SYNTHESIS OF SOME NEW SPIROPYRAZOLO[4,5-c]-BENZODIAZEPINES AND SPIROPYRAZOLO[4,5-c]-BENZOXAZEPINES

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Abstract
3-Methylpyrazolin-5-ones **1a,b** reacted with cyclic ketone **2a-d** in the presence of fused sodium acetate to give the corres-ponding cycloalkylidene derivatives **3a-h**. Reaction of compounds **3a-h** with o-phenylenediamine and o-aminophenol in ethanol and few drops of piperidine gave the benzodiazepines **4a-h** and benzoxazepine derivatives **5a-h** respectively. All the synthesized derivatives were identified by conventional methods (IR, ^{1}H NMR) and elemental analyses.

Introduction

The structure activity relationship on benzodiazepines, benzoxazepines had been studied (1-5). Diazepines have strong central depressant, anticonvu-lsant and anxiolylic activity (6-10). Also spiroheterocycles were used as nitric oxide synthesis inhibitors (11), photoisomerization (12,13) and potential topical agents for vaginal infection (14). It is of interest to note that pyrazoles are reported as well known pharmaceuticals (15-18). From this point of view and in continuation to our previous work (19-23), we report herein the synthesis of some new spiropyrazolo[4,5-c]benzodiaze-pines and spiropyrazolo[4,5-c]benzoxazepines.

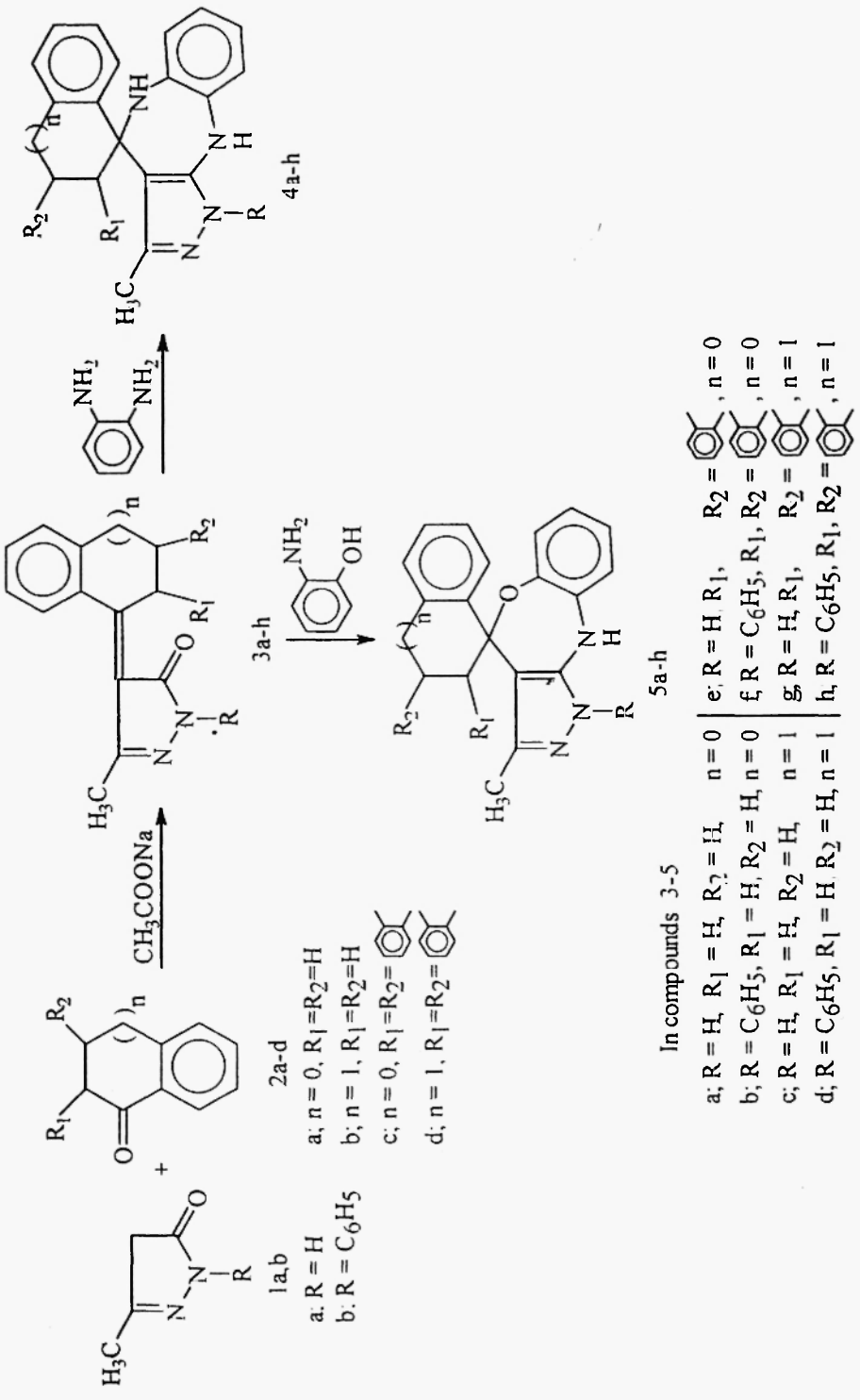
Experimental

The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a Pye-Unicam SP 200 G spectrophotometer. ^{1}H NMR spectra were measured on an EM-360 90 MHz NMR spectrophotometer. Microanalyses were determined on a Perkin-Elmer 240 C microanalyser. EI Mass spectra were recorded on a varian MAT 311A spectrometer.

Synthesis of 3-methyl-4-cycloalkylidenepyrazolin-5-ones 3a-h:

General Procedure:

A mixture of 3-methylpyrazolin-5-ones 1a,b (0.01 mole) and the appropriate cyclic ketone 2a-d (0.012 mole) was fused in the presence of anhydrous sodium acetate (0.012 mole) for 30


CH3COONa
3a-h
4a-h
1a,b
a: R = H
b: R = C6H5
2a-d
a; n = 0, R1=R2=H
b; n = 1, R1=R2=H
c; n = 0, R1=R2=
d; n = 1, R1=R2=
5a-h
In compounds 3-5
a; R = H, R1 = H, R2 = H, n = 0
b; R = C6H5, R1 = H, R2 = H, n = 0
c; R = H, R1 = H, R2 = H, n = 1
d; R = C6H5, R1 = H, R2 = H, n = 1
e; R = H, R1, R2 = , n = 0
f; R = C6H5, R1, R2 = , n = 0
g; R = H, R1, R2 = , n = 1
h; R = C6H5, R1, R2 = , n = 1

Scheme 1

Table (I) Physical Data of Spiropyrazolo[4,5-c]benzodiazepines **4a-h** and Spiropyrazolo[4,5-c]benzoxazepines **5a-h**.

Compound No.	Yield (%)	MP (°C)	Molecular formula (Solvent of Crystallization)	IR (KBr), cm^{-1}	^{1}H-NMR (DMSO-d_6), δ (TMS)
4a	70	166-168	$C_{19}H_{18}N_4$ (ethanol)	3175 (NH), 3050 (CH arom), 2900 (CH aliph)	2.30 (3H, s, CH_3), 2.40-2.60 (4H, m, $2CH_2$), 6.90-7.75 (8H, m, arom), 9.60 (3H, s, NH).
4b	75	280-282	$C_{25}H_{22}N_4$ (ethanol)	3175 (NH), 3050 (CH arom), 2890 (CH aliph)	2.30 (3H, s, CH_3) 2.40-2.60 (4H, m, $2CH_2$), 6.90-7.75 (13H, m, $2CH_2$), 6.90-7.75 (13H, m, arom), 9.60 (2H, s, NH).
4c	72	320-322	$C_{20}H_{20}N_4$ (ethanol)	3180 (NH), 3050 (CH arom), 2900 (CH aliph)	2.30 (3H, s, CH_3) 2.40-2.80 (6H, m, $3CH_2$), 7.10-8.40 (8H, m, arom), 9.60 (3H, s, NH).
4d	70	218-220	$C_{26}H_{24}N_4$ (ethanol)	3180 (NH), 3050 (CH arom), 2900 (CH aliph)	2.30 (3H, s, CH_3) 2.40-2.80 (6H, H, $3CH_2$), 7.110-7.90 (13H, m, arom), 9.60 (2H, s, NH).
4e	65	168-170	$C_{23}H_{18}N_4$ (ethanol)	3200 (NH), 3050 (CH arom), 2900 (CH aliph), 1610 (C=N)	2.30 (3H, s, CH_3) 7.10-8.40 (12H, m, arom), 9.65 (3H, s, NH).
4f	70	240-242	$C_{27}H_{22}N_4$ (ethanol)	3180 (NH), 3040 (CH arom), 2990 (CH aliph), 1620 (C=N)	2.30 (3H, s, CH_3) 2.60 (2H, s, CH_2, 7.20-8.10 (12H, m, arom), 9.60 (3H, s, NH).
4g	66	163-165	$C_{24}H_{20}N_4$ (ethanol)	3200 (NH), 3040 (CH arom), 2890 (CH aliph), 1610 (C=N)	2.30 (3H, s, CH_3) 2.60 (2H, s, CH_2), 7.20-8.20 (17H, m, arom), 9.60 (2H, s, NH).

Table (I) (Continued).

4h	69	216-218	$C_{30}H_{24}N_4$ (ethanol)	3180 (NH), 3050 (CH arom), 2900 (CH aliph), 1620 (C=N)	2.30 (3H, s, CH_3) 2.60 (2H, s, CH_2), 7.20-8.20 (17H, m, arom), 9.60 (2H, s, NH).
5a	75	184-186	$C_{19}H_{17}N_3O$ (ethanol)	3175 (NH), 3050 (CH arom), 2900 (CH aliph), 1610 (C=N)	2.30 (3H, s, CH_3) 2.40-2.60 (4H, m, $2CH_2$). 7.10-8.10 (8H, m, arom), 9.60 (2H, s, NH).
5b	70	144-146	$C_{23}H_{21}N_3O$ (ethanol)	3180 (NH), 3050 (CH arom), 2890 (CH aliph), 1620 (C=N)	2.30 (3H, s, CH_3) 2.40-2.60 (4H, m, $2CH_2$). 7.00-8.30 (13H, m, arom), 9.80 (1H, s, NH).
5c	72	172-4	$C_{20}H_{21}N_3O$ (ethanol)	3175(NH), 3040 (CH arom), 2900 (CH aliph), 1610 (C=N)	2.30 (3H, s, CH_3) 2.40-2.60 (6H, m, $3CH_2$). 7.20-8.30 (8H, m, arom), 9.60 (2H, s, NH).
5d	65	157-159	$C_{23}H_{23}N_3O$ (ethanol)	3180 (NH), 3050 (CH arom), 2900 (CH aliph), 1620 (C=N)	2.30 (3H, s, CH_3) 2.40-2.60 (6H, m, $3CH_2$). 7.20-8.30 (13H, m, arom), 9.80 (1H, s, NH).
5e	63	180-182	$C_{23}H_{17}N_3O$ (ethanol)	3200 (NH), 3040 (CH arom), 2890 (CH aliph), 1610 (C=N)	2.30 (3H, s, CH_3) 7.10-8.30 (12H, m, arom), 9.60 (2H, s, NH).
5f	66	320-322	$C_{29}H_{21}N_3O$ (ethanol)	3180 (NH), 3050 (CH arom), 2900 (CH aliph), 1620 (C=N)	2.30 (3H, s, CH_3) 7.10-8.30 (17H, m, arom), 9.80 (1H, s, NH).
5g	65	178-80	$C_{24}H_{19}N_3O$ (ethanol)	3175 (NH), 3050 (CH arom), 2900 (CH aliph), 1610 (C=N)	2.30 (3H, s, CH_3) 2.70 (2H, s, CH_2), 7.20-8.10 (12H, m, arom), 9.80 (2H, s, NH).
5h	67	196-198	$C_{30}H_{23}N_3O$ (ethanol)	3180 (NH), 3040 (CH arom), 2900 (CH aliph), 1620 (C=N)	2.30 (3H, s, CH_3) 2.60 (2H, s, CH_2), 7.10-8.20 (17H, m, arom), 9.80 (1H, s, NH).

min at 200°C. The reaction mixture was allowed to cool to room temperature, poured into water (200 ml), whereby the products 3a-h were precipitated, filtered and recrystallized from ethanol (Table I).

Synthesis of spiropyrazolo[4,5-c]benzodiazepines 4a-h and spironyra-zolo-[4,5-c]benzoxazepines 5a-h:

General Procedure:

A mixture of each compound 3a-h (0.01 mole), o-phenylenediamine and/or o-aminophenol (0.01 mole) and few drops of piperidine was refluxed in ethanol (50 ml) for 4 hrs., then glacial acetic acid (10 ml) was added to the reaction mixture and heating was continued further for 2 hr. The reaction mixture cooled to room temperature, left overnight and the resultant solid filtered and recrystallized from ethanol (Table I).

Results and Discussions

3-Methyl-4-cycloalkylidenepyrazolin-5-ones 3a-h were prepared by the interaction of 3-methylpyrazolin-5-ones 1a,b with 1-indanone 2a, 1-tetralone 2b, flourenone 2c and anthrone 2d in the presence of fused sodium acetate. The structures of compounds 3a-h were established from their elemental analyses and spectroscopic data (Table I).

Interaction of 3a-h with o-phenylenediamine and/or o-aminophenol in ethanol in the presence of piperidine as a basic catalyst gave the corresponding spiropyrazolobenzodiazepines 4a-h and spiropyrazolobenzox-azepines 5a-h respectively (Scheme 1). The structures of compounds 4a-h were confirmed on the basis of their elemental analysis and spectroscopic data (Table I). Also the structures of the spiropyrazolobenzodiazepine derivatives 5a-h were established from their elemental analysis and spectroscopic data (Table I).

Conclusions

This work reports a facile method for the synthesis of spiropyrazolo-benzodiazepines and spiropyrazolobenzoxazepine derivatives.

References

(1) L.H. Sternack, J. Med. Chem. 1, 22 (1979).

(2) S.J. Childress in Burger's Medicinal Chemistry, ed. M.E. Wolff, 4th ed., John Wiely, New York, Part III, 990 (1981).

(3) Y.D. Kulkarni, S.H.R. Abdi, V.L. Sharma, J. Ind. Chem. Soc. 63, 425 (1986).

(4) Z. Vejdelek, Z. Polivka, M. Protiva, Collect. Czechosl. Chem. Comm. 50, 1064 (1985).

(5) R.A. Mane, D.B. Ingle, Ind. J. chem. 21B, 973 (1982).

(6) M. Babbini, M. Gaiardi, M. Bartolett, Life Sci. 25, 15 91979).

(7) C. Braestrup, R. Albrechtsen, R.F. Squires, Nature (London) 269, 702 (1977); Chem. Abstr. 88, 45132 (1978).

(8) S.E. File, S. Pellow, Psychopharmacology, 80, 166 (1983).

(9) B.A. Weissman, J. Cott, S.M. Paul, P. Skolnick, Eur. J. Pharmacol. 90, 144 91983).

(10) S.E. File, A.R. Green, D.J. Nutt, N.D. Vincent, Psychopharmacology 82, 199 (1984).

(11) P. Hamley, T. Mclnally, A. Tinker, PCT Int. Appl. WO 9846, 611 (CL. CO7D491 10) 22 Oct. 1998, SE Appl. 97/1, 396, 15 Apr. 1997, 32 pp; Chem. Abstr. 129, 316237t (1998).

(12) L.A. Paquette, T. Lowinger, D.G. Bolin and B.M. Branan, J. Org. Chem. 61, 7486 (1996).

(13) A. Trani, C. Dallanoce, G. Panzone, F. Ripamanti, B.P. goldstein, R. Ciabatti, J. Med. Chem. 40, 967 (1997).

(14) I. Crista and I. Panea, Stud. Univ. Bab. bolyai, Chem. 40, 171(1995); Chem. Abstr. 128, 127985s (1998).

(15) F.T. coppe, M.M. Fawzi, J. Heterocycl. chem. 34, 1693 (1977).

(16) A. Steinmetz, L.F. Tietze, Ger Offen. DE 19, 627, 002 (CL. CO7D231/22) 8 Jan. 1998, Appl. 19, 627, 002, 5 Jul 1996, 14 pp; Chem. Abstr. 128, 114946e (1998).

(17) Y. Suzuki, Y. Takemura, K. Iwamoto, T. Higashino, A. Miyashito, Chem. Pharm. Bull., 46, 199 (1998).

(18) S.S. Bhagwat, C. Lee, M.D. Cowart, J. Mckie, A.L. Grillot, PCT Int. Appl. WO 9846, 605 (CL. CO7D471/04) 22 Oct. 1998, US Appl. 818, 216, 16 Apr. 1997, 172 pp; Chem. Abstr. 129, 316240b (1998).

(19) A.A. Al-Ahmadi and M.F. El-Zohry, Heteroatom Chemistry, 7(3), 171 (1996).

(20) M.S. Al-Thebeiti and M.F. El-Zohry, Indian Journal of Chemistry, 37B, 804 (1998).

(21) M.S. Al-Thebeiti and M.F. El-Zohry, Heterocycles 41(11), 2475 (1995).

(22) M.F. El-Zohry, A.A. Al-Ahmadi and F.A. Aquily, Phosphorus, Sulfur and Silicon, 2000 in press.

(23) M.F. El-Zohry, A.A. Al-Ahmadi and F.A. Aquily, Heterocyclic Communications, 2000 in press.

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