Synthesis and spectral studies of 1, 5-benzodiazepines derivatives From β-diketones/β-ketoesters

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***Abstract*: Synthesis of 1,5-benzodiazepines derivatives was achieved by Diazotization of 7-aminocephalosporanic acid (1) with sodium nitrite in presence of mineral acid form diazonium salt (2). The resulting product (2) was treated with different β-diketones (3a-c) to form new derivatives of various β-diketones(4a-c). The derivatives of β-diketones(4a-c) are finally treated with o-phenylenediamine (o-PDA) to obtained 1,5-benzodiazepines derivatives, (5a-c). All the newly synthesized compound were characterized by elemental analysis and spectral studies.**

***Keywords*: 1, 5-benzodiazepines, mineral acids,β-diketones/β-ketoester, o-phenylenediamine (o-PDA).**

Introduction:

Benzodiazepines are important members of heterocyclic compounds. Benzodiazepines have attracted attention as an important class of heterocyclic in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, anti-anxiety,analgesic, sedative, antidepressive and hypotic agents,[1] as well as anti-inflammatory agents,[2].

Benzodiazepines derivatives are also commercially used as dyes for acrylic fibers,[3]. 1,5-benzodiazepine are valuable synthons for the preparations of fused ring compound,such as triazolo-,oxadiazolo-,furano-benzodiazepine.[4] despite their importance from a pharmacologicaland synthetic point of view, few methods for the preparations of benzodiazepines are reported in the literature.[5-7]Although many methods for the synthesizing benzodiazepine ring system have been reported, they continue to receive a great deal attention.[8-10]

These compound are synthesized by the condensation of o-phenylenediamine (o-PDA) with β-diketones.[11] All these methods have disadvantages, such as extreme reaction condition and also several side-reaction. Surface mediated solid phase reaction are of growing interest [12] because of their ease of execution and work-up, mild reactions conditions. Previously, efforts were made to explore the utility of surface-mediated reaction.[13-15]

Heterocycles used as Scaffolds in medicinal chemistry is devoted to benzodiazepines derivatives.They exhibit useful pharmacological properties and clinical application.[16-19]

Azo compound form a large class of synthetic products which have been used as avaluable dyes, these being obtained by coupling diazonium salt with phenols or bases. These azocompound gained early recognituon as therapeutic agents and are used in the treatment of burns,surface wounds and ulcers[20].There dental surgical and urinary antiseptic action[21] are well known.

It was planned to introduce an azo group in the dialkyl/diaryl β-diketone molecule to study the effect of this group on their pathological properties[22]. Science dialkyl/diaryl β-diketones with azo group are well known for their antibacterial activities[23].

β-Diketones are of ample importance as they serve as precursors for the synthesis of a large number of pharmacologically active heterocyclic compounds such as diazepines[24], benzodiazepines[25], pyrazoles[26], isoxazoles, thiazepines and bezothiazepines[27]. β-diketones have been studied extensively till date as they are also found to occur in nature with various biological properties and can be synthesized in the laboratory by a number of methods.

Realising the medicinal properties of the above mentioned compounds *viz*. (7-ACA, β-diketones and β-ketoesters) encouraged us to synthesize various novel substituted β-diketones and β-ketoesters as precursors with 7-ACA derivative.

All these newly synthesized β-diketones and β-ketoester were reacted with different nitrogen nucleophile *viz*.o-phenylenediamine (o-PDA) to get various new benzodiazepines.

Result s and Discussions:

Diazonium salt of 7-aminocephlosporanic acid **(1)** was formed in the presence of $NaNO_2$/HCl at 0.5^0C. Diazonium salt **(2)** was condensed with different β-diketones/β- ketoesters **(3a-c)** in the presence of mineral acids. The newly synthesized β-diketones /β- ketoesters **(4a-c)** were condensed with o-phenylenediamine (o-PDA) to get various new 1,5-benzodiazepines derivatives **(5a-c) scheme-1.**

Experimental:

All the melting point were determined in open capillary tubes and are uncorrected. The ^{1}H-NMR 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 IR spectra were recorded on a Nicolet-Megna-FT-IR-550 spectrometer in KBr pellets. The purity of the newly synthesized compound was checked by TLC. Satisfactory C,H,N, analyser were obtained for all the compound.

Synthesis of compounds

Preparation of 3-[(acetyloxy) methyl]-7-[(E)-chlorodiazenyl]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid)(2)

Pure 7-Aminocephalosporanic acid (2.72g., 0.01 M) HCl (3.64 ml, 0.1M) and 3ml.water was taken in a round bottomed flask and stirred it 10 minute on a magnetic stirrer at temperature of 0-5º C. Then added $NaNO_2$ (0.759 g, 0.01 M) and 3ml water solution, temperature of the reaction mixture was maintained between 0-5º C. Thus diazonium salt remained in the solution.

Synthesis of 3-[(acetyloxy) methyl]-7-[(E)-(2,4-dioxopentan-3-yl/1,3-dioxo-1-phenylbutan-2-yl/1,3-dioxo-1,3-diphenylpropan-2-yl)diazenyl]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (4a-c)

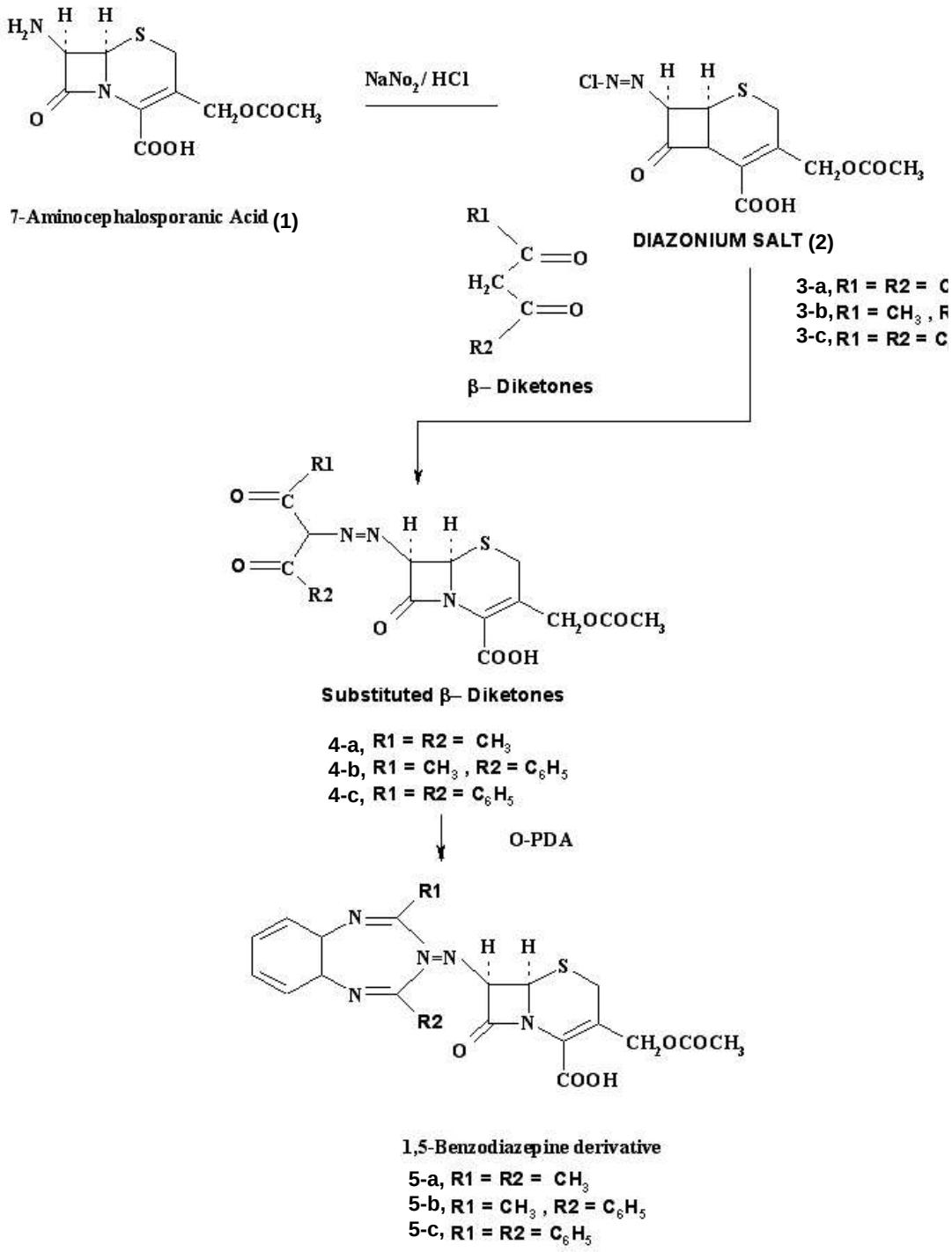
Placed sodium methoxide(1.0g.,0.02M)and β-diketones/β-ketoesters **(3a-c)**(0.01mole) in a dry round bottomed flask fitted with a guard tube and stirred it for one hour on a magnetic stirrer at a temperature of 50°C, until a creamy mass was obtained. The compound **(2)** (1.60g, 0.005M) was then added in small portions and dry toluene (5 ml) was added as solvent to affect proper stirring of the reaction mixture. The reaction mixture was refluxed at 100°C for about twenty hours. The completion of the reaction was monitored through TLC. When the reaction was completed, the reaction mixture was cooled and toluene was removed under reduced pressure. The reaction mixture was extracted with chloroform and then chloroform layer was washed thrice with water. The chloroform layer was then dried over sodium sulphate and filtered. The chloroform was distilled off and the viscous mass was precipitatedby using a mixture of ethylacetate and petroleum ether (2:8). The crude product was recrystallized fromabsolute alcohol. Purity of diketone was checked through TLC using benzene: ethanol: ammonia (7: 2: 1) upper layer as mobile phase.

Synthesis of 3-[(acetyloxy)methyl]-7-[(E)-(2,4-dimethyl/2-methyl-4-phenyl/2,4-diphenyl)-3H-1,5-benzodiazepine)diazenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (5a-c)

Placed β-diketone **(4a-c)** (2g., 0.005M) dry ethanol (10 ml) and glacial acetic acid (4 ml) in a two necked round bottomed flask equipped with a condenser and a dropping funnel. A solution of recrystallized o-phenylenediamine (0.54g., 0.005M) in dry ethanol (5ml.) was added dropwise through dropping funnel with continuous stirring. The progress of the reaction was checked through TLC. The reaction mixture was refluxed for four hours and then cooled to room temperature. The reaction mixture was kept overnight in refrigerator. The crude product separated out, was recrystallized from acetone. Purity of the compound was checked through TLC using - benzene : ethanol : ammonia (7 : 2 : 1) upper layer as mobile phase.

Table 1
Physical and analytical data of compound 4a-c

Compound	R^1	R^2	Melting point(^{0}C)	Yields(%)	Molecular formula
4a	CH_3	CH_3	175	45	$C_{15}H_{17}N_3O_7S$
4b	CH_3	C_6H_5	180	60	$C_{20}H_{19}N_3O_7S$
4c	C_6H_5	C_6H_5	185	50	$C_{25}H_{21}N_3O_7S$



Scheme-1

Spectral Data:

Synthesis of 3-[(acetyloxy)methyl]-7-[(E)-(2,4-dimethyl-3H-1,5-benzodiazepine) diazenyl] -8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (5a)

m.p. 180^{0}C; yield; 40% Anal.Calcd for $C_{21}H_{23}N_5O_5S$: C,55.13;H,5.07;N,15.31.Found: C,55.02; H,5.16; N,15.24. IR (KBr,cm^{-1}): 3340, 2900, 2550, 2120, 1700, 1245.^{1}H-NMR ($CDCl_3$): δ 2.056 (3H,s O-CH_3), 2.088 (6H,s CH_3-C), 3.388 & 3.574 (2H,dd,dd -NH), 4.503 (2H,s CH_2-C=O), 5.029 (1H,s –CH=), 5.151 (1H,d C-H), 5.571 (1H,d C-H), 7.366-7.637 (4H,m Ar-H). ^{13}C-NMR 15.6, 19.10, 29.11, 41.97,55.7, 76.2, 98.69, 135, 139.7, 171.2, 172.5, 180.2,

Synthesis of 3-[(acetyloxy)methyl]-7-[(E)-(2-methyl-4-phenyl-3H-1,5-benzodiazepine) diazenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (5b)

m.p. 175^{0}C; yield; 48% Anal.Calcd for $C_{26}H_{25}N_5O_5S$: C,60.10;H,4.85;N,13.48. Found: C,60.18; H,4.80; N,13.39.IR (KBr,cm^{-1}): 3360, 3040, 2945, 2552, 2130, 1720, 1240.^{1}H-NMR ($CDCl_3$): δ 2.056 (3H,s O-CH_3), 2.082 (3H,s CH_3-C), 3.388 & 3.574 (2H,dd,dd -NH), 4.503 (2H,s CH_2-C=O), 5.013 (1H,s C-H), 5.413 (1H,d –CH=), 5.764(1H,d C-H), 7.516-8.044 (9H,m Ar-H).^{13}C-NMR 15.40, 18.75, 29.24, 42.40, 54.20, 76.45, 99.50, 134.01, 139.45, 172.25, 173.40, 181.24.

Synthesis of 3-[(acetyloxy)methyl]–7-[(E)-(2,4-diphenyl)-3H-1,5-benzodiazepine)diazenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (5c)

m.p. 175^{0}C; yield; 43% Anal.Calcd for $C_{31}H_{27}N_5O_5S$: C,64.01;H,4.68;N,120.4. Found: C,64.12; H,4.59; N,12.14. IR (KBr, cm^{-1}): 3365, 3060, 2900, 2545, 2135, 1730, 1248.^{1}H-NMR ($CDCl_3$): δ 2.056 (3H,s O-CH_3),3.424 & 3.506 (2H,dd,dd -NH), 4.504 (2H,s CH_2-C=O), 5.018 (1H,s C-H), 5.413 (1H,d –CH=), 5.764(1H,d C-H), 7.450-8.044 (14H,m Ar-H).^{13}C-NMR 14.85, 18.20, 28.76, 43.26, 55.12, 75.36, 98.35, 133.65, 138.45, 173.55, 174.28, 180.44.

Conclusion:

In Conclusion this new method for the synthesis of 1,5-benzodiazepines were found clean and had operational simplicity. This simple and reproducible method affords various 1,5-benzodiazepines with short reaction times,excellent yields and without the formation of undesirable by products. More extensive study is needed to confirm the preliminary results and mode of action studied are required to be able to optimize the effectiveness of this series of compound **(5a-c).**

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References

1. (a) H Schutz,Benzodiazepines, Springer, Heidelberg, 1982; (b) J K Landquist,inComprehensive *Heterocyclic Chemistry*, Vol. 1, A R Katritzky, C W Rees, Eds.,Pergamon, Oxford, 1984, p. 166; (c) R I Fryer, in Comprehensive *HeterocyclicChemistry*, Vol. 50, E C Taylor, Ed., Wiley, NewYork, 1991, Chapter II; (d) L O Randall, B Kappel, in Benzodiazepines, S Garattini, E Musini, L O Randall, Eds.,Raven Press, New York, 1973, p. 27
2. J R de Baun, F M Pallos, D R Baker, US 3,978, 227 (1976) (*CA* **86** 5498d)
3. R C Harris, J M Straley, US 1,537,757 (1968) (*CA* **73** 100054w)
4. (a) M C Aversa, A Ferlazzo, P Gionnetto, F H Kohnke, Synthesis(1986) 230; (b) M Essaber, A Hasnaoui, A Benharref, J P Lavergne, *Synth. Commun.* **28** (1998) 4097; (c)A M EI-Sayed, H Abdel-Ghany, A M M EI-Saghier, *Synth. Commun.* **29** (1999) 3561;(d) A Chimirri, S Grasso, R Ottana, G Romeo, M Zappala, *J. Heterocycl. Chem.* **27**(1990) 371
5. D I Jung, T W Choi, Y Y Kim, I S Kim, M Y Park, Y G Lee, and D H Jung,*Synth. Commun*., **29,** 1941 (1999).
6. J S Yadav, B V S Reddy, B Eshwaraian, and K Anuradha, *Green Chem*., **4,** 592 (2002)
7. M Pozarentzi, J Stephanidou-Stephanatou, and C A Tsoleridis, *Tetrahedron Lett.*,**43,** 1755 (2002).
8. (a) Sanghetti, J N; Kokare, N D; Shinde, D B Sulfanic acid catalyzed solvent-free synthesis of 1,5-Benzodiazepine derivatives. *Chinese Chem. Lett.* **2007**, 18, 1305-1308.
9. Kusanur Raviraj A ; Ghate, M; Kulkarni M V Synthesis of spiro[indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents. *J. Chem. Sci.,* **2004**, 116, 265-270.
10. Kidwai, M; Ruby, M K and Venkataramanan R A facile synthesis of substituted benzodiazepines usingsolid support. *Chem. Heterocyclic Comp*. **2004**, 40, 631-634.
11. W Ried, E Torinus, *Chem. Ber*. **92** (1959) 2902
12. (a) A Fadel, R Yefash, J Saluan, Synthesis(1987) 37; (b) G Rosini, R Galarini, E Marotta, R Righi, *J. Org. Chem*. **55** (1990) 781; (c) M Kodomari, T Sakamoto, S Yoshitomi, *J. Chem. Soc*., *Chem. Commun*. (1990) 701; (d) P J Kropp, K A Duas, S D Crawford, M W Tubergren, K D Kepler, S L Craig, V P Wilson, *J. Am. Chem. Soc*.**112** (1990) 7433; (e) G Hondrogiannis, R M Pagni, G W Kabalka, P Anisoki, R Kurt,*Tetrahedron Lett.* **31** (1990) 5433; (f) H K Pantney, *Tetrahedron Lett*. **32** (1991) 2259;(g) F Pauter, M Daudon, *Tetrahedron Lett*. **32** (1991) 1457
13. A R Sardarian, B Kaboudin, *Synth. Commun*. **27** (1997) 543
14. A R Sardarian, B Kaboudin, *Tetrahedron Lett*. **38** (1997) 2543
15. B Kaboudin, *J. Chem. Rev*. (1999) 402
16. Sanna, P Carta, A Nikookar, M E Synthesis and Antitubercular activity of 3-arylsubstituted-2-(1H(2H) benzotriazol-1(2)-yl) acrylonitriles. Eur. *J. Med. Chem*, **2000**, 35, 535-543.
17. Kopanska, K Najda, A Zebrowska, J Chomicz, L Piekarczyk, J Myjak, P and Bretner, M.Synthesis and activity of 1H-benzimidazole and 1H-benzotriazole derivatives as inhibitors ofAcanthamoeba castellanii. Bioorg. *Med. Chem.,* **2004**, 12, 2617-2624.
18. Boido, A Vazzana, I Mattioli, F Sparatore, F Antiinflammatory and antinociceptive activities ofsome benzotriazolylalkanoic acid. *Il Farmaco*, **2003**, 58, 33-44.
19. Biagi, B Calderone, V Giorgi, I Livi, O Scartoni, V Baragatti, B Martinotti, E.Some structuralchanges on triazolyl-Benzotriazoles and triazolyl-Benzimidezolones aspotentialpotassium channelactivators. *Il Farmaco*, **2001**, 56, 841-849.
20. Burger,'A Medicinal Chemistry', Vol. 1, p. 668, John Wiley, New York, 1970.
21. A Goerner and H L Haley, J Lab,*Clin. Med*., 16,957.1931.
22. "Chemical constitution and biological activity" E. and F.N. Spon Ltd., London, 349, 1953.
23. J C Sheehan and K R H Logn, *J.A. Chem. Soc.*,79, 1262, 1957.
24. R Unny, P Joshi, M P Dobhal and Y C Joshi, *Hetreocyclic Commun*., 9,171, 2003.
25. J Bhagwan, Y C Joshi, R P Tyagi, B C Joshi, H N Mangal, (Department of chemistry,University of Rajasthan, Jaipur-302004,India). *J. Inst. Chem*.(India) 55,58-60, 1983.
26. S Nigam, Y C Joshi and P Joshi, *Heterocyclic Commun*., 9, 405, 2003.
27. M Padwad and V N Ingle, *J.Indian Chem.Soc*.,76,161,1999.