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EXPEDIENT PROTOCOL FOR THE INSTALLATION OF THIADIAZOLE ON 2-POSITION OF 1,4-BENZODIAZEPIN-5-CARBOXAMIDE THROUGH A PHENOXYL SPACER

NAVJEET KAUR

Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India

ABSTRACT

An efficient novel single step strategy for the heteroannulation of 2-chloro-1,4-benzodiazepine ring, substituted in its 5-position with a carboxamido group (5), has been developed to allow the easy installation of thiadiazole (8) ring through thiosemicarbazone (7) intermediate. In this communication, exceedingly facile single step expedient protocols based on the versatility and reactivity of corresponding intermediate thiosemicarbazone (7), derived from 5-carboxamido-1,4-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (5) have been developed to provide an easy installation of the thiadiazole (8) privileged template at 2-position of 5-carboxamido-1,4-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide, through a phenoxyl spacer.

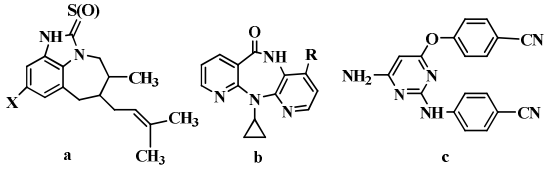
KEYWORDS: 1,4-benzodiazepine, aminothiadiazole, phenoxyl spacer, and thiosemicarbazone.

**Corresponding author*

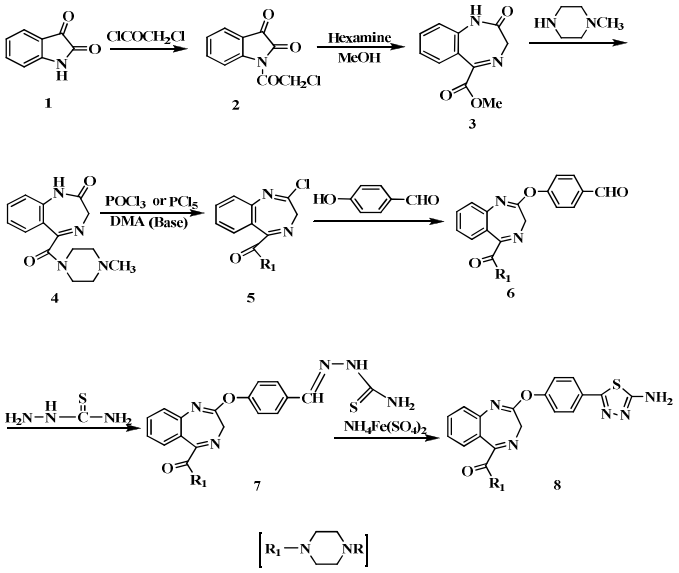
NAVJEET KAUR
Department of Chemistry, Banasthali University,
Banasthali-304022 (Rajasthan), India

INTRODUCTION

Eversince, 1,4-benzodiazepines have been recognized as 'privileged medicinal scaffolds' by virtue of their ability to provide ligands to a number of functionally and structurally discrete biological receptors, the interest on the various facets of the chemistry of these materials has expanded exponentially, thereafter.[1-3] On account of their impressive biological properties such as psychopharmacological,[4] anticancer,[5] anti-HIV[6] etc. (to name a few) this nucleus has remained in the mainstay as evergreen medicinal scaffold from which potential drug candidates can be expected.[7-9] Recently, the privileged[10] molecular framework of benzodiazepines has been actively studied in view of their ability to provide ligands to a number functionally and structurally discrete biological receptors.[11-14] The advent of anti-HIV (Human Immunodeficiency Virus) activity in 1,4-benzodiazepine derivative [TIBO[15] (a) (4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one)], the dipyrido diazepine derivative (Nevirapine)[16] (b), pyrimidine derivative (Etravirine)[17] (c) and in thiadiazole derivatives,[18] prompted us to explore the possibility of developing some such analogues of 1,4-benzodiazepines which contained in its nucleus the vital fragments of etravirine together with thiadiazole scaffold on the premise that their presence in tandem in the same molecular framework could contribute significantly to provide a beneficial effect on the overall biological efficacy in the resulting molecules.[19-22]



As a part of our endeavor to create novel heterocyclic scaffolds of biological interest through the simple and straightforward expedient routes, we explored the feasibility of the application of the corresponding thiosemicarbazone (7) based cyclization reactions in the incorporation of the thiadiazole based privileged template on to the 1,4-benzodiazepine nucleus (3) at its 2-position, through a phenoxyl spacer to generate by utilizing the synthetic plan depicted in scheme 1.



Scheme-1

EXPERIMENTAL

All melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 intrachord. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Brucker Avance 400 MHz spectrophotometer with TMS as internal standard (chemical shifts are expressed in δ ppm). The mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene-methanol mixture (9:1). N-chloroacetylisatin (2) (m.p. 210-11°C) and methyl-1,3-dihydro-2*H*-[1,4]-benzodiazepin-2-one-5-carboxylate (3) (m.p. 173-75°C) were prepared according to the reported procedure for their preparation in the literature.[26-27]

Preparation of N-chloroacetyl isatin (2) from isatin (1)

Isatin (1) (10 g, 0.068 mol) was vigorously refluxed with chloroacetyl chloride (70 ml, 0.090 mol) for 10 h and the mixture was cooled for 2 h in an ice-bath. The precipitate was filtered, washed with 20 ml portion of ether, then air-dried and recrystallised with ethyl acetate to give 2 (10.00 g, yield 66%, m.p. 210-11˚C).

Preparation of methyl-1,3- dihydro-2H-[1,4]-benzodiazepin-2-one-5-carboxylate (3)

N-chloroacetyl isatin (2)**,** (2.23 g, 0.01 mol) and hexamethylenetetramine (hexamine) (1.40 g, 0.01mol) was taken in dry methanol (20 ml) and the reaction mixture was refluxed for 14 h. Progress of reaction was checked by TLC. After completion of reaction, the solvent was removed under reduced pressure and the solid was chromatographed over alumina (neutral) in C_6H_6: MeOH (9.5:0.5) as an eluant. The product obtained was recrystallised from benzene to give 3 (1.25 g, yield 55%, mp.173-75°C).

Preparation of 1,3-dihydro-[2H]-[1,4]-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (4)

Methyl-1,3-dihydro-[*2H*]-[1,4]-benzodiazepin-2-one-5-carboxylate (3) (10.9 g, 0.05 mol) and N-methyl piperazine (5.0 g, 0.05 mol) were taken in ethanol (100 mL). The reaction mixture was refluxed for 12 h on the water bath. The completion of the reaction was checked by TLC. The mixture was cooled and poured on crushed ice, the resulting solid was filtered washed with dilute ethanol dried and recrystallized from ethanol-chloroform mixture (1:9), to give 4 **(**12.37 g, 75%, m.p. 257-258°C). IR (KBr) cm^{-1}: 3330 (NH str.), 2950 (C-H str. ArH), 1675 (C=O str.), 1660 (C=C str. ArH), 1590 (C=N str.), 1580 (NH bend.), 1430 (C-H bending, CH_3), 1140 (C-N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.0 (s, 1H), 7.27-7.86 (m, *J*=7.2 Hz, 4H), 3.60 (s, 2H), 3.20 (t, *J*=7.4 Hz, 4H), 2.27 (t, *J*=7.2 Hz, 4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2-45.4, 47.3-47.5, 49.5-49.7, 82.3-82.5, 113.0-113.2, 117.7-117.9, 125.4-125.6, 116.7-116.9, 128.2-128.4, 126.5-126.7, 149.5-149.7, 158.2-158.4, 164.5-164.7; MS: [M$^+$]: 286, Anal. calcd. for $C_{15}H_{18}N_4O_2$: C, 62.79; H, 6.31; N, 19.54. Found: C, 62.92; H, 6.33; N, 19.48.

Preparation of 2-chloro-[1,4]-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (5)

A solution of 4 (10 g, 0.06 mol), $POCl_3$ (5 mL, 0.06 mol), N,N-dimethylaniline (14 mL, 0.1 mol), and benzene (100 mL) were refluxed for 7 h and allowed to cool overnight. The cold reaction mixture was poured into ice water (100 mL) and stirred for 30 min until the reaction mixture reached to room temperature. It was then extracted with ether and the solvent layer was washed with water and brine, dried (over anh. $MgSO_4$), filtered, and evaporated. Trituration with ether gave 5 (8.0 g, 75%, m.p. 120-122°C). IR (KBr) cm^{-1}: 2955 (C-H str. ArH), 1680 (C=O str.), 1590 (C=C str. ArH), 1570 (C=N str.), 1435 (C-H bending, CH_3), 1140 (C-N str.), 710 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33-7.83 (m, *J*=7.2 Hz, 4H), 3.60 (s, 2H), 3.20 (t, *J*=7.4 Hz, 4H), 2.27 (t, *J*=7.5 Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2-45.4, 46.0-46.2, 47.8-48.0, 95.3-95.5, 116.6-116.8, 127.8-128.0, 126.5-126.7, 157.2-157.4, 124.6-124.9, 165.2-165.4, 152.5-152.7, 125.3-125.5, 131.1-131.3, 132.7-132.9, 136.6-136.8, 148.6-148.8, 138.5-138.7, 149.4-149.6, 158.3-158.5, 164.6-164.8; MS: [M$^+$]: 304, Anal. calcd. for $C_{15}H_{17}ClN_4O$: C, 59.24; H, 5.65; N, 18.34. Found: C, 59.11; H, 5.67; N, 18.28.

Preparation of 2-[4'-formylphenoxyl)-[1,4]-benzodiazepin-5-[-4''-methylpiperazinyl]-carboxamide (6)

To a solution of 5 (1 g, 0.003 mol) and parahydroxybenzaldehyde (0.38 g, 0.0035 mol) in DMF (5 mL) was slowly added potassium-tert-butoxide (0.67 g, 0.006) at ice-water bath, then stirred at room temperature for 5 h until reaction was completed. Then mixture was poured into ice water and pH was adjusted to 6 with 5% aqueous HCl and the mixture extracted with EtOAc three times. After removal of organic solvent in vacuo, crude product was purified by TLC or a silica column (eluent: petroleum ether/EtOAc) to give **6,** (0.83 g, 65%, m.p. 172-173°C).

IR (KBr) cm^{-1}: 3015 (C-H str. ArH), 1680 (free C=O str.), 1635 (C=N str.), 1585 (C=C str. ArH), 1430 (C-H bending, CH_3), 1210 (C-N str.), 1110 (C-O str.); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 9.80-9.82 (s, 1H), 7.40-7.73 (m, *J*=7.2 Hz, 4H), 6.81-7.90 (m, *J*=7.2 Hz, 4H), 3.6 (s, 2H), 3.24 (t, *J*=7.2 Hz, 4H), 2.28 (t, *J*=7.2 Hz, 4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 43.0-43.2, 44.7-44.9, 46.4-46.6, 83.7-83.9, 103.3-103.5, 108.1-108.3, 118.2-118.4, 123.3-123.5, 124.6-124.8, 126.4-126.6, 133.3-133.5, 137.7-137.9, 147.2-147.4, 138.5-138.7, 158.1-158.3, 159.4-159.6, 163.5-163.7, 166.3-166.5, 163.8-164.0, 170.6-170.8; MS: *m/z*: 390 (13%) [M^+], Anal. calcd. for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.42. Found: C, 67.48; H, 5.70; N, 14.35.

Preparation of 2-[4'-(benzylidenethiosemicarbazone)phenoxyl)-[1,4]-benzodiazepin-5-[-4''-methylpiperazinyl]-carboxamide (7)

A solution of 6 (1.17 g, 0.003 mol) and thiosemicarbazide (0.78 g, 0.0033 mol) in ethanol (6 mL) was heated to reflux for 3 h and monitored by TLC ($CHCl_3$/CH_3OH/AcOH 3:1:0.05). After reaction mixture was cooled, the solid was filtered out, washed with ethanol, and dried to give yellow solid of 7, (1.25 g, 90%, m.p. 255-257°C). IR (KBr) cm^{-1}: 3360-95 (NH str.), 2990 (C-H str. ArH), 1685 (free C=O str.), 1620-1630 (C=N str.), 1570 (C=C str. ArH), 1590 (NH_2 bending), 1480 (C-H bending CH_3), 1170 (C-N str.), 1120 (C-O str.), 1040 (C=S str.), 690 (C-S str.); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.50 (s, 2H), 8.30 (s, 1H), 7.35-7.81 (m, *J*=7.2 Hz, 4H), 7.02-7.50 (m, *J*=7.2 Hz, 4H), 3.6 (s, 2H), 3.20 (t, *J*=7.4 Hz, 4H), 2.27 (t, *J*=7.4 Hz, 4H), 2.26 (s, 3H), 2.20 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2-45.3, 47.1-47.3, 48.7-48.9, 116.1-116.2, 127.1-127.2, 123.5-123.6, 126.4-126.6, 132.2-132.4, 130.3-130.5, 147.3-147.5, 132.5-132.7, 156.3-156.5, 147.7-147.9, 158.1-158.3, 164.4-164.6; MS: [M^+]: 463; Anal. calcd. for $C_{23}H_{25}N_7O_2S$: C, 59.59; H, 5.44; N, 21.15; S, 6.92. Found: C, 59.67; H, 5.45; N, 21.22; S, 6.93.

Preparation of 2-[4'-(5''-amino-1'',2'',4''-thiadiazol-2''-yl)phenoxyl]-[1,4]-benzodiazepin-5-[4'''-methyl-piperazinyl-carboxamide (8)

Thiosemicarbazone 7 (0.740 g, 0.0016 mol) and ammonium ferric sulfate (3.2 g, 0.006 mol) were soluble in H_2O (10 ml), and the mixture was heated to reflux for 10 h. The mixture was then poured into ice-water, basified with 10% NaOH aq to pH 5, and extracted with EtOAc three times. Next, organic solvent was removed in vacuo, and residue was purified by a silica gel column ($CHCl_3$/CH_3OH/AcOH 9:1:0.02) to obtain 8, (0.546 g, 77%, m.p. 240-42°C). IR (KBr) cm^{-1}: 2990 (C-H str. ArH), 1690 (free C=O str.), 1600-1620 (C=N str.), 1610 (C=C str. ArH), 1580 (NH_2 bending), 1470 (C-H bending CH_3), 1170 (C-N str.), 1150 (C-O str.), 750 (C-S str.); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35-7.81 (m, *J*=7.1 Hz, 4H), 7.22 (s, 2H), 6.81-7.62 (m, *J*=7.2 Hz, 4H), 3.6 (s, 2H), 3.20 (t, *J*=7.3 Hz, 4H), 2.27 (t, *J*=7.4 Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2-45.4, 47.3-47.5, 48.0-48.2, 49.7-49.9, 116.4-116.6, 128.6-128.8, 127.3-127.5, 155.2-155.4, 129.7-129.9, 130.1-130.3, 132.4-132.6, 148.3-148.5, 158.2-158.4, 161.5-161.7, 164.8-165.0, 174.2-174.4; MS: [M^+]: 461; Anal. calcd. for $C_{23}H_{23}N_7O_2S$: C, 59.85; H, 5.02; N, 21.24; S, 6.95. Found: C, 59.70; H, 5.01; N, 21.18; S, 6.96.

RESULTS AND DISCUSSION

Ubiquity of 1,4-benzodiazepines in chemical literature is undoubtedly a consequence of multifarious biological response which they elicit in combating a variety of body ailments. Impressive medicinal properties endow with

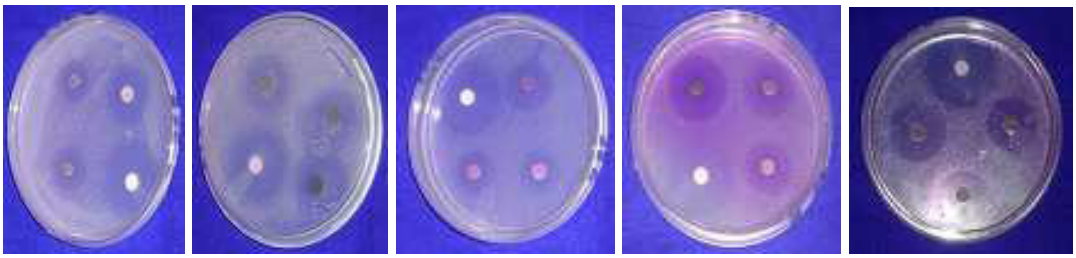
this nucleus has placed them to the class of 'privileged heterocyclic scaffolds' from which useful potential drugs can be expected.[23-25] The potential of isatin (1) in the synthesis of heterocyclic compounds through the expansion of its ring to give the six or seven membered heterocyclic rings has been well established in the literature. This feature of isatin has been very elegantly exploited by Ogata and Matsumoto[26-27] to develop a highly innovative technique for the synthesis of 5-methylcarboxylate substituted derivatives of 1,4-benzodiazepin-2-one from the reaction of 1-chloroacetylisatin with methanolic solution of hexamine.[28-29] This methodology was applied by us to obtain the 5-carbomethoxy substituted analogue of 1,4-benzodiazepin-2-one (3) in an acceptable yield. Treatment of the carbomethoxy function of 3 with N-methylpiperazine[30] formed the corresponding 5-carboxamide derivative (4). The NH-C=O group on face 'a' of the 1,4-benzodiazepine nucleus (4) had the potential to provide an easy access to the corresponding 2-Cl from its reaction with $POCl_3$.[31] The 2-Cl atom (an iminochloride species) was highly reactive species activated for nucleophilic attack. This 2-chloro analogue (5) on treatment with p-hydroxybenzaldehyde resulted the incorporation of p-oxybenzaldehyde substituent on its 2-position (6). The thiosemicarbazone derivative (7) of the aldehyde reacted smoothly with ammonium ferrous sulphate to give the corresponding aminothiadiazole derivative (8).

BIOLOGICAL STUDIES:[32-35]

Condensed heterocyclic systems containing thiadiazoles and 1,4-benzodiazepines have attracted the attention of chemists owing to these nuclei having been identified in the literature as the most active pharmacophores in drug design and synthesis. It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exert a profound influence on the biological profiles of that molecule. All the compounds were screened for their antimicrobial activity by disc diffusion method at 100, 200 and 400 µg/mL concentrations in DMF against *Pseudomonas aeruginosa* (MTCC 1688) and *Bacillus cerus* (MTCC 1305) and antifungal activity against *Macrophomina phaseolina* (MTCC 166) and *Fusarium solani* (MTCC 350). The stock solutions of standard and test compounds were prepared in DMF and subsequent dilutions were made with the same solvent. The zone of inhibition and activity index were determined in comparison of the standard drugs 'Streptomyacin' and 'fluconazol'. The outcome of this study is presented in tabular form in table 1. All these compounds were active against the bacterial and fungal strains.

Table 1
Antibacterial and antifungal activity of compounds 4-8

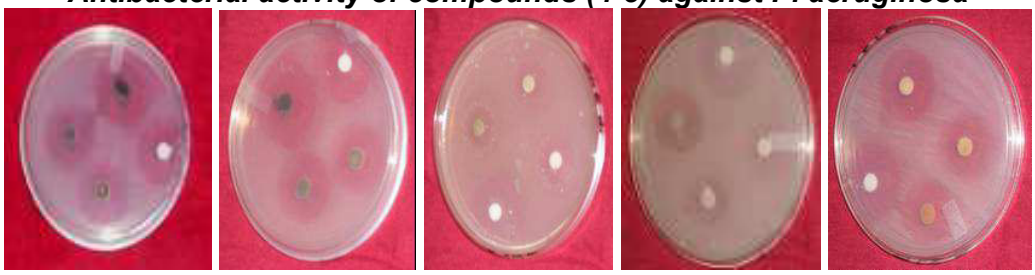
Comp. No.	*Pseudomonas aeruginosa*		*Bacillus cerus*		*Macrophomina phaseolina*		*Fusarium solani*	
	Zone of inhibition	% activity Compared to the standard	Zone of inhibition	% activity Compared to the standard	Zone of inhibition	% activity Compared to the standard	Zone of inhibition	% activity Compared to the standard
4	14	56.0	22.3	92.9	22.3	85.7	20.3	78.0
	12	60.0	16.2	90.0	20..5	93.1	17.6	80.0
	07	46.6	10.3	85.8	16.5	97.0	14.2	71.0
5	23	92.0	22.5	93.7	23	88.4	23.6	90.7
	18	90.0	17	94.4	21.2	96.3	20.5	93.1
	14	93.3	11.5	95.8	16.7	98.2	18.7	93.5
6	24.5	98.0	20	83.3	22	84.6	20.2	77.6
	19	95.0	16.5	91.6	20.5	93.1	15.1	68.6
	14.3	95.3	10.5	87.5	15	88.2	13.6	68.0
7	23.1	92.4	21.9	91.2	25.3	97.3	25.0	96.1
	17.9	89.5	17	94.4	16	72.7	21.2	96.3
	13.8	92.0	11	91.6	11	64.7	19.0	95.0
8	24.2	96.8	23.9	99.5	24.5	94.2	24.0	92.3
	18.8	94	17.6	97.7	19	86.3	21.0	95.4
	14.2	94.6	11.6	96.6	14	82.3	18.9	94.5



Antifungal activity of compounds (4-8) against M. phaseolina

Antifungal activity of compounds (4-8) against F. solani

Antibacterial activity of compounds (4-8) against P. aeruginosa



Antibacterial activity of compounds (4-8) against B.cerus

CONCLUSION

We devised an efficient one step synthetic protocol to the formation of corresponding 2-(oxy)-substituted analogues, of the privileged nucleus of 1,4-benzodiazepine. Firstly, it established the versatility of the one-pot synthetic protocol to the preparation of 1,4-benzodiazepine. Secondly, it provided an easy access to the formation of their thiadiazole derivative through thiosemicarbazone derivatives of biological interest in high purity and yield. In summary, two noteworthy features on the synthesis have been evident from our study. The cytotoxic properties of pyrrolo-[2,1-c][1,4]-benzodiazepine class of antibiotics have been implicated due to the intercalation of DNA with the C_{11} function of these molecules. In this context, the synthesis of C_2-substituted (C_{11} in the case of pyrrolo-

[2,1-c][1,4]-benzodiazepine) was of immense significance. In this context the proposed strategy on the one hand, has sought to provide a convenient one step synthetic entry to the heterocycles such as thiadiazole ring on the C_2 of 1,4-benzodiazepine nucleus from the corresponding thiosemicarbazone derivatives.

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