Synthesis, spectral studies and biological activity of *3H*-1, 5-benzodiazepine derivatives

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Abstract

Chlorination of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-*7H*-pyrazolo [4,3-*d*] pyrimidin-7-one **(1)** with $POCl_3$, afforded 5-(2-ethoxyphenyl)-1-methyl-7-chloro-*1H*-pyrazolo [4,3-*d*] pyrimidine **(2)**. Further, compound **2** condensed with different β-diketones/ β-ketoesters **3a-e**, to obtain new β-diketones/ β-ketoesters **4a-e**. These β-diketones/ β-ketoesters **4a-e** were condensed with *o*-phenylenediamine (o-PDA) to give biologically active *3H*-1, 5-benzodiazepines **5a-e**.

Keywords- Pyrazolo [4,3-*d*] pyrimidin-7-one, β-diketones/ β-ketoesters, *p*-toluenesulfonic acid, *o*-phenylenediamine, 1,5-benzodiazepines, antimicrobial and anthelmintic activities

Introduction

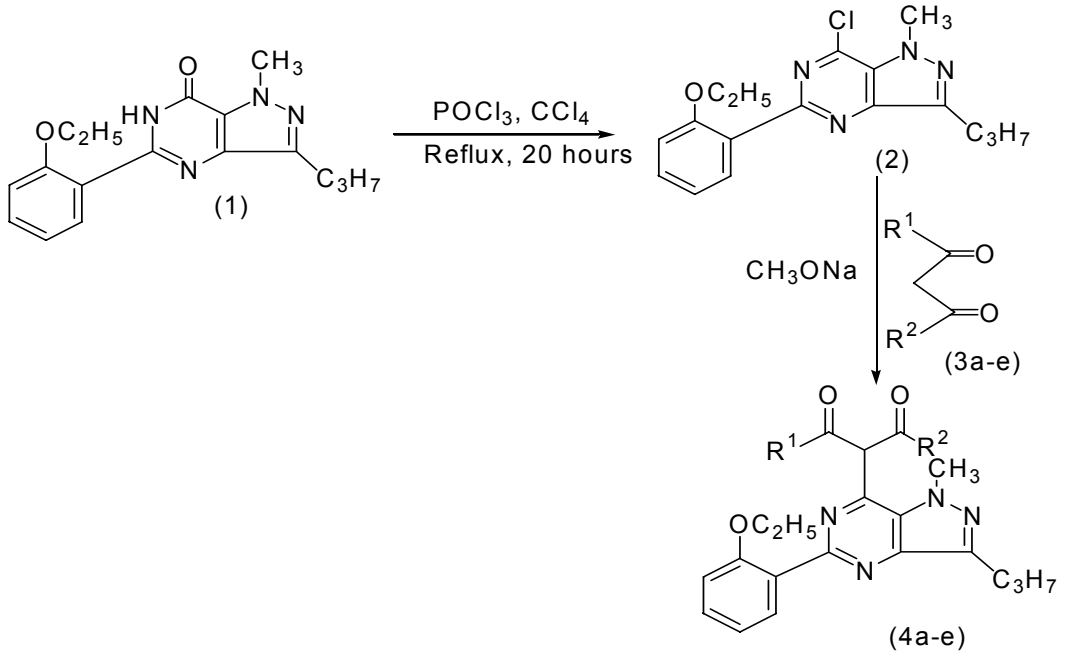
Benzodiazepines have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, anti-anxiety, analgesic, sedative, anti-depressive, hypnotic agents[1] as well as anti-inflammatory agents[2]. Other than their biological importance, benzodiazepine derivatives are also commercially used as dyes for acrylic fibres[3]. Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be used in preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-,or furano-benzodiazepines[4]. Research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. Generally, these compounds are synthesized by the condensation of *o*-phenylenediamines with α, β-unsaturated carbonyl compounds[5], β-haloketones, or ketones[6]. A variety of reagents, such as BF_3-etherate, $NaBH_4$, polyphosphoric acid, or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Al_2O_3/P_2O_5, or AcOH under microwave and in ionic liquids[7] have been utilized for the condensation reaction. Most recently, this condensation has been reported also to proceed in the presence of CAN, (bromodimethyl)sulfonium bromide, organic acids, and $AgNO_3$[8]. However, all of these methods have problems such as drastic reaction conditions and several side-reactions. Surface-mediated solid phase reactions are of growing interest[9] because of their ease of execution and work-up,

mild reaction conditions, rate of reaction, selectivity, high yields, lack of solvents and low cost in comparison with their homogeneous counterparts. As a part of our efforts to explore the utility of surface-mediated reactions, [10-12] we report here a new method for the preparation of 1, 5-benzodiazepine derivatives with β-diketones and β-ketoesters. It was found that a mixture of *p*-toluenesulfonic acid/celite under solvent-free conditions was capable of producing high yields of 1, 5-benzodiazepines **5a-e** by condensation of *o*-phenylenediamine with dicarbonyl compounds **4a-e** under mild conditions.

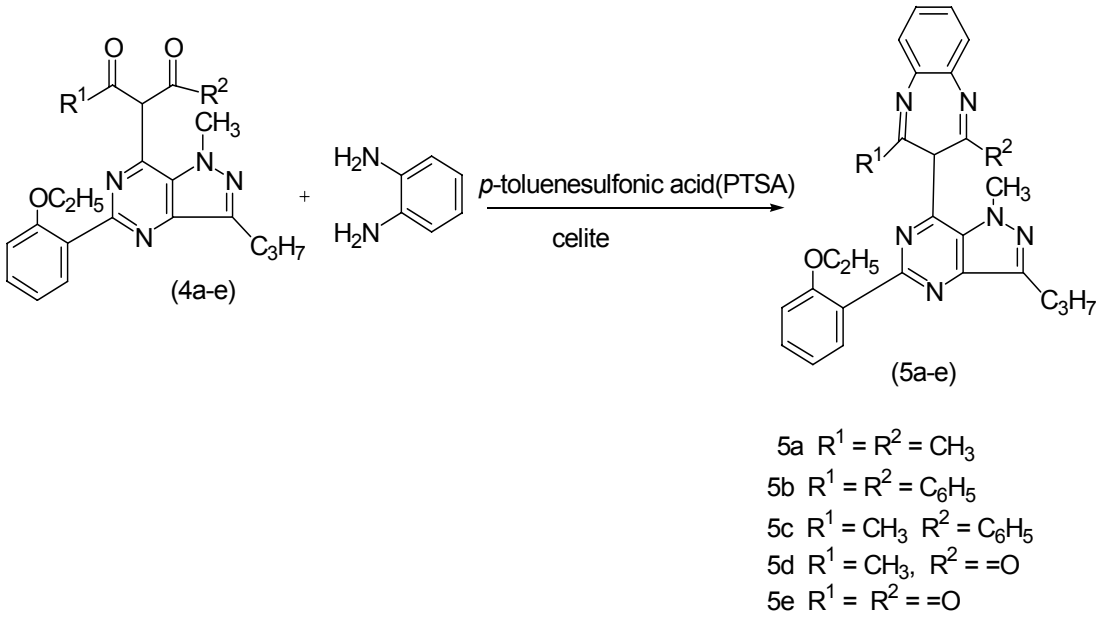
We are interested in the synthesis pyrazolo [4, 3-*d*] pyrimidin-7-one containing 1, 5-benzodiazepines due to the importance of this class of compound in medicinal chemistry. Substituted pyrazolopyrimidinones are potent and selective inhibitors of type 5 cyclic gaunosine-3′, 5′-monophosphate phosphodiesterase (cGMP) PDE-5[13, 14] and, as such, have utility in the treatment of male erectile dysfunction (MED)[15] and female sexual dysfunction (FSD). They also have found use in the treatment of male sexual impotence, with reduced side effects[16]. Substituted pyrazolopyrimidinones are useful also as CNS stimulant, bronchodilator, cardiotonic[17], herbicide[18] and antiviral[19]agents.

Results and Discussion

As an avenue to such species, 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-*7H*-pyrazolo [4,3-*d*]pyrimidin-7-one **(1)** was chlorinated with $POCl_3$ to afford the chlorinated compound **2**. The latter was condensed with different β-diketones/ β-ketoesters **3a-e** in the presence of sodium methoxide to yield β-diketones/ β-ketoesters **4a-e** (Scheme 1). The condensation of the newly synthesized β-diketones/ β-ketoesters **4a-e** with *o*-phenylenediamine (*o*-PDA) in the presence of *p*-toluenesulfonic acid/celite under solvent free conditions, afforeded *3H*-1,5-benzodiazepines **5a-e** (Scheme 2).



Scheme 1



Scheme 2

Antimicrobial and anthelmintic activities of compounds 5a-e

The newly synthesized benzodiazepine compounds **5a-e** have been screened for antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger* and *Candida albicans* by the cup-plate method[20, 21]. Crofloxin and Ciclopiroxolamine were used as standards for comparison of antibacterial and antifungal activities, respectively. The results indicate that these compounds were active against all the four organisms. The anthelmintic activity was carried out on earthworms *Pherituma posthuma* by a technique as described by Bagavant *et al.*[22] with slight modification. Piperazine citrate was used as the standard drug. The results of antimicrobial and anthelmintic activity are reported in Table 1.

Table 1. Antimicrobial and anthelmintic activities of compounds **5a-e**

Compd.	Antibacterial activity zone of inhibition (in mm)		Antifungal activity zone of inhibition (in mm)		Anthelmintic activity (in min.)	
	A. aureus	K.pneumoniae	*A. niger*	*C. albicans*	Paralysis	Death
5a	11	10	15	18	95	90
5b	10	10	16	17	90	120
5c	21	24	25	28	105	120
5d	12	15	15	11	90	110
5e	14	09	10	19	85	105

Experimental Section

General Procedures. All the melting points are uncorrected. The IR spectra were recorded on a Nicolet-Megna-FT-IR-550 spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were run on model DRX 300 at 300.13 MHz in $CDCl_3$ using TMS as internal standard. The purity of the newly synthesized compounds was checked by TLC.

Synthesis of 5-[2-ethoxyphenyl]-1-methyl-7-chloro-*1H*-pyrazolo [4,3-*d*) pyrimidine (2)

To 5-[2-ethoxyphenyl]-1-methyl-3-propyl-1,6-dihydro-*7H*-pyrimidin-7-one (3.12g, 0.01mol) in CCl_4 (50 mL) in a two neck round bottom flask, was added drop wise $POCl_3$ (10 mL, excess) at 0°C. After complete addition, the reaction mixture was heated on a water bath for 20 hours. The reaction was monitored through TLC. After completion of the reaction, unreacted $POCl_3$ was removed under reduced pressure. The reaction mass was poured into ice and was extracted with chloroform (2x 50mL). The chloroform layer was separated and evaporated, to yield a colourless solid. The product was purified by column chromatography on silica gel using pet ether: ethyl acetate (50:50) as eluent and crystallized from methanol. Purity of compound was checked

through TLC using ethyl acetate: acetone (8:2) system as the mobile phase; mp 165°C, yield 2.5g, 70%.

Synthesis of 3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-*1H*-pyrazolo[4,3-*d*] pyrimidin-7-yl-]-1,3-dimethyl1,3-diphenyl/1-phenyl,3-methyl/1-methyl,3-ethoxy/ 1,3-diethoxy propane-1,3-dione (4a-e)

Sodium methoxide (0.54g, 0.01mol) and β-diketones/ β-ketoesters **3a-e** (0.01mol) were placed in a dry round bottom flask and stirred for one hour on a magnetic stirrer at a temperature of 50°C and a creamy mass was obtained. The chloride derivative **2** (3.19g, 0.01mol) was then added, followed by dry toluene as solvent to effect proper stirring of the reaction mass. The reaction mixture was heated for six hours at 80°C with stirring. The progress of the reaction was monitored through TLC. After reaction was complete, the reaction mixture was cooled and toluene was removed. The reaction mixture was extracted using chloroform (2x50mL) and washed with water as to remove the salt. The chloroform layer was dried using anhydrous sodium sulphate. Chloroform was evaporated to get solid compound. The product was purified by column chromatography on silica gel using pet. ether: ethyl acetate (50:50) as eluent and crystallized with ethyl acetate and acetone mixture. Purity of the compound was checked through TLC using 7:2:1 (benzene: ethanol: ammonia) upper layer as the mobile phase.

Synthesis of *3H*-1, 5-benzodiazepines 5a-e: General procedure

1,3-Diketones/1,3-ketoesters **4a-e** (0.01mol) along with p-toluenesulfonic acid/celite (prepared by adding *p*-toluenesulfonic acid (1g) and celite(1g) in acetone, stirred for 0.5h on magnetic stirrer and then acetone removed by vacuum) mixed in a mortar for 10 minutes, To the aforesaid mixture was added *o*-phenylenediamine (1.08g, 0.01mol), heated on a water bath at 60 ^{0}C for 30 minutes. The reaction mixture was extracted with dichloromethane (2x100mL), dried over (Na_2SO_4), and the solvent was evaporated to give the crude products. The crude products were washed with ether to remove unreacted dicarbonyl compounds. The crude product was recrystallized from pet. ether: ethyl acetate (1:1). Purity of the compound was checked through TLC using 7:2:1 (benzene: ethanol: ammonia) upper layer as the mobile phase. Spectral data for selected products **5a-e**.

3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-*1H*-pyrazolo[4, 3-*d*] pyrimidin-7-yl]-2, 4-dimethyl-*3H*-1, 5-benzodiazepine (5a). M.p. 183°C; yield 85.7%; Anal. Calcd. $C_{27}H_{30}N_6O$: C, 71.37; H, 6.61; N, 18.50. Found: C, 71.26; H, 6.60; N, 18.49. IR (KBr): 3060, 2945, 1590, 1480, 1250, 1020 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.03 (t, *J* = 8.46 Hz, 3H), 1.60 (m, *J* = 7.25 Hz, 2H), 1.64 (t, *J* = 6.98 Hz,3H), 2.30 (s, 6H), 2.55 (t, *J* = 8.34 Hz, 2H), 3.80 (s, 3H), 4.40 (q, *J* = 8.12 Hz, 2H), 6.05 (s, 1H), 7.4-8.0 (m, *J* = 7.36 Hz, 8H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 162.56, 149.94, 132-128, 75.32, 67.85, 53.20, 40.37, 29.26, 15.85, 14.70; LCMS: 455.5671 ($M+H^+$).

3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-*1H*-pyrazolo[4,3-d]pyrimidin-7-yl]-2,4-diphenyl-*3H*-1,5-benzodiazepine (5b). M.p. 219°C; yield 86.3%; Anal. Calcd. $C_{37}H_{34}N_6O$: C, 77.35; H, 6.09; N, 14.63. Found: C, 76.99; H, 6.10; N, 14.59. IR (KBr): 3040, 2900, 1585, 1492, 1240,

1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, *J* = 8.45 Hz , 3H), 1.65 (m, *J* = 7.86 Hz, 2H), 2.55 (t, *J* = 7.46 Hz, 2H), 1.65 (t, *J* = 6.95 Hz,3H), 4.42 (q, *J* = 8.75 Hz, 2H), 3.80 (s, 3H), 6.0 (s, 1H), 7.6-8.1 (m, *J* = 7.66 Hz,18H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.50, 148.95, 132-127, 76.37, 66.36, 54.20, 41.25, 29.50, 15.84, 14.64; LCMS: 579.7059($M+H^+$).

3-[5-(2-ethoxyphenyl)-1-methyl-3-propyl-*1H*-pyrazolo[4,3-d]pyrimidin-7-yl-2-methyl-4-phenyl-*3H*-1,5-benzodiazepine (5c). M.p. 211°C; yield 83.7% Anal. Calcd. $C_{32}H_{32}N_6O$: C, 74.41;H, 6.02; N, 16.27. Found: C, 74.31; H, 6.15; N, 16.10. IR(KBr):3050, 2930, 1585, 1260, 1040 cm^{-1}; ^{1}HNMR (300 MHz, CDCl3): δ 1.03 (t, *J* = 8.32 Hz, 3H), 1.65 (m, *J* = 7.85 Hz, 2H), 1.69 (t, *J* = 9.05 Hz, 3H), 2.55 (t, *J* = 7.65 Hz, 2H), 3.80 (s, 3H), 4.42 (q, *J* = 8.75 Hz, 2H), 6.0 (s, 1H), 2.35 (s, 3H), 7.6-8.1 (m, *J* = 7.95 Hz, 13H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.23, 149.90,132-128, 75.34, 68.36, 54.03, 40.32, 29.54, 15.84, 14.66 ; LCMS: 517.6365($M+H^+$).

3-[5-(2-ethoxyphenyl)}-1-methyl-3-propyl-*1H*-pyrazolo[4,3-d]pyrimidin-7-yl]-4-methyl-1,3-dihydro-*3H*-1,5-benzodiazepine-2-one (5d). M.p. 189°C; yield 82.3% ; Anal. Calcd. $C_{26}H_{28}N_6O_2$: C, 68.12; H, 6.11; N, 18.34. Found: C, 68.10; H, 6.03; N, 18.29. IR (KBr):3040, 2900, 1580, 1490, 1260, 1045 cm^{-1},^1H NMR (300MHz, $CDCl_3$): δ 1.03 (t, *J* = 8.37 Hz, 3H), 1.60(t, *J* = 8.23 Hz, 3H), 1.65 (m, *J* = 8.15 Hz, 2H), 2.55 (t, *J* = 7.95 Hz, 2H), 2.50 (s, 3H), 3.80 (s, 3H), 4.44 (q, *J* = 7.65 Hz, 2H), 5.8 (s, 1H), 7.3-8.0 (m, *J* = 7.65 Hz, 4H), 8.75 (s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 165.34, 158.454, 149.12, 134-126, 75.85, 68.34, 54.37, 40.35, 28.60, 15.74, 14.47; LCMS: 457.5399($M+H^+$).

3-[5-(2-ethoxyphenyl)}-1-methyl-3-propyl-*1H*-pyrazolo[4,3-d]pyrimidin-7-yl]-1,5-dihydro-*3H*-1,5-benzodiazepine-2,4-dione (5e). M.p. 203°C; yield 85.4%; Anal. Calcd. $C_{25}H_{26}N_6O_2$: C, 65.50; H, 5.69; N, 18.34. Found: C, 65.49; H, 5.61; N, 8.17. IR (KBr): 3050, 2920, 1560, 1490, 1250, 1030 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 1.02 (t, *J* = 8.35 Hz, 3H), 1.64(t, *J* = 7.65 Hz, 1.70 (m, *J* = 7.95 Hz,2H), 2.55 (t, *J* = 6.98 Hz, 2H), 3.80 (s, 3H),4.40 (q, *J* = 7.35 Hz, 2H), 6.10 (s, 1H), 7.5-8.0 (m, *J* = 7.85 Hz, 8H), 8.65 s, 2H); ^{13}C NMR (300MHz, $CDCl_3$): δ 165.5, 157.56, 145.8,133-128, 75.37, 68.39, 54.34, 40.34, 29.57, 15.81, 14.66; LCMS: 443.5129($M+H^+$).

Acknowledgements

The authors are thankful to the Head, Department of Chemistry, University of Rajasthan, Jaipur for providing laboratory facilities. The authors are thankful also to Central Drug Research Institute, Lucknow for providing spectral data. One of them (Rajesh Kumar) is thankful to the UGC for the award of Senior Research Fellowship.

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