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Synthesis and antimicrobial, antifungal and anthelmintic activities of 3*H*-1,5-benzodiazepine derivatives

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Abstract: The diazonium salt of 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide in the presence of sodium hydroxide was condensed with different *β*-diketones/*β*-ketoesters, **3a**–**e**, to obtain new *β*-diketones/*β*-ketoesters, **4a**–**e**. The *β*-diketones/*β*-ketoesters **4a**–**e** were condensed with *o*-phenylenediamine (*o*-PDA) in presence of *p*-toluenesulfonic acid/SiO_2 to give biologically active 3*H*-1,5--benzodiazepines, **5a**–**e**. All the newly synthesized compounds were characterized by elemental analysis and spectral studies. The compounds **5a**–**e** were screened for their antimicrobial, antifungal and anthelmintic activities.

Keywords: 1,5-benzodiazepines; *β*-diketones/*β*-ketoesters; substituted pyrazole; *p*-toluenesulfonic acid.

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, antidepressive and hypnotic agents,[1] as well as anti-inflammatory agents.[2] Other than their biological importance, benzodiazepines derivatives are also commercially used as dyes for acrylic fibers.[3] Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be used in the 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 also been reported to proceed in the presence of CAN, bromodimethylsulfonium bromide, organic acids and $AgNO_3$.[8]

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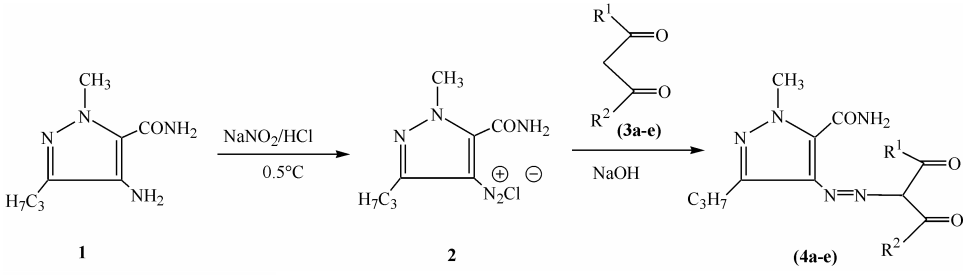
However, all these methods have disadvantages, such as extreme reaction conditions and also several side-reactions. Surface-mediated solid phase reactions are of growing interest[9] because of their ease of execution and work-up, mild reaction conditions, rate of reaction, selectivity, high yields, lack of solvents and low cost in comparison to their homogeneous counter parts. Previously, efforts were made to explore the utility of surface-mediated reaction.[10–12]

Herein, a new method for the preparation of 1,5-benzodiazepine derivatives with *β*-diketones and *β*-ketoesters is reported. It was found that a mixture of *p*-toluenesulfonic acid/SiO_2 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.

Our interest laid in the synthesis the pyrazole moiety containing 1,5-benzodiazepines, as pyrazoles are known to have significant pharmacological properties. They exhibit antimicrobial,[13] anti-inflammatory,[14] antiviral[15] and pesticidal activity.[16] Substituted pyrazoles are useful for their cardiovascular,[17] antitumor[18] and hypolipemic activity. It is interesting to note that pyrazoles are reported as well known pharmaceuticals.[19–21]

RESULTS AND DISCUSSION

Diazonium salt of 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide was formed in the presence $NaNO_2$/HCl at 0–5.0 °C. Diazonium salt was condensed with different *β*-diketones/*β*-ketoesters in the presence of sodium hydroxide (Scheme 1). The newly synthesized *β*-diketones/*β*-ketoesters **4a**–**e** were condensed with *o*-phenylenediamine (*o*-PDA) in the presence of *p*-toluenesulfonic acid, to obtain 3*H*-1,5-benzodiazepines **5a**–**e** (Scheme 2).



1 **2** **(4a-e)**

3a/4a $R^1 = R^2 = CH_3$

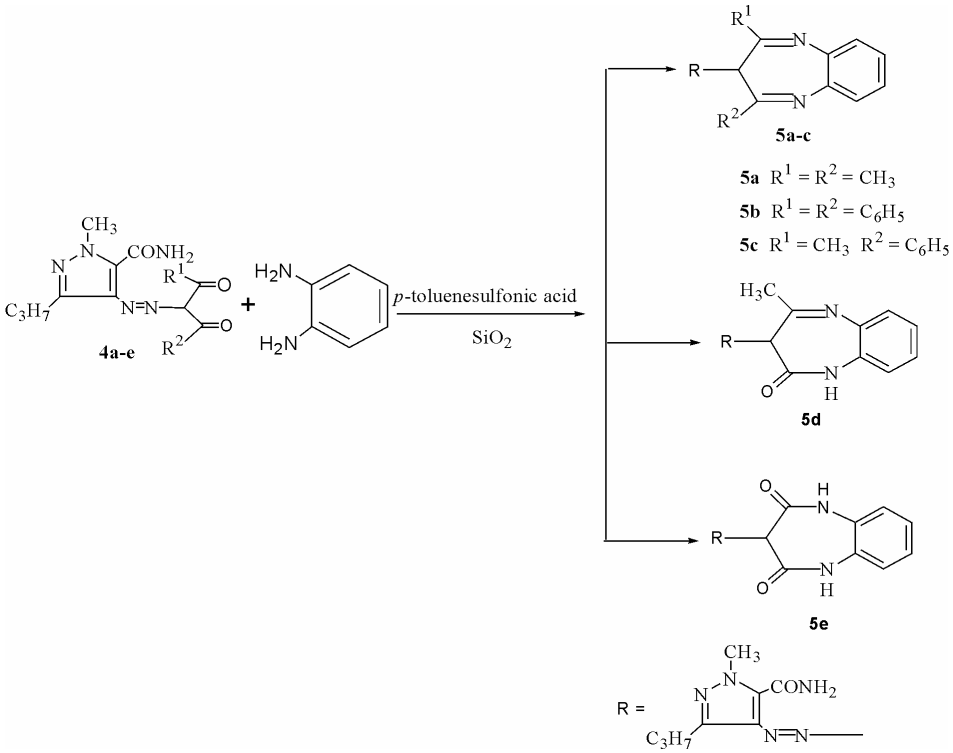
3b/4b $R^1 = R^2 = C_6H_5$

3c/4c $R^1 = CH_3$ $R^2 = C_6H_5$

3d/4d $R^1 = CH_3$, $R^2 = OC_2H_5$

3e/4e $R^1 = R^2 = OC_2H_5$

Scheme 1.



Scheme 2.

Spectral Analysis

*4-[(2,4-Dimethyl-3*H*-1,5-benzodiazepin-3-yl)azo]-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**5a**)*: Yield: 88 %; m.p. 215 °C; Anal. Calcd. for $C_{19}H_{23}N_7O$: C, 62.46; H, 6.30; N, 26.84. Found: C, 62.32; H, 6.20; N, 26.74. IR (KBr, cm^{-1}): 3400, 3450, 3050, 2930, 1680, 1585, 1435. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 1.03 (3H, *t*, CH_3, J = 7.86 Hz), 1.66 (2H, *m*, CH_2, J = 8.25 Hz), 2.15 (6H, *s*, CH_3), 2.55 (2H, *t*, CH_2, J = 7.89 Hz), 3.35 (1H, *s*, CH=), 3.80 (3H, *s*, N−CH_3), 7.55–7.80 (4H, *m*, Ar–H, J = 7.55 Hz), 8.1 (2H, *s*, $CONH_2$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 15.80 (CH_3−C=N), 18.71 (CH_3), 28.95 (CH_2), 40.38 (CH_2), 40.58 (N−CH_3), 134.65 (C=N), 140–144.7 (Ar–C), 169.79 ($CONH_2$). LCMS: 366 (M + H^+).

*4-[(2,4-Diphenyl-3*H*-1,5-benzodiazepin-3-yl)azo]-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**5b**)*: Yield: 76.6 %; m.p. 245 °C; Anal. Calcd. for $C_{29}H_{27}N_7O$: C, 71.16; H, 5.72; N, 20.04. Found: C, 71.00; H, 5.68; N, 20.04. IR (KBr, cm^{-1}): 3405, 3520, 3045, 2925, 1680, 1620, 1448. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 1.03 (3H, *t*, CH_3, J = 7.86 Hz), 1.66 (2H, *m*, CH_2, J = 8.25 Hz), 2.53 (2H, *t*, CH_2, J = 7.89 Hz), 3.42 (1H, *s*, CH=), 3.80 (3H, *s*, N−CH_3) , 7.62–7.95 (14H, *m*, Ar–H, J = 7.55 Hz), 8.20 (2H, *s*, $CONH_2$). ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 15.68

(CH_3), 27.57 (CH_2), 39.37 (N−CH_3), 41.37 (CH_2), 135.00–143.67 (Ar–C), 166.23 (C=N), 166.87 ($CONH_2$). LCMS: 490 ($M + H^+$).

*4-[(2-Methyl-4-phenyl-3*H*-1,5-benzodiazepin-3-yl)azo]-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**5c**)*: Yield: 82 %, m.p.256 °C; Anal. Calcd. for $C_{24}H_{25}N_7O$: C, 67.45; H, 5.89; N, 22.70. Found: C, 67.44; H, 5.90; N, 22.73. IR (KBr, cm^{-1}): 3415, 3485, 3030, 2910, 1685, 1435. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 1.02 (3H, *t*, CH_3, J = 7.86 Hz), 1.65 (2H, *m*, CH_2, J = 8.25 Hz), 2.20 (3H, *s*, CH_3), 2.54 (2H, *t*, CH_2, J = 7.89 Hz), 3.40 (1H, *s*, CH=), 3.86 (3H, *s*, N−CH_3), 7.50––7.80 (4H, *m*, Ar–H, J = 7.55 Hz), 8.20 (2H, *s*, $CONH_2$), 10.25 (1H, *s*, N–H). ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 15.77 (CH_3–C = N), 18.52 (CH_3), 28.61 (CH_2), 38.75 (N–CH_3), 40.04 (CH_2), 140.00–147.45 (Ar–C), 159.23 (–C–), 164.70 (C=N), 167.25 ($CONH_2$). LCMS: 428 ($M + H^+$).

*4-[(2,3-Dihydro-4-methyl-2-oxo-1*H*-1,5-benzodiazepin-3-yl)azo]-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**5d**)*: Yield: 77 %; m.p. 230 °C; Anal. Calcd. for $C_{18}H_{21}N_7O_2$: C, 58.85; H, 5.99; N, 26.70. Found: C, 58.83; H, 5.97; N, 26.67. IR (KBr, cm^{-1}): 3420, 3480, 3040, 2915, 1685, 1430. ^{1}H-NMR (300 MHz; $CDCl_3$; δ, ppm): 1.02 (3H, *t*, CH_3, J = 7.86 Hz) , 1.65 (2H, *m*, CH_2, J = 8.25 Hz), 2.20 (3H, *s*, CH_3), 2.54 (2H, *t*, CH_2, J = 7.89 Hz), 3.4 (1H, *s*, CH=), 3.85 (3H, *s*, N–CH_3), 7.50–7.80 (4H, *m*, Ar–H, J = 7.55 Hz), 8.2 (2H, *s*, $CONH_2$), 10.25 (1H, *s*, N–H). ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 15.74 (CH_3–C=N), 18.54 (CH_3), 28.65 (CH_2), 38.58 (N–CH_3), 40.07 (CH_2), 140.00–147.79 (Ar–C), 159.56 (−C−), 164.77 (C=N), 167.20 ($CONH_2$). LCMS: 368 ($M + H^+$).

*4-[(2,3,4,5-tetrahydro-2,4-dioxo-1*H*-1,5-benzodiazepin-3-yl)azo]-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**5e**)*: Yield: 51.5 %; m.p. 205 °C; Anal. Calcd. for $C_{17}H_{19}N_7O_3$: C, 55.28; H, 5.42; N, 26.55. Found: C, 55.24; H, 5.32; N, 26.45. IR (KBr, cm^{-1}) 3430, 3500, 3020, 2930, 1685, 1595, 1437. ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 1.04 (3H, *t*, CH_3, J = 7.86 Hz), 1.66 (2H, *m*, CH_2, J = 8.25Hz), 2.55 (2H, *t*, CH_2, J = 7.89 Hz), 3.42 (1H, *s*, CH=), 3.80 (3H, *s*, N–CH_3), 7.5–7.8 (4H, *m*, Ar–H, J = = 7.55 Hz), 8.15 (2H, *s*, $CONH_2$), 10.20 (2H, *s*, N–H). ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 16.78 (CH_3), 29.92 (CH_2), 41.32 (CH_2), 37.59 (N–CH_3), 138–145 (Ar–C), 163.74 (C=N), 166.28 ($CONH_2$). LCMS: 370 ($M + H^+$).

*Antimicrobial and anthelmintic activities of compounds **5a–e***

The newly synthesized diazepine compounds were screened for antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger* and *Candida albicans* by the cup-plate method.[22,23] Crofloxin and ciclopiroxolamine were used as standards for comparison of the antibacterial and antifungal activities, respectively. The results indicate that these compounds were active against all the four organisms. The anthelmintic activity was tested on earth worms *Pherituma posthuma,* by a technique described by Bagavant *et al.*[24] with modification. Piperazine citrate was used as the standard drug. The results of the antimicrobial and anthelmintic activity are re-

ported in Table I. Compound **5c** exhibited greater antimicrobial and antifungal activities than the standard drugs, whereas compounds **5d** and **5e** showed significant anthelmintic activity.

EXPERIMENTAL

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Nicolet-Megna-FT-IR-550 spectrometer in KBr pellets. The ^{1}H- and ^{13}C-NMR spectra were run on a model DRX 300 instrument at 300.13 and 75 MHz, respectively, in $CDCl_3$ using TMS as an internal standard. The mass spectra were obtained on an LCMS instrument. The purity of the newly synthesized compounds was checked by TLC. Satisfactory C, H, N analyses were obtained for all the compounds.

TABLE I. Antimicrobial and anthelmintic activities of compounds **5a**–**e**

Compd.	Antibacterial activity zone of inhibition, mm		Antifungal activity zone of inhibition, mm		Anthelmintic activity, min	
	A. aurens	*K. pneumoniae*	*A. niger*	*C. albicans*	Paralysis	Death
5a	11	10	15	18	95	90
5b	10	10	16	17	90	120
5c	22	24	25	28	105	112
5d	12	15	15	11	102	124
5e	14	9	10	19	105	129
Std.	24	26	22	24	100	125

Synthesis of β-*diketones and* β-*ketoesters (**4a**–**e**)*

The diazonium salt was condensed with *β*-diketones and *β*-ketoesters **3a**–**e** (0.010 M) in the presence of NaOH by continuously stirring the reaction mixture for 6–8 h at 60 °C. The progress of the reaction was monitored periodically by TLC. After completion of the reaction, the reaction mass was poured into ice, acidified and extracted into chloroform (2×50 ml). The solvent was evaporated and the residue dried under vacuum. After crystallization using petroleum ether and ethyl acetate, the purity of the compound was checked through TLC using 7:2:1 benzene:ethanol:ammonia as the mobile phase.

Synthesis of 3H-*1,5-benzodiazepines (**5a**–**e**)*

The 1,3-diketones/1,3-ketoesters **4a**–**e** (0.010 M) and *p*-toluenesulfonic acid/SiO_2 (*p*-toluenesulfonic acid (1.0 g) and silica gel (1.0 g) in acetone were stirred for 0.5 h on a magnetic stirrer and then the acetone was removed under vacuum) were mixed in a mortar for 10 min. To this mixture in a conical flask, *o*-phenylenediamine (0.010 M) was added. The reaction mixture was heated on a water bath at 60 °C for 30 min. The reaction mixture was washed with dichloromethane (2×50 ml), dried over Na_2SO_4 and the solvent evaporated to give the crude products. The crude products were washed with ether to remove the unreacted dicarbonyl compounds and then crystallized from petroleum ether:ethyl acetate (1:1). The purity of the compounds was checked by TLC using 7:2:1 benzene:ethanol:ammonia as the mobile phase.

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ИЗВОД

СИНТЕЗА И АНТИМИКРОБНА, АНТИФУНГАЛНА И АНТИХЕЛМИТИНСКА АКТИВНОСТ 3*H*-1,5-БЕНЗОДИАЗЕПИНСКИХ ДЕРИВАТА

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Диазонијум со 4-амино-1-метил-3-пропил-1*H*-пиразол-5-карбоксамида кондензована је са различитим *β*-дикетонима/*β*-кетоестрима **3a**–**e** у присуству натријум-хидроксида дајући нове *β*-дикетоне/*β*-кетоестре **4a**–**e**. Ови *β*-дикетони/*β*-кетоестри **4a**–**e** кондензовани су са *o*-фенилендиамином (*o*-PDA) у присуству *p*-толуенсулфонске киселине/SiO_2 при чему се граде биолошки активни 3*H*-1,5-бензодиазепини **5a**–**e**. Новодобијена једињења окарактерисана су на основу елементалних анализа и спектралних података. Једињења **5a**–**e** су тестирана на антимикробну, антифунгалну и антихелмитинску активност.

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