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A clean, simple and efficient synthesis of 1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl] (aryl)methyl)acetamides via chlorosulfonic acid as catalyst: A green protocol

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Abstract: We reported a green, simple and efficient method for the synthesis of 1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl](aryl)methyl)acetamides employing a multi-component and one-pot condensation reaction of aryl aldehydes, benzo[1,3]dioxol-5-ol, and acetonitrile in the presence of catalytic amounts of chlorosulfonic acid at ambient temperature. To a magnetically stirred solution of benzo[1,3]dioxol-5-ol (2 mmol) and aldehyde in acetonitrile was added chlorosulfonic acid at room temperature. The reaction mixture was then stirred for 1 h. The mixture was poured into 50 mL ice-water. The solid product was filtered, washed with ice-water to give the pure product. The structures of compounds were deduced from elemental analysis and their IR, ^{1}H NMR, ^{13}C NMR spectra. This new protocol offers advantages such as mild reaction conditions, short reaction time, easy work-up, and use of an inexpensive and non-toxic catalyst, high yields of biological active products and does not involve any hazardous solvent. Therefore, this procedure could be classified as green chemistry.

Keywords: Benzo[1,3]dioxol-5-ol, $ClSO_3H$, MCRs, Green chemistry.

Introduction

Acetamido- or amino-ketone derivatives are important for their biological and pharmaceutical properties [1,2] and in the preparation of antibiotic drugs such as nikkomycine or neopolyoxines [3,4].Three-component reaction between acetophenone derivatives, as enolic systems, aromatic aldehydes and acetonitrile has been used for the synthesis of β-acetamidoketones [5]. This reaction usually has been carried out in the presence of excess amount of acetyl chloride and catalyzed by different Brönsted or Lewis acids. Similar catalytic reaction has been reported between other enolic compounds such as 2-naphthol, aromatic aldehydes and acetonitrile [6].

Three-component reaction between an enolic system such as acetophenone or β-dicarbonyl compounds, an aryl aldehyde and acetonitrile is known as the modified Dakin-West reaction. This reaction is usually carried out in the presence of an excess amount of acetyl chloride and catalyzed by an acid. A number of catalysts such as $CoCl_2$, montmorilonit K-10 clay [7], H_2SO_4/SiO_2 [8], Heteropoly acids [9] and silica sulfuric acid [10] have been employed to effect this transformation. We reported the reaction between 2-naphthol derivatives with aromatic aldehydes and acetonitrile promoted by chlorosulfonic acid affording acetamidoalkylnaphthol [11]. We also reported pseudo-three-component reaction between electron-deficient aromatic aldehydes and acetonitrile in the presence of chlorosulfonic acid producing symmetrical *N*,*N*'-bisamide derivatives [12]. Here we wish to report that

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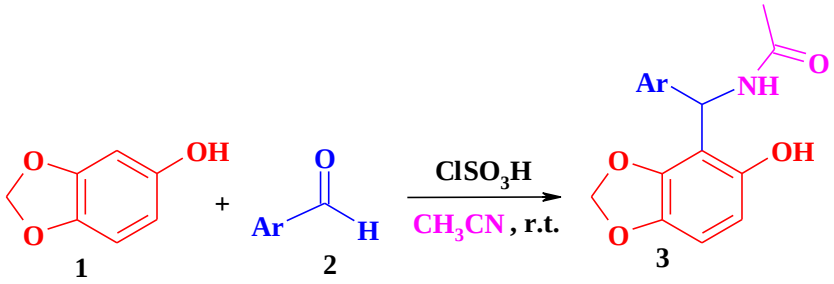
the similar three-component reaction between benzo[1,3]dioxol-5-ol, aryl aldehydes and acetonitrile in the presence of chlorosulfonic acid at ambient temperature.

Result and Discussion

One-pot, three-component reaction between benzo[1,3]dioxol-5-ol **1**, aryl aldehydes **2** and acetonitrile in the presence of chlorosulfonic acid affords 1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl](aryl)methyl)acetamides **3** in nearly quantitative yields (Scheme **1** and Table **1**).

Compounds **5h-l** was new and their structures were deduced by their ^{1}H, ^{13}C-NMR and IR spectroscopy and elemental analyses (Table **1**).

The structures of compounds **3a-f** were deduced from elemental analysis and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectra of compounds **3a–f** are fairly similar and display molecular ion peaks. For example, the mass spectrum of compound **3a** showing a molecular ion peak at *m/z* 285 confirmed that compound **3a** is a condensation product of benzo[1,3]dioxol-5-ol **1**, aryl aldehydes **2** and acetonitrile.



Scheme 1: Synthesis of 1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl](aryl)methyl)acetamides

Table 1: Yields of a series of 1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl](aryl)methyl) acetamides (3) (Scheme **1**)

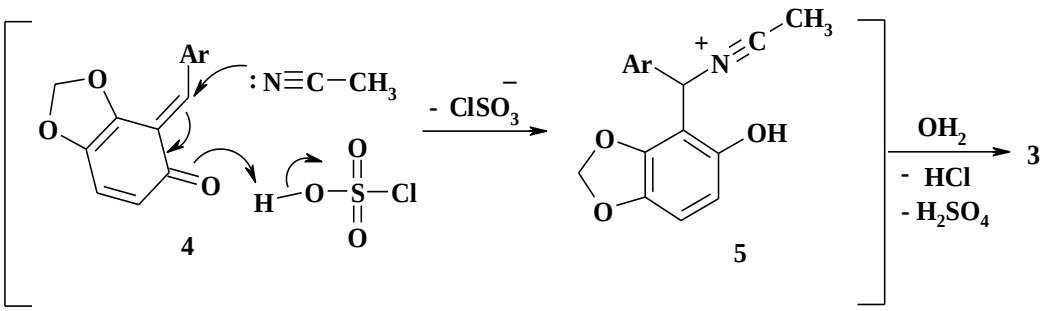
Entry	Ar	Product	Yield%[a]	m.p./°C
1	C_6H_5	**3a**	90	234-236
2	4-ClC_6H_4	**3b**	91	242-244
3	4-BrC_6H_4	**3c**	89	251-253
4	4-$NO_2C_6H_4$	**3d**	93	210-212
5	3-$NO_2C_6H_4$	**3e**	85	218-220
6	4-MeC_6H_4	**3f**	85	204-206

[a] Yields refer to the pure isolated products.

The ^{1}H NMR spectrum of 3a exhibits two sharp lines at δ = 2.15 and 6.15 ppm for the protons of methyl and methylene groups. The methine and NH protons couple each other and two doublets are observed for them at 7.11 and 8.54 ppm respectively. When the ^{1}H NMR spectrum is recorded after addition of some D_2O to the DMSO-d_6 solution of 3a the doublet related to NH proton was disappeared and the doublet related to methine proton was converted to a singlet. Aromatic protons resonate as multiples at δ = 7.24-7.58 ppm. The proton of hydroxy group resonates 9.98 ppm. The ^{13}C NMR spectrum of compound 3a shows 14 distinct

signals in consistent with the proposed structure. The IR spectrum showed two absorption bonds at 3475 and 3275 cm^{-1} for NH and OH groups. The carbonyl stretching vibrations observed as strong absorption bonds at 1631 cm^{-1}.

Although we didn't study the mechanism of the reaction, but a reasonable possibility is presented in Scheme **2**. Acetonitrile attacks to the condensation product of benzo[1,3]dioxol-5-ol and aldehyde in the presence of chlorosulfonic acid to afford the cation **5** which hydrolyzes to product **3**.



Scheme 2: Suggested mechanism for formation of compound **3**.

Conclusions

In conclusion here we reported a simple and efficient one-pot synthesis of 1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl](aryl)methyl)acetamides by three-component reaction between benzo[1,3]dioxol-5-ol, aryl aldehydes and acetonitrile in the presence of chlorosulfonic acid at ambient temperature. The advantages of this method are mild reaction conditions, short reaction time, easy work-up, and use of an inexpensive and non-toxic catalyst, high yields of biological active products and does not involve any hazardous solvent. Therefore, this procedure could be classified as green chemistry.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analysis were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra of selected compounds were recorded on a Shimadzu IR-470 spectrometer in KBr discs. ^{1}H and ^{13}CNMR spectra were obtained on a Bruker DRX-500 Avance spectrometer in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure for preparation of compounds **3a-f**:

To a magnetically stirred solution of benzo[1,3]dioxol-5-ol (2 mmol) and aldehyde (2 mmol) in acetonitrile (15 ml) was added chlorosulfonic acid (4 mmol) at room temperature. The reaction mixture was then stirred for 1 h. The mixture was poured into 50 mL ice-water. The solid product was filtered, washed with ice-water to give the pure product.

1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl](phenyl) methyl)acetamide **(3a):**

Yellow powder; m.p. 234-236° C; IR (KBr) (ν_{max} cm^{-1}): 3475, 3275, 1631; ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.15 (3H, s, CH_3), 6.15 (2H, s, CH_2), 7.11 (1H, d, $^{3}J_{HH}$ = 8Hz, CH), 7.24-7.58 (5H, m, aromatic), 7.85 (1H, d, $^{3}J_{HH}$ = 8Hz, Ar), 8.15 (1 H, d, $^{3}J_{HH}$ = 8Hz, Ar), 8.54 (1H, d, $^{3}J_{HH}$ = 8Hz, NH), 9.98 (1H, broad s, OH)ppm.; ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 24.53 (CH_3), 50.23 (CH), 106.80 (CH_2), 123.28, 124.51, 127.12, 130.25, 135.41, 137.15, 139.43, 145.93, 147.81, 151.26, 169.45 (NC=O)ppm.; EIMS: 285 (M^{+}, 7), Analyses: Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%. Found: C, 67.45; H, 5.38; N, 5.03.

1-[N-(4-chlorophenyl)(5-hydroxybenzo[d][1,3] dioxol-4-yl]methyl)acetamide **(3b):**

Yellow powder; m.p. 242-244° C; IR (KBr) (ν_{max} cm^{-1}): 3395, 3190, 1666; ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.08 (3H, s, CH_3), 5.95 (2H, s, CH_2) , 7.66-7.45 (5H, m, aromatic and NCH), 7.78 (1H, d, $^{3}J_{HH}$ = 8Hz, Ar), 8.08 (1H, d, $^{3}J_{HH}$ = 8Hz, Ar) , 8.33 (1H, d, $^{3}J_{HH}$ = 8Hz,

NH) , 9.84 (1H, broad s, OH)ppm.; ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 24.51 (CH_3), 51.22 (CH), 105.78 (CH_2), 124.04, 125.31, 127.93, 131.64, 136.16, 136.92, 138.52, 144.28, 146.90, 152.24, 171.41 (NC=O)ppm.; EIMS: 319 (M^+, 10); Analyses: Calcd. for $C_{16}H_{14}ClNO_4$: C, 60.10; H, 4.41; N, 4.38%. Found: C, 60.21; H, 4.53; N, 4.50.

1-[N-(4-bromophenyl)(5-hydroxybenzo[d][1,3]dioxol -4-yl)methyl]acetamide **(3c):**

Yellow powder; m.p. 251-253^o C; IR (KBr) (ν_{max} cm^{-1}): 3419, 3284, 1629; ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.97 (3H, s, CH_3), 6.11 (2H, s, CH_2) , 7.65-7.77 (5H, m, aromatic and NCH), 7.93 (1H, d, $^3J_{HH}$ = 8Hz, Ar) , 8.15 (1 H, d, $^3J_{HH}$ = 8Hz, Ar), 8.41 (1H, d, $^3J_{HH}$ = 8Hz, NH), 10.11(1H, broad s, OH)ppm.; ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 24.23 (CH_3), 50.63 (CH), 106.07 (CH_2) , 126.18, 127.17, 128.11, 129.15, 134.19, 135.11, 136.18, 137.05, 146.08, 150.08, 172.27 (NC=O**)**ppm.; EIMS: 363 (M^+, 5); Analyses: Calcd. for $C_{16}H_{14}$ $BrNO_4$: C, 52.77; H, 3.87; N, 3.85%. Found: C, 52.90; H, 3.96; N, 3.98.

1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl)(4-nitrophenyl)methyl)]acetamide **(3d):**

Yellow powder; m.p. 210-212^o C; IR (KBr) (ν_{max} cm^{-1}): 3470, 3395, 1635; ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.12 (3H, s, CH_3), 6.06 (2H, s, CH_2) , 7.63-7.74 (5H, m, aromatic and NCH), 7.81 (1H, d, $^3J_{HH}$ = 8Hz, Ar), 8.12 (1H, d, $^3J_{HH}$ = 8Hz, Ar) , 8.38 (1H, d, $^3J_{HH}$ = 8Hz, NH), 10.05 (1H, broad s, OH)ppm.; ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 24.61 (CH_3), 51.74 (CH), 105.93 (CH_2), 125.12, 126.75, 130.12, 133.73, 136.77, 137.11, 139.11, 145.23, 147.13, 151.11, 168.91(NC=O)ppm.; EIMS: 330 (M^+, 12); Analyses: Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48%. Found: C, 58.32; H, 4.40; N, 8.57.

1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl)(3-nitrophenyl)methyl]acetamide **(3e):**

Yellow powder; m.p. 218-220^o C; IR (KBr) (ν_{max} cm^{-1}): 3372, 3264, 1627; ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.17 (3H, s, CH_3), 6.14 (2H, s, CH_2) , 7.59-7.67 (5H, m, aromatic and NCH), 7.73 (1H, d, $^3J_{HH}$ = 8Hz, Ar), 7.99 (1H, d, $^3J_{HH}$ = 8Hz, Ar), 8.21 (1H, d, $^3J_{HH}$ = 8Hz, NH), 9.94 (1 H, broad s, OH)ppm.; ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 24.21 (CH_3), 50.83 (CH), 105.74 (CH_2), 122.14, 123.91, 127.68, 129.81, 134.18., 135.19, 135.95, 137.12, 139.64, 146.14 ,147.91, 150.27, 169.07 (NC=O)ppm.; EIMS: 330 (M^+, 10), Analyses: Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48%. Found: C, 58.29; H, 4.38; N, 8.55.

1-[N-(5-hydroxybenzo[d][1,3]dioxol-4-yl)(p-tolyl)methyl]acetamide **(3f):**

Yellow powder; m.p. 204-206^o C; IR (KBr) (ν_{max} cm^{-1}): 3300, 3165, 1679; ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.91 (3H, s, CH_3), 2.11 (3H, s, CH_3), 6.07 (2H, s, CH_2) , 7.38-7.51 (5H, m, aromatic and NCH), 7.64 (1H, d, $^3J_{HH}$ = 8Hz, Ar), 7.79 (1H, d, $^3J_{HH}$ = 8Hz, Ar), 8.24 (1H, d, $^3J_{HH}$ = 8Hz, NH), 9.94 (1H, broad s, OH)ppm.; ^{13}C NMR (125.8 MHz, d_6-DMSO): δ 22.17 (CH_3), 24.23 (CH_3), 49.24 (CH), 106.03 (CH_2), 123.17, 124.31, 129.93, 135.18, 136.92, 137.69, 143.13, 144.51, 148.73, 172.14 (NC=O)ppm.; EIMS: 299 (M^+, 4), Analyses: Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68%. Found: C, 68.33; H, 5.81; N, 4.76.

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References

[1] Casimir, J. R.; Turreta, C.; Ettouati, L.; Paris, J., *Tetrahedron Lett.*, **1995**, *36*, 4797.
[2] Godfrey, A. G.; Brooks, D.A.; Hay, L. A.; Peters, M.; McCarthy, J. R.; Mitchell, D., *J. Org. Chem.* **2003**, *68*, 2623.
[3] Dähn, U.; Hagenmaier, H.; Höhne, H.; König, W. A.; Wolf G.; Zöhner, H., *Arch. Microbiol*. **1976**, *107*, 249.
[4] Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura G.; Isono, K., *Agric. Biol. Chem.* **1980**, *44*, 1709.
[5] Maghsoodlou, M. T.; Hassankhani, A.; Shaterian, H.R.; Habibi-Khorasani S.; Mosaddegh, E., *Tetrahedron Lett.* **2007**, *48*, 1729.
[6] Shaterian, H. R.; Yarahmadi, H., *Tetrahedron Lett*. **2008**, *49*, 1297.
[7] Bahulayan, D.; Das S. K.; Iqbal, J., *J. Org. Chem.*, **2003**, *68*, 5735.
[8] Khodaei, M. M.; Khosropour A. R.; Fattahpour, P., *Tetrahedron Lett*., **2005**, *46*, 2105.
[9] Rafiee, E.; Shahbazi, F.; Joshaghani M.; Tork, F., *J. Molec. Cat. A.* **2005**, *242*, 129.
[10] Rafiee, E.; Tork F.; Joshaghani, M., *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1221.
[11] Anary-Abbasinejad, M.; Hassanabadi, A.; Kamali-Gharamaleki, M.; Saidipoor A.; Anaraki-Ardakani, H., *J. Chem. Res*. **2007**, 644.

[12] Anary-Abbasinejad, M.; Mosslemin M. H.; Hassanabadi, A., *J. Chem. Res.* **2009**, 218.