Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(5):1281-1285

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

A new chemistry of 2,3-dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one

Srinivasa Reddy Konda[1,2*], Buchi Reddy Reguri[3] and Mukkanti Kagg[2]

[1]Brundavan Laboratories Pvt Ltd, No. 305, Yellareddyguda Road, Hyderabad
[2]Centre for Pharmaceutical Sciences, JNT University, Kukatpally, Hyderabad, India
[3]IPCA Laboratories Ltd, 142 AB, Kandivli Industrial Estate, Mumbai, India

---

ABSTRACT

In view of several synthetic and biological, pharmacological applications of benzocycloheptene-5-one derivatives, the present work aimed to achieve 2,3-dimethyl-6-(1-phenyl but-3-enyl)-6,7,8,9-tetrahydro benzocyclohepten-5-ones (9a-c);1-(9,10-dimethyl-4-phenyl-6,7,-dihydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-2-yl)pyrrolidine-2,5-dione (11) and 2-(9,10-dimethyl-4-phenyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d] pyridine-2-yl) isoindole-1,3-dione (12).

Keywords: Benzocycloheptene-5-one derivatives, 2,3-dimethyl-6-(1-phenyl but-3-enyl)-6,7,8,9-tetrahydro benzocyclohepten-5-ones, Friedel-Crafts acylation, zinc-amalgam, MCM-41(H)

INTRODUCTION

The conjugate addition of allylsilanes to electrophilic alkanes, referred to as the Sakurai-Hosomi reaction has been recognized as particularly efficient method of carbon-carbon bond formation and has been extensively applied in organic synthesis[1], especially in natural product synthesis. Lewis acids such as $TiCl_4$, $AlCl_3$ and $BF_3.OEt_2$ have been employed as the most effective promoters for these conjugate allylation[2]. Subsequently, modified reagents such as allylbarium[3], allyl copper[4] and allylindium reagents have been developed to avoid strongly acidic conditions. With these modified reagents the allylation of acyclic enones is far more difficult than that of cyclic ketones. Recently, organotantalum reagents have also been developed for allylation of organotin compounds.

EXPERIMENTAL SECTION

Preparation of 5-(3,4-dimethyl phenyl)-5-oxo-pentanoic acid (3):
Compound **3** was prepared by the method of Anderson *et al.*,[45] with some modifications. Ortho benzoveratrole (1 equivalent) was added slowly to an ice-cooled suspension of $AlCl_3$ (2.2) equivalents) in dichloromethane (36 mL) after complete addition the glutaric anhydride (1 equivalent) was added to the reaction mixture. The resulting solution was refluxed until TLC showed completion of the reaction (2.5 h). The mixture was poured in to ice-water and separated by dichloromethane (DCM). Separated organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was dissolved in DCM and filtered over silica gel to remove the dicarboxylic acid formed during work up then give yellow color solid. Yield: 68.9%, m.p. 119-120°C (lit.,[45] m.p.117-118°C). IR (KBr): υ_{max} , 1679.4-1701.47(ester C=O), 2926.08(-COOH) cm^{-1}. ^1H NMR (300MHz, $CDCl_3$):δ 2.00-2.10 (m, 2H, -CH_2-), 2.30 (s, 6H, 2 x CH_3), 2.50 (t, 2H, -CH_2-), 3.00 (t, 2H, -CH_2-), 7.15 (d, 1H, Ar-H), 7.65 (d,1H, Ar-H), 7.69 (s, 1H, Ar-H). EI-MS: *m/z* =220(M^+).

Preparation of 5-(3,4-dimethyl phenyl)- pentanoic acid (4):
Mossy zinc (1.55 g) free from its oxides was amalgamated by shaking it with a mixture of mercuric chloride (0.15 g), conc. hydrochloric acid (1 ml) and distilled water (2.35 mL) for 15 min. aqueous portion was decanted off and

the residue washed thoroughly with water. A mixture containing amalgamated zinc, distilled water (1.5 mL) toluene (2 mL), acetic acid (4.5 mL), conc. hydrochloric acid (2.7 mL) and compound **3** (1.09 g, 3.75 m.mole) was refluxed for 48 h with addition of fresh conc. hydrochloric acid (40 mL) at ten-hour interval. The reaction mixture was cooled, the organic layer separated and the aq. layer extracted with benzene (2 x 20 mL). The combined organic layer was washed with water to neutrality and dried (Na_2SO_4). Solvent removal under reduced pressure and distillation under high vacuum gave (95%) of 5 - (3, 4-dimethyl phenyl)-pentanoic acid (**4**). It was recrystallized from benzene as colourless prisms, Yield: 50%, m.p. 68-69°C (lit.,[45] m.p.65-66°C). IR (KBr): υ_{max} 1703.90, 2857.17, 2924.10 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 1.60-1.70 (m, 4H, -CH_2-), 2.20 (s, 6H, 2 x-CH_3), 2.30-2.40 (m, 2H, -CH_2COOH), 2.50-2.60 (m, 2H, $ArCH_2$-), 6.80-7.00 (m, 3H, Ar-H). EI-MS:*m/z* = 206(M^+).

Preparation of 2, 3-dimethyl-6, 7, 8, 9-tetrahydrobenzocyclohepten-5-one (5):
Polyphosphoric acid was prepared by heating a mixture of phosphorous pent oxide (7 g) and orthophosphoric acid (3.5 mL, 86%) on a steam-bath for 1 hr with occasional shaking. To this was added **4** (10.0 g, 0.042 mole). The color of the reaction mixture immediately changed to deep red. This mixture was heated on a steam-bath for 1 h, poured over crushed ice with stirring and the solid separated was filtered and washed successively with aq. sodium carbonate and water. The crude product thus obtained was purified by distillation under high vacuum to furnish 8 g (86.6%) of 2,3-dimethyl-6,7,8,9-tetrahydro-5-(H)-benzocyclohepten-5-one (**5**). A portion crystallized from ethyl acetate-n-hexane, Yield: 76.9%, m.p. 52°C. IR (KBr): υ_{max} 1672.92(ArCOR) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75-1.90 (m, 4H, -CH_2-), 2.3 (s, 6H, 2 x CH_3), 2.7 (t, 2H, -CH_2 CO), 2.85 (t, 2H, -CH_2 Ar), 6.90 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H). EI-MS: *m/z* = 188(M^+).

General procedure for the preparation of benzylidene derivatives:
A mixture of 2, 3-dimethyl-6, 7, 8, 9-tetrahydro-benzocycloheptene-5-one (**5**, 0.35 g, 2 mmole), benzaldehyde (0.22 g, 2 mmol) in ethanolic KOH (5%) was stirred at room temperature for ½ h. During this period the product was formed. The reaction mixture was neutralized with acetic acid and diluted with water. The solid thus obtained was filtered and washed thoroughly with water and dried. Recrystalization from methanol gave following yellow colour solid products:

6-Benzylidene-2, 3 dimethyl-6, 7, 8, 9-tetrahydro-benzocyclohepten-5-one (7a): Yield: 95%, m.p.128-130°C. IR (KBr): υ_{max} 1660.16cm^{-1}(ArCOR) , ^1H NMR (300MHz, $CDCl_3$) : δ 2-2.1 (m, 2H, -CH_2-), 2.3 (s, 6H, 2 x –CH_3), 2.6 (t, 2H, -CH_2-), 2.8-2.9 (t, 2H, -CH_2-), 6.9 (s, 1H, Ar-H), 7.3-7.6 (m, 8H, Ar-H&-CH=), 7.8 (s, 1H, Ar-H). EI-MS: m/z 276 ($M^{+\cdot}$).

6-(4-Chlorobenzylidene)-2, 3-dimethyl 6, 7, 8, 9-tetrahydroben-zocyclohepten-5-one (7b): Yield: 95%, m.p-119-121^{0}C (KBr): υ_{max} 1658.58 cm^{-1} (ArCOR). ^1H NMR (200MHz,$CDCl_3$) : δ2-2.1 (m, 2H, -CH_2-), 2.3 (s, 6H, 2x CH_3), 2.5-2.6 (t, 2H, –CH_2-), 2.80-2.90 (t, 2H, -CH2-), 6.95 (s, 1H, Ar-H), 7.39 (d, 4H, Ar-H), 7.5 (s, 1H, -CH=), 7.7 (s,1H, ArH). EI-MS: m/z 310 (M^+).

6-(4-Bromo benzylidene)-2, 3-dimethyl-6, 7, 8, 9-tetrahydro benzocyclohepten-5-one (7c): Yield: 96%, m.p-112-113^{0}C. IR (KBr): $\upsilon_{Max:}$ 1668.39 cm^{-1} (ArCOR). ^1H NMR ($CDCl_3$) : δ 1.99-2.1 (m, 2H, -CH_2-), 2.30 (s, 6H, 2 x –CH_3), 2.50-2.60 (t, 2H, -CH_2-), 2.80-2.90 (t, 2H, -CH_2-), 6.95 (s, 2H, ArH), 7.30-7.40 (d, 2H, Ar-H), 7.50-7.60 (d, 2H, Ar-H), 7.7 (s, 1H, ArH). EI-MS: m/z 355 (M^+).

General Procedure for the preparation of phenyl butenyltetrahydro benzocyclohepten-5-one derivatives (9a-c):
To a stirred solution of the *α,β*-unsaturated ketone (**7a**, 1 mmol), and MCM-41(H) (2 mmol) in dichloromethane (10 mL), allyltrimethylsilane (1.5 mmol) was added slowly at 0 ^{0}C and the mixture stirred at room temperature for the appropriate time. After complete conversion as indicated by TLC, the reaction mixture was quenched with water (2X15 ml). The combined extracts were washed with a 15% solution of sodium thiosulphate, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The following resulting products were purified by column chromatography on silica gel:

2,3-Dimethyl-6-(1-Phenyl but-3-enyl)-6, 7, 8, 9-tetrahydro benzocycloheptene-5-one (9a): Yield: 57.3% IR (KBr): υ_{max} 1679.82 cm^{-1} (ArCOR). ^1H NMR (200MHz, $CDCl_3$) : δ 1.6 (m, 2H, -CH_2-), 1.8-2.1 (m, 2H, -CH_2), 2.1 (s, 3H, -CH_3), 2.2 (s, 3H, -CH_3), 2.60 (t, 2H, -CH_2), 2.80 (m, 2H, -CH_2 allylic), 3(m, H, -CH), 3.5(m,H,_CH_2), 4.8-5(m, 2H,-CH_2), 5.5(m, H, -CH), 6.8-7.8(m, 7H, ArH). EI-MS: m/z 318 ($M^{+\cdot}$).

2,3-Dimethyl 6-[1-(4-chlorophenyl) but-3-enyl]-6, 7, 8, 9-tetrahydro benzocycloheptene-5-one (9b): Yield: 52.3% IR (KBr): υ_{max} : 1668.39 cm^{-1} (ArCOR). ^1H NMR (300MHz,$CDCl_3$) : δ 1.6 (m, 2H, -CH_2-), 2.00 (m, 2H, -

CH_2), 2.1-2.4 (m, 6H, 2 x CH_3), 2.6 (t, 2H, -CH_2), 2.8 (t, 2H, -CH_2allylic), 3.00 (m, 1H, -CH), 4.8-5 (m, 2H, -CH_2), 5.5 (m, 1H, -CH), 6.8-7.7 (m, 6H, ArH). EI- MS: m/z 352 ($M^{+\cdot}$).

2,3-Dimethyl 6-[1-(4-bromophenyl) but-3-enyl)-6, 7, 8, 9-tetrahydro benzocycloheptene-5-one (9c): Yield:51.23% IR (KBr): υ_{max} 1668.39 cm^{-1} (ArCOR). ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.6 (m, 2H, -CH_2-), 2 (m, 2H, -CH_2), 2.1-2.4 (m, 6H, 2 x CH_3), 2.6 (t, 2H, -CH_3), 2.8 (t, 2H, -CH_2 allylic), 3 (m, 2H, -CH), 3.4 (m, H, -CH), 4.8-5(m, 2H,-CH_2), 5.5(m, H, -CH), 6.8-7.8(m, 7H, ArH). MS: m/z 397 ($M^{+\cdot}$).

Preparation of 9, 10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo [6, 7] cyclohepta [1, 2-d] pyrimidin-2-ylamine (10):
A mixture of 6-benzylidine-2,3-dimethyl-6,7,8,9-tetrahydro benzocyclohepten-5-one (**7a**, 0.262 g, 1 mmol) and guanidine hydrochloride (1 mmol) were refluxed together in 5% ethanolic KOH (8 mL) for 3 h. Progress of the reaction was monitored by TLC. The excess of solvent was removed under vacuum, extracted with chloroform and washed with water; the combined organic layers were dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a gummy product, which was purified by refluxing in hexane for 10 min and filtered. Yield: 50%, m.p-210-211 ^{0}C.IR (KBr): υ_{max} 3187.64 (-NH_2) cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.1-2.35 (m, 10 H, 2 x -CH_2-, 2 x CH_3), 2.6 (t, 2H, -CH_2), 5.20 (s, 2H, -NH_2), 7 (s, 1H, ArH), 7.4-7.6 (m, 6H, ArH). EI-MS: m/z 315 ($M^{+\cdot}$)

Preparation of 1-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta [1,2-d] pyrimidin-2-yl)-pyrrolidine-2,5-dione(11):
9,10-Dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*] pyrimidine-2-ylamine (**10**,0.3 g, 1 mmol) and a large exess of succinic anhydride (2.20 g, 22 mmol) were homogeneously mixed. The mixture was heated at 180 ^{0}C for 1 h in presence of MCM-41(H) (2 mmol) in a 50 mL RB flask. After cooling the residue was treated with ether to remove color impurities and filtered the solid product. Yield: 80.3%, m.p-122-123 ^{0}C.IR (KBr): υ_{max} 1783.97(C=O), 1865.46(C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1-2.35 (m, 10 H, 2 x -CH_2-, 2 x CH_3), 2.6 (t, 2H, -CH_2), 5.2 (s, 2H, -NH_2), 7 (s, 1H, ArH), 7.4-7.6 (m, 6H, ArH). ESI-MS: m/z 372 ($M^{+\cdot}$)

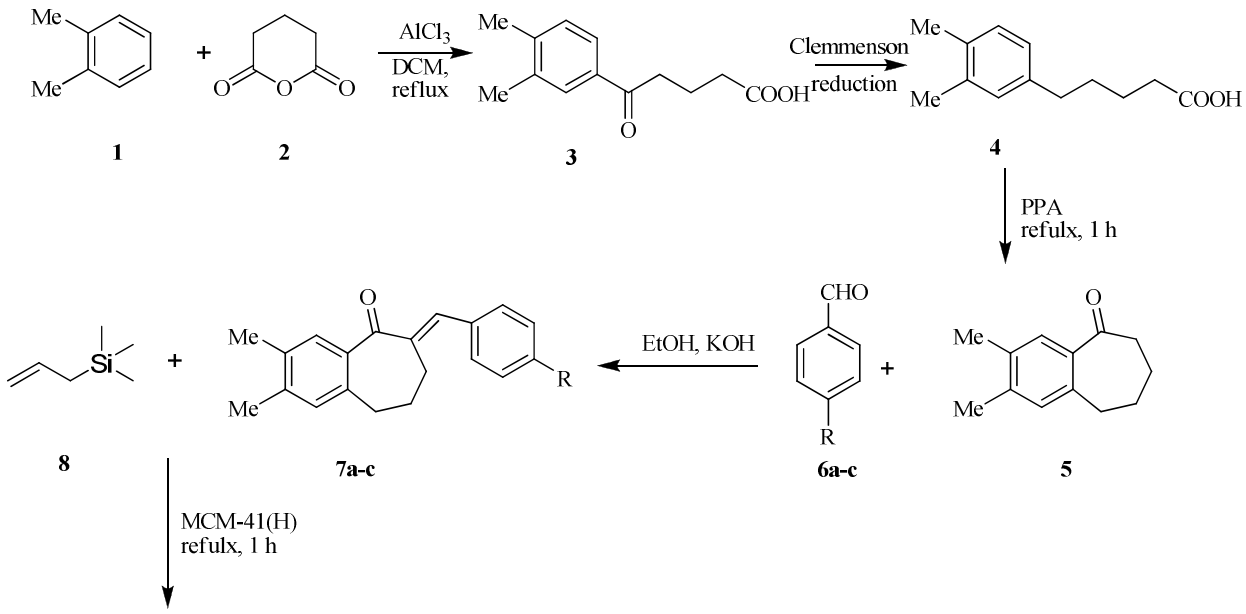
Preparation of 2-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-2-yl)-pyrrolidine-2,5-dione (12): 9,10-Dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-2-ylamine **(11,** 0.3 g, 1 mmol) and a large exess of pthalic anhydride (4.73 g, 32 mmol) were homogeneously mixed. The mixture was heated at 180 ^{0}C for 1 h in presence of MCM-41(H) (2 mmol) in a 50 mL RB flask. After cooling the residue was treated with ether to remove color impurities and filtered the solid product. Yield: 65.7%, m.p-133-134 ^{0}C IR (KBr): υ_{max} 1850.92 (C=O), 1765.40 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 6H, 2 x -CH_3), 2.4 (m, 2H, -CH_2), 2.6 (t, 2H, -CH_2), 2.7 (t, 2H, -CH_2), 7 (s, 1H, ArH), 7.5 (d, 5H, ArH), 7.6 (s, 1H, Ar-H), 7.7(m, 2H, ArH), 7.8 (m, 2H, ArH) EI= MS: m/z 451 ($M^{+\cdot}$).

RESULTS AND DISCUSSION

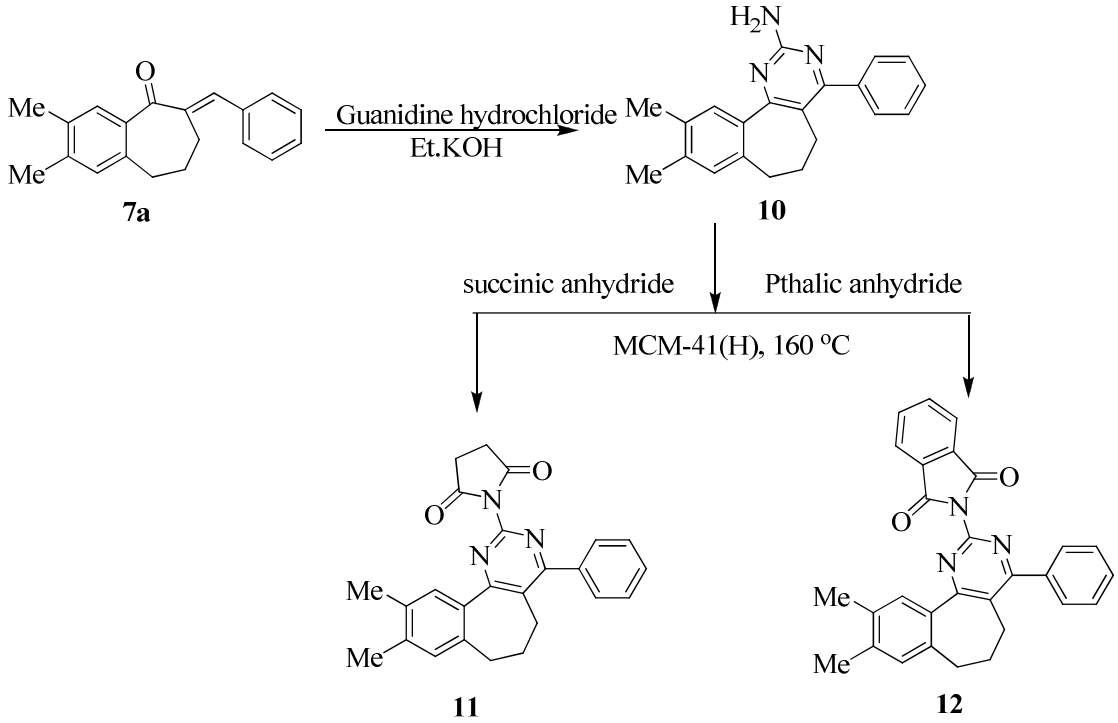
In view of several synthetic and biological, pharmacological applications of benzocycloheptene-5-one derivatives, the present work aimed to achieve 2,3-dimethyl-6-(1-phenyl but-3-enyl)-6,7,8,9-tetrahydro benzocyclohepten-5-ones (**9a-c**); 1-(9,10-dimethyl-4-phenyl-6,7,-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)pyrrolidine-2,5-dione (**11**) and 2-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*] pyridine-2-yl) isoindole-1,3-dione (**12**).

In the first part of our study Friedel-Crafts acylation of *o*-xylene (**1**) with glutaric anhydride (**2**) furnished γ-(benzoyl)-butyric acid (**3**), which on Clemmenson reduction with zinc-amalgam followed by cyclization with excess freshly prepared polyphosphoric acid gave 2,3-dimethyl-6,7,8,9-tetrahydro-*5H*-benzocyclohepten-5-one (**5**).

The next key intermediate 6-benzylidene-2,3-dimethyl-6,7,8,9-tetrahydro benzocyclohepten-5-one derivatives **(7a-c)**was obtained from the reaction of 2,3-dimethyl-6,7,8,9-tetrahydro benzocycloheptene-5-one (**5)**with various benzaldehydes**(6a-c)** in reasonable good yields. Finally the targeted 2,3-dimethyl-6-(1-phenyl but-3-enyl)-6,7,8,9-tetrahydro benzocyclohepten-5-one derivatives (**9a-c) (Scheme 1)** were obtained from the reaction of benzylidene derivatives **(10a-c)** with allyltrimethylsilane in the presence of recyclable MCM-41(H). The structures were confirmed by their spectral analysis.



Scheme 1



Scheme 2

In the other hand 6-arylidene-3-methyl-6, 7, 8, 9-tetrahydro-5*H*-benzocyclohepten-5-one **(7a)** was treated with appropriate aromatic aldehyde (9a), which on reaction with guanidine hydrochloride in alkaline medium to yield corresponding 9, 10- dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[*d*]-2-amine **(10)** in good yield.

Amino compound **10** when treated with succinic anhydride, pthalic anhydride in the presence of catalytic amount of MCM-41(H) at 160 ^{0}Cfor 1 h afforded 1-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*] pyrimidin-2-yl) pyrrolidine-2,5-dione (**11**) and 2-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*] pyrimidin-2-yl) isoindole-1,3-dione(**12**) in good yield and their structures were confirmed by IR, ^{1}H NMR and mass spectral data **(Scheme 2)**

CONCLUSION

Amino compound treated with succinic anhydride, pthalic anhydride in the presence of catalytic amount of MCM-41(H) afforded 1-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*] pyrimidin-2-yl) pyrrolidine-2,5-dione and 2-(9,10-dimethyl-4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*] pyrimidin-2-yl) isoindole-1,3-dione in good yield and their structures were confirmed by IR, ^{1}H NMR and mass spectral data**.**

Acknowledgements
The authors K S Reddy *Brundavan Laboratories* thank for the financial support and encouragement

REFERENCES

[1] a) E. Colvin, *Silicon in Organic Synthesis*; Butterworth: London, **1981**, 97,b) A. Hosomi. Acc. Chem. Res., 1988, 21, 200; c) E. Langkopf, D. Schinzer, *Chem. Rev*., **1995**, 95, 1375.
[2] a) A. Hosomi, H. Sakurai, *J. Am. Chem. Soc*., **1977**, 99, 1673; b) I. Fleming, J. Dunogues, R. Smithers, *Org. React.*,**1989**, 37, 57.
[3] A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.*,**1994**, 116, 6130.
[4] 4. a) B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, R. A. J. Smith, *J. Am. Chem. Soc.*,**1990**, 112, 4404; b) B. H. Lipshutz, C. Hackmann, *J. Org. Chem.*,**1994**, 59, 7437.
[5] J. S. Yadav, B. V. S. Reddy, K. Sadasiv, G. Satheesh, *Tetrahedron Lettrs.*,**2002**, 43, 9695.
[6] P. H. Lee, H. A. K. Lee, S. Sung, S. Kim, *Tetrahedron Lettrs.*,**2001**, 42, 37.
[7] P. H. Lee, H.Ahn, K. Lee, S. Sung, S. Chang, *J. Org. Chem.*,**2001**, 66, 8646.
[8] Brugnatelli, Giorn. Fis.Chim.Storia.Nat. (Pavia), *decadaseconda*, **1818**, 1, 117.
[9] Grimaux, *Compt. Rend.*,**1878**, 87, 752.
[10] Pinner, *Chem. Ber.*,**1885**, 18, 759.
[11] G. H. Hitchings, G. B. Elion, H. Vander Werff, E. A. Falco, *J. Biol. Chem.*,**1948**, 174, 765.
[12] P. B. Russell, G. H. Hitchings, H. Vander Werff, *Nature*, **1948**, 164, 107.
[13] R. Truhaut, M. De Clercq, S. Lambin, Y. Lund, M. Robert, Rev. Franc. Etudes.*Clin.Biol.*,**1962**, 7, 177.
[14] D. E. O'Brien, C. W. Noell, R. K. Robins, C. C. Cheng, *J. Med. Chem.*,**1966**, 9, 121.
[15] C. K. Banks, *J. Am. Chem. Soc.*,**1944**, 66, 1131.
[16] E. Profft, H. Raddatz, *Arch. Pharm.***1962**, 295, 649.
[17] J. S. Beeck, C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T. W. Chu, D. H. Olson, E. W. Sheppared, S. B. Sheppared, Mc Cullen, J. B. Higgins, J. L. Schlenker, *J. Am. Chem. Soc.*,**1992**, 114, 1083.
[18] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. S. Beck, *Nature*,**1992**, 359, 710.
[19] X. S. Zhao, G. Q. Luand, G. J. Millar, *Ind. Eng. Chem. Res.*, **1996**, 35, 2075.
[20] A. Corma, A. Martinez, V. Martinez-Soria, J. B. Montoni, *J. Catal.*,**1995**, 25, 153.