

GREEN SYNTHESIS OF BIOACTIVE 2-PHENYLIMIDAZO [4,5-*f*][1,10]-PHENANTHROLINE

Arshia Parveen

Assistant Professor,

Department of Chemistry, B. Raghunath ACS College, Parbhani, 431401 India.

ABSTRACT:

An efficient and one pot method for smooth conversion of substituted aldehydes and 1,10,phenanthroline-5-dione into a range of 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline have been synthesized in very good yield under solvent-free conditions by grinding 1,10,phenanthroline-5dione, aromatic aldehydes and ammonium acetate in the presence of [HBim] BF₄ ionic liquid as a catalyst as well as solvent . The ionic liquid can be recycled and reused several times. 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline was synthesized and tested for antibacterial effects against *Bacillus Subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The antibacterial screening of the synthesized compounds were performed in vitro by the filter paper disc diffusion method. The short reaction time, clean reaction, and easy workup make this protocol green and practically economical attractive and efficient.

KEYWORD:-2-phenylimidazo [4,5-*f*] [1,10]- phenanthroline, aldehydes, 1,10,phenanthroline-5-dione , ammonium acetate , antibacterial activity.

INTRODUCTION:-

2-phenylimidazo [4,5-*f*] [1,10]- phenanthroline possess synthetically challenging scaffold skeleton and is a basic structure of several synthetic drugs .The heterocyclic compounds with fused Imidazo-Phenanthroline ring system represent an important class of ligand used as a Convenient Modular Platform for the Preparation of Heteroleptic Cu(I) Photosensitizers. In addition, the substituted imidazole ring systems are substantially used in ionic liquids¹ that have been given a new approach to "Green Chemistry". Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazoles from 1, 2-dicarbonyl compound, various aldehydes and ammonia to obtain the imidazoles.²⁻³

The Ru(II) metal complexes of 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline has been attracted considerable attention of chemist for many years⁴, because their utilities in DNA structure prob⁵⁻⁶.

Many ammine complexes of ruthenium (II) tend to bind selectively to imine sites in biomolecules because of their nitrogen lone pairs that are available for metal ion coordination. . Consequently, ruthenium complexes often selectively conjugate the histidyl nitrogen of imidazole on proteins and the N7 site on the imidazole ring of purine nucleotides. These heterocyclic structures forms the skeleton of natural alkaloids⁷ which act as

neuromuscular blocking agent⁸, reversible inhibitors of the H⁺, K⁺, ATPase enzyme⁹ with a potent anti-secretory activity¹⁰ and sedative hypnotics of the nervous system.¹¹ Literature survey shows that synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline has various routes like from 1,10-phenanthroline-5,6-dione with aldehyde in the presence of ammonium acetate in acetic acid¹² and anhydrous ZnCl₂ mediated the formation of 2-4,5-diphenyl-2-pyridin-2-yl-1H-imidazol-1-yl in methanol¹³ and molecular iodine¹⁴. Most routes involve reaction of a 2-amino methyl pyridine with acylation followed by cyclization with phosphorus oxy chloride or polyphosphoric acid¹⁵ or thiocyclation followed by ring closure using DCC or mercuric salts¹⁶ Imidazo-[1,5-a]-pyridines were also obtained from 2-cynopyridine by the Vilsmeier reaction¹⁷ or by reaction with Schiff bases in the presence of three steps from the dipyrindyl ketone.¹⁸⁻²², using nitriles and esters²³ also reported by using potassium ferrocyanide²⁴. Siddiqui et al²⁵⁻²⁶. However these methods require prolong and exotic reaction condition. Thus the development of a new method for the synthesis of imidazoles derivatives would be highly desirable. We have already reported the synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline at room temperature²⁷. But now we extend our work to study and find out the catalytic amount of ionic liquid used with respect to the isolated yield of the desired product and its antimicrobial activity. Initially, a systematic study was carried out for catalytic evaluation of complex for 2-phenylimidazo [4,5-f] [1,10]-phenanthroline, benzaldehyde and ammonium acetate (**Table 1**). The enhancement of mol% of [HBim]BF₄ enhance the yield of the product and reduce the reaction time (entry 1-5). The reaction went to completion in 10-30 minutes at room temperature with 10 mol% [HBim]BF₄. Accordingly, 10 mol% was sufficient to catalyze the reaction. As per shown in the **Figure:01** rate enhancement with high yield was observed when higher molar ratios of ionic liquid were used. However, no product formation was observed in absence of [HBim]BF₄.

Table 1: Catalytic evaluation of [HBim]BF₄ for the synthesis of 3a

Entry	[HBim]BF ₄ (mol %)	Time (Sec)	Yield ^{a,b} (%)
1	0	180	00
2	2	80	65
3	5	68	90
4	10	18	98
5	15	15	94

^a: Reaction Condition; 1,10-phenanthroline-5,6-dione,(1mmol),benzaldehyde (1 mmol), ammonium acetate (2.5 mmol),RT Room temperature

^b: Isolated yield after column chromatography

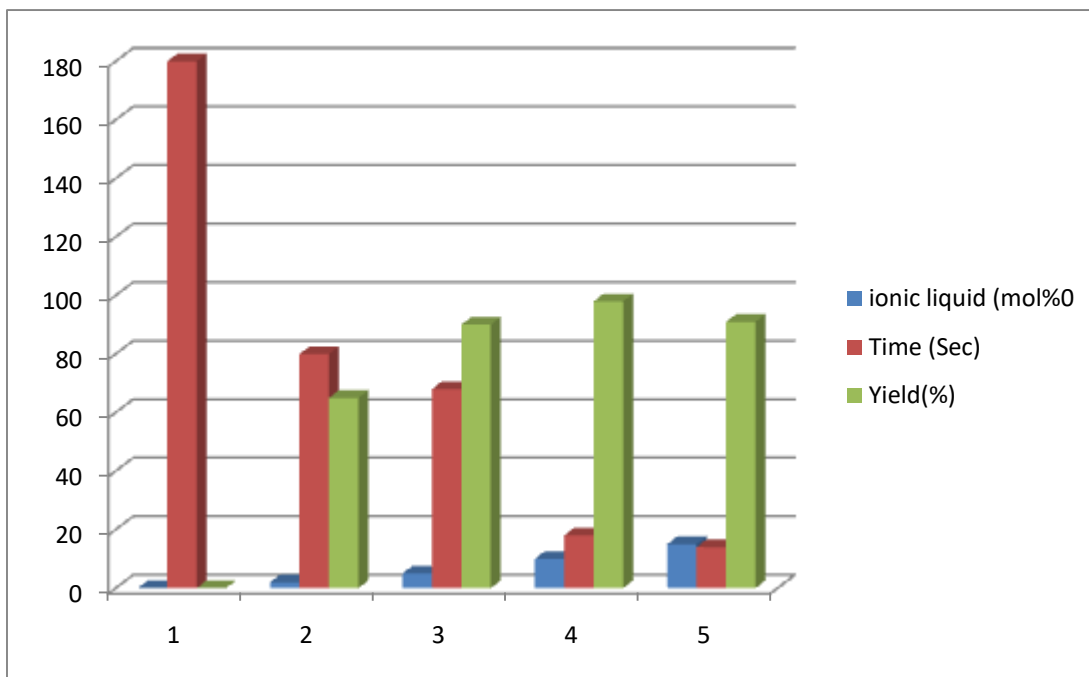
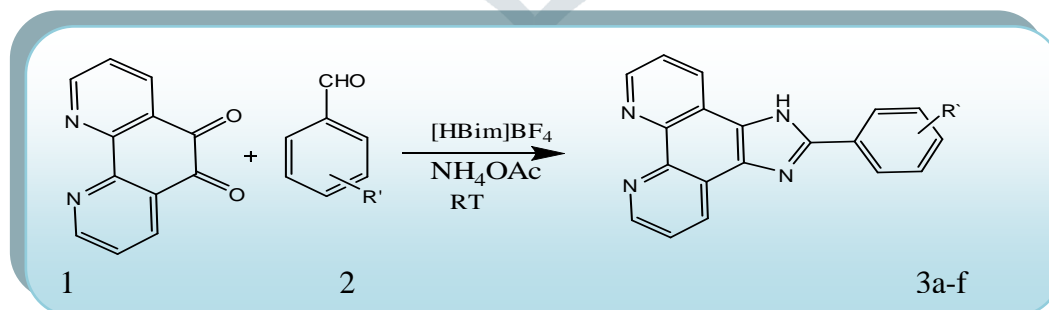


Figure:-1 Catalytic evaluation of [HBim]BF₄ for the synthesis of 3a

Material and Methods:

Synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline²⁷ :

mixture of benzaldehyde(1mmol)1,10-phenanthroline-5,6-dione,(1mmol),NH₄OAc(2.5mmol) and [HBim]BF₄ (10mmol) were ground together in a mortar with a pestle at room temperature for appropriate time as shown in table-1 .Completion of reaction is confirmed by TLC the mixture was further purified by column chromatography by using methanol : benzene and recrystallised from methanol. Recently ionic liquid has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformation²⁸offering the corresponding products in excellent yield with high selectivity.

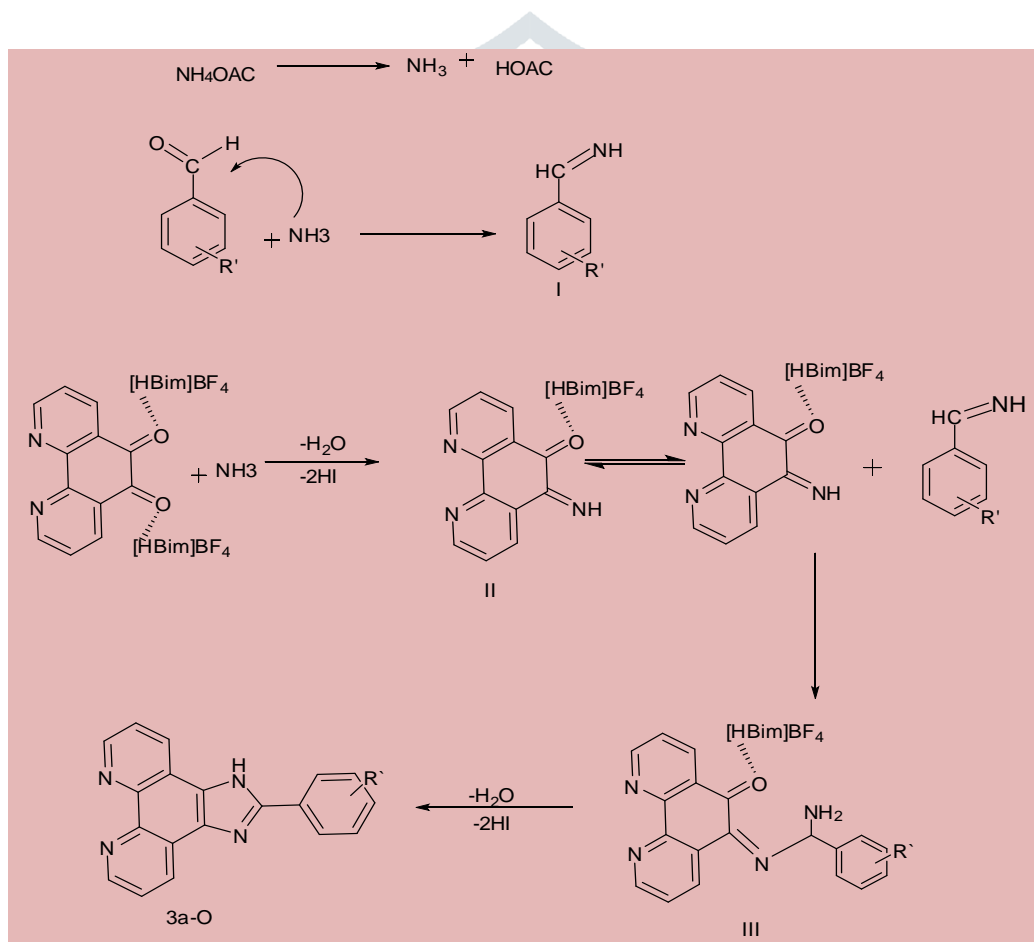


Schem-1 Synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline

The mild Lewis acidity associated with ionic liquid enhanced its usage in organic synthesis to realize several organic transformation using stoichiometric levels to catalytic amount. Owing to numerous advantages associated with this eco-friendly element, ionic liquid has been explored as a powerful catalyst for various

organic transformations. During the course of our studies towards the development of new routes to the synthesis of biologically active heterocycles.

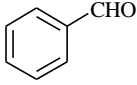
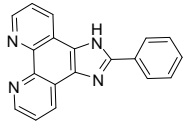
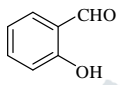
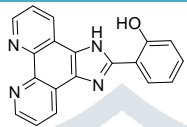
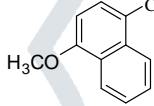
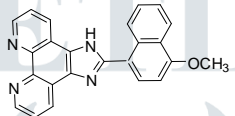
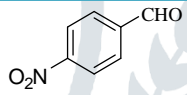
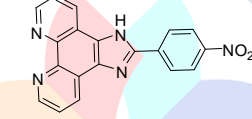
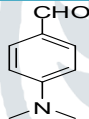
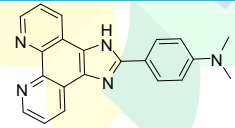
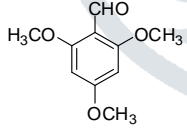
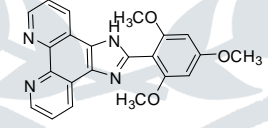
The ammonium acetate is acting as a nitrogen source for the formation of imines I. Due to the high selectivity the [HBim]BF₄ ionic liquid attached to the both carbonyl group of 1,10-phenanthroline give an intermediate II which cyclized to form product via intermediate III as mention in scheme-2. By getting this result, we have extended this protocol to a variety of aldehydes and summarized in Table 1. This protocol is rapid and efficient for the preparation of several 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline from both electrons efficient as well as electron deficient aromatic aldehydes. Electron-withdrawing groups enhance the rate of the reaction as compare to the electron-donating group.



Schem-2 Possible mechanism of the synthesis of 3a-f

Aliphatic aldehydes were also used as starting carbonyl compounds for the same reaction. The *ortho* and *para* substituents activate the aromatic ring of aldehydes and increase the rate of the reaction. While *meta* substitution requires somewhat greater time as compared to the *o/p* substituent's. A nearly stoichiometric amount of ammonium acetate was used in the course of the reaction, whereas previously a many-fold excess of ammonium acetate was required. This is an additional advantage of the novel methodology. Here we report an easy procedure for synthesizing of 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline catalyzed by inexpensive and nontoxic $[\text{HBim}]\text{BF}_4$ in the presence of ammonium acetate under solvent free condition with excellent yield and easy work up

Table-1: Synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline 3a :

Entry	Aldehyde	^a Product	Time (sec).	^b Yield (%)
3a			18	82
3b			23	89
3c			18	88
3d			12	82
3e			18	85
3f			20	89

^aProducts were characterized by ¹H NMR, ¹³C NMR, Mass, elemental analysis and comparison with authentic sample, ^bIsolated yield after column chromatography.

Result and discussion:-

In conclusion, [HBim]BF₄ was found to be a mild and effective catalyst for the formation of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline in excellent yields. The uses of this inexpensive and easily available catalyst under solvent-free conditions make this protocol green and economically attractive. The simple work-up procedure, mild reaction conditions, selectivity, and very good yields make our methodology a valid contribution to the existing processes in the field of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline derivatives synthesis.

The formation of 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline are confirmed by spectral analysis. The IR spectra of 4-N,N-dimethyl-2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline shows absorption at 1687,2257 and 3355cm⁻¹ corresponding to the C=N, NH and tertiary amino group respectively. The ¹HNMR spectra shows 1H(s) δ=2.0, for NH gr, 6H(s) δ=3.00 for methyl group, 4H(d) δ=6.65-7.30 for aromatic benzene, 4H(d) δ=8.00-8.81, 2(H) δ=7.26 mass 207(M⁺), 185, 165, 127. These result shows the confirmation of the formation 4-N,N-dimethyl-2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline(3e).

EXPERIMENTAL:

General procedure for the synthesis of 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline(3a-f):

A mixture of benzaldehyde (1mmol), 1,10-phenanthroline 5,6-dione(1mmol), ammonium acetate (20mmol) and [HBim]BF₄ (10mmol) were grind together in a mortar with pestle at room temperature for appropriate time **Table-1** after completion of reaction confirmed by TLC . The crude was further purified by column chromatography by using petroleum ether: ethyl acetate (9:1) eluent and get the corresponding 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline . The products **3(a-f)** were confirmed by comparison with authentic sample, ¹H NMR, ¹³C NMR, mass, elemental analysis and melting points.

ANTIMICROBIAL ACTIVITY

The antibacterial activities of the synthesized compounds 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline were studied against four bacteria, viz. *Bacillus subtilis* (G+), *Escherichia coli* (G-), *Staphylococcus aureus* (G+) and *Pseudomonas aeruginosa* (G-). For the detection of antibacterial activities, the filter paper discs diffusion method was used²⁹. Streptomycin sulphate was used as positive control. Nutrient agar (NA) was used as basal medium for test bacteria. The discs were prepared by impregnating them in methanol solution of each sample (1 mg/1 mL). Each culture was prepared to a turbidity equivalent to McFarland and spread on the test tube. The paper disc containing the compound was placed on the agar surface previously inoculated with suspension of each microbes to be tested. All determinations were made in duplicate. Inhibition diameter was determined after incubation at 37°C ± 1 for 24 h. The antimicrobial activity was indicated by the presence of the clear inhibition zones around each disc.

The antibacterial activity of compounds (3d) and (3e) has been assayed at the concentration 1000 µg/mL against four human pathogenic bacteria. Among them two were gram-positive and the other two were gram negative. The inhibitory effect of compounds (3d) and (3e) against these organisms are given in Table 2. The screening results indicate that only compound (3d) was active against a gram-negative bacteria, *Escherichia coli* with a mean zone of inhibition 12.5 ± 0.3 mm (table 2).

Determination of the minimum inhibitory concentration (MIC) :

The active sample in the disc diffusion method was then tested for its activity by the serial dilution method to determine the minimum inhibition concentration (MIC-value). The MIC value obtained for 2-phenylimidazo [4,5-*f*] [1,10]-phenanthroline was 1000 µg/mL against *Escherichia coli*.



Fig 02:- Diameter of the zone of inhibition (mm)

Table 2. Antibacterial screening for the compounds (3d) and (3e)

Organism	chalcones	2-phenylimidazo [4,5-f] [1,10]- phenanthroline	Streptomycin sulphate
Bacillus subtilis	—	—	22.0 ± 0.3
Staphylococcus aureus	—	—	22.5 ± 0.7
Escherichia coli	—	12.5 ± 0.3	
Pseudomonas aeruginosa	—	—	22.0 ± 0.0 22.0 ± 0.0

Acknowledgment: Author thankful to Dept. of Chemistry and Dr. V.Y.Sonawane Principal of B. Raghunath ACS College Parbhani for valuable support.

References:

- (a) Wasserscheid P, Keim W. *Angew Chem Int Ed Eng.* 2000; 39: 37872. (b) Bourissou D, Guerret O, Ggabbai FT, Bertrand G. *Chem Rev.* 2000; 100.
- Radziszewki B. *Chem Ber.* 1882; 15: 1493.
- Japp F R, Robinson HH. *Chem Bar.* 1882; 15: 1268.
- Donoghue KA, Kelly JM, Kruger PE. *Dalton Trans.* 2004; 1.
- Metcalfe, C.; Thomas, J. A.; *Chem. Soc. Rev.* 2003; 32: 215
- Tan LF, Chao H, Liu YJ, Sun B, Wei WJ. *L.N.* 2005; 13: 4693.

7. Biachi G, Rodrigues A, Yakurshigi K. *J. Org. Chem* 1989; **54**:4497.
8. Bolger L, Brittain RJ, Jack D, Jackson MR, Martin LE, Mills J, Poynter D, Tyers MB. *Nature (London)* 1972; **238**:354.
9. Zito SW, Martlnez MJ. *Biol. Chem* 1980; **225**:8645.
10. Jansonius JN, Eichele G, Ford GC, Picot D, Thaller C, Vicent M G, In Transaminases; Christen P, Metzler DE. *Eds Wiley: New York*, 1985; **110**.
11. Arbilla S, Allen J, Wick A, Langer S. *Eur. J. Pharmacol.* 1986; **130**:257.
12. Steck E A, Day AR. *J. Am. Chem. Soc.* 1943; **65**:452
13. Michael GB, Derek AT, Kiranmoy C, Shubhamoy C, Dipankar D. *New. J. Chem.* 2004; **28**:32-32.
14. Arshia Parveen., Sk Md Rafi, Shaikh. Kabeer A, Deshmukh SP, Pawar RP. *ARKIVO* .2007; **14**:12-18.
15. (a) Bower JD, Ramage GR., *J. Chem. Soc.* 1955:2834, PS, Joshi PN, Chavan SP, Chaphekar GM, *Green Chem.* 2004; **6**: 308-309.
16. Bourdais J, Omar A. M. E. *J. Heterocycl. Chem.* 1980; **17**:555. (b) ElKhadem HS, Kawai J, Sartz DL. *Heterocycles*. 1989; **28**:239.
17. Sasaki K, Tsurumori A, Hirota T. *J. Chem. Soc. Perkin Trans.* 1998; 3851.
18. Palacios F, Alonso C, Rubiales G. *Tetrahedron*. 1995; **51**:3683.
19. Kartritzky AR, Qiu G. *J. Org. Chem.* 2001; 662862.
20. (a) Krapcho AP, Powell JR. *Tetrahedron Lett.* 1986; **27**:3713. (b) Grigg R, Kennewell P, Savic V, Sridharan V. *Tetrahedron*. 1992; **48**:10423
21. Wang J, Dyers L, Mason R. Jr, Amoyaw P Jr, Bu XR. *J. Org. Chem.* 2005; **70**:2353.
22. Bluhm ME, Ciesielski M, Gorls H, Walter O, Doring M. *Angew. Chem. Int. Ed.* 2002; **41**:2962.
23. Grimmett MR, *Pergamon: New York*. 1996; **3**:77.
24. Shahed Ali *Arch. Appl. Sci. Res.* 2010; **2 (5)**: 397
25. a) Siddiqui SA, Potewar TM, Lahoti R J, Srinivasan KV. *Synthesis*. 2006; 2849
b) Bhosale RS, Sarda SR, Ardhapure SS, Jadhav WN, Bhusare SR, Pawar RP. *Tetrahedron Letters*. 2005; **46**:7183.
26. Jarikote DV, Siddiqui SA, Rajgopal R, Thomas D, Lahoti RJ, Srinivasan KV. *Tetrahedron Lett.* 2003; **44**:1835.
27. Parveen et al, *J Adv Sci Res*, 2013, 4(2): 42-47
28. a) Rajgopal R, Jarikote DV, Lahoti RJ, Thomas D, Srinivasan KV. *Tetrahedron Lett.* 2003; **44**:1615;
b) Gholap AR, Venkatesan K, Thomas D, Lahoti RJ Srinivasan KV. *Green Chem.* 2004; **6**:147-150.
c) Panchgalle SP, Kalkote UR, Nipahadkar PS, Joshi PN, Chavan SP, Chaphekar GM, *Green Chem.* 2004; **6**: 308-309.
29. M. Tsukayama, Y. Kawamura, T. Ishizuka, S. Hayas and F. Torii, *Heterocycles*, **2003**, 60 (12), 2775.