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Efficient one pot synthesis of [1,2,4]triazolo[4,3-α][1,4] benzodiazepines derivatives

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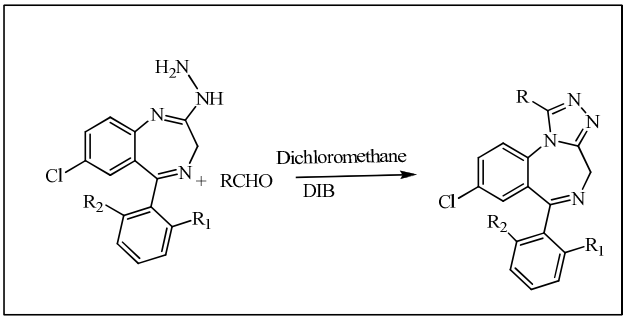
ABSTRACT

Efficient one pot synthesis of [1,2,4]triazolo[4,3-α][1,4]benzodiazepines derivatives. chloro-6-phenyl-1-(substituted)-4H-[1,2,4]triazolo[4,3-α][1,4]benzodiazepine were efficiently synthesized by oxidative cyclization reaction of 2-hydrazino-1,4-benzodiazepines with various aldehydes in presence of diacetoxy iodobenzene.



INTRODUCTION

Benzodiazepine have been shown to be very good scaffold for medicinal chemistry. In addition to the well known sedative[1] tranquilizer, diuretic, muscle-relaxant,[2] anticovasculant, anxolytic activity and novel application are continuously emerging.[3-7] Five atom heterocyclic fused benzodiazepine ring system occupy prominent place among drugs for CNS disorder.[8] The introduction of alprazolam (**entry 3a**), triazolam, brotizolam and etizolam in chemotherapy has enhanced the interest in the preparation of five atom heterocyclic fused benzodiazepine ring

system. 4H-[1,2,4]triazolo[4,3-α] [1,4] benzodiazepine have not been object of new synthetic development in the last few years and recent reports on their preparation use only classical method.[9] This fact joined us to circumstance part of literature covered, so carry out studies improve the synthetic methodology, improved classical organic reaction, shortening reaction time and improved yield as well promote new reaction. The most widely used method was reaction of 1,4-benzodiazepine-2-thione with aryl or alkyl acid hydrazide in alcohol to give 2-acyl/aryl-hydrazino-1,4-benzodiazepine derivative which undergo dehydrative cyclization at high temperature to give **3**.[8a-9] Another approach where reaction of 2-hydrazino-1,4–benzodiazepine with ortho ester in alcohol presence of catalytic amount of acid to give 4H-[1,2,4]-triazolo[4,3-α][1,4] benzodiazepine **3**.[10]

Most of these synthetic approaches suffer from drawback such as harsh reaction conditions (high temperature) and multistep synthesis. N-Aryl-hydrazino-1,4-benzodiazepine derivative never undergo complete cyclization even in high boiling solvent (n-butanol) making it difficult to isolate the product from starting material. In literature heterocyclic substituted imino hydrazones undergo oxidative cyclization, thus forming imidazo[1,5-a]pyridines, imidazo[1,5-a]imidazoles, imidazo[1,5-a]isochinolines and 1,2,4-triazolo[4,3-a]pyridines.[11-15] (reference cited in them) as our part of our studies dealing with oxidative cyclization in synthesis[16]. We herein report a simple efficient method of oxidative heterocyclization reaction of 2-hydrazino-1,4-benzodiazepines with various aldehydes in presence of DIB (diacetoxyiodobenzene).

EXPERIMENTAL SECTION

Melting points were recorded on a Philip Harris C4954718 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz and 50 MHz respectively. Chemical shifts d are in parts per million (ppm) measured in $CDCl_3$ as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a "Perkin-Elmer"RX-1FT-IR" Spectrophotometer and elemental analyses were carried out on an Exeter analytical model CE440 (CHN) and a Leco elemental analyzer Truspec (CHNSO). Mass spectra were recorded on MS-3200Q trap spectrometer.

General experimental procedure for synthesis of 8-chloro-6-phenyl-1-(substituted)-4H-[1,2,4]triazolo[4,3-α] [1,4]benzodiazepine:

A solution of 2-hydrazino-1, 4-benzodiazepine 2.89 gm (1mmole), benzaldehyde1.06 gm (1mmole) in 20 ml dichloromethane stirred reaction for 30 min, followed by addition Diacetoxy iodobenzene 4.82 gm (1.5 mmol) continued stirring reaction for 30 min. Progress of reaction monitored on TLC. Hexane: ethyl acetate [1:1], upon the completion of reaction washed organic layer with 10% aq. sodium bicarbonate solution & dried over sodium sulphate. Distilled solvent on rota evaporator crude residue was obtained purified by flash chromatography with methylene chloride /ethyl acetate as solvent. Identical procedure was employed to prepare 4H-[1,2,4]triazolo-[4,3-α][1,4] benzodiazepine as shown in Table 2.

8-Chloro-1-methyl-6-phenyl-4H-[1, 2, 4] triazolo[4, 3-α] [1, 4]benzodiazepine (3a).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 2.65 (s, 3H, CH_3), 4.06 (d (J=14),, 1H, CH_2), 5.45 (d (J=14), 1H, CH_2), 7.27-7.54 (m, 7H, Ar-H) 7.64-7.69 (m, 1H, Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 11.93, 46.04, 124.60, 128.13, 129.03, 130.0, 130.59, 131.01, 131.79, 132.01, 132.92, 138.30, 149.95, 154.69, 167.74 MS (EI): m/z (m+1 =309, m+2 =311). Anal. Calcd. For $C_{17}H_{13}ClN_4$**:** C, 66.12, H, 4.21, N, 18.15. Found: C, 65.82, H, 4.36, N, 18.28.

8-Chloro-1, 6-diphenyl-4H-[1,2,4] triazolo[4, 3-α] [1,4]benzodiazepine (3d).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.12 (d, 1H, J=10Hz, CH_2), 5.54 (d, 1H, J=10Hz CH_2), 7.25-7.30 (m, 5H, Ar-H), 7.32 (d, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 7.61-7.84

(m, 5H, Ar-H), ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 46.30, 124.90, 127.50, 128.13, 129.20, 129.52, 130.52, 131.00, 131.22, 131.34, 131.66, 132.92, 133.20, 134.40, 138.40, 150.50, 154.70, 166.30. MS (EI): m/z= (m+1= 371.4, m+Na= 393.3). FT-IR (KBr): cm^{-1} 3055.0, 2926.0, 1608.5, 1482.2, 1018.3. Anal. Calcd. For $C_{22}H_{15}ClN_4$: C, 71.25, H, 4.048, N, 15.11, Found: C, 71.60, H, 3.90, N, 14.91.

8-Chloro-6-phenyl-1-(4-flurophenyl)-4H-[1, 2, 4] triazolo [4,3-α] [1,4]benzodiazepine (3e).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.14 (d (J=12),, 1H, CH_2), 5.54 (d (J=12), 1H, CH_2), 7.18-7.28 (m, 5H, Ar-H), 7.31 (d, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.48 (d, 2H, Ar-H), 7.54 (d, 1H, Ar-H), 7.87 (d, 2H,Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 46.26, 116.09, 122.34, 126.04, 128.51, 129.19, 130.37, 130.55, 131.06, 131.30, 132.64, 133.28, 138.28, 152.20, 156.86, 161.30, 166.30, 168.26. MS (EI): m/z= (m+1= 389.2, m+Na =411.4). Anal. Calcd. For $C_{22}H_{14}FClN_4$: C, 67.95, H, 3.60, N, 14.41. Found: C, 67.90, H, 3.59, N, 14.66.

8-Chloro-6-phenyl-1-(4-chlorophenyl)-4H-[1, 2, 4]triazolo[4,3-α] [1, 4]benzodiazepine (3f).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.95 (d (J=13.2), 1H, CH2), 5.511 (d (J=13.2), 1H, CH2) 6.77(d, 1H Ar-H), 6.80-6.96(m, 3H, Ar-H), 7.18-7.43 (m, 8H, Ar-H): ^{13}CNMR(50MHz, $CDCl_3$): δ (ppm): 46.24, 124.69, 126.02, 128.46, 129.15, 129.28, 129.54, 130.34, 131.01, 131.26, 131.38, 132.58, 133.25, 136.58, 138.21, 152.06, 156.98, 168.16. MS (EI): m/z= (m+1 =405, m+4= 408, m+Na =427) Anal. Calcd. For $C_{22}H_{14}Cl_2N_4$: C, 65.34, H, 3.46, N, 13.86. Found: C, 65.34, H, 3.43, N, 13.83.

8-Chloro-6-phenyl-1-(4-bromophenyl)-4H-[1, 2, 4]triazolo[4,3-α] [1, 4] benzodiazepine (3g).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.13 (d (J=12), 1H,-CH2), 5.53 (d (J=12), 1H,-CH2), 6.94 (d, 1H, Ar-H), 7.40-7.50 (m, 7H, Ar-H), 7.58-7.67 (m, 4H, Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 45.58, 124.23, 124.56, 125.56, 127.84, 128.59, 129.20, 129.27, 129.56, 130.35, 131.06, 131.21, 131.60, 132.57, 137.64, 151.51, 156.30, 167.62; MS (EI):m/z= (m+1 =451, m+4= 453, m+Na =471, 473), Anal. Calcd. For $C_{22}H_{14}BrClN_4$: C, 58.73, H, 3.11, N, 12.45, Found: C, 58.62, H, 3.08, N, 12.49.

8-Chloro-6-phenyl-1-(4-methoxyphenyl)-4H-[1, 2, 4]triazolo[4,3-α] [1,4]benzodiazepine (3h).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.87 (s, 3H -OCH3), 4.13 (d (J=14), 1H, CH2), 5.51 (d (J=14), 1H, -CH2), 6.94-7.02 (m, 3H, Ar-H), 7.36-7.53 (m, 6H, Ar-H) 7.61-7.86 (m 3H, Ar-H), MS (EI): m/z= (m+1= 401, m+2= 402, m+Na= 423). Anal. Calcd. For $C_{23}H_{16}ClN_4O$: C, 69.08, H, 4.00, N, 14.00, Found: C, 69.18, H, 3.98, N, 14.10.

8-Chloro-6-phenyl-1-(4-hydroxyphenyl)-4H-[1,2,4]triazolo[4,3-α] [1,4]benzodiazepine (3i).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.10 (d, 1H, -CH2), 5.50 (d, 1H, -CH2), 5.63(s, 1H, OH), 6.86(d, 2H,Ar-H), 7.20(d, 1H, Ar-H), 7.69-7.71(m, 6H, Ar-H), 7.64-7.85(m, 3H, Ar-H).
Anal. Calcd. For $C_{22}H_{15}ClN_4O$: C, 68.30, H, 3.88, N, 14.48. Found: C, 68.15, H, 3.80, N, 14.40.

8-Chloro-6-phenyl-1-(pyridin-4-yl)-4H-[1, 2, 4]triazolo[4,3-α] [1, 4]benzodiazepine (3j).

^{1}H NMR (200MHz, $CDCl_3$) δ (ppm): 4.07(d, (J=12.4) 1H, CH2), 5.48 (d, (J=12.4) 1H, CH2), 6.99 (d, 1H, Ar-H), 7.29-7.51 (m, 5H, Ar-H), 7.54(m, 2H, Ar-H), 7.65(d, 2H, Ar-H), 8.77(d, 2H, Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 46.40, 121.30, 125.00, 128.8, 129.20, 130.5, 131.00, 131.10, 131.30, 131.80, 134.00, 134.4, 139.00, 149.80, 153.00, 155.3, 168.60. MS (EI): m/z= (m+1= 372.38, m+3= 374.4, M+Na= 394.5); FT-IR:(KBr)cm^{-1}:3040.0, 2962.0, 1614.5, 1480.2, And 1026.3; Anal. Calcd. For $C_{21}H_{14}ClN_5$: C, 67.83, H, 3.76, N, 18.84 Found: C, 67.43, H, 3.64, N, 18.64.

8-Chloro-6-phenyl-1-(pyridin-3-yl)-4H-[1,2, 4] triazolo[4,3-α] [1,4]benzodiazepine (3k).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 4.20 (d (J=12.8) , 1H, CH2), 5.60 (d(J=12.8), 1H, CH2), 6.97 (d, 1H, Ar-H), 7.29-7.57 (m, 6H, Ar-H), 7.65-7.67 (m, 2H, Ar-H), 8.06 (d, 1H, Ar-H), 8.72 (d, 1H, Ar-H), 8.77(d, 1H, Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 45.42, 122.06, 123.17, 125.33, 127.90, 128.57, 129.70, 130.39, 130.69, 131.07, 131.57, 132.73, 135.12, 137.53, 147.93, 149.80, 150.47, 156.50, 167.64; Anal. Calcd. For $C_{21}H_{14}ClN_5$: C, 67.83, H, 3.76, N, 18.84 Found: C, 67.73, H, 3.68, N, 18.84.

8-Chloro-6-phenyl-1-(2-methyl pyridin-3-yl)-4H-[1,2 4]triazolo[4,3-α] [1, 4] benzodiazepine (3l).

^{1}H NMR (200 MHz , $CDCl_3$): δ (ppm): 2.60 (s, 3H, CH3) , 4.10 (d(J=12.8), 1H, -CH2), 5.42 (d(J=12.8), 1H,-CH2), 6.93 (d, 1H, Ar-H), 7.34-7.49 (m, 6H, Ar-H), 7.53-7.58 (m, 2H, Ar-H), 7.80(m, 1H, Ar-H), 8.56(m, 1H, Ar-H); Anal. Calcd: For $C_{22}H_{16}ClN_5$: C, 68.48, H, 4.15, N, 18.15, Found: C, 68.38, H, 3.97, N, 18.28.

8-Chloro-6-phenyl-1-(4-nitrophenyl)-4H-[1, 2, 4]triazolo[4,3-α] [1,4]benzodiazepine (3m).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.07 (d(J=14), 1H, -CH2), 5.45 (d (J=14), 1H, -CH2), 6.84 (d, 1H, Ar-H), 7.34-7.46 (m, 5H, Ar-H), 7.54-7.71 (m, 2H , Ar-H), 7.80 (d, 2H, Ar-H), 8.22 (d, 2H, Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$):45.41, 122.02, 123.49, 125.52, 127.84, 128.88, 129.69, 130.48, 130.78, 131.07, 131.50, 132.94, 137.46, 147.91, 150.2, 156.89, 167.70, 172.42; FT-IR: (KBr): cm^{-1} 3041.5and 2964.1(–CHstr), 1614.3(–C = N), 1540, 1330(N=O), 1481.2 (–CH2), 1026.1 cm–1 (Ar–Cl). MS (EI): m/z= 415 (m+1=416, m+2= 417, m+Na= 438, m-1= 414): Anal. Calcd. For $C_{22}H_{14}ClN_5O_2$: C, 63.53,H, 3.36, N, 16.84. Found: C, 63.58, H, 3.32, N, 16.76.

***8-Chloro-6-phenyl-1-(3-nitrophenyl)-4H-[1, 2,4]triazolo[4,3-α][1,4]benzodiazepine* (3n).**

^{1}H NMR (200 MHz,$CDCl_3$) δ (ppm): 4.20 (d(J=14), 1H, CH_2), 5.49 (d(J=14), 1H, CH_2), 7.01 (d, 1H, Ar-H), 7.44-7.52 (m, 5H, Ar-H), 7.58-7.75 (m, 3H, Ar-H), 7.81 (d, 1H, Ar-H), 8.35 (d, 1H, Ar-H), 8.54 (d, 1H, Ar-H); Anal. Calcd. For $C_{22}H_{14}ClN_5O_2$: C, 63.53, H, 3.36, N, 16.84 Found: 63.48, H, 3.29, N, 16.88.

8-Chloro-6-phenyl-1-(3,5-bistrifluromethylphenyl)-4H-[1,2,4] triazolo[4,3-α] [1,4] benzodiazepine (3o).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.20 (d(J=12), 1H, -CH2), 5.49 (d(J=12), 1H, -CH2), 7.01(d, 1H), 7.49-7.64(m, 7H), 8.02(s, 1H), 8.08(s, 2H); MS (EI): m/z= (m+1=507.6, m+2=509.7, m+Na =529).

8-Chloro-6-phenyl-1-(2-furyl)-4H-[1,2,4] triazolo[4,3-α] [1, 4 benzodiazepine (3p).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.22 (d, 1H,-CH2), 5.64 (d, 1H, -CH2), 6.57 (dd, 1H, Ar-H), 6.92 (d, 1H, Ar-H),7.13 (s, 1H, Ar-H), 7.20-7.26 (m, 6H, Ar-H), 7.36 (d, 1H, Ar-H), 7.61 (d,1H, Ar-H): Anal. Calcd. For $C_{20}H_{13}ClN_4$: C, 66.57, H, 3.60, N, 15.53.Found: C, 66.32, H, 3.78, N, 15.49.

8-Chloro-6-(2-fluoro phenyl-1-(pyridin-4-yl)-4H-[1,2,4]triazolo[4,3-α] [1,4] benzodiazepine (3q).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.22 (d(J=10.44), 1H, CH_2), 5.64 (d(J=10.44), 1H, CH_2), 7.03-7.11 (m, 2H, Ar-H), 7.31 (t, 1H, Ar-H),7.36-7.44 (m, 3H, Ar-H), 7.54 (d, 1H, Ar-H), 8.01 (d, 2H, Ar-H), 8.72 (d, 2H, Ar-H): ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 46.32, 116.29, 122.19, 124.91, 125.94, 126.87, 126.40, 130.80, 131.55, 131.94, 132.96, 133.03, 133.72, 134.00, 134.31, 150.70, 151.33, 157.59, 160.42, 165.40. MS (EI): m/z= 389.5(m+1= 390); FT-IR: (KBr) cm^{-1}: 3041.5, 2964, 1613, 1478, 1079, 1026.12. Anal. Calc. for $C_{21}H_{13}ClFN_5$: C, 53.91, H, 3.33, N, 17.97 Found: 53.95, H, 3.37, N, 17.98.

8-Chloro-6-(2-fluorophenyl)-1-pyridin-3-yl-4H-[1,2,4]triazolo[4,3-α][1,4]benzodiazepine (3r).

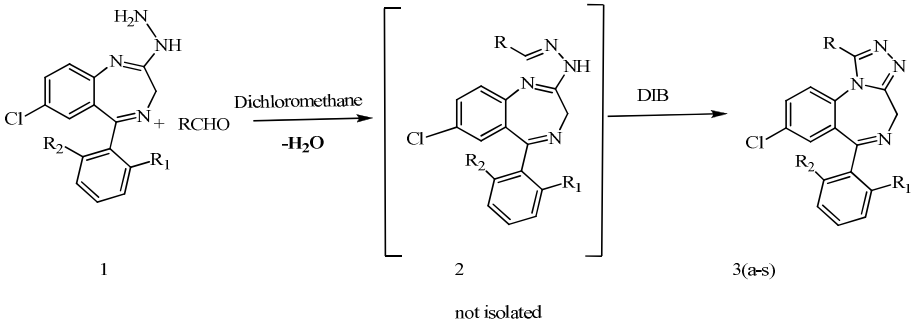
^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.17 (d (J=10.4)1H, –CH_2), 5.60 (d (J=10.4), 1H, CH_2), 6.94 (d, 1H, Ar–H), 7.05-7.28 (m, 2H, Ar–H), 7.30 (m, 3H, Ar–H), 7.48 (s, 1H, Ar–H), 7.74 (s, 1H, Ar–H), 7.87 (d, 1H, Ar–H), 8.70 (d, 1H, Ar–H), 8.76 (s, 1H, Ar-H): ^{13}C NMR: ($CDCl_3$, 50 MHz) δ(ppm):47.31, 117.17, 123.74, 124.56, 125.65, 126.55, 127.77, 127.86, 130.56, 131.67, 131.88, 132.46, 132.85, 133.72, 133.78, 134.96, 136.59, 149.89, 151.79, 152.18, 159.12
162.23, 166.25 MS: m/z (m+1= 391 m+2=392,) Anal. Calc. For $C_{21}H_{13}ClFN_5$: C, 53.91, H, 3.33, N, 17.97 Found: C, 53.95, 3.45, N, 17.96

8-Chloro-6-(2-fluorophenyl)-1-(4-fluorophenyl)-4H-[1,2, 4]triazolo[4,3-α][1, 4]benzodiazepine (3s).

^{1}H NMR: (200 MHz, $CDCl_3$) δ (ppm): 4.20 (d (J=12.2), 1H, CH_2), 5.58 (d (J=12.2) 1H, CH2), 6.96 (d, 1H, Ar–H), 7.05 (d ,1H, Ar–H), 7.13 (dd , 2H, Ar–H), 7.45 (m, 2H, Ar–H), 7.52 (dd, 2H, Ar–H), 7.59 (m, 1H, Ar–H): ^{13}C NMR: ($CDCl_3$,50MHz) δ (ppm): 46.40, 116.24, 116.30, 116.40, 116.53, 122.43,124.84, 125.99, 126.96, 127.11, 129.46, 130.51, 130.63,130.84, 131.32, 131.96, 132.80, 132.91, 133.78, 154.69, 165.43, 165.58. FT-IR: (KBr): cm^{-1} 3065.5 and 2925.8 (–CH stretch), 1610.5(–C = N), 1481(–CH2), 1231.5 (Ar–F), 1103.2 (Ar–Cl);
Anal. Calc. for $C_{22}H_{13}ClF_2N_4$: C, 64.94, H, 3.19, N, 13.77 Found: 64.84, H, 3.09, N, 13.75.

RESULT AND DISCUSSION

DIB are most interesting oxidant in organic synthesis, as they are stable in different solvents, commercially available and have been used for oxidation processes [17] imino-hydrazone cyclization reaction1,2,4-triazolo[4,3-a]pyridines and 1,2,4-triazolo[4,3-a]quinolines as antibacterial agents.[18] We have explored the possibility of using DIB as an oxidant for oxidative cyclization of hydrazino **2** derivatives to afford compounds **3a-s Scheme 1.**



Scheme 1: Synthesis of 8-chloro-6-phenyl-1-(substituted)-4H-[1,2,4]triazolo[4,3-α][1,4] benzodiazepineby oxidative cyclization

Table 1: Effect of different oxidant on the oxidative cyclization of hydrazone 2 for entry 3d

Entry no	reagent	Yield %
1	IBX	No reaction
2	NCS/DBU	35
3	CAN	55
4	$PhI(OAc)_2$	80
5	DDQ	Undesired produc
6	MnO2	30
7	KMnO4	30
8	$Pb(OAc)_4$	70

To assess the efficacy DIB over different oxidants for the oxidative cyclization of 2 with different oxidants were performed using reaction of benzaldehyde and 2-hydrazino-1, 4-benzodiazepine 1 as model reaction (entry 1d). Dichloromethane were used as solvent for all reactions. IBX in dichloromethane failed to oxidize the substrate, while DDQ led to rapid disappearance of starting material, albeit with no desired product formation. NCS/DBU, MnO_2, $KMnO_4$ in dichloromethane, abtained of the desired product in low yield. Lead (IV) acetate giving good yield but required excess quantity. However, this method has some restrictions as

regards their applicability and toxicity. Thus it is obvious from this study that oxidizing performance of DIB was superior in this oxidizing cyclization protocol Table1

Heterocyclization was carried out in dichloromethane because good solubility of hydrazino1,4-benzodiazepine **1**, after the hydrazino 1,4-benzodiazepine **1** had been dissolved, added one equivalent of aldehyde stirred at room temperature for 30 min followed by addition of 1.5 equivalents of DIB continued stirring at room temperature. The reaction had been completed within 30 min when its initially pale yellow colour turned to violet due to the overwhelming tendency of iodobenzene for reductive elimination. Washed reaction mixture with aq.bicarbonate sol, distilled solvent and crude product were purified by column chromatography and yield are given in Table 2.

Table 2: DIB mediated synthesis of 8-chloro-6-phenyl-1-(substituted)-4H-[1,2,4]triazolo[4,3-α][1,4]benzodiazepine (3a-s)

Entry	R	R_1	R_2	Yield %	Melting Point ^{0}C
3a	CH_3	H	H	69	228-230 [228-228.5][8b]
3b	C_2H_5	H	H	72	231-233 [231.5-232.5] [8b]
3c	n-C_3H_7	H	H	70	175-178 [176-176.5] [8b]
3d	C_6H_5	H	H	80	194-196 [193.5-194.5] [8b]
3e	4-F-C_6H_4	H	H	75	135-138
3f	4-Cl-C_6H_4	H	H	80	235-237
3g	4-Br-C_6H_4	H	H	78	245-247
3h	4-OMe C_6H_4	H	H	69	142-145
3i	4-OH-C_6H_4	H	H	65	235-240
3j	4-pyridyl	H	H	68	163-165
3k	3-Pyridyl	H	H	75	191-194
3l	2CH_3-3pyridyl	H	H	80	135-138
3m	4-NO_2-C_6H_5	H	H	70	287-289
3n	3-NO_2-C_6H_5	H	H	74	295-296
3o	3,5-CF_3-C_6H_3	H	H	55	211-214
3p	2-furyl	H	H	40	165-167
3q	4-pyridyl	F	H	65	205-208 [204-206] [9a]
3r	3-pyridyl	F	H	63	175-178[178-180] [9a]
3s	4-F-C_6H_4	F	H	79	153-157 (154-156) [9a]

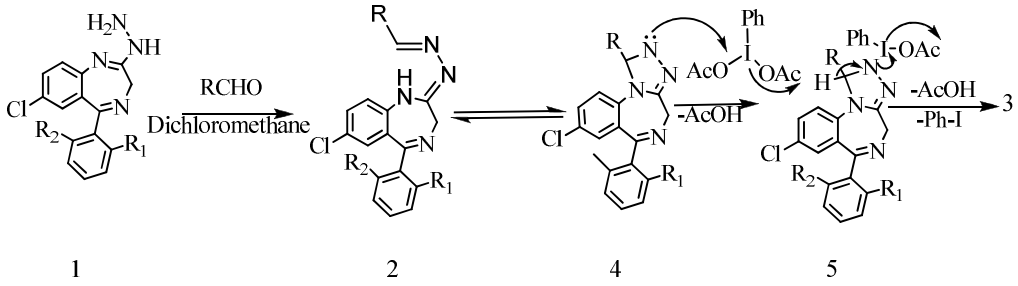
[a] Reactions were carried out on a 1-mmol scale in Dichloromethane at room temperature with DIB (1:5 equiv). [b]Yields obtained after column chromatography. [C]melting point in [ ] Square bracket are reported in literature

As reported in Table 2, Comparison of the reactivities of the tested imino hydrazones (aldazine) **2** indicates that the cyclization is not strongly affected by the substituent R. The reactivity to remains unchanged when the phenyl group in the hydrazones is replaced by an n-alkyl residue.

In addition, hydrazones of donor-substituted benzaldehyde (R-methoxyphenyl and 4-hydroxy-phenyl) and those bearing an acceptor substituent R4-chloro-phenyl,R4 bromophenyl), R-3,5-bistrifluromethyl phenyl, 4-nitrophenyl and 3-nitrophenyl) yielded triazoles under similar conditions. Functionalities of the substrate are maintained, even when substituents susceptible to

oxidation, e.g. a hydroxy group, are considered. On the other hand, the influence of the nature of the heterocyclic moiety is more significant. If the [–NH–N] CH group is attached to a six-membered nitrogen containing ring, the triazoles are obtained in a smooth reaction. The lower selectivity in the oxidation of indicates that a five-membered ring is less favorable however, the yield is low.

As regarding the mechanism concern oxidative cyclization undergo as earlier described in literature.[19] Possible mechanism using DIB is depicted in **Scheme 2**.



Scheme 2: Possible mechanism using DIB.

First step is reaction 2-Hydrazino-1,4-benzodiazepine **1** with aldehyde to give intermediate **2**. Ligand–exchange reaction between electrophilic DIB and **2** will generate putative intermediate **4**. The overwhelming tendency of Iodobenzene for reductive elimination from intermediate **5** will give compound **3**.

CONCLUSION

In conclusion this investigation constitute a robust and efficient route for construction of triazolo [4,3α] [1,4] benzodiazepine by oxidative cyclization using of DIB. This method stands as a feasible alternative for convenient access to this class of Heterocycle.

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