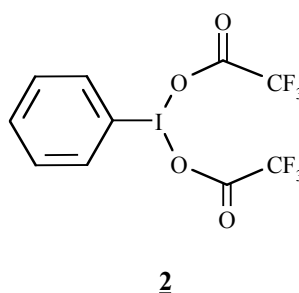
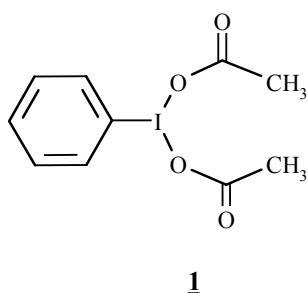


Trivalent iodine chemistry

A review of some compounds used as mild oxidising agents and their applications in modern organic synthesis

Introduction

In the last years, there has been considerable attention on hypervalent iodine compounds in organic synthesis. A lot of contributors^{1,2} have reviewed a wide range of applications of these powerful and selective oxidising agents. Although numerous reagents are mentioned for related studies, this article will focus on two trivalent iodine compounds which are developed industrially by the French company SIMAFEX : **Diacetoxy-Iodo-Benzene 1 (DIB)** is one of the first reagent of this family to be investigated, and is the synthetic precursor to several related compounds; among these derivatives, **[Bis(trifluoroacetoxy)iodo] benzene (BTI) 2** plays a key role by offering several interesting applications in modern organic synthesis.

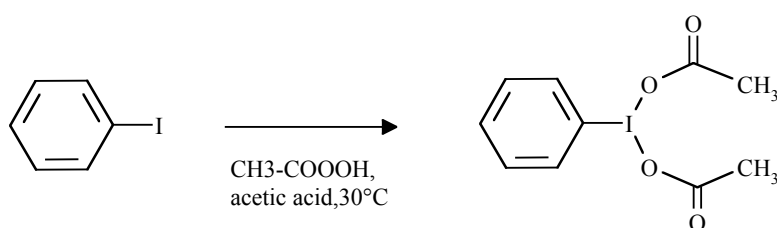


It has been observed that trivalent iodine compounds' synthetic properties are often similar to those of lead and thallium derivatives, somehow with better yields and improved toxicity, which make them more compatible in a pharmaceutical production environment.

The aim of this article is to give an overview of the possible applications of such reagents. The commonly used reactions are described, as well as practical examples from the literature.

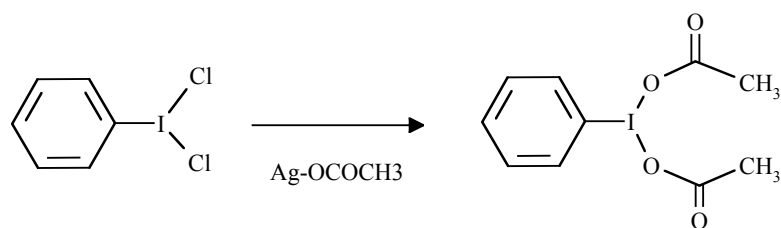
Synthesis and derivatives

Several paths are described for the synthesis of **1**. Iodobenzene may be used as a starting material, and then oxidised by peracetic acid in acetic acid³ with a conversion yield of 85 %, as follows :



The reaction with peracetic acid is exothermic, and can be considered dangerous if not carefully controlled. This method may be used for toluenic and xylenic derivatives. Sodium perborate⁴ in acetic acid is also a useful reagent for the synthesis of **1**.

Another route, known as the safest process for the synthesis of **1**, was investigated by Alcock⁵, starting from dichloro-iodobenzene in presence of silver salts :



Karele⁶ performed an analogous synthesis in two steps from iodobenzene, using thionyl chloride to yield dichloro-iodobenzene, then aqueous acetic acid in pyridin to convert it to **1**.

Other syntheses of **1** are described but their application field seems limited in an industrial environment, due to production costs and feasibility.

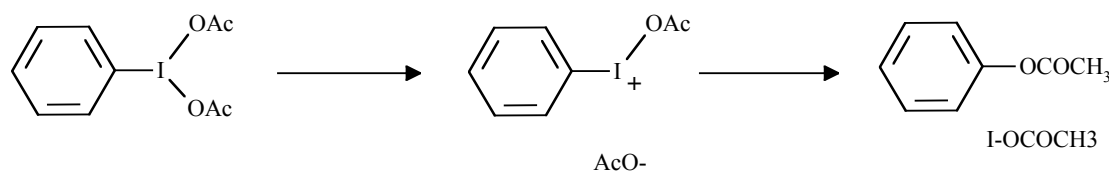
Since the structure of trivalent iodine compounds enables a ligand exchange on iodine, it has been possible to use **1** as a precursor in the synthesis of numerous derivatives. The reaction of **1** with trifluoroacetic acid provides an efficient synthesis of **2**. In the same way, two promising derivatives **3** (**hydroxy-tosyl-iodobenzene**) and **4** (hydroxymesyl-iodobenzene) were synthesized⁷, following Koser's method :



Stability

Leffler⁸ has observed that **DIB 1** is likely to decompose in various products. The following hypothesis about the mechanism of decomposition was proposed :

- The main decomposition reaction is related to a nucleophilic displacement :



I-OCOCH₃ then decomposes to methyl iodide and carbon dioxide.

- In aromatic solvents, **1** is subjected to a homolytic cleavage (free-radical reaction). Iodobenzene has been isolated as a product of this reaction.
- Another possibility is a radical-induced reaction yielding acetic acid as a residue.

Substituent effect :

Parasubstitution on iodosobenzene diacetate increases the decomposition rate.

Temperature effect :

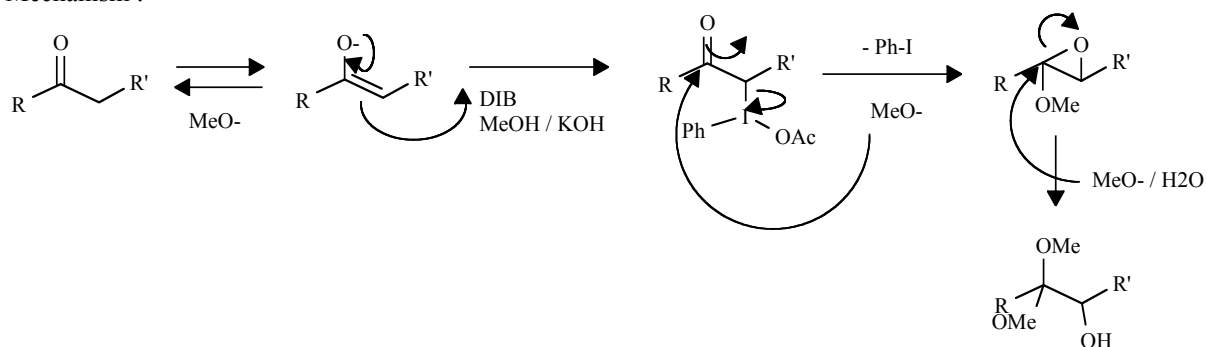
When trivalent iodine compounds are heated above 160°C, generally they become relatively unstable.

Main reactions and related mechanisms. Typical applications

In this section, general reactions using **DIB 1** and **BTI 2** are described with some related mechanisms and applications.

- Oxidation of enolizable ketones to α -hydroxy-dimethyl-acetals⁹*

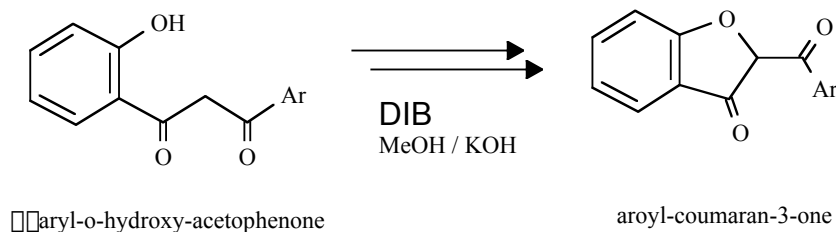
Mechanism :



α -hydroxy-dimethyl-acetals are building-blocks in the synthesis of "O"-containing heterocycles, when intramolecular participation by a suitably placed hydroxyl group occurs. Several potentially oxidisable groups are unaffected in this reaction, since the mechanism is selective.

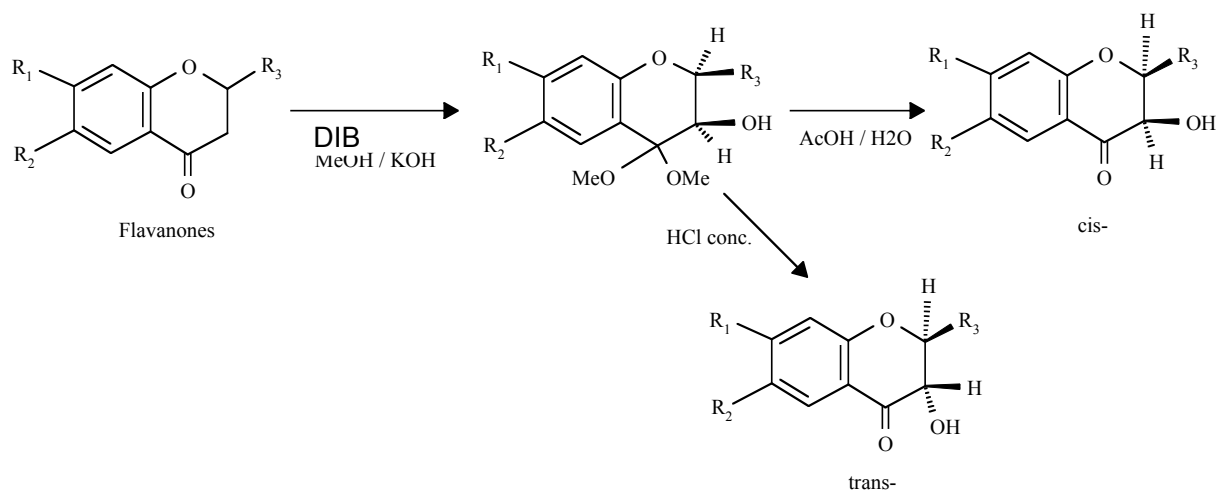
→ Typical applications :

1) Synthesis of disubstituted coumaran-3-ones, aroyl-coumaran-3-ones, aurones, isoaurones



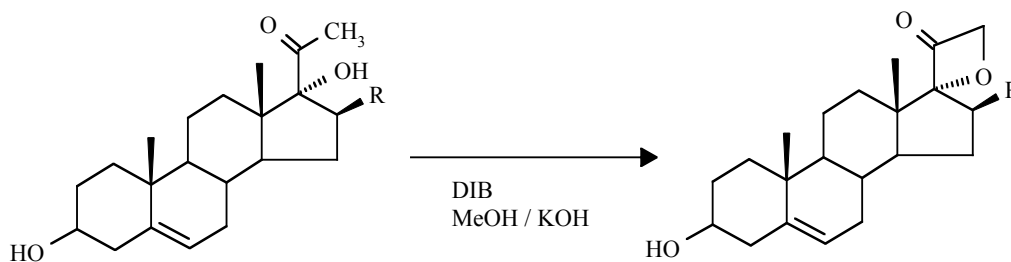
The reaction is selective and does not yield ylides as a by-product from diketones, as it is established for other reactions.

2) Regio- and stereoselective synthesis of cis- and trans- 3-hydroxy-flavanones and 2-furyl analogues (possible application to chromanones, and their 2-furyl derivatives)



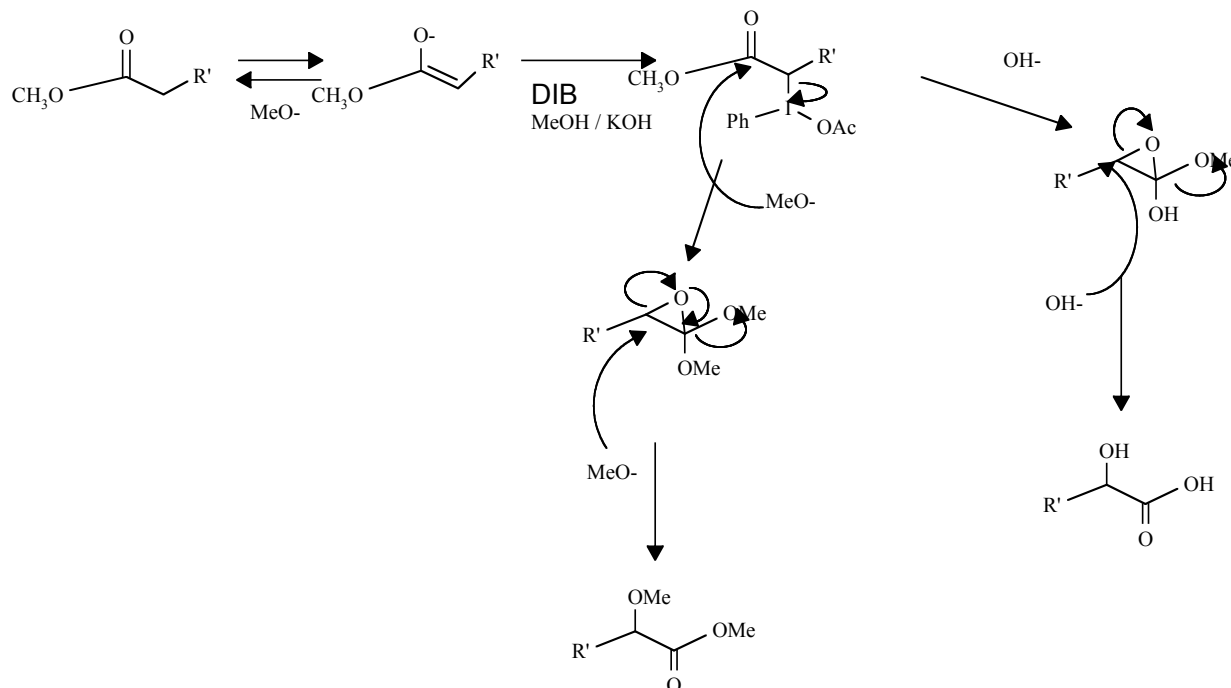
3) C3-hydroxylation of α , β -unsaturated-ketones, such as chromones, flavones, and α -naphthoflavones.

4) Synthesis of steroidal spiro-oxetan-3-ones : in this reaction, the use of **DIB** favours the intramolecular nucleophilic action of C17- α -hydroxyl-group on the intermolecular attack by methoxide.



• α -hydroxylation or α -methoxylation of esters¹⁰

Mechanism :

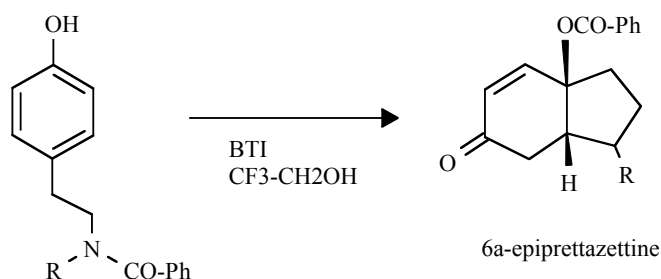


• Oxidation of phenolic derivatives¹¹

Phenolic derivatives are oxidised in mild conditions in quinones. **DIB** is a soft alternative to the use of toxic substances such as lead or thallium derivatives.

→ Typical applications :

This reaction is widely used for oxidative coupling.



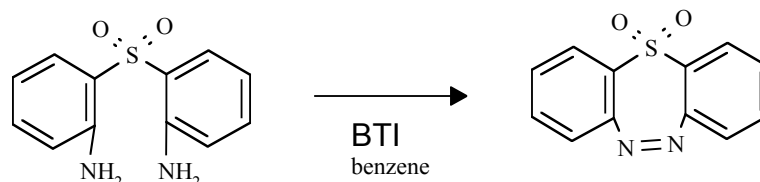
Key-step in the synthesis of epipretazettine¹².

Another interesting application is the conversion of reticuline to salutaridine¹³ and related products with **DIB** in trifluoroacetic acid.

It is also to mention that the oxidation of phenolic derivatives does not occur if such molecules bear electron-withdrawing groups (see below : phenyliodination of phenols and phenol ethers).

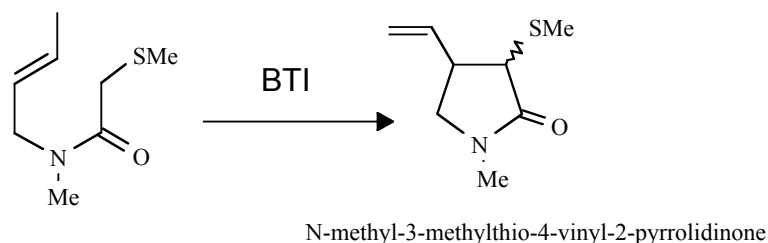
- **Oxidation of amines**

It has been reported that **DIB** has the ability to oxidise aromatic amines to azo compounds in variable yield. Intramolecular azo group formation is a useful reaction for the formation of dibenzo [c,f] diazepine¹⁴ :

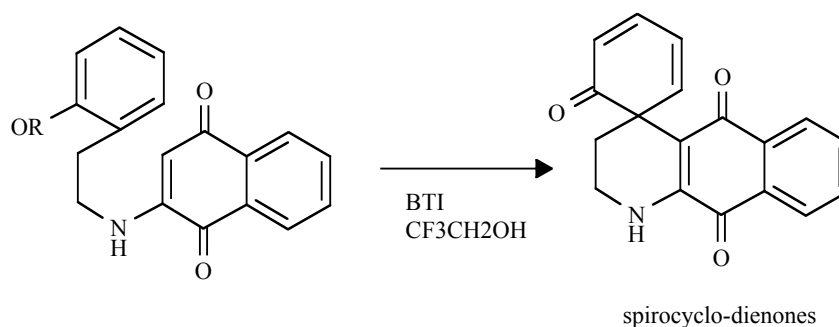


The oxidative coupling can lead to intramolecular cyclisation, an example of which is given in the synthesis of sporidesmin A¹⁵.

In the presence of **BTI**, α -methylthioamides undergo a Pummerer-type rearrangement leading to the formation of nitrogen-containing heterocycles¹⁶ :



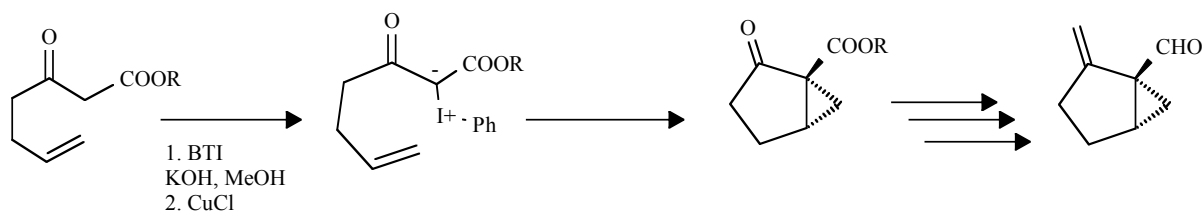
More generally, T.Kitamura and Y. Fujiwara² have presented the applications of **DIB** and **BTI** in the chemical pathway of various heterocycles and natural products, such as alkaloids, spirocyclo-dienones, spirocyclic isoxazolines... Oxidation can result in an aryl-aryl coupling, an oxidative cyclisation (cyclisation of phenolic oximes is reported), with interesting asymmetric properties in some cases.



- **Reactions with α -dicarbonyl systems : formation of iodonium ylides and intramolecular cyclopropanation**

A Copper (I) chloride - catalyzed reaction on the corresponding iodonium ylide enables an intramolecular cyclopropanation.

An asymmetric synthesis of a vitamin D - synthon employed this intramolecular cyclopropanation¹⁷ :



- *Addition on alkenes and ketones²*

Vicinal functionalized alkanes are readily obtained by the reaction of **DIB** or related hypervalent iodine reagents on alkenes. Virtually, a variety of nucleophilic agents can be introduced by using this method, since ligand exchange is made possible on iodine.

- *Promoted substitution²*

Such reactions are initiated by electrophilic addition of hypervalent iodine reagents. The intermediate iodine species undergo a displacement by nucleophilic agents leading to the final products.

Substitution is a common way of synthesis of diaryliodonium salts. When these salts are made unstable by the effect of aromatic substituents, the iodine intermediate complex is subjected to the attack of nucleophiles on the aromatic ring.

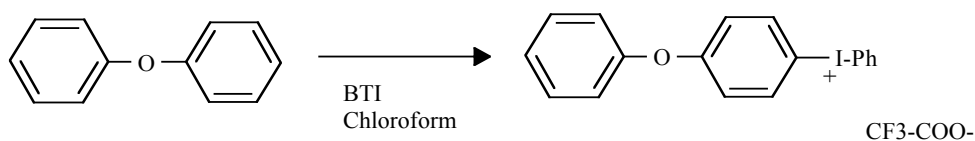
Intramolecular nucleophilic substitution may occur by using **BTI**. In this manner, the synthesis of 2,3-dihydroazepines, sulfur-containing heterocycles, and quinone imine ketals were performed.

As we have seen earlier, hypervalent iodine reagents enable the α -hydroxylation or α -methoxylation of ketones. Acetophenone derivatives and α -diketones also undergo an α -acetoxylation with **DIB** in acetic acid, with a similar mechanism (electrophilic addition, followed by a nucleophilic displacement) :



- *Phenyliodination of phenols and phenol ethers¹⁸*

We have mentioned already that phenols bearing electron-withdrawing groups undergo no oxidation with hypervalent iodine reagents, but they rather react to give 1,4-iodonium dipoles or iodonium salts.

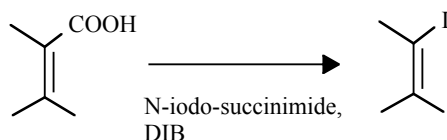


Upon reaction with **BTI**, 4-alkoxy-phenol ethers can be converted oxidatively by various nucleophiles into 2-substituted derivatives. Such reactions are oxidations proceeding through radical cations.

- *Alternative to the Hunsdiecker reaction¹⁹*

Through the Hunsdiecker reaction, it is possible to perform in presence of silver salts, a decarboxylation followed by a simultaneous halogenation on a carboxylic acid. This reaction is very useful and selective in organic synthesis.

It has been reported that **DIB** may be an alternative reagent for the Hunsdiecker reaction :



□,□-unsaturated carboxylic acids undergo an oxidative iodo-decarboxylation by this reaction. One may imagine to use in these reactions the toluenic analogue of DIB to avoid formation of undesirable benzene .

Numerous other reactions are described in related papers : mild oxidation of sulfur compounds and alcohols, dethioacetalization (**BTI** converts selectively thioacetals to the corresponding carbonyl function while other functional groups such as esters, nitriles, secondary amides, alcohols, halides, alkenes, thioesters, alkynes, remain unaffected by this transformation), carbon-carbon bond cleavage, transannular carbocyclization of dienes, formation of alkynyl esters from pyrazolones, generation of alkoxy radicals under irradiation. Since industrial applications are more difficult to appreciate, we have not further described these reactions.

Conclusion

Hypervalent iodine chemistry has gained significance in the synthesis of complex substances.

It has been observed that the use of trivalent iodine reagents is often an interesting alternative to lead and thallium derivatives, the toxicity of which makes them incompatible in a pharmaceutical environment.

Although no systematic studies has been far directed to investigate the full potential of this reagent, we have reviewed in the works of numerous contributors and their co-workers a wide number of applicative reactions of trivalent iodine reagents.

The oxidative properties of these reagents, enabling powerful coupling reactions and mild oxidations, have been used for the development of simpler synthetic procedures for compounds of biological importance²⁰.

Interesting applications with the use of substitution and addition reactions have been studied. The possibility of ligand exchange on the iodine let us think about virtual possibilities of synthesizing new compounds by such reactions.

Since each iodine reagent has selective properties, we may think about the design of specific compounds compatible with market needs, derived from the industrially available **DIB** and **BTI**, and expect this selective chemistry to play a wider role in organic synthesis.

References

1. Publications of A. Varvoglis ; Reviews in *Synthesis*, Sept.1984, 709
2. T. Kitamura ; Y. Fujiwara ; *Org. prep. and procedures int.*, **29** (4), 1997, 409
3. J.G. Sharefkin ; H. Saltzmann ; Organic syntheses, 660
4. A. Mc Killop ; D. Kemp ; *Tetrahedron*, **45** (11), 1989, 3299
5. N.W. Alcock ; T.D. Waddington ; *J.Am.Chem.Soc.*, 1963, 4103
6. B. Karele ; O. Neilands ; *Latv. Psr. Zinat. Akad. Vestis, Khim Ser.*, **5**, 1970, 587
7. G.F. Koser ; R.H. Wettach ; *J.Org.Chem.*, **41**, 1976, 3609 / **42**, 1977, 1476
8. J.E. Leffler ; L.J. Story ; *J.Am.Chem.Soc.*, May 1967, 2333
9. Om Prakash ; Shiv. P. Singh ; *Aldrichimica Acta*, Vol.27, **1**, 1994, 15
10. R.M. Moriarty *et al.* ; *Tet. Lett.*, **22** (29), 1981, 2747
11. A. Pelter ; S. Glgendy ; *Tet. Lett.*, **29**, 1988, 677
12. D.J. White ; W.K.M. Chong ; K. Thiring ; *J.Org.Chem*, **48**, 1983, 2300
13. Y. Kita *et al.* ; *Tet. Lett.*, **30**, 1989, 1119
14. H.H. Smarzt ; R. Infante ; *J.Org.Chem.*, **26**, 1961, 4173
15. V. Kishi *et al.* ; *J.Am.Chem.Soc.*, **95**, 1973, 6493
16. Y. Tamura *et al.* ; *J.Chem.Pharma.Bull.Jpn*, **35**, 1986, 1061
17. R.M. Moriarty ; J. Kim ; L. Guo ; *Tet. Lett.*, **34**, 1993, 4129
18. S. Spyroudis ; A. Varvoglis ; *Am.J.Chem.Soc.*, Perkin trans., **1**, 1984, 135
19. A. Graven *et al.* ; *J.Org.Chem.*, **59**, 1994, 3543
20. Om Prakash ; R.M. Moriarty ; *Contemp. Org. Syn*, Vol.2, n°2, 1995, 121