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Archives of Applied Science Research, 2011, 3 (1): 139-144

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ISSN 0975-508X
CODEN (USA) AASRC9

Microwave assisted green chemistry approach to the synthesis of some novel N_1-amino-methyl-substituted 1,4-Benzodiazepine derivatives

Veena Yadav, Nishant Yadav

Department of Chemistry, Kurukshetra University, Kurukshetra (India)

ABSTRACT

*An efficient microwave assisted protocol for the exclusive one pot synthesis of N-amino-methyl substituted 1,4- benzodiazepine derivatives **4(a-f)** and **5(a-f)** by the reaction of N-amino-methyl substituted isatoic anhydride **1(a-f)** with glycine and L-proline respectively has been described. Treatment of N-amino-methyl substituted isatoic anhydride **1(a-f)** with amino acids glycine and L-proline afforded **4(a-f)** and **5(a-f)** respectively in excellent yield. The derivatives of N-amino-methyl substituted 1,4-benzodiazepine **4(a-f)** and **5(a-f)** were screened for their in-vitro antimicrobial activities against bacterial species (E.coli and B.subtilis) and fungal species (A.niger and A.flavus) by Agar-well assay method against the standard drugs (ciprofloxacin for bacteria and fluconazol for fungi).*

Key words: Microwave assisted organic synthesis, Isatoic anhydrides, sec. amines, glycine, L-proline, Mannich bases.

INTRODUCTION

The use of microwave irradiation for carriying out organic reaction has been well established and has recently been reviewed[1]. The application of the solvent free technology coupled with the recyclability of mineral support has led to the development of many reaction procedures, which are environment friendly, falling in the domain of green chemistry[2].

Secondary amines like pyrrolidine, morpholine, piperazine etc. are well known for their antimicrobial activities[3-13]. Condensed heterocyclic systems containing the 1,4-benzodiazepine moieties have attracted the attention of the chemists owing to this nuclei having been identified in the literature[14-20] as the most promising 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 profile of that molecules. Based on these observations, it could be anticipated that incorporation of the bioactive 1,4-benzodiazepine moiety with various biological active secondary amines could produce interesting series of compounds with enhanced biological activity. Ubiquity of isatoic anhydride and 1,4-benzodiazepine in the chemical literature[12] is undoubtedly a consequence of multifarious

biological response, which they elicit in combinating a variety of body ailments. The recent demonstration that some of their derivatives can serves as potential agents in the control and treatment of AIDS has stimulated further interest in these molecules from yet another perspectives and prompted us to synthesize some novel compounds containing these pharmacophores, on the premise that their presence in tandem in a single molecular framework can contribute significantly to the biological activity in the resulting molecules. As a part of an on going endeavour to create novel heterocyclic scaffolds with anticipated biological activity from studies on the synthesis of the novel N-amino-methyl substituted 1,4-benzodiazepine derivatives.

MATERIALS AND METHODS

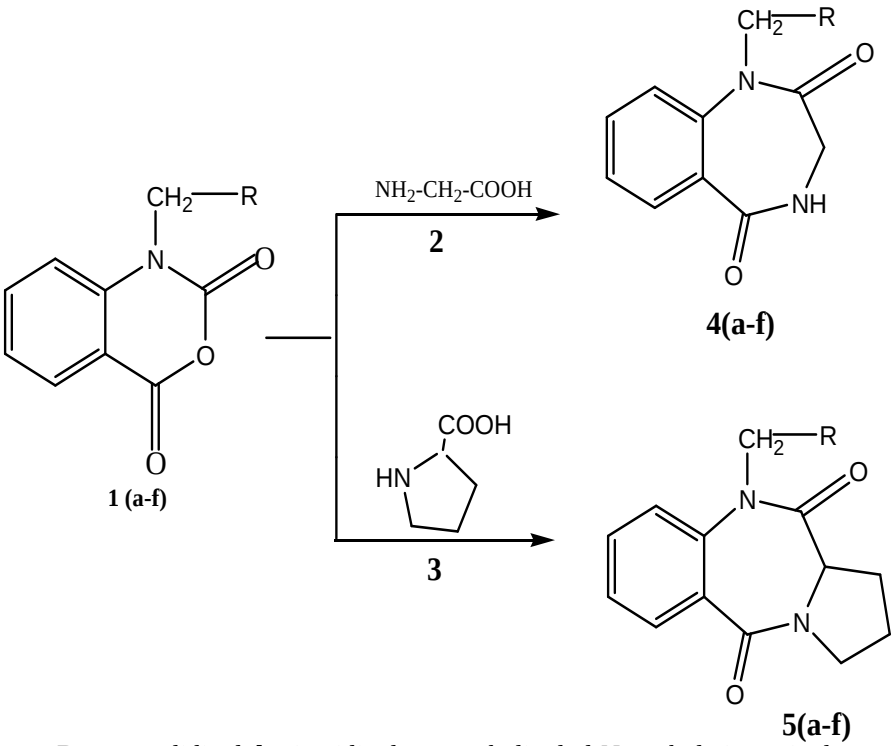
Experimental

Melting points were determined in an open glass capillaries and are uncorrected. TLC was done on silica gel 'G' coated glass plates using benzene: methanol (9.5:0.5) as eluent of the reations. IR spectra on KBr were recorded on FTIR-8400S, CE (SHIMADZU). ^{1}H NMR spectra were recorded on Model AC-300F (Bruker) using $CDCl_3$ as solvent and TMS as an internal standard. Basic alumina used as aluminium oxide, basic, mesh size (100-300) Min. 90%, pH=10.

General procedure for the preparation of 4(a-f):

Solution phase microwave assisted method-

A solution of compund (0.001M) **1a** and glycine (0.005M) in glacial acetic acid was taken in a 100ml borocil conical flask with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 110^{0}C for 8 min. and then 720 W for 6 min. with short interval of 1 min. to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0^{o}C for I hour and the resulting solid obtained was filtered and recrystallised from ethanol to give **4a**.The compounds **4(b-f)** and **5(a-f)** were prepared by adopting the same procedure.



R=**a**-pyrrolidinyl, **b**-piperidinyl**, c**-morpholinyl, d-N-methyl piperazinyl,

e-N-phenyl piperazinyl, f-N-benzyl piperzinyl,

(Scheme-1)

Solid phase microwave assisted method

A sullry of eqimolar quantities of N-amino-methyl-substituted isatoic anhydride (.001M) **1a**, glycine (0.005M) was absorbed over basic alumina (20%) by weight of reactant via a solution in ethanol (5ml). The dride slurry was powered and the free flowing powered was placed in a 100 ml borosil beaker and irradiated at 390 W microwave power for 7 min. and then at 680 W for 5 min until the completion of the reaction monitored by TLC. The recyclable in organic solid support was separated by extraction the product with ethyl acetate .The solvent was evaporated and solid obtained was recrystallized from DCM and dride to give **4a**. The compounds **4(b-f)** and **5(a-f)** were prepared by adopting the same procedure.

Table-1: Physical data of compounds 4(a-f) and 5(a-f)

Comp.	Molecular Weight	M. P. (°C)	N Analysis (%) (Calcd./Found)
4a	259	170	16.20/16.17
4b	273	177	15.37/15.41
4c	275	185	15.26/15.30
4d	288	165	19.43/19.48
4e	351	176	15.99/16.02
4f	365	175	15.37/15.33
5a	390	181	14.04/14.07
5b	313	178	13.41/13.37
5c	315	171	13.32/13.36
5d	328	166	17.06/17.11
5e	390	179	14.35/14.30
5f	404	177	13.85/13.89

RESULT AND CONCLUSION

N-amino-alkyl substituted isatoic anhydrides **1(a-f)** reacted with glycine and L-proline to give N-amino-methyl substituted 1,4-benzodiazepine derivatives **4(a-f)** and **5(a-f) (Scheme-1)**.

To our knowledge, there has been no report on the synthesis N-amino-methyl substituted 1,4-benzodiazepine derivatives from the reaction of N-amino-alkyl substituted isatoic anhydride with sec. amine on a solid support under MW conditions and therefore, an efficient microwave assisted protocol for the exclusive one pot synthesis of N-amino-methyl substituted 1,4-benzodiazepine derivatives **4(a-f)** and **5(a-f)** from the reaction N-amino-alkyl substituted isatoic anhydride with glycine and N-proline has been described in this paper **(Scheme-1)**.

All the synthesized compounds gave satisfactory results of nitrogen analysis. IR and ^{1}H-NMR spectral data were found to be consistent to the assigned structures. The physical and analytical data of the compounds are presented in Table-1.

Table 2: Spectral data of compounds 4(a-f) and 5(a-f)

Comp.	IR(KBr) cm-1	1H NMR (ppm)	MS: m/z
4a	3180, 1720, 1460	8.0(1H,t,NH); 1.59(4H,m,CH_2) 7.28-8.00(4H,m,ArH);	260.14(100%)259.13(15.4%);;261.14(1.5%) 260.13(1.1%)
4b	3160 ,1719, 1460	8.0(1H,t,NH); 1.59(6H,m,CH_2)	274.15(100%),273.15(16.5%),275.15(1.8%),2 74.14(1.1%)
4c	3093 ,1643, 1450	8.0(1H,t,NH); 3.67(4H,t,CH_2)	276.13(100%),275.13(15.5%),277.13(1.9%),2 76.12(1.1%)
4d	3090 ,1650, 1430	8.0(1H,t,NH); 2.27(3H,s,CH_3) 2.46(8H,m,CH_2)	289.16(100%),288.16(18.0%),290.17(1.3%)
4e	3016 ,1689, 1452,1286	8.0(1H,t,NH); 6.00-8.00(8H,m,ArH);	350.17(100.0%), 351.18(22.0%),352.18(2.7%), 351.17(1.5%)
4f	3010 ,1680, 1452,1280	8.0(1H,t,NH); 7.06-8.00(8H,m,ArH); 3.62(2H,s,CH_2)	364.19(100%),365.19(24.3%),366.20(2.5%),
5a	3055 ,1690 1471,1286	1.6-3.40(2H,t,CH_2) 1.59(4H,m,CH_2)	300.17(100.0%),390.16(18.7%),301.17(2.1%), 300.16(1.1%)
5b	3050 ,1670, 1470,1260	1.6(2H,m,CH_2) 3.40(2H,t,CH_2) 1.50(6H,m,CH_2)	314.18(100%),313.18(20.7%),315.19(1.9%),
5c	3170,1620, 1496,1280	3.67(4H,t,CH_2) 2.37(4H,t,CH_2) 4.23(2H,s,CH_2)	316.16(100.0%),315.16(19.9%),317.17(1.7%),
5d	3110 ,1610, 1460,1270	2.46(8H,t,CH_2) 2.27(3H,s,CH_3)	329.19(100.0%),328.19(21.0%),330.20(1.9%),
5e	3093 ,1643, 1450,1296	3.45(4H,t,CH_2) 2.59(4H,t,CH_2) 6.59-7.08(5H,m,Ar-H)	391.21(100.0%),390.21(25.3%),392.21(3.8%),
5f	3090 ,1640, 1450,1290	2.46(8H,t,CH_2) 3.62(2H,s,CH_2) 7.06-7.8(9H,m,Ar-H)	405.22(100.0%),404.22(22.7%),406.23(3.7%),

The antibacterial activity was evaluated against two pathogenic strains (*E.coli*. and *B.subtilis*).The zone of inhibition and activity index were determined by comparison with the standard drug ciprofloxacin. The outcome of this study is presented in table-**3**. The antibacterial screening against *B.subtilis* showed that amongst the compounds **4(a-f)** and **5(a-f)** the compound **4c** and **5c** displayed highest activity. The remaining compounds showed only moderate activity. The antifungal activity was evaluated against two pathogenic strains (*A.niger* and *A.flavus).*The zone of inhibition and activity index were determined by comparison with the standard drug fluconazol. The outcome of this study is presented in table-3. The antifungal screening against *A.niger* showed that amongst the compounds **4(a-f)** and **5(a-f)** the compound **4f** and **5f** exhibited highest activity.

Table:3

S.N	Conc. In (µg/ml)	(E. coli) Zone of inhibition	(B.subtilis) Zone of inhibition	(A. niger) Zone of inhibition	(A. flavus) Zone of inhibition
4a	400	09.0	08.5	08.0	09.0
	200	08.0	07.0	07.5	08.5
	100	07.4	06.0	06.3	07.0
4b	400	11.0	11.2	11.5	11.5
	200	10.5	10.2	10.0	10.5
	100	10.0	10.5	09.5	09.0
4c	400	16.5	14.7	11.7	11.5
	200	15.7	15.7	10.5	10.5
	100	14.5	15.4	10.0	10.6
4d	400	12.0	12.2	12.3	12.4
	200	12.5	12.0	12.0	12.5
	100	12.0	11.5	11.7	11.0
4e	400	11.2	11.5	11.5	11.5
	200	10.5	10.5	10.6	10.5
	100	10.0	10.0	10.5	10.0
4f	400	12.8	12.5	17.7	15.5
	200	12.5	12.0	15.6	14.8
	100	12.0	11.8	14.8	16.5
5a	400	11.5	11.0	11.7	11.6
	200	10.5	10.0	10.5	10.6
	100	10.0	09.5	09.6	10.0
5b	400	10.3	09.0	07.0	10.2
	200	08.2	08.5	08.9	11.0
	100	09.6	10.0	07.5	09.1
5c	400	16.0	15.5	13.5	13.0
	200	15.6	13.0	13.0	12.6
	100	14.0	14.1	12.6	12.0
5d	400	11.2	10.0	10.1	09.1
	200	12.1	09.0	09.0	07.5
	100	10.5	08.8	08.5	09.0
5e	400	10.2	10.0	10.1	09.1
	200	09.1	07.0	09.0	07.5
	100	10.5	09.8	08.5	09.0
5f	400	15.2	12.0	15.1	15.1
	200	15.1	12.0	15.0	14.5
	100	14.5	11.8	14.5	14.0
***Standard Antibacteria**	400	26	18	28	30
	200	26	18	28	30
	100	26	18	28	30
***Standard Antifungal**	400	26	-	-	-
	200	26			
	100	26			

Acknowledgement

The authors wish to thank CDRI, Lucknow and Punjab University Chandigarh (India) for providing ^{1}H NMR spectral data.

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