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MTSA on Neutral Alumina as an Efficient Catalyst for the Synthesis of Substituted 1,5-Benzodiazepines in the Solid State

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ABSTRACT

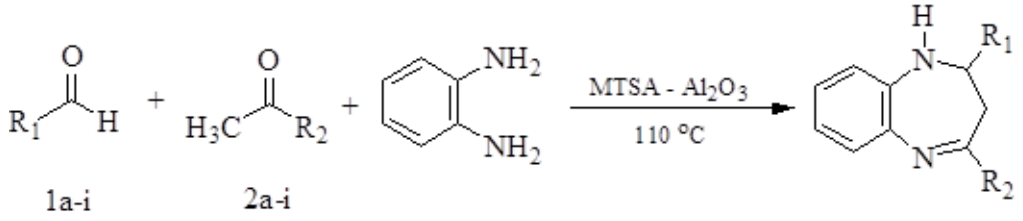
A simple and versatile method for the synthesis of substituted 1,5-benzodiazepines on MTSA-Neutral Al_2O_3 in the solid state is reported. The substituted 1,5-benzodiazepines were prepared by the three component reaction of substituted aldehydes, substituted acetophenones and o-phenylenediamine in the solid state. The chemical structure of the newly synthesized compounds has been confirmed by IR, 1H NMR, mass spectra and elemental analysis.

Keywords: MTSA-neutral alumina, 1.5-benzodiazepines, o-phenylenediamine, Solid state

INTRODUCTION

Benzodiazepines receive considerable attention because of their important biological activities [1]. They show anticancer [2], anticonvulsant [3], antimicrobial, antioxidant, antihelmintic and antibacterial activities [4]. Also 1,5-benzodiazepines are key intermediates for various fused ring systems such as triazolo-, oxadiazolo-, oxazino-or furanobenzodiazepines [5-7]. Benzodiazepines also find use in as dyes for acrylic fibres in photography [8]. Owing to their versatile importance, various methods in literature have been reported. These methods involve acid catalysed cyclocondensation of o-phenylenediamine with α,β-unsaturated carbonyl compounds [9] ketones [10], using piperidine-AcOH [11], $Ga(OTf)_3$ [12], HPW/SiO_2 [13], MoO_3/SiO_2 [14], sulphated zirconia [15] and use of microwave irradiation technique [16]. Unfortunately many of these catalysts suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yield and tedious workup procedure.

Therefore, here in this methodology melamine trisulphonic acid on neutral alumina as a solid support is reported.



1a-i 2a-i 3a - i

1a: R_1=3-$NO_2C_6H_5$, R_2=-C_6H_5

1b: R_1=4-ClC_6H_5, R_2=-C_6H_5

1c: R_1=3-$OCH_3C_6H_5$, R_2=-C_6H_5

1d: R_1=2-ClC_6H_5, R_2=4-ClC_6H_5

1e: R_1=2-OHC_6H_5, R_2=4-$NH_2C_6H_5$

1f: R_1=H, R_2=-C_6H_5

1g: R_1=4-$NO_2C_6H_5$, R_2=3-$NO_2C_6H_5$

1h: R_1=4-$NO_2C_6H_5$, R_2=4-$OCH_3C_6H_5$

1i: R_1=2-ClC_6H_5, R_2=4-$OCH_3C_6H_5$.

The catalysts was prepared by adsorbing MTSA [17] (5% w/w) on neutral alumina and activation of the air-dried mixture in a hot air oven at 110ºC for 6 h. The catalyst was reactivated, each time before use. Subsequent reactions of substituted aldehydes 1a-i, substituted acetophenone 2a-j and o-phenylenediamine with stoichiometric amount of MTSA-Al_2O_3 were carried out in a thermostatically controlled hot air oven at 110ºC for 1-2 h. The resulting products 3 a-I (70-88%) were isolated with dichloromethane, purified by column chromatography and analysed by spectral methods such as HREIMS, IR, ^{1}H NMR and ^{13}C NMR (Table 1).

Table 1: Reaction of substituted aldehydes, substituted acetophenones and o-phenylenediamine at 110ºC

Entry	R_1	R_2	Time (h)	Yield (%)	m.p. (°C)
3a	3-$NO_2C_6H_5$	-C_6H_5	1.5	75	128
3b	4-ClC_6H_5	-C_6H_5	1.3	70	117
3c	3-$OCH_3C_6H_5$	-C_6H_5	2	72	60
3d	2-ClC_6H_5	4-ClC_6H_5	1.5	70	59
3e	2-OHC_6H_5	4-$NH_2C_6H_5$	1	80	59
3	-C_6H_5	-C_6H_5	1	85	77
3g	4-$NO_2C_6H_5$	3-$NO_2C_6H_5$	2	70	69
3h	4-$NO_2C_6H_5$	4-$OCH_3C_6H_5$	1.2	75	95
3i	2-ClC_6H_5	4-$OCH_3C_6H_5$	1.5	78	55

Experiments were performed to ascertain the effect of temperature and the catalyst amount on the rate of the reaction. It was observed that at 110ºC and in the presence of 5% (w/w) of the catalyst, the reaction proceeded towards the formation of 1,5-benzodiazepines in short reaction time and high yield. Increase in the amount of the catalyst did not have any effect on the yield and the reaction time.

The reusability of the catalyst is one of the most important benefits. The catalyst can be recovered and reused for five additional times without a considerable change in the reaction times and yield.

MATERIALS AND METHODS

Reagents and chemicals

Melting points were determined with an electrothermal melting point apparatus and are uncorrected. FTIR spectra were obtained on a Nicolet Magna 550 Fourier transform Infrared spectrophotometer as KBr disc. 1H and 13C NMR spectra (400 MHz, 100 MHz) were recorded on a Brucker Advance DRX-400 spectrometer. Elemental analysis was carried out on an EA2400II elemental analyser.

General method for the synthesis of substituted 1,5-benzodiazepines (3a-3i)

Substituted aldehydes (1a-i), substituted acetophenones (2a-2i) and o-phenylenediamine in the molar ratio (1:1:1) with stoichiometric amount of MTSA-Al_2O_3 were grinded in pestle-mortar. Then the mixture was transferred in a stoppered round bottom flask and kept in a hot air oven at 110ºC for 1-2 h. The resulting products 3a-3i (70-88% yield) was isolated with dichloromethane, purified by column chromatography over silica gel.

Spectral data

3a. 2-(3′-Nitrophenyl)-4-phenyl-1H-benzo[b][1,5]diazepine

Dark brown crystals. IR: υ_{max} 3360, 3050, 1591, 1563, 1272, 804 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ 3.36(1H, NH, s, D_2O exchangeable), 7.25-8.61 (14H, m, Ar-H).

^{13}C-NMR: δ 81.0, 116.6, 119.1, 119.2, 120.3, 124.1, 127.1, 127.8, 128, 130, 132.2, 136, 140, 147, 163.

HREIMS (m/z): 341.90, 342[M+1]$^+$, 296.12, 265.09, 220.09, 145.06.

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.82; H, 4.40; N, 12.29.

3b. 2-(4′-Chlorophenyl)-4-phenyl-1H-benzo[b][1,5]diazepine

Creamy crystals IR: υ_{max} 3406, 3067, 1586, 1555, 1271, 680 cm^{-1}.

^{1}H-NMR ($CDCl_3$-d_6): δ 3.82(1H, s, NH), 7.22-8.04(14H, m, Ar-H). ^{13}C-NMR δ: 81.2, 116.3, 119.3, 122.1, 125.3, 130.2, 140.1., 147.6, 163.3.

HREIMS (m/z): 330.09, 331[M+1]$^+$, 296.13, 254.08, 220.09, 144.06.

Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.53; Cl, 10.68; N, 8.47%.

Found: C; 76.21, H; 4.48, Cl; 10.50, N; 8.41.

3c. 2-(3'-Methoxyphenyl)-4-phenyl-1H-benzo[b][1,5]diazepine

Yellow amorphous solid; IR: υ_{max} 3403, 3060, 2925, 1587, 1556, 1256, 1098 cm^{-1}.

^{1}H-NMR (DMSO-d_6) δ: 3.31(3H, s, OCH_3), 4.32(1H, s, NH), 6.96 – 8.09(14H, m, Ar-H).

^{13}C-NMR: δ 54.1, 81.2, 109.4, 111.3, 117.5, 119.3, 127.8, 128.2, 137.2, 148.3, 163.4.

HREIMS (m/z): 326.13, 327 $[M+1]^+$, 296.13, 250.10, 220.08, 144.04.

Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.54; N, 8.57.

Found: C; 80.91, H; 5.52, N; 8.56.

3d. 2-(2'-Chlorophenyl)-4-(4''-Chlorophenyl)-1H-benzo[b][1,5]diazepine

Dark brown crystals; IR: $\upsilon_{max.}$ 3386, 3059, 1597, 1537, 1271, 771 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ4.22(1H,s,N-H),7.25-8.61(13h,m,Ar-H).

^{13}C-NMR δ: 80.9, 115.4, 119.2, 121.6, 126.4, 127.2, 127.3, 130.0, 134.1, 137.1, 147.7, 162.8.

HREIMS (m/z): 364.01, 365$[M+1]^+$, 330.00, 296.13, 220.10, 144.07, 265.09.

Anal. Calcd. for $C_{21}H_{14}Cl_2N_2$: C, 69.04; H, 3.87; Cl, 19.42; N, 7.68.

Found: C; 69.01, H; 3.82, Cl; 19.38, N; 7.64.

3e. 4-(4'-Aminophenyl)-2-(2''-hydroxyphenyl)-1H-benzo[b][1,5]diazepine

Black crystals; IR: υ_{max} 3595, 3486, 3070, 1535, 1523, 1269 cm^{-1}.

^{1}H-NMR (DMSO-d_6); δ 6.14 (2H, s, NH_2), 3.47 (1H, s, N-H), 7.14-8.08 (13H, m, Ar-H), 10.4 (1H, s, OH).

^{13}C-NMR δ: 80.6, 107.9, 114.3, 114.6, 116.6, 118.2, 121.2, 126.4, 128.3, 140.1, 147.6, 147.8, 157.2, 162.8.

HREIMS (m/z): 328.38, 329$[M+1]^+$, 311.13, 296.13, 220.10, 144.07.

Anal. Calcd. for $C_{21}H_{18}N_3O$: C, 77.04; H, 5.23; N, 12.84.

Found: C; 77.01, H; 5.20, N; 12.81.

3f. 2,3-dihydro-2,4-diphenyl-1H-benzene[b][1,5] diazepine

Light yellow crystals. IR: υ_{max} 3387, 3060, 1568, 1550, 1270 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.9(d, 2H, CH_2), 2.2(t, 1H, CH), 3.9(s, 1H, NH), 6.9–7.2(8H, Ar-H), 7.4-7.8(4H, Ar-H), 7.8-8(2H, Ar-H).

^{13}C-NMR ($CDCl_3$) δ: 38.2, 63.4, 113.6, 122.4, 125.9, 126.2, 127.3, 128.1, 128.9, 129.7, 132.4, 142.3, 144.8, 163.3

HREIMS (m/z): 298.38(M+), 299.25(M+1).

Anal. for $C_{21}H_{18}N_2$: C, 84.5; H, 6.04; N, 9.3.

Found: C; 84.1, H; 6.01, N; 9.0.

3g: 4-(3'-Nitrophenyl)-2-(4''-nitrophenyl)-1H-benzo[b][1,5]diazepine

Black crystals, IR: υ_{max} 3390, 3082, 1548, 1532, 1347, 854 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 4.17(1H, s, N -H), 7.23 – 8.64(12H, m, Ar-H).

^{13}C-NMR: δ 81.2, 115.8, 118.8, 121.4, 121.8, 123.1, 126.2, 127.0, 127.9, 132.8, 137.2, 140.2, 146.5, 147.8, 163.2.

HREIMS (m/s): 386.33, 387$[M+1]^+$, 341.1, 296.1, 220.1, 144.0.

Anal. Calcd. for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50.

Found: C; 65.26, H; 3.62, N; 14.47.

3h. 4-(4'-Methoxyphenyl)-2-(4''-nitophenyl-1H-benzo[b][1,5]diazepine

Brown crystals, IR: υ_{max} 3405, 3095, 2985, 1587, 1549, 1296, 1049, 856 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 3.30(3H, s, OCH3), 4.06(1H, s, N-H), 7.25-8.6(13H, m, Ar-H).

^{13}C-NMR: δ 54.9, 80.9, 113.4, 115.8, 118.8, 120.0, 124.1, 126.1, 126.8, 137.1, 140.2, 147.8, 161.8, 163.2.

HREIMS (m/z): 371.37, 372$(M+1)^+$, 326.14, 296.13, 220.10, 144.07.

Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; C, H,4.61; N, 11.31.

Found: C; 71.13, H; 4.59, N; 11.28.

3i. 2-(2'-Chlorophenyl)-4-(4''-methyloxyphenyl)-1H-benzo[b][1,5]diazepine

Light yellow crystals, IR: 3385, 3096, 2985, 1586, 1538, 1296, 1047, 758 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 3.10(3H, s, OCH_3), 4.17(1H, s, N-H), 7.23-8.64(13H, m, Ar-H).

^{13}C-NMR: δ 54.2, 80.9, 113.1, 118.6, 122.1, 125.4, 126.2, 126.9, 129.1, 137.2, 140.2, 162.1, 162.8.

HREIMS (m/z): 360.1, 361 $[M+1]^+$, 326.14, 296.13, 220.10, 144.07.

Anal. Calcd. for $C_{22}H_{17}ClN_2O$: C, 73.23, H; 4.75, Cl; 9.83.

Found: C; 73.19, H; 4.72, Cl; 9.80, N; 7.74.

CONCLUSION

In short, an efficient method for the synthesis of substituted 1,5-benzodiazepines catalysed by MTSA–Al_2O_3 is reported. Moreover, short reaction times, high yields, ease of preparation, easy work-up procedure, low toxicity and reusability of the catalyst are the other advantages of this method.

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