HETEROCYCLES, Vol. 60, No. 10, 2003, pp. 2349 - 2354
Received, 29th May, 2003, Accepted, 22nd August, 2003, Published online, 25th August, 2003

SHORT SYNTHESES OF MELATONIN

Helmut M. Hügel* and Faizul Nurlawis

RMIT University, Department of Applied Chemistry, GPO Box 2476V
Melbourne 3001 Victoria Australia E-mail: helmut.hugel@rmit.edu.au
Fax:+61396391321

Abstract - The chemistry concerning the most recent syntheses of melatonin (*N*-acetyl-5-methoxytryptamine) is described.

INTRODUCTION

Biological time is measured in Circadian rhythms on a scale of 24 hours and these rhythms are generated by molecular mechanisms that are present in many different tissues around the body. This concert of rhythms is synchronized by the master clock found in the brain which controls time-dependent rhythms according to light impacting from the environment. The production of melatonin is an expression of Circadian rhythmic activity and may also reflect Circadian control by the master clock.

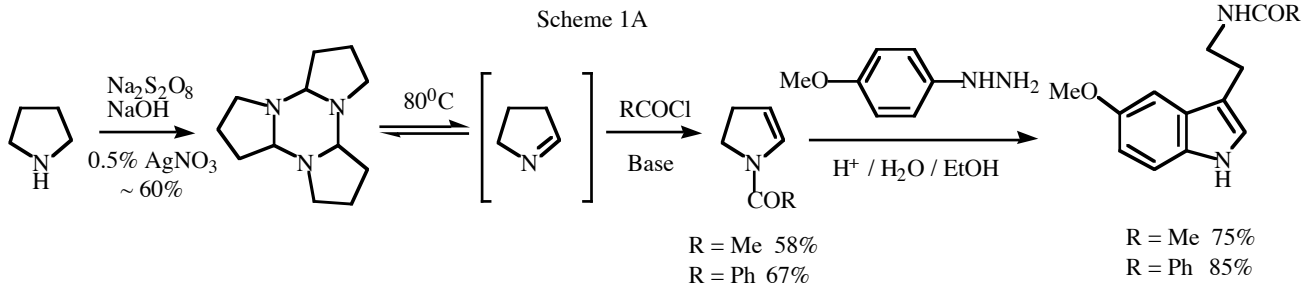
Melatonin Synthesis

For the laboratory synthesis of melatonin[1] (*N*-acetyl-5-methoxytryptamine), the preparation of 5-methoxytryptamine in a one pot reaction is desirable but this has been a low yielding reaction because of the problems associated with making the required aminobutanal. Two research groups have developed different strategies to improve this chemistry.

Marais and Holzapfel,[2] by generating cyclic enamides and carbinolamines which act as surrogates for *N*-acylbutanal and Sheldon and coworkers[3] who used catalytic conditions to selectively hydroformylate *N*-allylacetamide to furnish the elusive 4-acetamidobutanal, have completed short syntheses of melatonin.

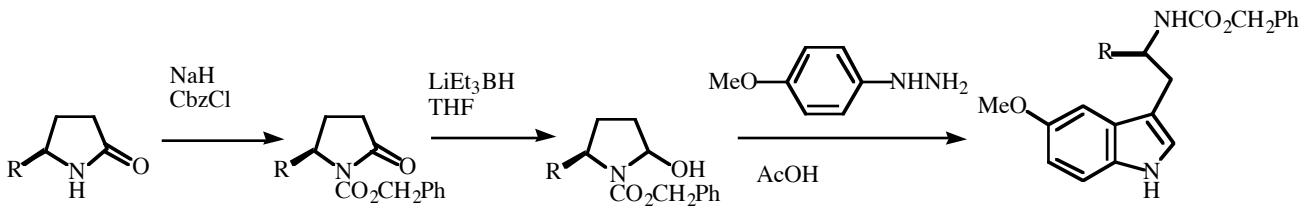
The cyclic enamides as synthetic equivalents of amino aldehydes were prepared from pyrrolidine by oxidation in aqueous alkaline peroxodisulfate and 0.5% silver nitrate to form the trimer which on heating with an acyl chloride directly formed the enamides. This was followed by Fischer-indole synthesis with *p*-methoxyphenylhydrazine hydrochloride in aqueous acetic acid-ethanol mixture under reflux for 20 min. Melatonin (Scheme 1A) was isolated in overall 26% yield.

Scheme 1A



An efficient extension of this approach was achieved by starting with 2-pyrrolidone and pyroglutamic acid (Scheme 1B) providing carbamate deriatives of 5-methoxytryptamine (80%) and l-tryptophan (87%).

Scheme 1B



R = H
R = CO_2H

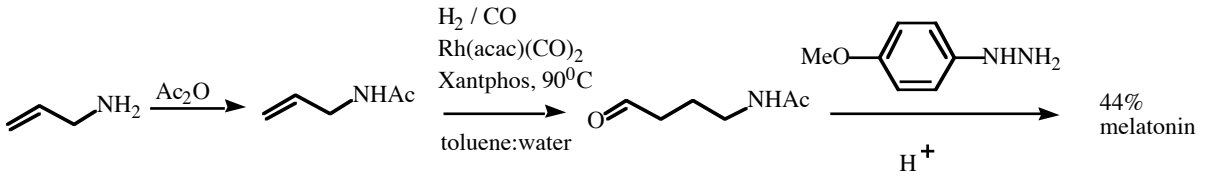
R = H
R = CO_2Bu-*t*

R = H (2 steps) 84%
R = CO_2Bu-*t* (2steps) 91%

R = H 95%
R = CO_2Bu-*t* >95%

The critical step in the second approach to melatonin synthesis was the investigation of the hydroformylation conditions required to selectively convert *N*-allylacetamide into *N*-acetylbutanal. Thus in a one pot reaction sequence (Scheme 2), allylamine was acetylated, regioselectively hydroformylated to provide *N*-acetylbutanal with the aid of Rh-Xantphos catalyst system in an inverted two phase toluene/water solvent system. Subsequent hydrazone formation with 4-methoxyphenylhydrazine and Fischer-indole synthesis yielded 44% melatonin when extracted from the aqueous phase. The experimental details are available as electronic supplementary information from supplied website.

Scheme 2

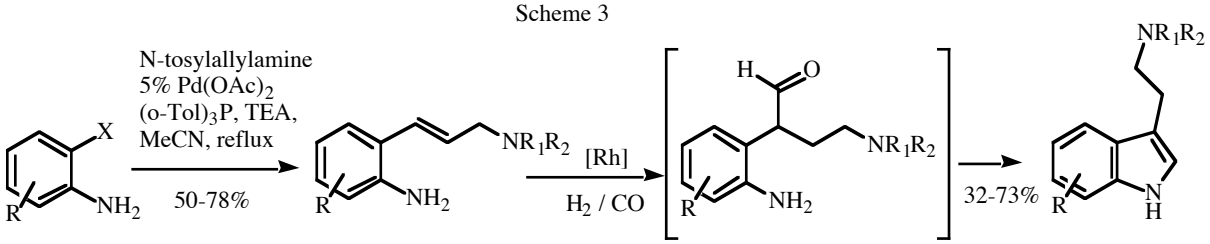


Xantphos = 4,5-is(diphenylphosphino)-9,9-dimethylxanthene

Furthermore, a method for regioselectively hydroformylating functionalized anilines has been developed by Dong and Busacca[4], leading to the syntheses of tryptamines and tryptophol. Employing the Heck reaction conditions, *meta*- and *para*- fuctionalized 2-haloanilines and *N*-tosylallylamine or *N*,*N*-di-Boc-allylamine with $Pd(OAc)_2$ catalysis were converted into Heck adducts which underwent hydroformylation in the presence of H_2/CO (1:1) and $HRh(CO)(PPh_3)_3$ to yield tryptamines or tryptophol (10 examples, yields 32-73%) (Scheme 3)

The application of this Heck and hydroformylation reaction sequence with 2-bromo-4-methoxyaniline and *N*-allylacetamide would make melatonin.

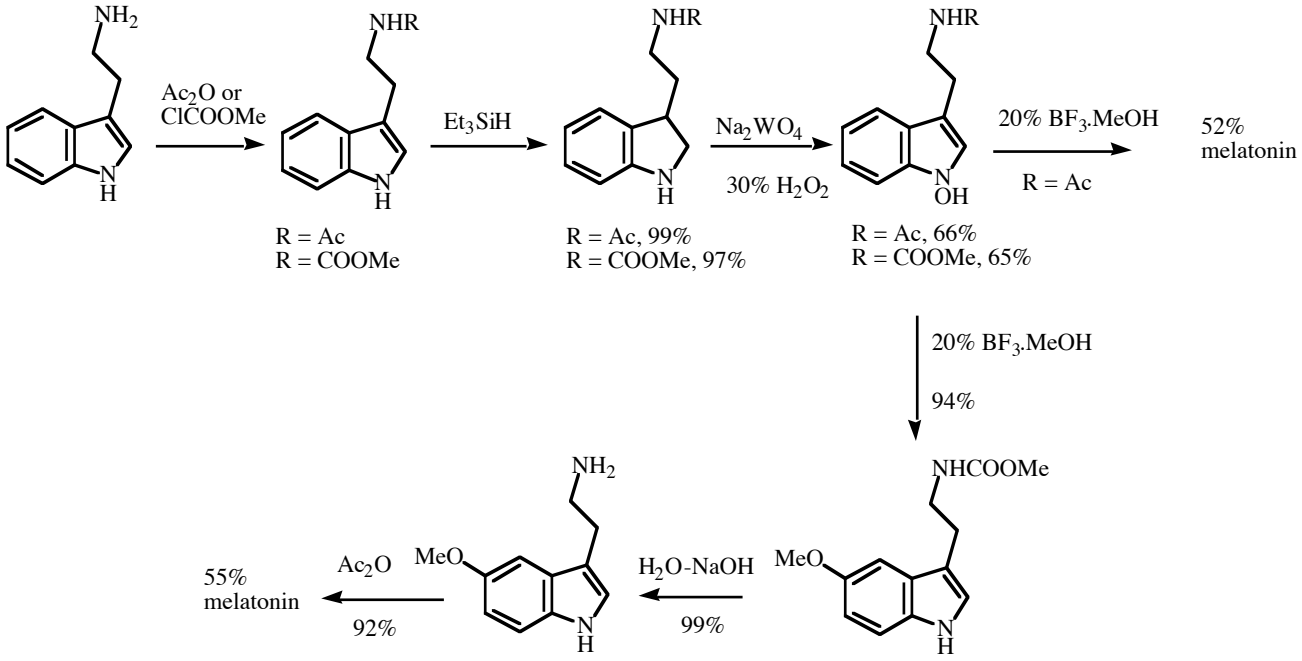
Scheme 3



X = Br or I
R = variable
R_1R_2 = $(BOC)_2$

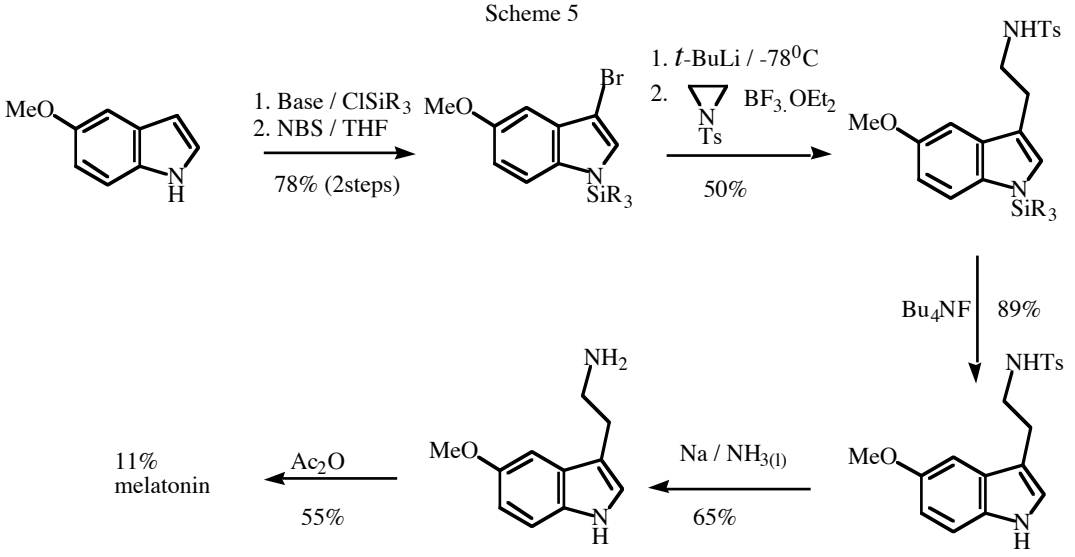
Somei and coworkers[5] have developed their *N*-hydroxyindole chemistry to transform tryptamine in six steps into melatonin with an overall 55% yield. In the key step, the introduction of the 5-methoxy group was achieved by reacting the substrate, 1-hydroxy-*N*-acetyltryptamine with 20 % BF_3-methanol solution and refluxing the mixture for 30-40 min. (Scheme 4).

Scheme 4



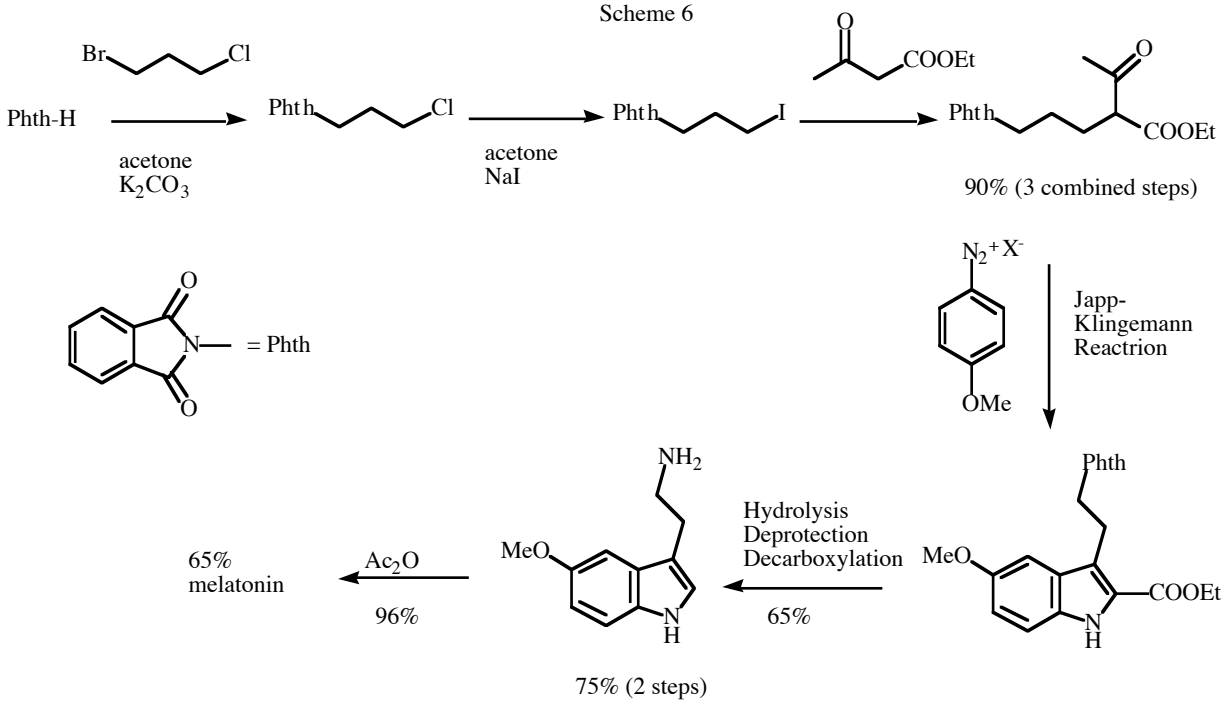
Amat and coworkers[6] recently described the preparation of 4-, 5-, and 6-methoxy substituted 3-lithio-1-(trialkylsilyl) indoles and their reaction with electrophiles. When *N*-tosyl aziridine was the electrophile (Scheme 5), their methodology produced melatonin in overall 11% yield.

Scheme 5



Om Reddy and coworkers[7] have revisited literature syntheses of melatonin with the objective of developing a cost effective and industrial process that avoids the use of expensive chemicals, is a short process, has no low yielding steps and requires limited purification of intermediates and products.

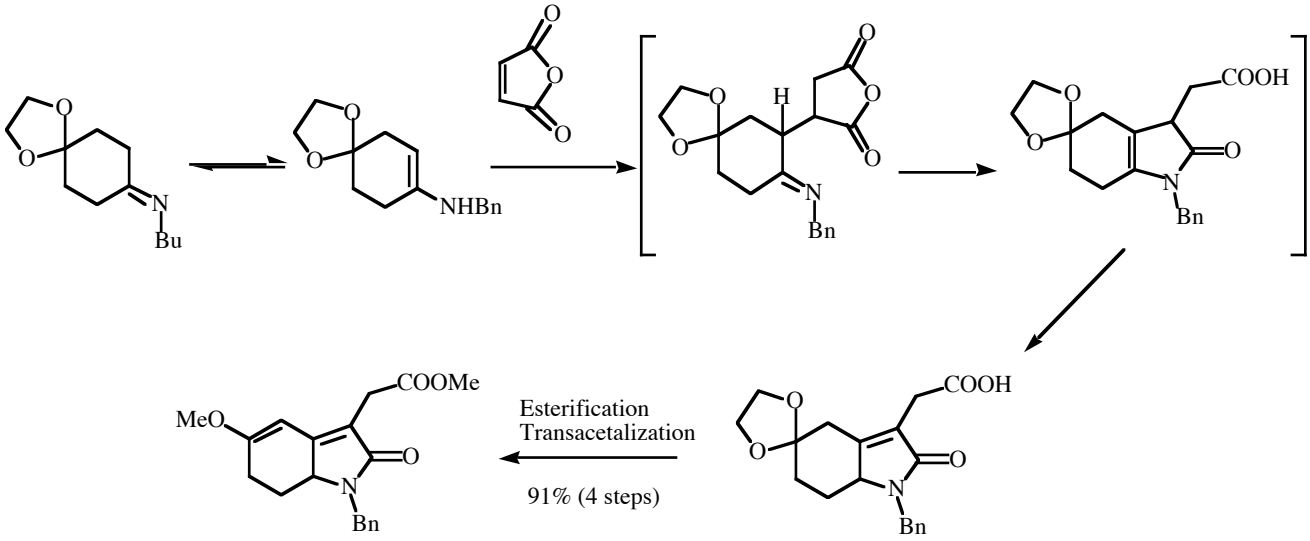
Scheme 6



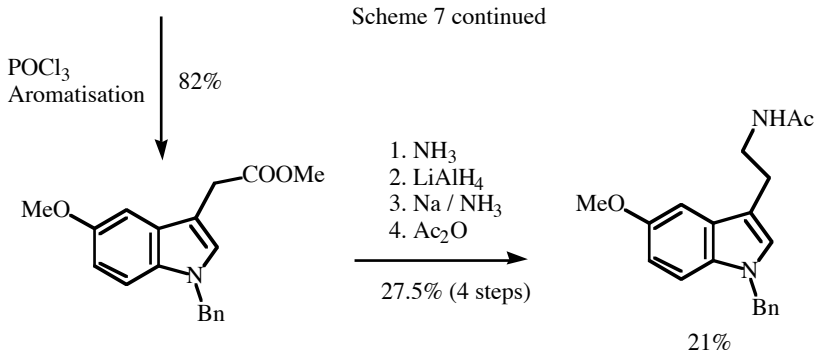
Using the Japp Klingemann reaction to form the tryptamine ring system, the six step process (Scheme 6) has been carefully optimized, yielded 65% melatonin in ~99.5% purity and has been performed on 5-10 kg scale.

In a new approach to the synthesis of melatonin and related compounds, Pfau and coworkers[8] found that the Michael addition of the *N*-cyclohexylimine of commercial1,4-cyclohexanedione mono- ethylene ketal with maleic anhydride as shown in Scheme 7 provides the indole-3-acetic acid skeleton. This was followed by the reaction sequence: esterification, transacetalization and aromatization which produced the key compound methyl 1-benzyl-5-methoxy-1 *H*-indole-3-acetate in 74% yield from the starting material without purification of the intermediates. Side chain transformations and indole-*N*-deprotection gave melatonin in around 20% overall yield.

Scheme 7

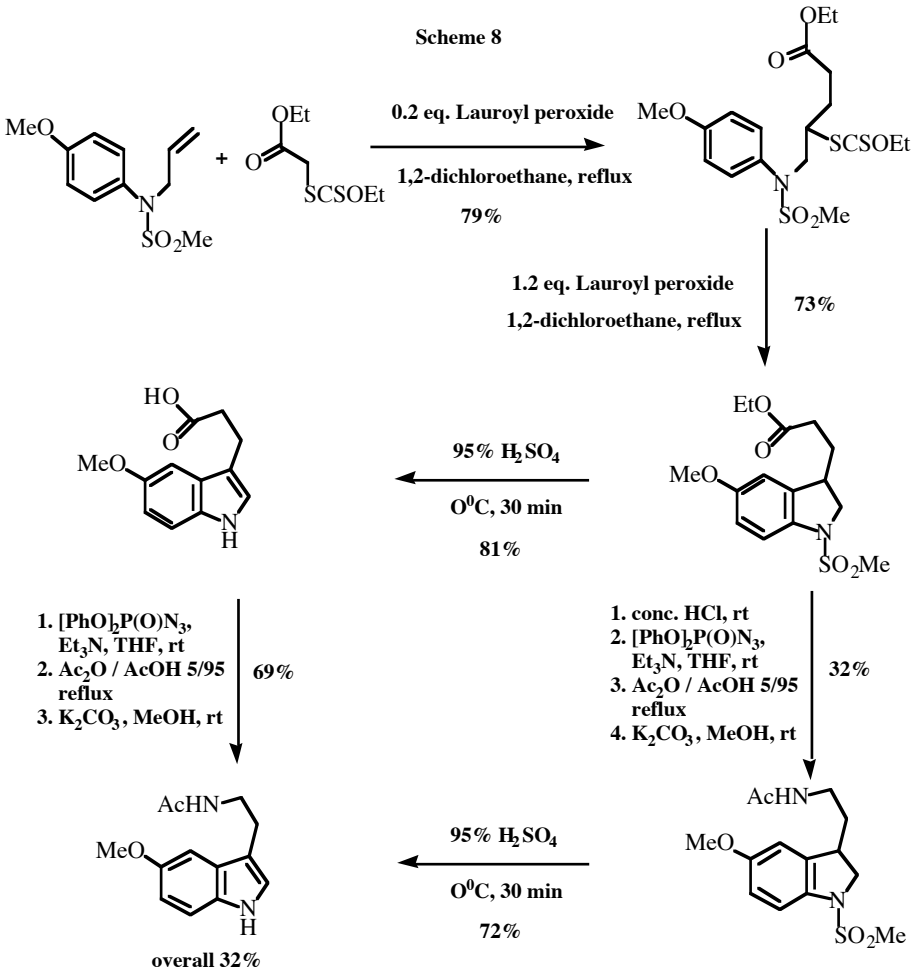


Scheme 7 continued



Sortais and coworkers[9] have applied their free radical reaction methodology to a route to indolines which was elaborated to give in seven steps a 32% overall yield of melatonin as illusrated in Scheme 8. The first step involved an intermolecular catalytic radical addition of a xanthate to a protected *N*-allylaniline which was followed by stoichiometric radical formation and indoline ring closure. The three carbon ester side chain was hydrolysed and the acid underwent a Curtius rearrangement using diphenylphosphoryl azide, in situ acetylation followed by simultaneous *N*-mesyl group deprotection / aromatization using 95% concentrated sulfuric acid. Alternatively, when the indoline ring was aromatized prior to the side chain refunctionalisation, the six step sequence gave slightly lower yields of melatonin.

Scheme 8



In the last five years, there have been new approaches and improvements to existing methods of tryptamine synthesis. This has translated into shorter routes and more efficient methods of melatonin synthesis as summarized in the Table.

Table

Novelty of Method	Synthetic Steps	% Melatonin	Researchers
Use of *N*-acetylbutanal surrogate	3	26	Marais *and* Holzapfel
Generation of *N*-acetylbutanal	3 steps, one pot	44	Sheldon *and* coworkers
Hydroformylation of anilines	3	32-73 [tryptamines]	Dong *and* Busacca
5-Methoxy group introduction	6	55	Somei *and* coworkers
Ethanamide side chain introduction	7	11	Amat *and* coworkers
Large scale synthesis	6	65	Om Reddy *et al.*
Michael addition, indole ring formation	9	21	Pfau *et al.*
Free radical synthesis of indolines	7	32	Sortais *and* coworkers

REFERENCES

1. H.M.Hügel and D.J. Kennaway, *Org. Prep. Proc. Int.,* 1995, **27**, 1.

2. W. Marais and C.W. Holzapfel, *Synth. Commun.,* 1998, **28**, 3681.

3. G. Verspui, G. Elbertse, F.A. Sheldon, M.A.P.J. Hacking and R.A. Sheldon, *Chem. Commun.*, 2000, 1363.

4. Y. Dong and C.A. Busacca, *J. Org. Chem.,* 1997**, 62**, 6464.

5. M.Somei, Y. Fukui, M. Hasegawa, N. Oshikiri and T. Hayashi, *Heterocycles*, 2000, **53**, 1725.

6. M. Amat, F. Seffar, N. Llor and J. Bosch, *Synthesis*, 2001, 267.

7. C. Prabhakar, N.V. Kumar, M.R. Reddy, M.R. Sarma and G. Om Reddy, *Organic Process Research & Development*, 1999, **3**, 155.

8. G. Revial, I. Jabin, S. Lim and M. Pfau, *J. Org. Chem.*, 2002, **67**, 2252.

9. B. Quiclet-Sire, B. Sortais and S.Z. Zard, Chem. Commun., 2002, 1692.