Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2015, 7(5):329-334
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

An eco-friendly solvent free one pot multi-component synthesis of Coumarin thiazolidinone derivatives

Santosh A. Jadhav[a], Mahesh G. Shioorkar[a], Omprakash S. Chavan[b], Rahul V. Chavan[c], D. B. Shinde[d] and R. K. Pardeshi*[e]

[a]*Department of Chemistry, Vivekanand College, Aurangabad (India)*
[b]*Department of Chemistry, Badrinarayan Barwale College, Jalna.(India)*
[c]*Department of Chemistry, Vasantrao Naik College, Aurangabad (India)*
[d]*Department of chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad. (India)*
[e]*Department of Chemistry, Sant. Ramdas. College, Ghansawangi, Jalna (India)*

ABSTRACT

*8-ethoxy-3-acetyl coumarin **1**, thiosemicarbazide **2** was condensed under microwave irradition gives 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinecarbothioamide **3** then **3**, chloroacetyl chloride **4**, substituted aryl aldehydes **5**, were condensed in presence of alum catalyst to formed 5-benzylidene-2-((E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl)ethylidene)hydrazono) thiazolidin-4-one **6**, by simple grinding technique at room temperature under solvent free condition. Synthesized compounds were confirmed by IR, NMR, Mass and CHN analysis.*

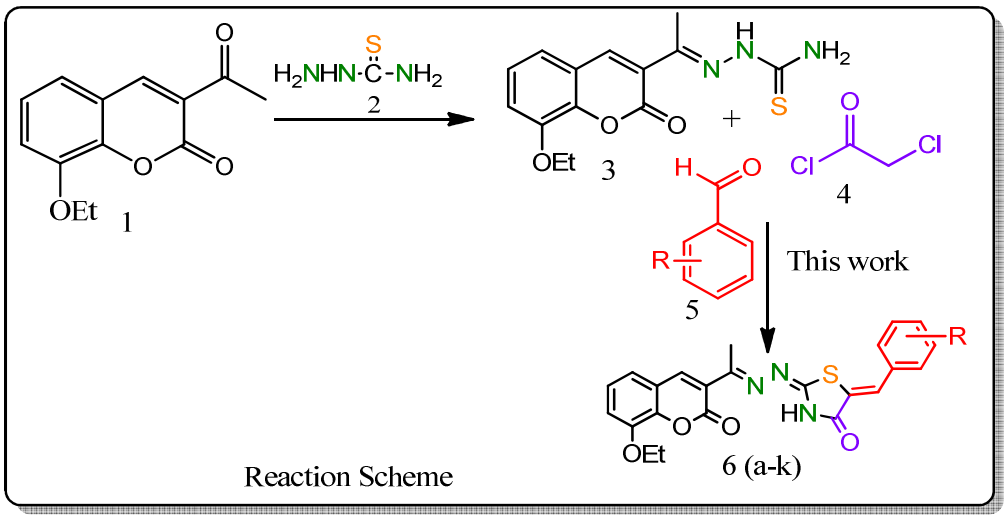
Keywords: Coumarin thiazolidinone, Green Synthesis, Knovenagel condensation reaction.

INTRODUCTION

Heterocyclic compounds widely occur in nature and are essential to life. In particular, Coumarin and its derivatives are used as additives in food, perfumes, cosmetics, pharmaceuticals, agrochemicals [1, 2], for their cardiothioc, anticancer, antiviral, properties [3, 4] and as laser dyes in the blue-green region. These types of dyes have been employed as labels for fluorescent energy transfer experiments [5, 6]. Coumarin compounds also form number of drugs, which are widely used in medicine as anticoagulant, anti arrhythmic, hypertensive and immune modulant agents [7].

Coumarin thiazolidinone derivatives plays an important role in chemistry, which is used as antifungal, antioxidant [8], antimicrobial [9], *in -vitro* cytotoxicity evaluation [10], antimicrobial [11] anticonvulsant and analgesic agent [12], Antitumer [13], antibacterial [14], anti-inflammatory [15] In our continuation of our research interest thiosemicarbazide moiety [16].

The application of solvent-free reaction conditions in organic chemistry has been explored extensively within the last decade. It was shown to be an efficient technique for various organic reactions. solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier workup, and in some cases enhancement of regio and stereo selectivity [18].



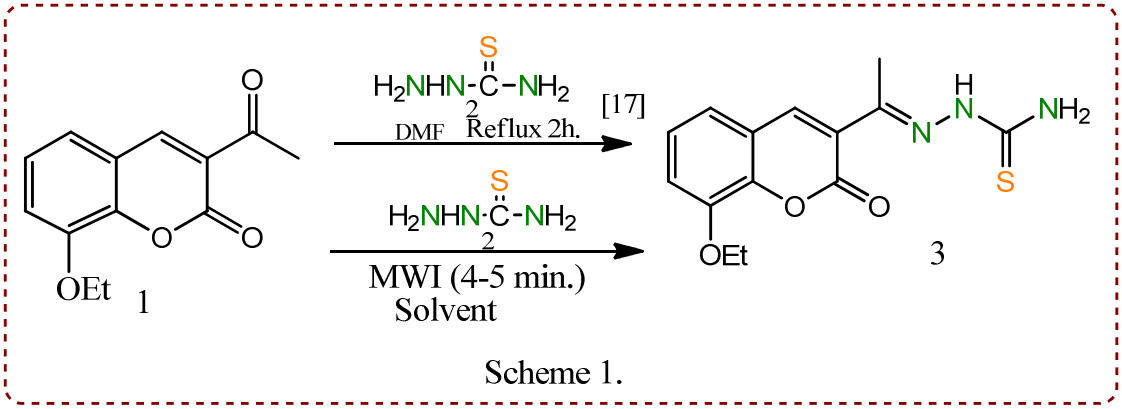
Alum [KAl(SO4)2.12H2O] has been found to be effective in the synthesis of cis-isoquinolic acids [19a], mono and disubstituted 2,3-dihydroquinazolin-4(1H)-ones[19b], dihydropyrimidines via Biginellireaction [19c] coumarins [19d],1,3,4-oxadiazoles [19e], dibenzoxanthenes [19f], 1,5-benzodiazepines,[19g], and trisubstituted imidazoles [19h].

Many research study reported for green grinding method with formation of carbon carbon or carbon heteroatom single as well as double bond, some of name reactions example is Grignard [20], Reformatsky [21], Dieckmann [22], Aldol reaction [23] and various other coupling type of reactions [24-26]. An environmentally benign process are requested for crucial perventation of pollution, enviro-economic factors, low cost and simplicity in processing these factors are beneficial to industries as well as environment [27]. However, there are no examples of the use of 'alum as a catalyst under solvent free grinding technique,' for the synthesis of Coumarin thiazolidinone derivatives, thus we choose environmentally benign process.

MATERIALS AND METHODS

All the compounds used in synthesis were of analytical grade, the melting points of the compounds were determined in open head capillary and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm-1 by using KBr pallet on FT-IR Perkin spectrophotometer. H^1 NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in DMSO-d_6. The values of chemical shift are expressed in δ ppm as a unit. All the compounds were checked for purity by thin layer chromatography (TLC).

REACTION SCHEME:



1. General Procedure for synthesis of 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazine carbothioamide 3 by microwave irradiation technique:

An equimolar amount of mixture of 8-ethoxy-3-acetyl coumarin (10 mmol) and thiosemicarbazide (10 mmol) in 10 m L of DMF was subjected to microwave irradiation for 4-5 min. at 400W. The progress reaction was monitored by TLC, After completion of reaction filtered off, washed with alcohol dried and recrystalised from ethyl alcohol, colorless needles was obtained (yield 86%) melting point range 216-222^{0}C

2. General Procedure for synthesis of 5-benzylidene-2-((E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl) ethylidene) hydrazono) thiazolidin-4-one 6 by grinding technique techniques:

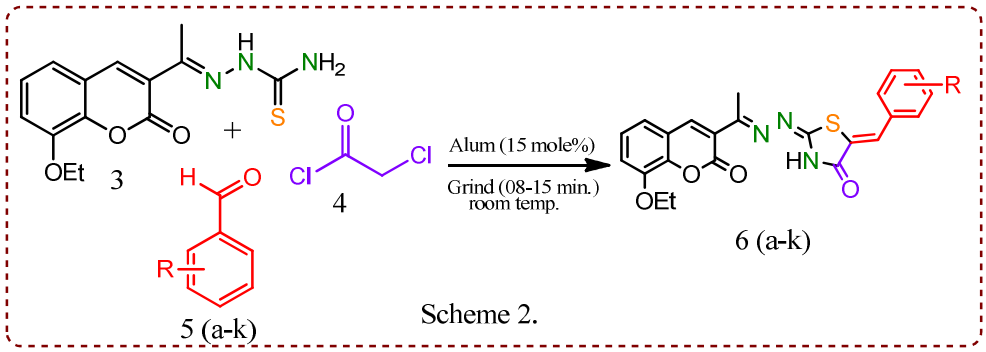
An equimolar amount of mixture of 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazine carbothioamide **3** (5 mmol), chloroacetyl chloride **4** (5mmol), substituted aryl aldehydes **5** (5mmol) and 15 mol% of alum [$KAl(SO_4)_2$.$12H_2O$] was grind in mortor by pestle for 8-15min.The progress reaction was monitored by TLC, After completion of reaction filtered off, washed with alcohol dried and recrystalised from ethyl alcohol, Pale yellow color product **6** was obtained (yield 80%) melting point 221^{0}C

Table 1. Optimization of catalyst with respect to yield and time:

Sr. No.	Catalyst	Mole %	Yield (%)[a] /Time (min.)
1.	Acetic acid	15	88/10
2.	Boric acid	15	60/15
3.	Oxalic acid	15	20/15
4.	Sodiumacetate-acetic acid	15	89/10
5.	Ammonium-acetate-acetic acid	15	70/15
6.	Pyridine-acetic acid	15	81/15
7.	Alum	15	**96/08**
8.	Alum	20	96/12
9.	Alum	10	80/15

[a] *Isolated yield*

Table 2. Synthesis of 5-benzylidene-2-((E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl) ethylidene) hydrazono) thiazolidin-4-one 6

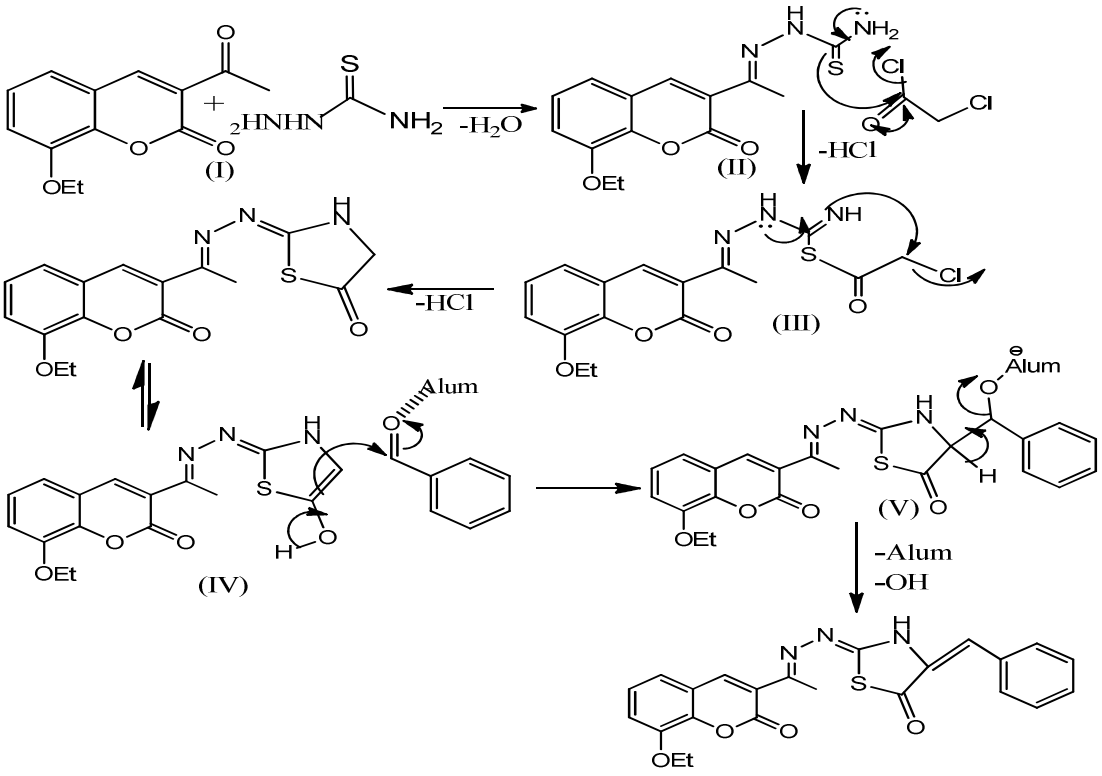


Scheme 2.

Sr. No.	Compound	R (Substituent)	Isolated yield(%)/Time(mi.)	Melting Point (^{0}C)		Color
				Found	Lit.	
1.	6a	H	93/10	210-214	-	Brown
2.	6b	4-OCH_3	**96/08**	221	218-222(17)	Pale brown
3.	6c	2,4(OCH_3)$_2$	91/10	218-223	-	Light brown
4.	6d	4-OH	86/12	199-205	-	Colorless
5.	6e	4-CH_3	92/10	243-247	-	Colorless
6.	6f	4-CN	89/10	221-226	-	Pale brown
7.	6g	4-Cl	83/15	217	-	Light brown
8.	6h	4-NO_2	81/12	240-250	-	Light yellow
9.	6i	Furyl (C_4H_3)	78/15	-	-	Brown grey
10	6j	3-NO_2	83/15	226-229	-	Light yellow

Reaction condition: 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazine carbothioamide (5 mmol), chloroacetyl chloride (5mmol), substituted aryl aldehydes (5mmol) and alum 15mol%

Possible mechanism:



Spectral data for compound (3) and (6):

2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinecarbothioamide 3 by grinding technique (3):

IR (KBr) υ (cm^{-1}): 3404, 3254, 3178, (NH andNH_2), 2979 (C-H aliphatic), 1729 (CO).; ^{1}H-NMR (DMSO-d_6) δ:8.54 (s, 2H), 7.02 (s, 1H), 2.04 (s, 3H), 7.52 (s, 1H), 7.39 (d, 1H), 7.37 (t, 1H), 7.17(d, 1H), 4.02 (qt., 2H), 1.30 (t. 3H) MS m/z (%): 305 (M^+, 42), 290 (100), 245 (23), 230 (27), 161 (24); Anal.calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; found: C, 55.09; H, 4.94; N, 13.78%.

5-benzylidene-2-((E)-(1-(8-ethoxy-2-oxo-2H-chromen-3yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)thiazolidin-4-one1 (6b):

IR (KBr) υ (cm−1): 2941 (CH aliphatic), 1685-1705 (CO), 1605 (N=C).; 1H-NMR (DMSO-d_6) δ: 1.45 (t, 3H, CH_3, J = 6.8Hz), 2.35 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.20 (q, 2H, CH_2, J = 6.7Hz), 7.56–7.81 (m, 7H, Ar-H), 8.29 (s, 1H, =CH-Ar), 8.42(s, 1H, 4-H), 12.43 (brs, 1H, NH).; Anal. calcd. for $C_{24}H_{21}N_3O_5S$: C, 62.19; H, 4.57; N, 9.05; found: C, 62.18; H, 4.58 N, 9.09%.

RESULTS AND DISCUSSION

Initially, simle condensation reaction carried out between acetyl coumarin and thiosemicarbazide in microwave irradiation expeditious obtained hydrazinecarbothioamide **3** Scheme 1 We optimized or screened of catalyst in a constant amount of mol % (15 mol%) for this multicomponent reaction of 2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinecarbothioamide3 (5 mmol), chloroacetyl chloride 4 (5mmol), substituted aryl aldehydes 5 (5mmol) an excellent yield was obtained (**Table 1**. Entry **7** as well as entry no.4 and 1), if we increased mole% of alum catalyst there is no too effect on the yield of product. (**Table 1.** entry no 8) gradually decreases yield of product in entry no. **9**.

The optimum conditions for the multicomponent synthesis of Coumarin thiazolidinone derivatives required the use of alum (15 mol%), simple grinding technique using the optimized reaction conditions, the scope and generality of this reaction were investigated (**Table 2, Scheme 2.**). an aromatic aldehydes with different functional groups such as hydroxyl, chloro, nitro methoxy, nitrile etc. were applied in the reaction, we observed that electronic effects on the

aldehydes had little influence on the yield and reaction time: arylaldehydes with electron-donating groups reacted rapidly, gives better yield (**Table 2**. entry no.**2**) than unsubstituted aryl aldehyde (**Table 2**. entry no.**1**.), the poor yield was obtained for electron withdrawing substituted aryl aldehyde. summarized in **Table 2**.entry 6,7,8,9,10. On the basis of the results obtained from Table 2. and according to proposed mechanism in **Scheme 2**.for the formation of Coumarin thiazolidinone derivatives

In all the cases, the Coumarin thiazolidinone derivatives precipitated under solvent free were obtained in excellent yields after recrystallization from ethanol. No side products were observed during the course of the reaction; thus we believed that the present methodology opens new possibilities for the green synthetic organic chemistry and could be an important addition to existing methodologies, in our experiments, the completion of reaction was confirmed by the disappearance of the starting on TLC and the structure of compounds (6a-k) were substantiated by IR, ^{1}HNMR and CHN analysis, The IR spectrum of representative compound **6,** shows a strong absorption band at the region 1685-1705 cm^{-1} which is due to a carbonyl group thiazolidinone moiety. ^{1}HNMR spectra of compound **6** show one singlet for the methylene proton *(1H)* in the range δ 8.26-8.31 ppm. and another one signal for the methylene proton *(1H)* δ 12.40 ppm (-NH) and another δ values. Thus conformed that coumarin thiazolidinone compound.

CONCLUSION

In conclusion, we have developed a convenient alum-catalyzed synthetic protocol for Coumarin thiazolidinone derivatives; an alum is commercially available and inexpensive. The time required for the completion of the reaction is obviously reduced and the yields of the products are increased. Hence, this route is economical and eco-friendly when compared to some of the other existing methods. An effort toward the synthesis of other important drug molecules with azoles moiety by grinding as well as microwave irradiation method is ongoing in our laboratory. Also work is in progress to obtain biological activity such as antibacterial, antifungal, and anticancer of these important compounds. Results in these areas will be presented in due course.

Acknowledgment
The authors are thankful to The Principal and Head, Department of Chemistry, Sant Ramdas College, Ghansawangi, Jalna (MS), India, for providing financial assistance for instrument help, also thankful to The Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, 431004 (MS), India, for given valuable instruction and comments.

REFERENCES

[1] Kennedy, R.O.; Thornes, R.D. Coumarins: Biology, Applications and Mode of Action; *Wiley & Sons: Chichester*, UK, **1997.**
[2] Murray, R.D.H.; Mendez, J.; Brown, S.A. The Natureal Coumarins; Occurrence, Chemistry and Biochemistry; *Wiley & Sons: New York, NY, USA*, **1982.**
[3] Egan, D.; Kennedy, R.O.; Moran, E.; Cox, D.; Prosser, E.; Thornes, R.D. The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. *Drug Metab. Rev*. **1990**, 22, 503–529.
[4] Gabor, M. The Pharmacology of Benzopyran Derivatives and Related Compounds; *Akademiai Kiado: Budapest*, *Hungary*, **1988**;. 91–126.
[5] Guilbault, G.G.; Practical Fluorescence. Theory, Methods and Techniques; Marcel Dekker: *New York, NY, USA*, **1973**; p. 354.
[6] Rathbone, D.L.; Wang, D.; Su, Y.; Billington, D.C. Molecular recognition by fluorescent imprinted polymers. *Tetrahedron Lett*. **2000**, 41, 123–126.
[7] Abyshev, A.Z.; Gindin, V.A.; Semenov, E.V.; Agaev, E.M.; Abdulla-zade, A.A.; Guseinov, A.B. Structure and biological properties of 2H-1-benzopyran-2-one (coumarin) derivatives. *Pharm. Chem. J*. **2006**, 40, 607–610.
[8] BojanSarkanj, Molnar M., Milan Cacic, *Food chemistry*, **2013**,139, (1-4), 488-495.
[9] Mulwad, Vinata V., Mir, Abid Ali, *Journal of Chemical Res*., **2008**,(5), 292-296.
[10] Vikas Goba, Jitender B., Vivek S., Manish K., *Chemistry & Biology Interface*, **2014**,(4,5) 281-286.
[11] Hany M. Mohamed Ashraf H. F. Abd El-Wahab, Kamal A. Ahmed, *Molecules*, **2012**, 17, 971-988.
[12] MA Bhat, N.Siddiqui, SA Khan, *Indian Journal of Pharm. Sciences*, **2006**, 68 1,120-124.
[13] Raev, L. E. Voinov I. Ivanov and D. Popov, (*Chem. Abstr*), 114, 74711 B. *Pharmazie*, **1990**, 4 , 696.
[14] Rama Ganesh C.K., Yadav D. Bodke, Venkatesh K.B. *Indian Journal of Chemistry*, **2010**,.49B,1151-1154.

[15] Ashish L. Asrondkar, Vrushali N. Patil, Neha U. Mishra, Anil S. Bobade and Abhay S. Chowdhary, *Der Pharma Chemica*, **2013**, 5(4), 288-292.
[16] Santosh A. Jadhav, Pardeshi R. K., Shioorkar M. G., Chavan O. S, *Der Pharma Chemica*, **2015**, 7 (2):127-131
[17] Hany M. Mohamed, Ashraf H. F., Ahmed H. Bedair, Fathy A. Eid, and Mostafa M. Khafagy, *Molecules* **2012**, 17, 971-988
[18] (a) K.F. Tanaka, Chem. Rev. **2000**, 100, 1025–1074; (b) D. Klemm, B. Heublein, H.P. Fink and A. Bohn, *Angew Chem. Int. Ed*. **2005**, 44, 3358–3393.
[19] (a) J. Azizian, A.A. Mohammadi, A.R. Karimi and M.R. Mohammadizadeh, *J. Org. Chem*. **2005**, 70, 350–352; (b) M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary and A.A. Mohammadi, *Tetrahedron Lett*. **2005**, 46, 6123–6126; (c) J. Azizian, A. A. Mohammadi, A. R. Karimi and M. R. Mohammadizadeh, *Appl.Catal. A. General* **2006**, 300, 85–88; (d) M. Dabiri, M. Baghbanzadeh, S. Kiani and Y. Vakilzadeh, *Monatsh. Chem.* **2007**, 138, 997–999; (e) M. Dabiri, M. Baghbanzadeh, and M. Bahramnejad, *Monatsh. Chem.*, **2007**, 138, 1253–1255; f) M. Dabiri, M. Baghbanzadeh, M.S. Nikcheh and E. Arzroomchilar, *Bioorg. Med. Chem. Lett*. **2008**, 18, 436–438; (g) D. Mahajan, T. Nagvi, R.L. Sharma, K.K. Kapoor, Aust. *J. Chem.* **2008**, 61, 159–162; (h) A.A. Mohammadi, M. Mivechi and H. Kefayati, *Monatsh.Chem*., **2008**, 139, 935–937.
[20] Toda F.; Takumi H.;Yamaguchi H.;*Chem.Exp*. **1989**, 4, 507.
[21] Tanaka K.; Kishigami S.; Toda F.; *J.Org. Chem*. **1991**, 56, 4333.
[22] Toda F.; Suzuki T.; Higa S.; *J. Chem. Soc. Perkin trans*. **1998**, 1, 3521.
[23] Toda F.; Tanaka Hummai.; *J. Chem. Soc. Perkin trans*. **1990**, 1, 3203.
[24] Toda F.; Tanaka K.; Iwata. S.; *J. Org. Chem*. **1989**, 54, 3007.
[25] Toda F.; Kiyoshige K.; Yagi. M.; *Angewante Chem, Int. Ed*. **1989**, 2, 320
[26] (a) Schmeyers T.; Toda F.; Boys J. Kaupp. G. *J. Chem Soc. Perkin trans*. **1998**, 2,989.; (b) Xiao J. P.; Wang Y. L.; Zau. Q. X.; Synth. Commun. **2001**, 31, 66.; (c) Wang Z. X.; Hua, L. Q.; *Green Chem*. **2004**, 60, 90.
[27] Tanaka K.; Toda F.; *Chem. Rev*. **2000**, 100, 1025.