BENZOTHIAZEPINE FUSED HETEROCYCLES VI : A CONVENIENT SYNTHESIS OF 2-ARYL-4-(4-HYDROXY-6-METHYL-2-PYRONE-3-YL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES USING MCM-41(H) ZEOLITE[†]

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Abstract : Simple and convenient procedures have been developed for the synthesis of 2-aryl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepines (**3a-e**) by the condensation reaction between 2-aminothiophenol (**1**) and 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones(**2a-e**) with MCM-41(H) Zeolite in ethanol.

Introduction :

A number of 1,5-benzothiazepines were found to exhibit wide range of pharmacological activities[1-10],like coronary, vasodilatory, tranquilizing, bactericidal, sedative, diuretic, CNS depressant, blood pressure depressant and non-hypnotic activities. Synthesis of this group of benzothiazepines has been intensely studied and numerous procedures are described in the literature[11-14].A recent successful approach has been investigated by Sucheta *et al* research group[15], modification of the known reaction conditions or the development of new procedures are important to get newer insight into the formation of these 1,5-benzothiazepines. In continuation of our ongoing and previous investigations[16-19] the present aim of this study was, therefore to introduce simple and convenient procedures for the synthesis of 2-aryl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepines by the reaction of 2-aminothiophenol with 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones (**2a-e**) [20] in the presence of MCM-41(H) zeolite[21-23]. The important features of the reaction is that the MCM-41(H) zeolite is recovered and can be recycled without substantial loss in the yield of product.

Chemistry :Reaction of 2-aminothiophenol (**1**) with alcoholic solution of 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones (**2a-e**) and MCM-41(H) zeolite in ethanol heated under reflux to give 2-aryl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepines (**3a-e**) in 76-88 % yield.

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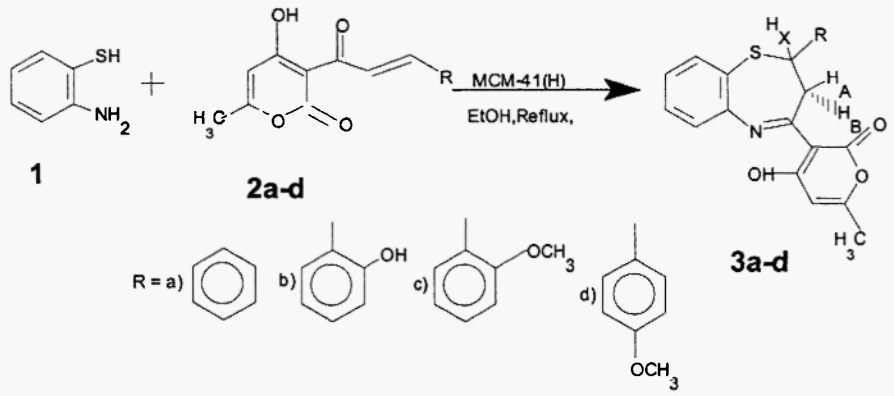
Structures of compounds synthesized have been elucidated by the elemental analysis, IR, ^{1}H-NMR and Mass spectral data. A C=N band characteristic for such 2,3-dihydro-1,5-bezothiazepines has been observed between 1565 and 1700 cm^{-1}. Chemical shift ,coupling constant values and multiplicity of protons attached to carbon C_2 and C_3 unequivocally (signals arising in **3a** due to typical ABX pattern. The spectrum contained three double doublets. The first one appeared at δ 2.75 integrating for one proton with coupling constant values , J_{ab}=14.3 Hz and J_{ax}=11.3 Hz. It was assigned to C_3-H_A. The second double doublet which appeared at δ 4.25 (1H) with coupling constant values J_{ab}=14.7 Hz and J_{ax}=5.7 Hz was attributed to C_2-H_x prove the structure of all reaction products.

In summary ,it can be concluded that we managed to introduce efficient procedures for the preparation of 1,5-benzothiazepines using MCM-41(H) zeolite due to its simplicity, excellent yields shorter times and easy workup.



Experimental :

Melting points were determined in open glass capillaries on Polmon melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini(200 MHz) spectrometer (chemical shift are recorded in δ ppm); internal standard was TMS and IR spectra were recorded in KBr on a Perkin-Elmer spectrometer .Elemental analysis were carried with a Carlo Erba Model 1106 Elemental Analyser.

2,3-Dihydro-1,5-benzothiazepines **(3a-e)** .

General Procedure :A mixture of 2-aminothiophenol (**1**, 0.1 mole), substituted-3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones (**2a-e**. 0.18 mole) MCM-41(H) zeolite(0.01 mole) and dry ethanol (50ml) were refluxed for 1-2 hr. The reaction mixture was allowed to cool to room temperature, diluted with ethanol (50ml) ,filtered [MCM-41(H)was washed thoroughly with ethanol (2x20 ml) and activated for recycle] .The combined ethanol phase was dried (Na_2SO_4) and the solvent was

removed in *vaccuo* to afford following products which were purified by column chromatography on silica gel eluted with hexane: EtOAc (1:4).

***2-Phenyl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepine* (3a)** :

Obtained as light yellow fluffy solid in 76% yield, m.p. 241-242°c(lit[15],m.p. 242°c), ^{1}H NMR ($CDCl_3$): δ 2.10(s,3H,CH_3), 2.75(dd,1H,J=14.3 &11.3 Hz, H_A), 4.25(dd,1H, J=14.3 &5.7 Hz, H_B) 5.25(dd,1H,J=14.3 &5.7 Hz, H_X), 5.80(s,1H, pyrone –H) and 7.20-7.85 (m.9H,arom-H).
MS: m/z 363(m+ 100%),330(55%), 272(70%),259(80%),217(40%),189(25%, 175(65%),103(80%).
Anal.cald. for $C_{21}H_{17}NO_3S$: C,69.40; H,4.68; N.3.85 %
Found : C,69.42; H,4.62; N,3.88 %

***2-(2-Hydroxy phenyl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepine* (3b)**

Obtained as yellow crystalline solid in 78% yield, m.p. 234°c(lit[15],m.p. 234°c), ^{1}H NMR ($CDCl_3$): δ 2.21(s,3H,CH_3), 3.63(dd,1H,J=15.1 &10.01 Hz, H_A), 4.26(dd,1H, J=15.0 &10.1 Hz, H_B), 5.25(dd,1H,J=10.0 &10.1 Hz, H_X), 5.81(s,1H, pyrone –H) and 6.80-7.69 (m.8H,arom-H).
Anal.cald. for $C_{21}H_{17}NO_4S$: C,66.49; H,4.48; N.3.69 %
Found : C,66.51; H,4.51; N,3.70 %

***2-(2-Methoxy phenyl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepine*(3c):**

Obtained as light yellow crystalline solid in 83% yield, m.p. 241°c(lit[15],m.p. 242°c), ^{1}H NMR ($CDCl_3$): δ 2.25(s,3H,CH_3), 3.81(s,3H,-OCH_3), 3.10(dd,1H,J=15.1 &12.5 Hz, H_A), 4.20(dd,1H, J=15.0 &5.1Hz,H_B), 5.20(dd,1H,J=12.5 &5.1 Hz, H_X), 5.71(s,1H, pyrone –H) and 6.68-7.81 (m.8H,arom-H).
Anal.cald. for $C_{22}H_{19}NO_4S$: C,67.18; H,4.83; N.3.56 %
Found : C,69.20; H,4.83; N,3.58 %

***2-(4-Methoxy phenyl-4-(4-hydroxy-6-methyl-2-pyrone-3-yl)-2,3-dihydro-1,5-benzothiazepine*(3d):**

Obtained as light yellow crystalline solid in 88% yield, m.p. 246°c(lit[15],m.p. 245°c), ^{1}H NMR ($CDCl_3$): δ 2.22(s,3H,CH_3), 2.66(dd,1H,J=15.0 &15.1 Hz, H_A), 3.88(s,3H,-OCH_3) 4.25(dd,1H, J=15.0 &5.0 Hz, H_B), 5.25(dd,1H,J=15.2 &5.2 Hz, H_X), 5.79(s,1H, pyrone –H) and 6.68-7.83 (m.8H,arom-H).
Anal.cald. for $C_{22}H_{19}NO_4S$: C,67.18; H,4.83; N.3.56 %
Found : C,67.15; H,4.80; N,3.58 %

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References :

1. B.A.Koechlin, M.A.Schwartz and L.G.Knol. "*Pharmacological Exp.Therapy*" **148**, 399 (1965)
2. H.W.Ruelins, J.M.Lee and M.E.Alburn,*Arch.Biochem.Biophys*,**III**, 376 (1965).
3. S.S.Walkenstein,R.Wiser and C.H.Gudmudsen,*J.Pharm.Sci.*, **53**, 1181 (1964)
4. J.A.F.Desilva, B.A.Koechlin and G.Badev, *J.Pharm.Sci.*, **55**, 692 (1966).
5. B.Z.Senkowski, M.S.Levin, J.R.Urbigkit and E.G.Wolishi, *Anal.Chem.*, **36**, 1991 (1964)
6. A.Baurer, K.K.Weber and P.Dannlberg, *Ger.Offen*, 2,306,770 (1974)
7. J.elks and C.R.Ganellin, *Dictionary of Drugs*, Chapman & Hall, 291 (1990).
8. J.K.Chakrabarti and E.T.David, *Ger.Pat*, 2,552,403, *Chem Abstr.*, **86**, 29893e (1976).
9. R.R.Gupta(Ed), "*Phenothiazines & 1,4-Benzothiazines – Chemical & Biomedical Aspects*", Elsevier, Amsterdam (1988).
10. C.Y.Ho, W.E.Hageman and F.J.Persico, *J.Med.Chem..*, **29**, 1118 (1986).
11. A.Levai, *Trends Heterocycl.Chem.*, **4**, 51 (1995).
12. A.Chimin, R.Gitto, S.Grasso, A.M.Maonforte and M.Zappala, *Adv.Heterocycl.Chem.*, **63**, 61 (1995).
13. A.Levai, *Heterocycl.Commun.*, **5**(4), 359 (1997).
14. A.levai, *Heterocycl.Commun.*, **3**(3), 211 (1997).
15. K.Sucheta, A.Prashant and N.Rama Rao, *Ind.J.Chem.*, **34B**, 893 (1995).
16. L.Nagarapu, R,Narendar and N.V.Rao, *Enantiomer*, **6**(6), 339 (2001).
17. L.Nagarapu and R.Narendar, *Heterocyclic Commun.*, **7**(3), 237 (2001).
18. L.Nagarapu and R.Narendar, *Ind.J.Chem.*, **37B**, 39 (1998).
19. L.Nagarapu and R.Narendar, *Heterocyclic.Commun.*, **7**(5), 433 (2001).
20. W.Richrad, H.Wiley, CH. Jarboe and H.G.Ellert, *J.Am.Chem.Soc.*, **77**, 5102 (1955).
21. 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.McCullen, J.B.Higgins and and J.L.. Schlenker, *J.Am.Chem.Soc.*, **114**, 10843 (1992).
22. C.T.Kresge, M.E.Leonowicz, W.J.Roth, J.C.Vartuli and J.S.Beck, *Nature*, **359**, 710 (1992).
23. X.S.Zhao, G.Q.Lu and G.J.Millar, *Ind.Eng.Chem.Res.*, **35**, 2075 (1996).

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