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Research Article

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An efficient synthetic method for the preparation of 2-phenylethanamine thiazoline using $Pd(PPh_3)_4$ as an effective catalyst under mild conditions

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ABSTRACT

An efficient synthetic method for the preparation of 2-phenylethanamine thiazoline with good yield is described by using $Pd(PPh_3)_4$ as an effective catalyst under mild conditions for deprotection of Allyloxy carbonyl (Alloc) group. The use of $(CH_3CO^2)_2Pd2^+$,$(C_{17}H_{14}O)_2Pd$, $C_{16}H_{24}Cl_2Ir_2$, $(COD)_2Ni$, $AuCl_3$ was unsuccessful whereas the use of iodine I_2 in presence of DMSO led to thiazole.

Keywords: Thiazoline, Peptide, Deprotection.

INTRODUCTION

Heterocyclic compounds represent one of the most active classes of compounds possessing awide spectrum ofbiological activities, including antibacterial, antifungal, and other biologicalactivities[1-6].

The development of five membredheterocycles adopting simple, facile and efficient methodologiesfrom readily reagents is one of the major challenges in organic syntheses [7]. Thiazolineheterocycles are found in many bioactive natural products of peptide origin[8]. This substructure confers conformartional rigidity and serves as recognition site for DNA, RNA, and protein binding. Thiazolines are biosynthesized from peptides by nucleophilic attack of the cysteine thiol group on the amide carbonyl group of the preceding residue, followed by dehydration[9]. Although the biosynthesis of thiazolines employs cysteine residues, most chemical syntheses use serine residues[10]. Here we report an efficient synthesis method of 2-phenylethanamine thiazolines methyl esterby treating Alloc-Phe-Cys(Trt)-OMe Dipeptidewhich are synthesized by coupling reaction between N-Alloc phenylalanine and trityl cysteine methyl ester**,** with hexaphenyloxodiphosphoniumtrifluromethanesulfonate. TheAlloc-amino thiazolines methyl ester obtainedare treated by using numerous catalysts to removeallyloxy carbonyl group(Alloc) in order to get the target molecule**6**(Scheme 1).

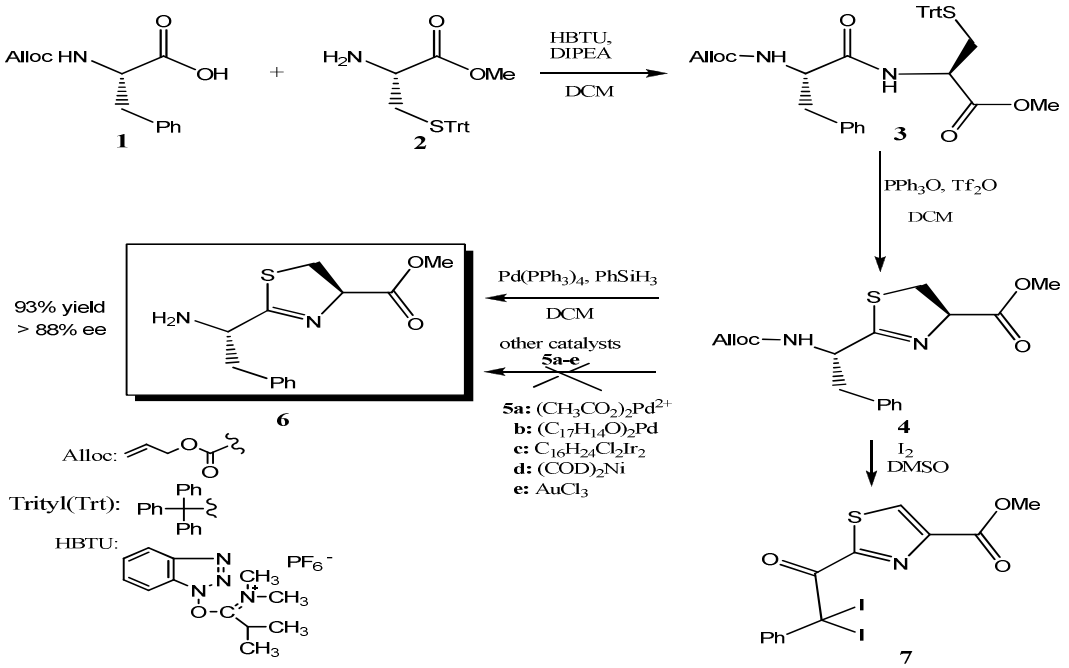
EXPERIMENTAL SECTION

MATERIAL

^1H NMR, ^{13}C NMR spectra on a BrukerAvance DPX400 MHz spectrometer with $CDCl_3$ as a solvent and TMS internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplate).Reserved-phase analytical HPLC were performed on a Waters Alliance separation module 2695 using a Waters XBridge BEH 130 C18 column (4.6×100 mm, 3.5 Mm) and a Waters 2998 PDA with a photodiode array detector with MeCN (0.036% TFA) and H2O (0.045% TFA).

Synthesis of Alloc-L-Phe-OH.*N*-Allocphenylalanine(1)

L-Phe-OH (3.31 g, 20.0 mmol) was dissolved in 2 N NaOH (10 mL). The solution was cooled in an ice-water bath then allylchloroformate (2.45 mL, 1.15 eq) and 2 N NaOH (11.5 mL, 1.15 eq) were added dropwise simultaneously. After completion of the addition the bath was removed and stirring went on for 45 min at rt. A white emulsion formed. The reaction mixture was acidified to pH ~ 2 by the addition of 2 N HCl, then ethyl acetate (150 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (150 mL). Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 3.5 g (quantitative yield 70%) of crude title compound. Crude product was used in next step without further purification. Data for these compounds were identical with those described earlier.[11]



Scheme 1

Synthesis of H-Cys(Trt)-Ome. Trityl cysteine methyl ester(2)

Fmoc-L-Cys(Trt)-OH (10.0 g, 17.1 mmol) was dissolved in CH_2Cl_2/MeOH 4:1 (150 mL). The solution was cooled in an ice-water bath then $TMSCHN_2$ (2.0 M in hexanes, 10 mL, 1.15 eq) was slowly added while stirring. Upon completion of the addition the ice-water bath was removed and the solutiuon was stirred at room temperature for 30 min. Volatiles were removed *in vacuo*. The white solid residue was taken up in EtOAc (150 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (150 mL), then water (150 mL) and finally brine (150 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield crude methyl ester. Crude ester was dissolved in CH_2Cl_2 (150 mL) then piperidine (15 mL) was added and the solution was stirred at room temperature for 1 h. Volatiles were removed *in vacuo* and the residue was azeotropically evaporated with PhMe (3 × 20 mL). Purification by silica flash column chromatography (hexanes/EtOAc 70:30 to 30:70) yielded 4.94 g (77%) of title compound as a pale yellow oil. The physical data were identical in all respect to those previously reported.[12]

Synthesis of Alloc-Phe-Cys(Trt)-OMe. Dipeptide(3)

Crude Alloc-L-Phe-OH (1.15 g, 4.6 mmol, 1.4 eq) was dissolved in dry CH_2Cl_2 (10 mL) under N_2 atmosphere. A solution of H-Cys(Trt)-OMe (1.25 g, 1 eq) in dry CH_2Cl_2 (10 mL) was added *via cannula* to the first solution. HBTU (2.51 g, 2 eq) was then added in one portion while stirring. Slow addition of DIPEA (2.3 mL, 4 eq) followed. The solution was stirred at rt for 1 h, then it was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NH_4Cl (2 × 50 mL), and finally brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica flash column chromatography (hexanes/EtOAc 80:20 to 60:40) yielded the title compound as a white solid (1.46 g, 74%).^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.56 (dd, *J* = 5.0, 12.5, 1H), 2.64 (dd, *J* = 5.8, 12.5, 1H), 3.02 (dd, *J* = 7.1, 13.9, 1H), 3.08 (dd,

J = 6.3, 13.9, 1H), 3.69 (s, 3H), 4.37 (m, 1H), 4.44 (ddd, J = 5.0, 5.8, 7.6, 1H), 4.54 (d, *J* = 5.6, 2H), 5.16 – 5.32 (m, 3H), 5.79 – 5.95 (m, 1H), 6.11 (d, *J* = 7.6, 1H), 7.10 – 7.46 (m, 20H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 155.8, 144.4 (3C), 136.3, 132.7, 129.6 (6C), 129.6 (2C), 128.9 (2C), 128.2 (6C), 127.2, 127.1 (3C), 118.0, 67.1, 66.1, 56.0, 52.8, 51.5, 38.8, 33.6.

Synthesis of Phe-Thiazoline-OMe. Thiazoline methyl ester (4)

PPh_3O (6.87g, 3 eq) was dissolved in dry CH_2Cl_2 (80 mL) under N_2 atmosphere. The solution was cooled in an ice-water bath then Tf_2O (2.07 mL, 1.5 eq) was added dropwise. Stirring went on at 0 °C for 15 min: a white precipitated formed. The mixture was then cooled to -20 °C and a solution of Alloc-Phe-Cys(Trt)-OMe (5g, 8.23 mmol, 1 eq) in dry CH_2Cl_2 (60 mL) was added over 40 min. Stirring went on at -20 °C for 2 h, then the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (150 mL). The mixture was allowed to warm to rt while stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). Combined organic layers were washed with brine (350 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica flash column chromatography (hexanes/EtOAc 90:10 to 70:30) yielded the title compound as colourless oil (1.9g, 76%).^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.24 (m, 5H), 5.99–5.89 (m, 1H), 5.50 (d, *J* = 7.6 Hz, 1H), 5.36–5.14 (m, 3H), 4.97–4.92 (m, 1H), 4.61–4.60 (m, 2H), 3.85 (s, 3H), 3.69 (dd, *J* = 8.8, 11.2 Hz, 1H), 3.59 (dd, *J* = 10.0, 11.2 Hz, 1H), 3.30 (dd, *J* = 6.0, 14.0 Hz, 1H), 3.16 (dd, *J* = 6.4, 13.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.2, 170.7, 155.3, 135.7, 132.6, 129.6 (2C), 128.4 (2C), 126.9, 117.6, 77.8, 65.7, 54.3, 52.7, 39.7, 35.4.

Procedure for the deprotection of Alloc group by Using $Pd(PPh_3)_4$ (Synthesis of 6)

To a stirred solution of substrate **4** (0.287 mmol) in DCM (25ml) were added $Pd(PPh_3)_4$ (0.028 mmol, 33.2 mg) and $PhSiH_3$ (1.72 mm0l, 0.21 mL). The reaction mixture was stirred at ambient temperature until the completion of the reaction (monitored by HPLC, 4h). After completion of the reaction, the mixture was washed with saturated aqueous $NaHCO_3$ (2.50 mL), and the organic layer was dried over Na_2SO_4. Evaporation of the volatiles followed by column chromatography on silica gel (Ethyl acetate/hexane 50:50 to 100:00) then (hexane/MeOH 90:10) afforded the desired product in yield 93%. HPLC, Gradient: 15 to 30 % MeCN: 8 min. 2 peaks at 5.464 min and 5.726 min.^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.22–7.14 (m, 5H), 5.01 (t, 1H), 4.06–4.03 (m, 1H), 3.71 (s, 3H), 3.52 (dd, J_1 = 12 Hz, J_2=10 Hz, 1H), 3.49 (dd, J_1 = 4 Hz, J_2=10 Hz, 1H) 3.40 (dd, J_1 = 4 Hz, J_2=4 Hz, 1H), 2.81 (t, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz), δ: 29.67, 30.90, 34.68, 42.09, 52.67, 128.59, 128.99, 129.37, 136.81, 171.05. HRMS m/z calcd for $C_{13}H_{16}N_2O_2S$ (M+H) 265.34, found 264.95

General procedures for the deprotection of Alloc group with other catalysts

The table 1 represents an optimization of reaction conditions and test reactions for these procedures.

Table 1

Entry	substrate	Reaction conditions	Yield of **5**[a]
1	**4**	$Pd(PPh_3)_4$, $PhSiH_3$, DCM	93%
2	**4**	$Pd(PPh_3)_4$, $(Et)_2NH$, DCM	complex mixture
3	**4**	$(CH_3CO_2)_2Pd^{2+}$, $PhSiH_3$, DCM	-
4	**4**	$(C_{17}H_{14}O)_2Pd$, $PhSiH_3$, DCM	-
5	**4**	$C_{16}H_{24}Cl_2Ir_2$, $PhSiH_3$, DCM	-
6	**4**	$(COD)_2Ni$, $PhSiH_3$, DCM	-
7	**4**	$(COD)_2Ni$, DCM	-
8	**4**	$(COD)_2Ni$, $PhSiH_3$, PPh_3(0.2 eq), DCM	-
9	**4**	$AuCl_3$, $PhSiH_3$, DCM	-
10	**4**	$AuCl_3$, DCM	-

[a] *HPLC detection*

Procedure A: Catalyst with nucleophile (See table 1)

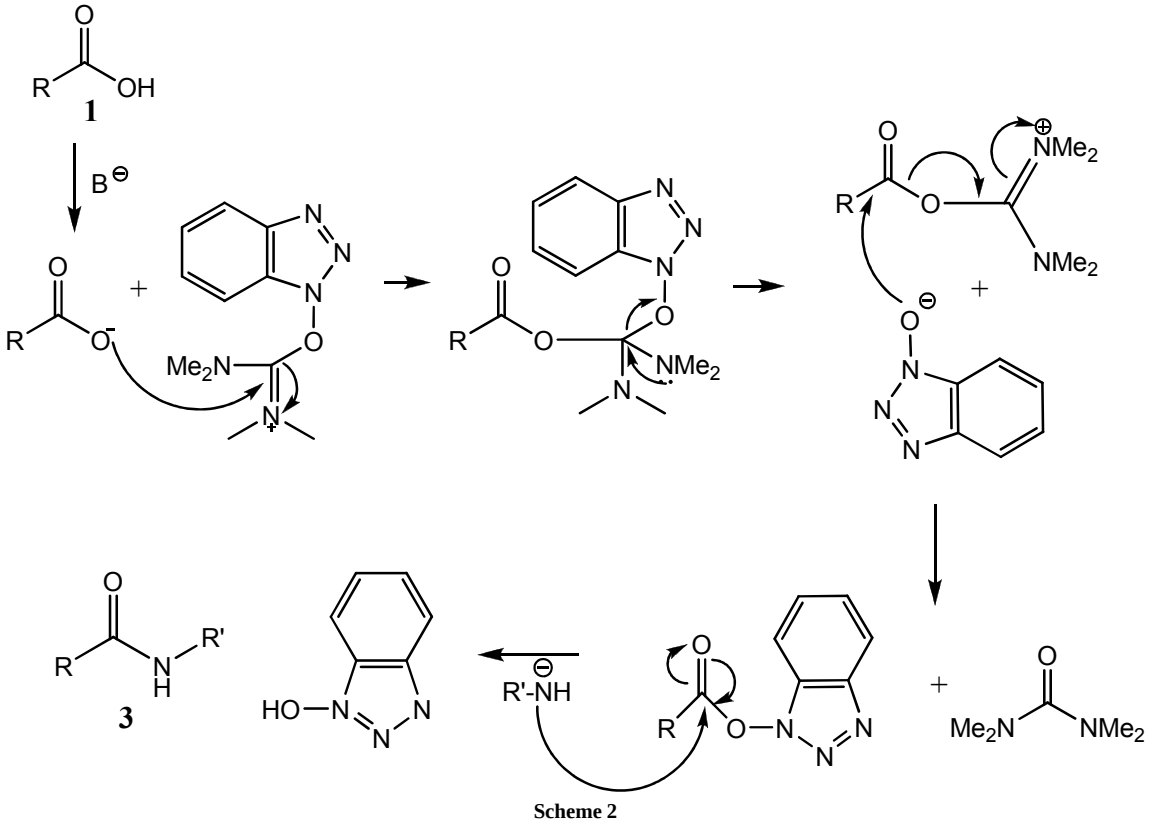
To a stirred solution of substrate **4** (0.086 mmol) in DCM (6ml) were added the catalyst (10 mol%) and the nucleophile (6 eq). The reaction mixture was stirred at ambient temperature for 3-4 h and was checked by HPLC. Gradient: 15 to 30 % MeCN: 8 min.

Procedure B: Catalyst without nucleophile (See table 1)
To a stirred solution of substrate **4** (0.086 mmol) in DCM (6ml) was added the catalyst (10 mol%). The reaction mixture was stirred at ambient temperature for 3-4 h and was checked by HPLC. Gradient: 15 to 30 % MeCN: 8 min.

Procedure for the deprotection of Alloc group by Using I_2
To a solution of compound **4** (0.114 mmol) in dimethyl sulphoxide (3 mL) was added a catalytic amount of iodine (0.068 mmol, 0.6eq). The reddish solution was heated (130 ˚C) for 22h. The reaction mixture was diluted with dilute hydrochloric acid 1M (5 mL) and extracted with ethyl acetate. The excess of iodine was destroyed by addition of sodium thiosulphate solution (10 mL) then washed with water (20 mL) followed by brine solution (20 mL). The crude mixture was purified by column chromatography over silica gel (hexane/EtOAc 80:20 to 50:50) to afford the byproduct **7** (11.3 mg).^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.6 (s, 1H), 7.36–7.24 (m, 5H), 3.9 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz), 32.1, 52.72, 129.33, 130.17(2C), 132.09, 134.15(2C), 135.24, 149.68, 160.95, 163.31, 184.96, 190.60.

RESULTS AND DISCUSSION

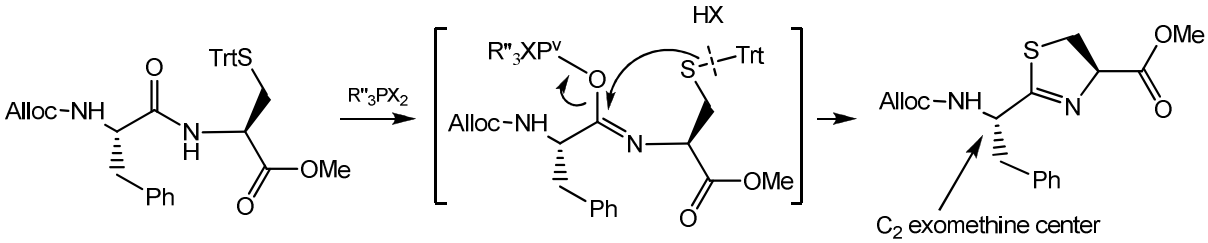
Synthesis of Dipeptide 3
In this typical peptide coupling reaction, the carboxylic acid moiety of the amino acid **1** is first activated by *O*-benzotriazol-1-yl-*N*,*N*,*N* ,*N* -tetramethyluroniumhexafluorophosphate (HTBU) in the presence of N,N-Diisopropylethylamine (DIPEA), and then reacted with the amino acid **2** to produce a desired peptide **3**. Proposed mechanism for the synthesis of Alloc-Phe-Cys(Trt)-OMe with HBTU reagent is illustrated in Scheme 2.



Scheme 2

Synthesis of 4
In this step, the dipepetide **3** is treated with hexaphenyloxodiphosphonium trifluoromethanesulfonate ($(Ph_3POPPh_3)^{2+}$, $2(CF_3SO_2O^-)$)[13] to activate the amide group. The reaction proceeds in high yield with retention of configuration at the C4- and C2-exomethine carbon atoms of the thiazolines. Dehydrocyclisation of a fully protected N-Alloc dipeptide residue requires activation of the amide bond, as well as deprotection of the side chain. We

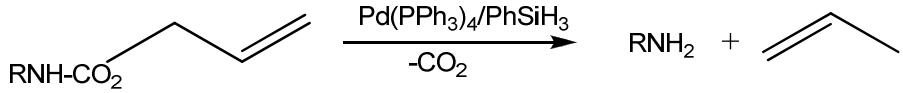
envisioned that the oxophilicity and Lewis acidity of phosphonium salts or phosphoranes should enable them to perform both transformations simultaneously(Scheme 3)



Scheme 3

Deprotection of Alloc group

The Alloc group is removed by using $Pd(PPh_3)_4$ in the presence of phenyltrihydrosilane (PhSiH3) as a neutral ally group scavenger[14]. The deprotection step involves a palladium-catalyzed transfer of the allyl unit to phenyltrihydrosilane (Nucleophiles) in the presence of a proton source (Scheme 4).The reaction of deprotection proceeds in high yield (93%)with retention of configuration at the C_4- and C_2-exomethine carbon atoms of the thiazoline (ee>88%). Whereas, the use of nucleophilic secondary amine such as diethylamine as the allyl acceptor leads to complex of mixture. The use of other catalysts such as $(CH_3CO^2)_2Pd2^+$, $(C_{17}H_{14}O)_2Pd$, $C_{16}H_{24}Cl_2Ir_2$, $(COD)_2Ni$, $AuCl_3$ was unsuccessful whereas the use of iodine I_2 in presence of DMSO led to thiazole.



Scheme 4

CONCLUSION

In this paper, we have reported an efficient route for the synthesis of phenylethaneaminethiazoline using $Pd(PPh_3)_4$. We have also shown that the followed catalysts:$(CH_3CO^2)_2Pd2^+$, $(C_{17}H_{14}O)_2Pd$, $C_{16}H_{24}Cl_2Ir_2$, $(COD)_2Ni$, $AuCl_3$are not useful for the removal of Alloc group.

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REFERENCES

[1] KF Ansari; C Lal. *J. Chem. Sci*.,**2009**, *121(6)*, 1017-1025.
[2] S Antus; K Gulacsi; L Juhasz; L Kiss; T Kurtan. *Pure Appl. Chem*. **2004**, *76(5)*, 1025-1032.
[3] TB Mostafa. *J. Am. Sci*. **2010**, *6(8)*, 512-524.
[4] AK Singh; G Mishra; K Jyoti. *J. Appl. Pharm. Sci*. **2011**, *1(5)*, 44-49.
[5] J Salimon; N Salih; H Hussien; E Yousif. *Eur. J. Sci. Res*. **2009**, *31(2)*, 256-264.
[6] PF Xu; ZH Zhang; XP Hui; ZY Zhang; RL Zheng. *J. Chin. Chem. Soc*. **2004**, *51(2)*, 315-319.
[7] A Padmaja; T Payani; K Mahesh. *IDIAN J. Chem*., **2008**, *47(B)*, 1713-1725.
[8] S Carmeli; RE Moore; GML Patterson; TH Corbett; FA Valeriote., *J. Am. Chem. Soc*., **1990,** 112*(22)*, 8195-8197.
[9] HM Patel; CT Wash. *Biochemistry*.,**2001**, 40*(30)*, 9023-9031.
[10] P Wipf; Y Uto. *J. Org. Chem*.,**2000**, 65*(4)*, 1037-1049.
[11] F Debaene; L Mejias; JL Harris; N Winssinger. *Tetrahedron*.,**2004**, *60(39)*, 8677-8690.
[12] X Liu; D Suh; J Call; GD Prestwich. *Bioconjugate Chem.*,**2004**, *15(2)*, 270–277.
[13] SL You; H Razavi; JW Kelly. *Angew. Chem. Int. Ed*., **2003**, 42*(1)*, 83-85.
[14] M Dessolin; MG Guillerez; N Thieriet; F Guibe; ALoffet. *Tetrahedron Lett*.,**1995**, 36*(32)*, 5741-5744.