrected. The physical data of synthesized compounds was summarized in the Table 1. Fluorescence spectra were recorded on PC based spectrofluorometer (JASCO Japan FP-750) and absorption spectra were measured on UV-Visible-NIR spectrophotometer (Shimadzu, Model UV-3600).

General procedure for the synthesis of polyhydroquinoline derivatives:
A mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and $GaCl_3$ (2 % mmol) (as the salt is very moisture sensitive, the weight may not be accurate) was stirred at room temperature in ethanol (7 mL) for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting product was purified by nonchromatographic technique that is by simple recrystalization in ethanol.

RESULTS AND DISCUSSION

In this article, we report the results of our studies involving the synthesis of polyhydroquinoline derivatives by reaction of aromatic aldehyde, dimedone, ethyl acetoacetate and ammonium acetate in presence of gallium chloride.

As a case study, a mixture of *p*-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and catalytic amount of $GaCl_3$ (as the salt is very moisture sensitive, the weight may not be accurate) was stirred at room temperature in ethanol (7 mL) for the appropriate time. After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting product was purified by recrystalization in ethanol and interpreted by spectral data. This prime success of the above reaction prompted us to find out the most favorable quantity of gallium chloride for the present transformation.

To optimize the quantity of gallium chloride, we have carried out the same reaction with various quantity (From 0.5 mol % to 2.5 mol %) of gallium chloride simultaneously. It has been observed that the 2 mol % catalyst is sufficient to get the almost quantitative yield (92 %) in very less time.

Subsequently, we have extended this methodology for the varieties of the substituted aromatic aldehydes. These variations not alter the theme of the protocol in terms of reaction time and yield. The results are summarized in Table 1

The gallium chloride have strong affinity towards the water molecules, as during the progress of the reaction two water molecules being formed which subsequently absorbed by the catalyst due to which the rate of the reaction increases tremendously to complete the reaction in shorter span of time.

All the synthesized compounds have been characterized by comparison of their physical constant with reported literature and representative compounds from their spectroscopic data.

Photo physical Study:
The steady state fluorescence and UV-Visible absorption was employed to investigate photophysical properties of the molecule in ethanol solvent. **Fig. 1** shows the absorption spectra of Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate have seen broad peak maximum at 372 nm in the range of 300-500 nm. The fluorescence quenching of salicylic acid with different amount of Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate (**Fig. 2**), it was observed that the fluorescence emission spectra lies in the range of 350-550 nm at λex = 310. It was also seen that

the fluorescence intensity at donor decreased along with red shift with increasing amount of said compound indicating that the formation of donor-acceptor complex at excited state. The possible mechanism between salicylic acid and the said compound represent the hydrogen bonding.

The kinetics of quenching of salicylic acid was studied by using Stern-Volmer relation (**Fig. 3**). The plot of Fo/F against concentration of quencher is shown in figure 3, where F and F_o are the fluorescence intensities in presence and absence of polyhydroquinline respectively. The Stern-Volmer plot is straight line with intercept having value one on Y-axis indicating validity of Stern-Volmer relation given by

$$F_o/F = 1+kq.\ \tau[Q] = 1+Ksv\ [Q] \qquad [1]$$

From the linear portion of the curve, the value of quenching rate constant kq obtained by following equation

$$Kq = Ksv/\tau \qquad [2]$$

Where, Ksv = Stern-Volmer constant obtained from slope i.e. 3757.1

The value of $\tau = 0.97x10^{-9}$ns (1 ns = 1 X 10^{-9} sec.) was measured on time resolved fluorimeter. The estimated value of kq was found to be $3.8x10^{-6}M^{-1}S^{-1}$

Table-I $GaCl_3$ catalyzed synthesis of polyhydroquinoline derivatives*

Entry	Aldehyde	Time (hrs)	Yield#	Physical constant (^oC)	
				Found	Literature
1	C_6H_5	2.00	90	203	188-190[20a]
2	3-NO_2-C_6H_4	3.30	94	178	177-178[20a]
3	4-Cl-C_6H_4	2.00	95	240	245-246[20c]
4	4-NO_2-C_6H_4	1.30	92	245	244-246[20c]
5	4-OH-C_6H_4	2.00	90	232	232-234[20c]
6	3,4,-$(OCH_3)_2$-C_6H_3	1.00	95	198	198-199[20c]
7	2-Cl-C_6H_4	3.15	89	206	208-210[20b]
8	2-Furyl	2.15	91	245	246-248[20c]
9	4-$CH_3C_6H_4$	2.30	93	260	261-262[20c]
10	C_6H_5CH=CH	3.00	88	204	204-206[20c]
11	4-MeO-C_6H_4	3.00	85	255	260-261[20b]
12	2-Thiophene	3.00	86	248	248-250[20b]
13	4-N,N$(CH_3)_2$-C_6H_4	3.00	88	222	222-223[20a]

**All reactions were performed at 1mmol scale in 7 mL ethanol. # Yields refer to pure isolated products.*

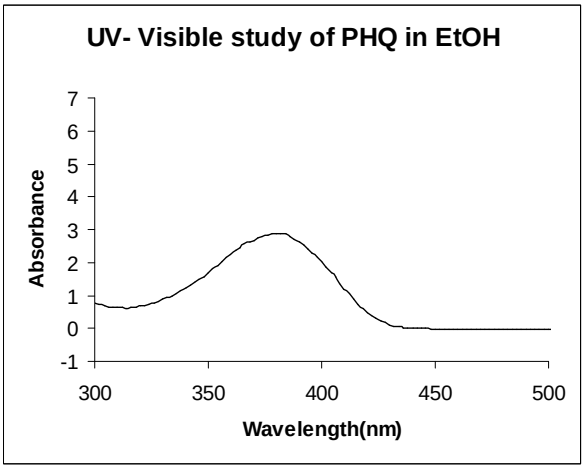


Figure-1 UV-Visible study of polyhydroquinoline in ethanol

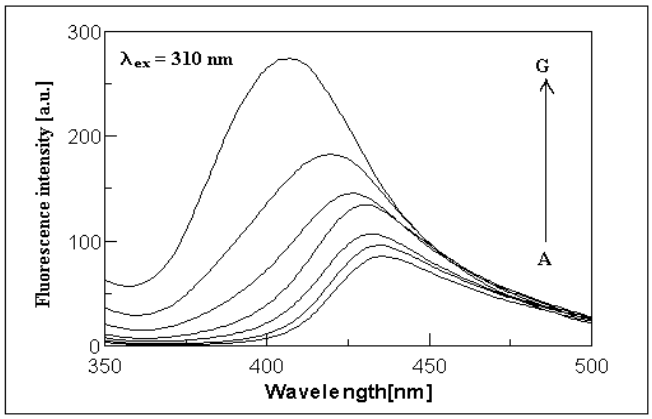


Figure 2 Fluorescence quenching of 2 x 10^{-5} M salicylic acid with varying concentrations of polyhydroquinoline from A to G 0.0 to 3 x 10^{-3}

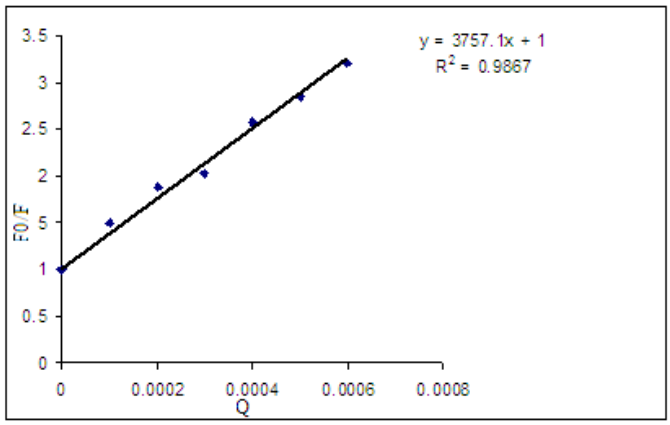


Figure 3 Stern-Volmer plot

CONCLUSION

We describe a mild and efficient route for the synthesis of polyhydroquinoline utilizing gallium chloride as a catalyst. The photophysical properties of representative compound were investigated by UV-Visible, fluorescence spectra, in ethanol solvent with varying concentration. The fluorescence of salicylic acid was found to be quenched and quenching is in accordance with Stern-Volmer relation.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorolphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (Entry 3)

IR (KBr): 3392, 3273, 2960, 1711, 1646, 1057, 831 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.92(s, 3H, -CH_3), 1.06(s, 3H, -CH_3), 1.16-1.21 (t, 3H, CH_2CH_3), 2.11-2.26 (m, 4H, 2×CH_2) 2.29(s, 3H, CH_3), 4.04-4.09 (q, 2H, CH_2CH_3), 5.01 (s, 1H, CH), 6.2 (s, 1H, -NH), 7.14–7.17 (m, 2H, ArH), 7.25-7.26(m, 2H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δppm: 195.52, 167.21, 148.20, 145.53, 141.63, 139.80, 131.58, 127.98, 111.85, 105.73, 59.90, 50.65, 41.04, 36.21, 32.69, 29.40, 27.08, 19.39, 14.19.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5(6*H*)-oxoquinolin-3-carboxylate. (Entry 4)

IR (KBr): 3273, 3201, 3075, 1703, 1646, 1340, 820 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$) δppm: 0.93 (s, 3H, CH_3), 1.01(s, 3H, CH_3), 1.11-1.17(t, 3H, CH_2CH_3), 2.10-214(m, 4H, 2×CH_2), 2.36 (s, 3H, -CH_3), 3.96-4.03 (q, 2H, -CH_2CH_3), 5.08(s, 1H, CH), 6.12(s, 1H, -NH), 7.40-7.44(m, 2H, ArH), 7.99-8.03(m, 2H, ArH)

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-hydroxyphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (entry 5)

IR (KBr): 3484, 3273, 2958, 1714, 1681, 1487, 1075, 831 cm^{-1} ^{1}HNMR(300 MHz, $CDCl_3$) δppm: 0.98 (s, 3H -CH_3), 1.07 (s, 3H, -CH_3), 1.16-1.22 (t, 3H, -CH_2CH_3), 2.19-2.33 (m, 4H, 2×CH_2) 2.39 (s, 3H -CH_3), 3.97-4.08 (q, 2H, -CH_2CH_3), 5.13 (s, 1H -CH), 6.17 (s, 1H, -NH), 7.49 (dd, 2H, Ar-H), 8.04-8.08 (dd, 2H, Ar-H) 8.15(s, 1H, Ar-OH).

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(3,4-dimethoxylphenyl)-5(6*H*) oxoquinolin -3-carboxylate. (Entry 6)

IR (KBr): 3285, 3075, 2930, 1688, 1634, 1030, 862 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δppm: (0.93 (s, 3H, CH_3), 1.06(s, 3H, CH_3), 1.20(t, 3H, CH_2CH_3), 2.13-2.18 (m, 4H, 2×CH_2) 2.36(s, 3H, CH_3), 3.79(s, 3H, -OCH_3), 3.82(s, 3H, OCH3), 4.04-4.11(q, 2H CH_2CH_3), 4.99(s, 1H, -CH), 6.66(d, 1H, Ar-H).6.0(s, 1H, -NH), 6.70(dd, 1H, ArH). (6.90(d, 1H, Ar-H).

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REFERENCES

[1] (a) R. A. Jains, P. J. Silver, D. J. Triggle, *Adv. Drug Res.*, **1987**, 16, 309. (b) F. Bossert, W. Vater, *Med. Res. Rev.*, **1989**, 9, 29. (c) N. Martin, C. Secoane, *Quim. Ind.*, **1990**, 36, 115.
[2] (a) U. Eisner, J. Kuthan, *Chem. Rev.*, **1972**, 72, 1. (b) D. M. Stout, A. I. Meyers, *Chem. Rev.*, **1982**, 82, 223. (c) F. Bossert, H. Meyers, E. Wehinger, *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 762. (d) J. Kuthan, A. Kurfurst, *Ind. Eng. Chen. Prod. Res. Dev.* **1982**, 211, 191.
[3] (a) R. J. Chorvat, K. J. Rorig, *J. Org. Chem.* **1988**, 53, 5779. (b) C. O. Kappe, W. M. F. Fabian, *Tetrahedron*, **1997**, 53, 2803. (c) C. O. Kappe, *Tetrahedron*, **1993**, 49, 6937.
[4] (a) S. Goldman, W. Geiger, *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 301. (b) S. Goldman, L. Born, S. Kazda, B. Pittel, M. Schramm, *J. Med. Chem.* **1990**, 33, 1559. (c) S. Goldman, J. Stoltefuss, *Angew. Chem. Int. Ed. Engl.*, **1991**, 30, 1559.
[5] (a) N. Schramm, G. Thomas, R. Towart, G. Franckowiak, *Nature, (London, U.K.)* **1983**, 303, 535. (b) A. M. Brown, D. L. Kunze, A. Yatani, *Natuer, (London, U.K.)* **1984**, 311, 570.
[6] (a) N. Martin, M. Quintero, J. L. Segura, C. Seoane, J. L. Soto, M. Morales, M. L. Suarez, *Ann. Chem.* **1991**, 827. (b) N. Martin, M. Quinteiro, C. Seoane, J. L. Soto, A. Mora, M. Suarez, E. Ochoa, A. Morales, J. Bosque, *J. Heterocycl. Chem.*, **1995**, 32, 235.
[7] (a) F. Bossert, H. Meyer, E. Wehinger *Angew. Chem., Int. Ed. Engl.* **1981,** 20, 762. (b) H. Nakayama, Y. Kasoaka, *Heterocycles.* **1996**, 42, 901. (c) D. Mauzeral, F.H. Westheimer, *J. Am. Chem. Soc.*, **1955**, 77, 2261. (d) Y. Sawada, H. Kayakiri, Y. Abe, T. Mizutani, N. Inamura, M. Asano, C. Hatori, I. Aramori, T. Oku, H. Tanak, *J. Med. Chem.*, **2004,** 47, 2853. (e) R. Shan, C. Velazquez, E. E. Knaus, *J. Med. Chem.*, **2004,** 47, 254.

[8] (a) V. Klusa, *Drugs Future*., **1995**, 20, 135. (b) R. G. Bretzel, C. C. Bollen, E. Maester, K. F. Federlin, *Am. J. Kidney. Dis*., **1993**, 21, 54. (c) R. G. Bretzel, C. C. Bollen, E. Maester, K. F. Federlin, *Drugs Future.*, **1992**, 17, 465. (d) R. Boer, V. Gekeler, *Drugs Future.*, **1995**, 20, 499.
[9] (a) T.L. Gilchrist, *Heterocyclic Chemistry*, Addison Wesley Longman: **1997**, *3rd Edition*. (b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles: Structure, Reaction, Syntheses and Applications*, *2nd Edition*; John Wiley & Sons, Inc.: Chichester, U.K., **2003**.
[10] (a) A. Domling, I. Ugi, *Angew. Chem., Int. Ed.* **2000**, 39, 3168. (b) S. Brase, C. Gil, K. Knepper, *Bioorg. Med. Chem.*, **2002**, 10, 2415. (c) R. V. A. Orra, M. de Greef, *Synthesis.* **2003**, 1471. (d) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.*, **2003**, 4101.
[11] J. B. Sainani, A. C. Shah, *Indian J. Chem., Sect. B.* **1994**, 33, 526.
[12] M. Sufirez, E. Ochoa, Y. Verdecia, B. Verdecia, L. Moran, N. Martin, M. Quinteiro, C. Seoane, J. L. Soto, H. Novoa, N. Blaton, O. M. Peters, *Tetrahedron*, **1999**, 55, 875.
[13] M. Li, Z. Zuo, L.Wen, Wang, S. *J. Comb. Chem*., **2008**, 10, 436.
[14] S. J. Tu, J. F. Zhou, X. Deng, P. J. Cai, H. Wang, J. C. Feng, *Chin. J. Org. Chem*., **2001**, 21, 313.
[15] B. Das, B. Ravikanth, R. Ramu, B. V. Rao, *Chem. Pharm. Bull*., **2006**, 54, 1044.
[16] (a) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.*, **2002**, 124, 10294.(b) H. Inoue, N. Chatani, S. Murai, *J. Org. Chem*., **2002**, 67, 1414. (c) M. Yamaguchi, T. Tsukagoshi, M. Arisawa, *J. Am. Chem. Soc*., **1999**, 121, 4074. (d N) Asao,. T. Asano, T. Ohishi, Y. Yamamoto, *J. Am. Chem. Soc.*, **2000,** 122, 4817.
[17] R. Amemiya, Y. Miyake, M.Yamaguchi, *Tetrahedron Lett.*, **2006,** 47, 1797.
[18] (a) M. B. Deshmukh, S. M. Salunkhe, D. R. Patil, P. V. Anbhule, *Euro. J. Med. Chem.*, **2009,** 44, 2651 (b) M. B. Deshmukh, P. V. Anbhule, S. D. Jadhav, S. S. Jagtap, D. R. Patil, S. M. Salunkhe, S. A. Sankpal *Indian J. Chem*., **2008,** 47B, 792.
[19] (a) S. N. Lad, U. S. Mote, P. V. Anbhule, S. R. Patil, G. B. Kolekar, *Bull. Chem. Soc. Ethiop.*, **2009,** 23(2), 231. (b) U. S. Mote, S. L. Bhatter, S. R. Patil, G. B. Kolekar, *J. Sol. Chem*., **2009**, 38, 619. (c) S. L. Bhatter, S. R. Patil, G. B. Kolekar, *J. Lumin.*, **2010**, 130, 355. (d) V. R. More, U. S. Mote, S. R. Patil, G. B. Kolekar, *J. Sol. Chem*., **2009**, 74(3), 771.
[20] (a) A. Kumar, R. A. Maurya, *Tetrahedron Lett*., **2007**, 48, 3887. (b) S. J. Ji, Z. Q. Jiang, J. Lu, T. P. Loh, *Tetrahedron Lett*., **2004**, 5, 0831. (c) M. Maheswara, V. Siddaiah, G.L.V. Damu, C.V. Rao, *Arkivoc*, **2006,** 201.