Asian Journal of Chemistry Vol. 12, No. 1 (2000), 286–288

NOTE

Novel And Convenient Synthesis of 1,4-Dihydro Pyridines

V.S. RAO, S.V.S. ARUN KUMAR GUPTA*, P. GIRIDHAR,
N. JAI GANESH and B.S. REDDY†
Chemistry Group, Birla Institute of Technology and Science, Pilani-333 031, India

Some novel 1,4-dihyropyridine fused/spiro systems were synthesized by the reaction of different types of α,β-unsaturated carbonyl/nitriles with 2,4-thiazolidinedione in the presence of excess of ammonium acetate at reflux condition. The structure of the compounds were assgined by spectral and elemental data.

The chemistry of heterocyclic compounds is one of the most well attended branches of organic chemistry. Amongst all heterocycles, the nitrogen and sulfur containing five or six member compounds and their fused/spiro systems, have been studied extensively in view of their pharmacological importance. Once such type of system is 1,4-dihyropyridine[1]. 1,4-Dihydropyridines are compounds with interesting synthetic[2], therapeutic[3] and bio-organic applications[4]. Amilodipine, nicardipine and nifidipine are the best suitable examples for such type of compounds. Although the chemistry of N-alkyl-1,4-dihydropyridines are well known but the reports on preparation of N-unsubstituted-1,4-dihydropyridine and its derivatives by methods other than the Hantszch synthesis are relatively scarce. Here we are reporting the synthesis of some novel fused, spiro-1,4-dihydropyridines by reaction of methylene group in the 2,4-thiazolidinedione with different types of α,β-unsaturated nitriles, carbonyls by Michael reaction followed by cyclization.

EXPERIMENTAL

Melting points were determined on Mel. Temp and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer spectrometer. PMR,s were determined in DMSO-d_6 and $CDCl_3$ on Varian-Gemini 200 spectrometer.

General Procedure for the preparation of II, IV and VI

A solution of 2,4-thiazolidinedione (0.01 mole) in ethanol 30 mL was treated with proper unsaturated compounds [*i.e.*, I, III, V] (0.01 mole) and ammonium acetate (0.08 mole) and was taken in a 250 mL round bottomed flask. The contents were refluxed for 5–8 h, concentrated, and the mixture was decomposed in

†Suven Pharmaceuticals, Hyderabad, India.

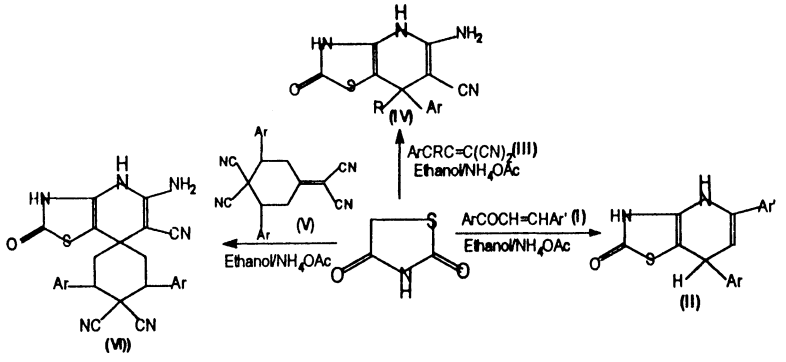
250 mL of chilled water under stirring and acidified with conc. hydrochloric acid. The solid thus separated was filtered and dried and recrystallised from ethylacetate-hexane (2 : 8).

(IIa) IR: ν_{max} (KBr): 3200 cm^{-1} ν(amide N—H); 815 cm^{-1}ν(C_6—H); 1560 cm^{-1} ν(amide carbonyl). NMR δ ppm ($CDCl_3$ + d_6-DMSO): 7.15–7.25 (m, 10H, Ar—H); 10.90 (b, 1H, amide N—H); 7.65 (b, 1H, N—H pyridyl); 4.50 (d, 1H, C_7—H); 5.22 (d, 1H, C_6—H).

(IVa) IR: ν_{max} (KBr): 3250 cm^{-1} ν(amide N—H); 3400–3300 cm^{-1} ν(NH_2); 2180 cm^{-1} ν(CN); 1580 cm^{-1} ν(amide carbonyl); NMR δ ppm ($CDCl_3$ + d_6-DMSO): 7.30 (s, 2H, NH_2); 7.48 (s, 1H, pyridyl N—H); 9.72 (s, 1H, amide N—H); 7.25 (m, 5H, Ar—H); 5.41 (s, 1H, C_7—H).

(VIa) IR: ν_{max} (KBr): 2150 cm^{-1} ν(CN); 3380–3200 cm^{-1} (a broad triplet band, the presence of N—H, NH_2); 1565 cm^{-1} ν(amide carbonyl). NMR δ ppm ($CDCl_3$ + d_6-DMSO): 7.25 (s, 2H, NH_2); 7.35 (s, 1H, pyridyl N—H); 10.10 (s, 1H, amide N—H); 7.15–7.65 (m, 10H, Ar—H); AMX pattern: H_A: 4.21, H_M: 3.86, H_X: 2.85; J_{Am}: 15.70, J_{AX}: 10.48, J_{MX}: 5.20.

2,4-Thiazolidinedione when reacts with ω-arylidieneacetophenone (I), undergoes Michael addition followed by cyclisation in the presence of excess of ammonium acetate in ethanol gives 5,7-diaryl-2-oxo-1-3-thiazolo-[4,5-b]-2,3,4,7-tetrahydropyridine (II). The IR spectrum of (II) shows a broad band of N—H stretching at 3400–3200 cm^{-1} and the presence of a sharp medium to weak band at 815 cm^{-1} indicates the presence of a vinyl proton at C-6 carbon[5]. The PMR spectrum of II shows two broad singlets at 8.8–10.1 δ ppm indicating the presence of N—H proton; a *gem* peak at the region of 4–6 δ ppm indicates the presence of protons at C—6 and C—7. All the aromatic protons are resonated at 7.0–7.6 δ ppm as a multiplet[6] (Scheme-1).



Scheme-1

α-cyano-acrylonitrile (III) and 1,1-dicyano-2,6-diaryl-4(2,2-dicyano)-cyclohexanone (V) is easily accessible through the Knoevenagel condensation of malononitrile with various araldehydes or acetophenones and cyclohexanones in the presence of piperidine in ethanol. (III) and (V) react readily with 2,4-

thiazolidinedione in the presence of excess of ammonium acetate at reflux temperature for 12 h yield 5-amino-2-oxo-7-aryl-2,3,4,7-tetrahydro[1,3]-thiazolo-[4,5-b]-pyridine-6-yl-cyanide (IV) and 5-amino-9,11-diaryl-2-oxo-4-azaspiro-7-[5,5]-undeca-2,3,4,7-terahydro-1,3-thiazolo-[4,5-b] pyridine-6,10,10-tricarbo-nitriles (VIII). The PMR spectra of all the spiro compounds showing AMX pattern confirm the cyclohexyl axial/equatorial ring protons. Compounds (V) and (VI) show a sharp singlet at 7.0–8.5 δ ppm for NH_2 protons and all aromatic protons are at 6.85–7.25 δ ppm as multiplets. Two separate broad singlets appear in the region 7.5–11.0 δ ppm indicating the presence of two N–H protons in the different environment[7, 8].

REFERENCES

1. Anshu Dandia, Alpana Kumar, Varinder Sehgal and Babita Rani, *Indian J. Chem.*, **35B**, 1314 (1996).
2. V. Eismer and Kuthan, *J. Chem. Rev.*, **72** , 1 (1972); D.M. Storet and A.I. Meyers, *Chem Rev.*, **82**, 223 (1982); A. Sausins and G. Dabar, *Heterocycles*, **27**, 291 (1988).
3. D.J. Triggle, in: Hansch (Ed.), Comprehensive Medicinal Chemistry, Pergmon, Oxford, Vol. 3, p. 1070 (1990).
4. O. Almarasson and T.C. Bruice, *J. Am. Chem. Soc.*, **115**, 2125 (1993).
5. G. Bhagawan and S.P. Choudari, *J. Indian Chem. Soc.*, **64**, 442 (1987).
6. D.B. Reddy, P.V. Raman Reddy, P. Padmavati and M.V. Raman Reddy, *Sulf. Lett.*, **13**, 83 (1991).
7. R.M. Abd El-Aam, F.M. Abd El-Latif and A.I.M. Korian, *Proc. Indian Acad. Sci. Chem.*, **110**, 433 (1998).
8. H. Abdel-Ghany, H.M. Moustafa and A. Khodairy, *Synth. Comm.*, **28**, 3431 (1998).

(*Received*: 15 June 1999; *Accepted*: 21 October 1999) AJC-1889