Mild and Efficient Phosphonitrilic Chloride mediated Synthesis for 1, 5-benzodiazepines

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Abstract- Phosphonitrilic chloride was found to be an efficient reagent for the preparation of 1,5-benzodiazepine derivatives of *o*-phenylenediamine and ketones. This method is an easy, rapid, and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives. The remarkable advantages offered by this method include green and reusable catalyst, mild reaction conditions, fast reaction rate, and excellent yield of products. This novel methodology maintains atom economy and an environmentally friendly approach.

I. INTRODUCTION

HHeterocyclic compounds containing five or six membered ring with one or more nitrogen atoms are always of great importance in the pharmaceutical sector because of having bioisosteric factor. In 1971 Sternbach introduced benzodiazepines as drug.[1] Meanwhile Benzodiazepine is widely used as a primary etiological agent for the acquired immunodeficiency syndrome against the human immunodeficiency virus type 1 (HIV-1).[2] The anti-HIV chemotherapy era has started a decade ago. In the search for more effective and safe chemotherapeutic agents there has been considerable interest in non-nucleoside reverse transcriptase inhibitors or NNRTI's.[3] It was found that a number of compounds representing various structural types inhibit HIV-1 reverse transcriptase (RTase). [4]

In the view of 1,5-Benzodiazepine derivatives have received significant attention because of their accessibility, easy functionalization, and potential pharmacological properties including anti-inflammatory, antianxiety, anticonvulsant, and hypnotic activities. [5] It represents a "privileged scaffold" found in compounds active against a variety of target types including peptide hormones, [6a] interleukin converting enzymes.[6b] and inhibitors of mitochondrial F1F0 adenosine triphosphate (ATP) hydrolase. [6c]

Consequently many methods has been developed for synthesis of1,5-Benzodiazepine derivatives , the area of biological interest in 1,5-benzodiazepines has been extended to various diseases such as cancer, [7a] viral infection, [7b] and cardiovascular disorders. [7c,d] These derivatives are also used as dyes for acrylic fibers in the photography industry. [8] Because of their wide range of pharmacological activity , industrial and synthetic applications, the synthesis of 1, 5-benzodiazepines has received increasing attention.

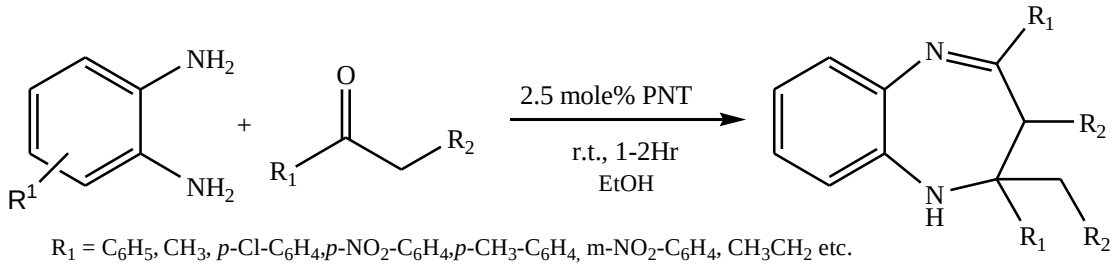
In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring compounds such as triazolo-[9] and oxadiazolo-benzodiazepines. [10] The general and simplest method for synthesis of 1,5-benzodiazepines involves the acid catalyzed reaction of *o*-pheneylenediamine with ketones, β-haloketones and α,β-unsaturated carbonyl compounds. Many catalysts have been reported in the literature for this reaction including BF_3-OEt_2,[11] polyphosphoricacid-$SiO2$,[12] $NaBH_4$,[13] $MgO/POCl_3$,[14] $Yb(OTf)_3$,[15] CH3COOH using microwave,[16] Al_2O_3-P_2O_5.[17] $ZnCl_2$, [18] cerium ammonium nitrate (CAN). [19]

However, many of them suffer from the drawbacks such as high temperature, drastic conditions, relatively expensive reagents, and nonenvironmental friendliness except for some methods.[20] In camparison with broad spectrum utility of 1,5-benzodiazepines in many field , their preparation methods are limited in number and the chemical processes often employ large amounts of hazardous and toxic solvents. The choice of pursuing a low-waste route and reusable reaction media to minimize the economic cost and environmental impact of a chemical process is becoming ever more urgent for the future, so there is pressure on organic chemists to investigate clean, economical, and environmentally safer methodologies. Due to wide range of biological application of 1,5-benzodiazepines, the development of efficient, clean and environmentally friendly protocols for the synthesis of 1,5- benzodiazepines are desirable.

Recently, Phosphonitrilic chloride trimer (PNT) has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. The Lewis acidity associated with Phosphonitrilic chloride trimer (PNT) enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amount. Owing to numerous advantages associated with this eco-friendly synthesis.

II. RESULTS AND DISCUSSION

In the present work, herein we wish to report PNT catalyzed efficient, simple and practical procedure for direct synthesis of 1,5-benzodiazepines through the reaction of o-phenylene diamine and ethyl methyl ketone (1:2) under stirring at room temperature in ethanol.



R_1 = C_6H_5, CH_3, *p*-Cl-C_6H_4,*p*-NO_2-C_6H_4,*p*-CH_3-C_6H_4, m-NO_2-C_6H_4, CH_3CH_2 etc.

R_2= H, CH_3. etc

R^1= H,4-CH_3, 4,5-diCH_3, 4-NO_2 etc.

Scheme 1

In our preliminarily investigation on model reaction of *o*-phenylene diamine and acetophenone , it was found that reaction could be finished under very simple reaction condition in the presence of catalytic amount of Phosphonitrilic chloride acid (PNT) and few (3 to 4) drop of EtOH as solvent which give desired 1,5-benzodiazepines product in good yield . The effect of solvent , catalyst, reaction time on the reaction was systematically investigated and result were summarized in **Table 1**. To optimize reaction condition to examine the effect of different solvent H_2O, CH_3CN, MeOH, THF, Toluene, DCM, Ethanol and molar ratio of the catalyst at different . The reaction was monitoring by TLC and the entire yield reported in **Table 1**

Table 1 Optimization of reaction condition

Entry	Solvent	Time (Hr)	Yield [a] %
1	H_2O	12 Hr	Nil
2	CH_3CN	10 Hr	Nil
3	MeOH	8 Hr	20 %
4	THF	12 Hr	45 %.
5	Toluene	8 Hr	Nil.
6	DCM	5 Hr	65 %
7	**Ethanol**	2 Hr	**Above 80 %**

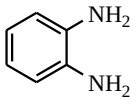
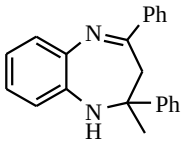
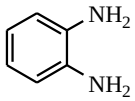
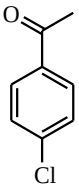
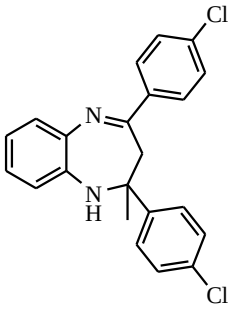
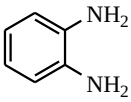
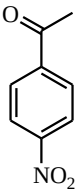
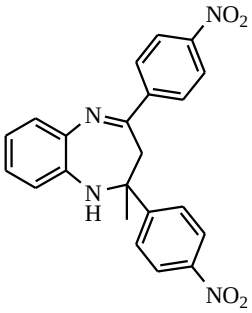
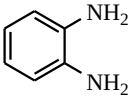
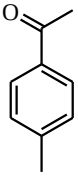
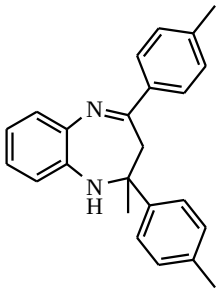
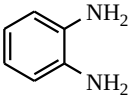
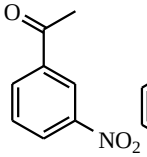
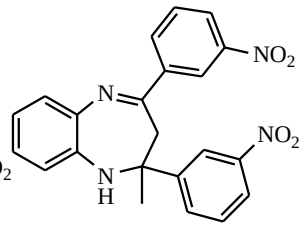
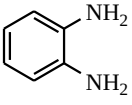
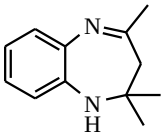
[a] Isolated Yield

As can be seen from Table 1, solvent play an important role in the model reaction. It was found that Ethanol is the best one among the solvent tested and reaction proceeded smoothly in the ethanol and gave desired product in 80% yield, while DCM afforded the product only in 65% yield. Use of H_2O, CH_3CN, MeOH, THF and Toluene as solvent led to slower reaction (**Table 1, Entry 1-5**). To our delight, above 80% of model product was isolated when the model reaction was carried out in the presence of ethanol at room temperature for 1 Hr stirring only. With respect to catalyst loading, when 1 mol% to 5 mol % of PNT was used, the reaction goes to completion gave a satisfactory result.

During the course of our further optimization of reaction condition, the reactions were generally complete in a matter of 1-2 hours. Meanwhile experimental data indicated that the reaction was not complete when reaction time was less than 1 Hr. However, no increase in yield was observed when the reaction time was prolong with respect to solvent **(Table 1)**. The optimized reaction conditions for the reaction were found to be PNT 2.5 mol % under stirring at room temperature for 1-2 Hr.

Having established the optimized reaction condition, we turn our attention to explore the scope of this protocol. The result are listed in **Table 2.**

Table 2 PNT catalyzed synthesis of 1, 5-benzodiazepines in ethanol[a.]

Entry	Substrate	Ketone	Product	Time (Hr)	Yield [b] %	M.P.^{o}C Reported	M.P.^{o}C Found
1				2	87	150-152	152
2				1.2	82	143-144	145
3				3	80	156-158	155
4				2.2	90	98-99	101
5				2.4	85	151-153	157
6				1.4	90	137-138	136

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From Table 2

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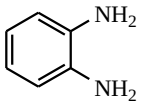
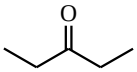
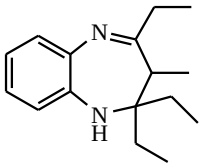
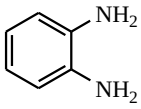
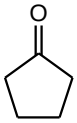
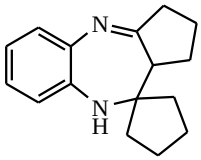
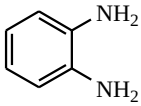
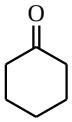
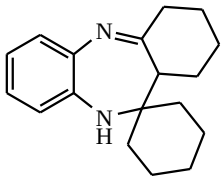
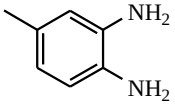
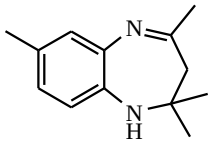
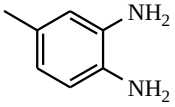
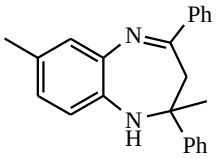
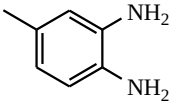
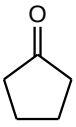
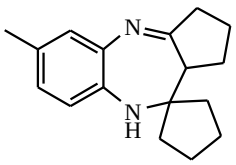
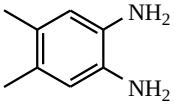
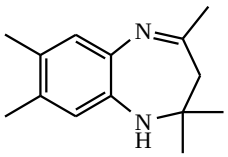
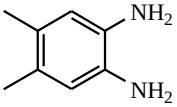
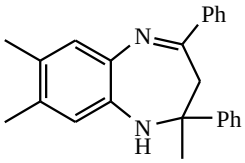
7				2	85	142-143	141
8				1.5	80	138-139	140
9				2.5	85	136-137	136
10				2	82	127-128	126
11				3	80	92-93	92
12				2	84	142-143	142
13				2.5	80	112-114	112
14				3	85	115-116	115

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From Table 2

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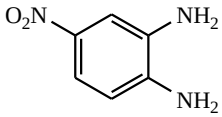
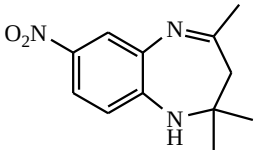
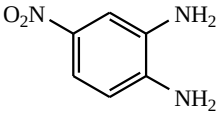
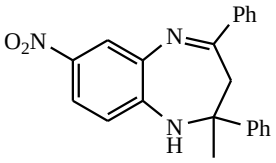
15				2.5	75	113-114	114
16				3	80	136-138	136

[a]Reaction Condition : o-phenylene diamine (1 mmole) , acetone (2 mmole) and Phosphonitrilic Chloride (Trimer) (2.5 mole %) in ethanol (2-4 drops) stir, 2 Hr R. T.
[b] Isolated Yield

As shown in the Table 2, in the most cases, o-phenylene diamine reacted with wide variety of substituted acetophenone completely and afforded the corresponding 1,5-benzodiazepines in good to excellent yield (**Table 2 , Entries 1-5**). Substituted acetophenone containing electron-donating or electron-withdrawing group on the benzene ring reacted with o-phenylene diamine smoothly under optimal condition to give the desired product. Furthermore, sterically demanding *ortho*-substituents hampered reaction so which are not shown in the **Table 2**.

To our delight cyclic ketones such as cyclopentanone, cyclohexanone whereas 3-pentanone (**Table 2, Entry 8, 9,7**) also reacted well and equally efficiently with similar success to afford fused ring 1, 5-benzodiazepines in high yields. Meanwhile substituted o-phenylene diamine with electron donating or electron withdrawing groups on the benzene ring reacted with ketone or cyclic ketone to generate corresponding product in high yield (**Table 2, Entry 10-16**) . It is important to note that substituted o-phenylene diamine with a strong electron withdrawing groups, such as nitro group on the benzene ring showed lower reactivity than those of ones with electron donating groups . (**Table 2, Entry 15-16**)

III. CONCLUSION

We have presented an elegant and simple methodology for the synthesis of 1, 5-benzodiazepine derivatives from o-phenylene diamine and cyclic or acyclic ketone in the presence of Phosphonitrilic Chloride by stirring in ethanol at room temperature. The reactions were performed smoothly to generate the corresponding products in high yields under the safe experimental condition and the procedure is simple and convenient. Furthermore, the catalyst is environmentally friendly and expensive. This method offer one of the important motifs for the synthesis of 1, 5-benzodiazepine, as natural product, biological active compounds and pharmaceutical agents.

Experimental Section

(a)General Experimental Procedure for the synthesis of 1, 5-benzodiazepine:

A mixture of *o*-phenylenediamine (1 mmol) and ketone (2. mmol) was stirred in the ethanol solvent at room temperature using Phosphonitrilic chloride (2 mol %) for an appropriate time as 2 Hr . The progress of the reaction was followed by TLC using 20%-40% EtOAc in *n*-Hexane as eluent. After completion of the reaction, the reaction mixture was separated from ethyl acetate (5ml) and water . The organic layer was evaporated and crud products were purified by recrystalization in *n*-Hexane or by column chromatography by silica gel using EtOAc : *n*-Hexane 20 : 80 as eluent.

Spectral analysis

2-methyl-2,4-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine [18] (Entry 1):

Yellow solid; M.P. 152 ^{0}C IR ($CHCl_3$, υ max): 3325, 2100, 1635, 1465, 1245, 1055, 815 cm^{-1}.; ^{1}H NMR ($CDCl_3$): δ 6.83–7.60 (m, 14H, ArH), 3.52 (s, 1H, NH), 2.96–3.15 (d, 2H, J = 13.2 Hz), 1.76 (s, 3H, CH_3).; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2 (C=N), 148.0, 140.5, 139.9, 130.2, 128.8, 128.5, 127.5, 126.7, 125.9, 122.1, 121.9, 74.2, 43.5, 30.3.Elemental Analysis: $C_{22}H_{20}N_2$ Calcd. C, 84.58; H, 6.45; N, 8.97. Found C, 84.43; H, 6.37; N,8.91.

4-(4-Chlorophenyl)-2- methyl-2,3-dihydro-*1H*-1,5-benzodiazepine[5c] (Entry 2):

M.P. 147^{0}C ^{1}H NMR (CDCl3): δ 6.84–7.53(m, 12H, ArH), 3.43 (s, 1H, NH), 2.87–3.09 (dd, 2H, J_1 = 12 Hz, J_2 = 12.8 Hz), 1.74 (s, 3H, CH3).

2-methyl-4-(4-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine[19] (Entry 3):
M.P. 155^{0}C ; ^{1}H NMR ($CDCl_3$): δ 6.90–8.08 (m, 12H, ArH), 3.64 (s, 1H, NH), 2.99–3.32 (m, 2H, CH_2), 1.85(s, 3H, CH_3). ;Elemental Analysis: $C_{22}H_{18}N_4O_4$ (402.13) calcd.: C, 65.66; H, 4.51; N, 13.92.Found: C, 65.37; H, 4.47; N, 14.01

2-methyl-4-(4-methyl phenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (Entry 4) [19]: M.P. 101^{0}C ;^{1}H NMR ($CDCl_3$): δ 6.81–7.59 (m, 12H, ArH), 3.52 (s, 1H, NH), 2.96–3.11 (m, 2H, CH_2), 2.34 (s, 3H,CH_3), 2.31 (s, 3H, CH_3), 1.74 (s, 3H, CH_3).;^{13}C NMR ($CDCl_3$):δ 168.1 (C=N), 145.5, 140.8, 140.5, 138.7, 137.4, 137.2, 129.5, 129.3,129.0, 127.6, 126.6, 125.7, 122.1, 122.0, 73.9, 43.3, 30.3, 21.8, 21.4.

2-methyl-4-(3-nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine[5c] (Entry 5):
Mp 157 ^{0}C;^{1}H NMR ($CDCl_3$, 400 MHz): δ6.92–8.48 (m, 12H, ArH), 3.56 (s, 1H, NH), 2.99–3.28 (m, 2H, CH_2), 1.87(s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 164.6 (C=N), 149.6, 148.7, 141.0, 139.8, 137.6, 133.0, 132.4, 130.0, 129.7, 129.4, 127.9, 124.9, 122.9, 122.7, 122.0, 121.3, 104.0, 74.6, 43.3, 37.6, 30.4. HRMS (m/z): calcd. For $C_{22}H_{18}N_4O_4$; 402.1328; found 402.1295.

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine[18] (Entry 6):
Pale Yellow Solid M.P. 136^{0}C .^{1}H NMR ($CDCl_3$): δ 7.12–7.14 (m, 1H, ArH), 6.96–7.01 (m, 2H, ArH), 6.72–6.74 (m, 1H, ArH), 2.97 (s, 1H, NH), 2.37(s, 3H, CH_3), 2.22 (s, 2H, CH_2), 1.34 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): δ 173.1 (C=N), 141.1, 138.3, 127.1, 125.9, 122.5, 122.2, 68.9,45.4, 30.8, 30.2;Elemental Analysis: $C_{18}H_{24}N_2$; Calcd. C,80.55; H, 9.01; N, 10.44. Found: C, 80.36; H,8.84; N, 10.31

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine[16b] (Entry 7):
M.P. 141 ^{0}C ;^{1}H NMR ($CDCl_3$): δ 6.59–7.34 (m, 4H, ArH), 3.85 (s, 1H, NH), 2.81–2.83 (m, 1H), 2.49–2.57(m, 2H), 1.52–1.56 (m, 2H), 1.20–1.37 (m, 4H), 0.68–0.96 (m, 10H).

10- Spirocyclopentane- 1, 2, 3, 9, 10, 10ahexahydro-1*H*-dibenzo[b]-cyclopenta [e] [1,4] -diazepine (Entry 8);Yellow solid; M. P. 140ºC; IR ($CHCl_3$, υmax): 3338, 2150, 1670, 1640, 1245, 1050, 850 cm^{-1} ;^{1}H NMR: ($CDCl_3$) δ 6.6–7.39 (m, 4H). 4.54 (brs, 1H), 2.30–2.61 (m, 3H), 1.3–1.92 (m, 12H). ;^{13}C NMR: ($CDCl_3$) δ 178,143.1, 139, 132.2, 128.6, 126.3, 119.4, 118.3, 66.7, 54.4, 39.3, 38.5, 34.4, 33.2, 28.7, 24.5, 24.1, 23.2.;Elemental Analysis: $C_{16}H_{20}N_2$ Calcd. C, 79.96; H, 8.39;N, 11.66. Found: C, 79.78; H, 8.24; N, 11.43

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo[b,e][1,4]
diazepine [16b] (Entry 9): Pale Yellow;M.P. 136^{0}C. ;IR($CHCl_3$, υmax): 3290, 2100, 1850, 1640, 1150, 945, 758 cm^{-1}.;^{1}H NMR ($CDCl_3$): δ 6.99–7.33 (m, 4H, ArH), 3.80 (br, 1H, NH), 2.87–3.24 (m, 3H), 1.55–2.75 (m, 16H).;HRMS (m/z): calcd. $C_{18}H_{24}N_2$; 268.1939, found 268.1929.

2, 2, 4-Trimethyl-2, 3-dihydro-8 -methyl-1*H*-1, 5-benzodiazepine (Entry 10)
Yellow solid; M. P. 126ºC ;IR ($CHCl_3$, υmax): 3325, 2800, 2200, 1665, 1450, 1150, 945, 850, 710 cm^{-1}.;^{1}H NMR ($CDCl_3$): δ 7.05– 7.10 (m, 1H), 6.70–6.80 (m, 1H), 6.65–6.75 (s, 1H), 2.80 (s, 3H), 2.23 (s, 3H), 2.19 (s, 2H), 1.30 (s,6H).;^{13}C NMR ($CDCl_3$) :δ174.3, 138.1, 136.7, 127, 126.6, 122.6, 67, 45.8, 30.8, 30.8, 30.4, 29.6, 20.9.;Elemental Analysis: $C_{13}H_{18}N_2$; Calcd. C, 77.18,H, 8.97, N, 13.85. Found C, 77.10, H, 8.78, N, 13.72.

2-Methyl-2, 4- diphenyl – 2 , 3 – dihydro – 8- methyl-1*H*-1,5-enzodiazepine (Entry 11)
Yellow solid; M. P. 92ºC: IR ($CHCl_3$, υmax): 3275, 2750, 2100, 1659, 1240, 1045, 935, 850, 745 cm^{-1}.; ^{1}H NMR($CDCl_3$): δ 6.70–7.69 (m, 13H), 3.5(brs, 1H), 3.13–3.17 (d, J= 13 Hz, 1H), 2.98–3.03 (d, J= 13 Hz, 1H), 2.41(s, 3H), 1.8 (s, 3H).;^{13}C NMR $CDCl_3$) : δ164.6, 136.9, 134, 131.2, 130.8, 129, 128.6, 128.5, 128.3, 128.2, 127.4, 126.3, 125.7, 123.5, 113.5, 51, 45.9, 28.7, 20.9.Elemental Analysis: $C_{23}H_{22}N_2$ Calcd. C, 84.63;H, 6.79; N, 8.58. Found C, 84.51; H, 6.65; N,8.42.

2, 2, 4- Trimethyl - 2, 3-dihydro – 7 , 8 -dimethyl-1H-1,5-benzodiazepine (Entry 13)
Yellow solid; M. P. 112ºC.;IR ($CHCl_3$, υmax): 3290, 2230, 1635, 1240, 1035, 850, 745.cm^{-1};^{1}H NMR($CDCl_3$): δ 6.52(s, 1H), 6.39 (s, 1H), 2.80 (brs, 1H), 2.34 (s, 3H), 2.22 (s, 2H), 2.20 (s, 3H), 2.19 (s, 3H), 1.35 (s, 6H).;^{13}C NMR($CDCl_3$): δ 171.3, 138.4, 135.5, 133.6, 129.9, 127.8, 122.8, 67.7, 45.3, 30.4, 30.3, 29.8, 19.1, 18.9.;
Elemnetal Analysis: $C_{14}H_{20}N_2$ Calcd. C, 77.73; H, 9.32; N, 12.95. Found C, 77.52; H, 9.15; N, 12.82.

2-Methyl- 2, 4-diphenyl-2 , 3 – dihydro – 7 ,8 -dimethyl-1H-1,5-benzodiazepine (entry 14): Pale yellow solid; M. P. 115ºC;IR($CHCl_3$, υmax): 3285, 2200, 1950, 1635, 1130, 1050, 940, 835 cm^{-1} ;^{1}H NMR($CDCl_3$): δ 7.50–7.60 (m, 4H), 7.30–7.18 (m, 6H), 7.15 (s, 1H), 6.6 (s, 1H), 3.45 (brs, 1H), 3.10 (d, J= 12.8 Hz, 1H), 2.90 (d, J= 12.8 Hz, 1H), 2.25 (s, 6H), 1.70 (s,3H).;^{13}C

NMR($CDCl_3$): δ 166.8, 147.8, 139.7, 137.6, 135.7, 134.8, 129.6, 129.4, 128.2, 127.8, 126.9, 126.8, 125.4, 122.3, 73, 43.2, 29.7, 19.3, 18.6.;Elemental Analysis: $C_{24}H_{24}N_2$ Calcd. C, 84.67;H, 7.11; N, 8.23. Found C, 84.42; H, 7.02; N,8.15.

2-Methyl-2, 4-diphenyl-2 , 3-dihydro-8-nitro- 1H-1,5-benzodiazepine (Entry 16):

Dark yellow solid; M. P. 136ºC; IR($CHCl_3$, υmax): 3300,2150, 1950,1651,1430,1250,1085,970, 850. cm^{-1}; ^{1}H NMR($CDCl_3$): δ 6.80–7.95 (m, 13H), 4.40(brs, 1H), 3.35 (d, J = 12.6 Hz, 1H), 3.05–3.15 (d, J =12.6 Hz, 1H), 1.80(s, 3H).

^{13}C NMR ($CDCl_3$): δ 168.4, 145, 136.9, 132.4, 130.8, 129, 128.6, 126.2, 121.2, 118.3, 60.8, 45.6, 29.2.;Elemental Analysis: $C_{22}H_{20}N_3O_2$;Calcd. C, 73.72; H, 5.62; N, 11.72. Found C,73.62; H, 5.51; N, 11.53.

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REFERENCES

[1] Sternbach L. H., (1971) Angew chem. Int Ed Engl, 10, , 34.

[2] De Clercq E. J. (1995) Med. Chem. 38 , 2491.

[3] (a) De Lucca, G.V., Otto M.J. ,(1992) Bioorg. Med. Chem. Lett. 2 , 1639.(b) Patel U.R. , Proudfoot J.R. (1992) J. Org. Chem. 57 , 4023(c) Proudfoot, J.R. (1995) Bioorg. Med. Chem. Lett. 5 , 163.

[4] (a) Artico M. , Silvestri R. , Pagnozzi E. , Stefancich G., Massa S. , Loi A.G ., Putzolu M.., Corrias S. , Spiga M.G. , La Colla P. (1996) Bioorg. Med. Chem. Lett. 4 , 837. (b) Vig R. , Mao C. , Venkatachalam T.K. , Tuel-Ahlgren L. , Sudbeck E.A., Uckun F.M. (1998) Bioorg. Med. Chem. Lett. 8, 1461. (c) Pauwels R. , Andries K. ,Desmyter J. , Schols D. , Kukla M. , Breslin H. Raeymaekers A. ,Van Gelder J. , Woestenborghs R. , Heykants J. , Schellekens, K., Janssen M.A. , De Clercq E. , Janssen P. (1990) Nature 343, 470.(d) Ho W. , Kukla M.J. , Breslin H.J. , Ludovici D.W. ,Grous P.P., Diamond C.J., Miranda, M. Rodgers J.D. , Ho C.Y. , DeClercq E. , Pauwels R., Andries K.,Janssen M.A.C. , Janssen P.A.J. (1995) J. Med. Chem. 38, 794.(e) Pfaendler, H.R. ; Weisner, F. (1995) Heterocycles (40 , 717.

[5] (a) Schutz, H. (1982) Benzodiazepines; Springer Verlag: Heidelberg, Germany (b) Landquist, J. K. (1984) In Comprehensive Heterocyclic Chemistry; Katritzky, A. R. and Rees, C. W. (Eds); Pergamon: Oxford Vol. 1, p. 116. (c) Orlov, V. D.,Desenko, S. M., Kolos, N. N. (1984), Chem. Heterocycl. Compd. 20, 106–111.

[6] (a) Werner W., Baumgart, J., Burckhardt G., Fleck W. F., Geller K., Gutsche W., Hanschmann H., Messerschmidt A., Roemer W. (1990) Biophys. Chem. 35, 271–285. (b) Herpin T. F., Van Kirk K. G., Salvino J. M., Yu S. T., Labaudinie`re, R. F. (2000) J. Comb. Chem. 5, 513–521. (c) Hamann, L. G., Ding C. Z., Miller A. V., Madsen C. S., Wang P., Stein P. D. Pudzianowski A. T., Green, D. W. Monshizadegan H. , Atwal K. S. (2004) Bioorg. Med. Chem. Lett. 14, 1031–1034.

[7] (a) Atwal K. S., Bergey J. L.,Hedberg A., Moreland S. (1987) J. Med. Chem. 30, 635–640.(b) Merluzzi V., Hargrave K. D., Labadia M., Grozinger K., Skoog M., Wu J. C., Shih C. K., Eckner K., Hattox S., Adams J., Rosenthal A. S.,Faanes R.,Eckner R. J., Koup R. A., Sullivan J. L. (1990) Science 250,1411–1413. (c) Di Braccio M., Grossi G., Roma G., Vargiu L., Mura M., Marongiu M. E. (2001) Eur. J. Med. Chem. 36, 935–949. (d) Tranquillini M. E., Cassara P. G., Corsi M., Curotto G., Donati D., Finizia G., Pentassuglia G., Polinelli S., Tarzia G., Ursini, A., Van Amsterdam, F. T. M. (1997) Arch.Pharm. 330, 353–357.

[8] Haris, R. C.; Straley, J. M. Cationic polymethine dyes for acrylic fibers. US Patent, 1537757, 1968; Chem. Abstr. 1970, 73, 100054w.

[9] Aversa M. C., Ferazzo A., Giannetto P., Kohnke F. H. (1986) Synthesis 230.

[10] Chimirri A., Grasso S., Ottana R., Romeo G., Zappala M. J. (1990) Heterocyclic Chem. 27, 371.

[11] Herbert J. A. L., Suschitzky H. (1974) J. Chem. Soc., Perkin Trans. 1 2657.

[12] Jung D. I., Choi T. W., Kim Y. Y., Kim I. S., Park Y. M., Lee Y. G., Jung D. H. (1999) Synth.Commun. 29, 1941.

[13] Morales H. R., Bulbarela A., Contreras R. (1986) Heterocycles 24, 135.

[14] Balakrishna M.S., Kaboudin B. (2001) Tetrahedron Lett. 42, 1127.

[15] Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. (2001) Tetrahedron Lett. 42. 3193.

[16] Minothora P., Julia S. S., Constantinos A. T. (2002) Tetrahedron Lett. 43, 1755. (b) Chen W. Y., Lu, J. (2005) Synlett 8, 1337–1339.

[17] Kaboudin B., Navaee K. (2001) Heterocycles 55. 1443.

[18] Pasha M. A., Jayashankara V. P. (2006) Heterocycles 68, 1017–1023.

[19] Varala R., Enugala R.,; Nuvula S., Adapa S. R. (2006) Synlett, 7,1009–1014.

[20] (a) Reddy B. M., Sreekanth P. M. (2003) Tetrahedron Lett. 44, 4447–4449.(b) Yadav J. S., Reddy B. V. S., Praveenkumar S., Nagaiah, K., Lingaiah, N.,Saiprasad P. S. (2004) Synthesis 6, 901–904. (c) Sivamurugan, V., Deepa K., Palanichamy M., Murugesan V. (2004) Synth. Commun. 34, 3833–3846.(d) De S. K., Gibbs R. A. (2005) Tetrahedron Lett. 46, 1811–1813. (e) Du Y., Tian F., Zhao W. (2006) Synth. Commun. 36, 1661–1669. (f) Jarikote D. V., Siddiqui S. A., Rajagopal R.., Daniel T., Lahoti R. J., Srinivasan K. V. (2003) Tetrahedron Lett. 44, 1835–1838. (g) Yadav J. S., Reddy B. V. S., Eshwaraian B., Anuradha K. (2002) Green chem.. 4, 592–594.

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