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D-Glucosamine, a natural aminosugar as organocatalyst for an ecofriendly direct aldol reaction of ketones with aromatic aldehydes in water

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Abstract: D-Glucosamine, one of the important sugars of natural origin catalyzes direct aldol reaction of different aromatic aldehydes with acyclic or cyclic ketones. Diastereo- and enantioselection varies with the substituent on the benzene ring of the aromatic aldehydes used.

Keywords: D-Glucosamine, direct aldol reaction, syn/anti isomers, enantioselection, diastereoselection

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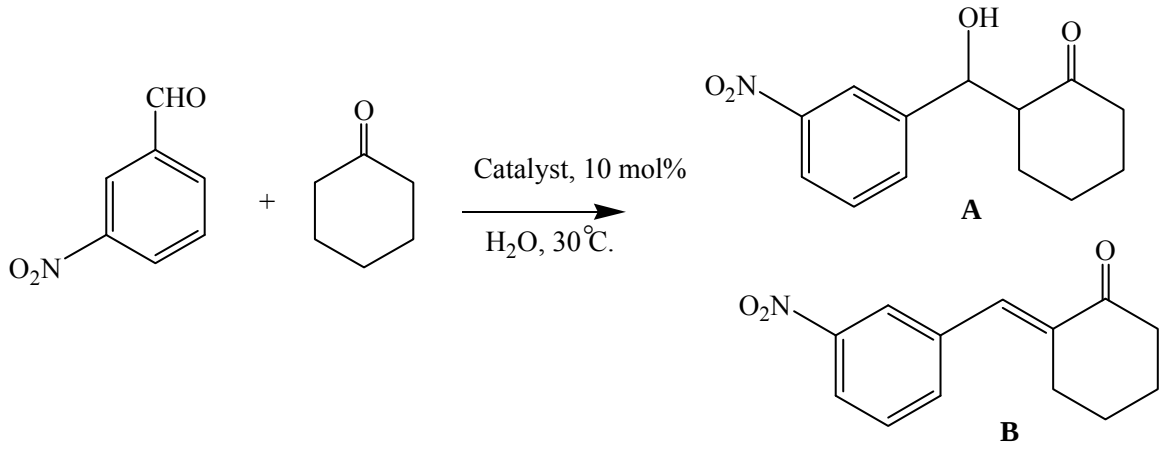
There are several methods to synthesize *β*-hydroxy carbonyl compounds commonly known as aldol adducts [1] as intermediates in organic synthesis of complex natural products and pharmaceuticals. Recently, organocatalytic direct aldol reaction between an aldehyde and a ketone catalyzed by different amines has been reported [2-5]. The use of amines in direct aldol reaction is known since long back [6]. In the past few years a number of chemically robust organocatalysts have successfully been used by group of Takabe, Barbas and Hayashi [7, 8] in asymmetric aldol reaction. However, early studies with amines as organocatalysts for direct aldol reaction in pure water are associated with several limitations [9-11]. The aldol condensation "in water" promoted by tryptophan, [12] small peptides, [13] pyrrolidine-based catalysts, [14] or proline-related systems [15-17] as organocatalyst was described for stereoselective reactions. However, in all the successful reactions either aqueous organic solvents or the use of surfactants, or dendritic systems are required which needs extra steps for chemical manipulation. A large excess of ketone is unnecessarily employed for every successful reaction in aqueous medium [18]. In few of the successful reactions in water, acid additives are required. In all these reactions it is presumed that amines form an imine enamine which adds to the aldehyde resulting the aldol adduct similar to the reaction mode of class I aldolases, [19, 20] which have extensively been studied [21-26]. Certain amines in combination with metal salts have also been used in aldol reactions [27-29].

The use of water as solvent during organic preparations has many advantages in terms of cost, safety, and environmental impact [30, 31]. Moreover, a natural organocatalyst soluble in water and compatible with substrates of aldol reaction is expected to offer

better results. As discussed above many natural amino acids did offer excellent results in direct aldol reaction in aqueous organic medium. However, there are scanty reports where natural amino sugars have been used as organocatalyst in direct aldol reaction. D-glucosamine, abundant in the cartilaginous tissues and the cartilage between joints in the human body play important role in the metabolic processes and is known to catalyze a number of reactions involved in connective tissue synthesis. Many other D-glucosamine derivatives in the body are known to play key role in biological reactions. Taking a clue from nature we thought that D-glucosamine may act as an organocatalyst in direct aldol and other organic reactions. The study is in continuation of our ongoing effort towards development of synthetic aminosugars as organocatalyst [32, 33]. During course of our studies Tsusui et al [34] reported the use of N- prolinamidyl derivative of D-glucosamine in direct aldol reaction, however there is no report on organocatalytic activity of D-glucosamine itself. It is a first report where application of a natural sugar, D-glucosamine in direct aqueous aldol reaction without any additive is reported to the best of our knowledge.

As shown in Scheme 1, reaction of 3- nitro benzaldehyde (1 equivalent) and cyclohexanone (1 equivalent) was studied under the catalytic influence of various organic catalysts. As shown in Table 1 (entry 1) Et_2NH did not give any product even after 20 hrs and the starting materials were recovered as such. However, Et_3N catalyzed the reaction at a much faster rate affording the insignificant (16%) amount of the required aldol adduct (A) and the dehydrated product (B) in 41% yield (Table 1, entry 2). DBU, a hindered organic base led to the formation of aldol adduct (A) in 14% yield only with 1:1

syn/anti ratio. The major product isolated again was found to be the dehydrated aldol condensation product (B) in 51% yield (Table 1, entry 3).



Scheme 1

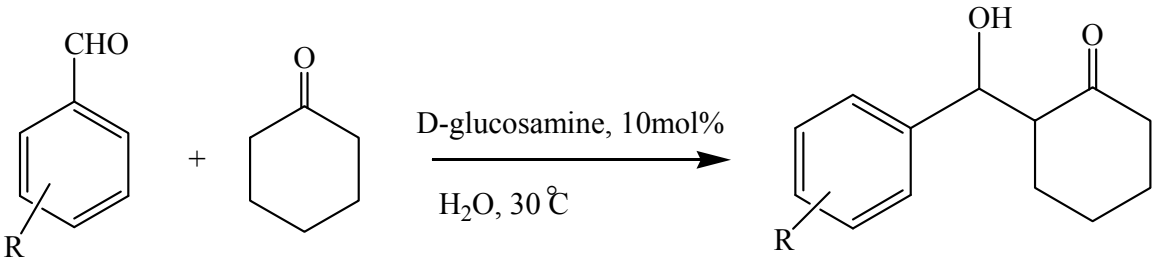
Table-1 Aldol reaction of cyclohexanone with 3-nitro benzaldehyde in presence of different bases

Entry	Organic base	Catalyst Mol %	Time (hrs)	% yield [a] isolated products		*syn*/*anti* ratio[b]
				A	B	
1	Et_2NH	10	20	No reaction	-	-
2	Et_3N	10	7	16	41	-
3	DBU	10	6	14	51	1:1
4	$NaHCO_3$	10	18	8	-	
5	D-Glucosamine	10	19	55	-	0.6:1
6	Ethanolamine	10	12	29	-	-
7	Piperidine	10	6	-	72	N.A.
8	Pyrrolidine	10	7	-	78	N.A.

[a]Isolated yields based on aromatic aldehydes; [b]determined on the basis of ^{1}HNMR spectra

D-Glucosamine (10 mol%, obtained by neutralization of its hydrochloride salt with $NaHCO_3$) catalyzed reaction and gave aldol adduct (A) exclusively in 55% yield (Table 1, entry 5) and no other products were observed (TLC). $NaHCO_3$ on the other hand, did not catalyze the reaction efficiently as only 8% of the aldol adduct (A) was isolated (table 1 entry 4). However, pyrrolidine and piperidine catalysed reactions resulted only dehydrated aldol condensation product (B) in good yields (Table 1, entries 7 and 8). The reaction with ethanolamine gave required product (A) in 29% yield only (Table 1, entry 6) and with very poor selection of *syn* and *anti* isomers.

The scope of D-glucosamine as an organocatalyst in direct aldol reaction was then extended with other aromatic aldehydes and cyclohexanone (Scheme 2, Table 2). As evident from Table 2 in all the reactions only aldol adducts were obtained in moderate to good yields. It is also evident that ratio of *syn* and *anti* aldol products varies with the nature and position of substituents in the benzene ring.



R= H, 4-NO_2, 2-NO_2, 4-Br, 3,4-di-OMe, 3,4,5-tri-OMe

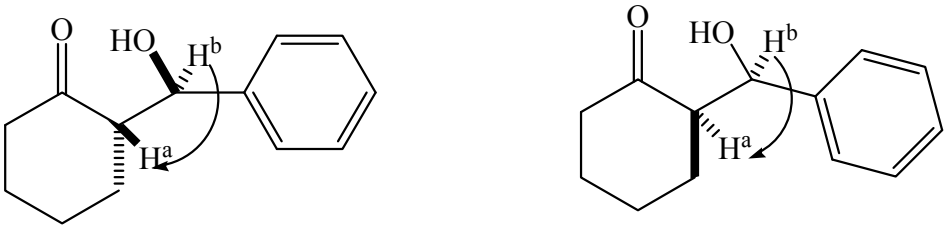
Scheme 2

The structures of syn: anti isomers and their ratios in the above products were determined on the basis of ^{1}H NMR spectrum. Measurement of the integration of the H^b signal in the two isomers indicated their ratios, while the *J* H^a, H^b established the geometry of the two isomers (Figure 1). In the *anti*-isomers *J* H^a, $H^b \geq 5.7$ *Hz* while in the *syn*- isomers *J* H^a, $H^b < 1$*Hz* (appeared as singlets). Further, the H^b in *anti* isomers always appears at a higher field (lower δ value) than that for the *syn* isomer. Our observation is based on the reports of *syn* and *anti* isomers of β-amino ketones recently reported [35]. In the ^{1}H NMR spectra of 2-[hydroxyl(3-nitrophenyl)methyl]-cyclohexanone, the signal for H^b of *anti* isomer appeared as *d* at δ =4.88 ppm (*J* = 8.4 Hz), while that of *syn* isomer appeared as *s* at δ =5.46 ppm. Similar pattern was found in all the *syn*- and *anti*-isomers.

Table 2. Aldol reaction of cyclohexanone with different aromatic aldehydes in presence of 10 mol% D-glucosamine at room temperature

Entry	R	Time (hrs)	% Yield[a]	Syn/Anti[b]
1	H	14	60	0.8:1
2	4-NO_2	11	75	4:1
3	2-NO_2	14	38	0.4:1
4	4-Br	17	65	4:1
6	3,4- Di-OMe	14	60	0.3:1
6	3,4,5 Tri-OMe	14	59	1.6:1

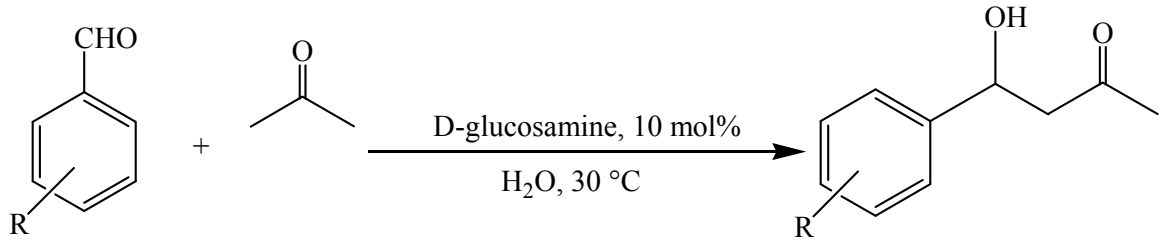
[a]isolated and unoptimized yields; [b]determined on the basis of ^{1}H NMR spectra



J Ha, Hb >5.6 Hz *J* Ha, Hb <1 Hz

Figure 1

The organocatalytic efficiency of D-glucosamine (10 mol%) on the reaction of various aromatic aldehydes with acetone (1 equivalent) in water at room temperature was also examined (Scheme 3). As shown in Table 3 (entries 1-6), the only isolable products were the aldol adducts, obtained in good to moderate yields with varying enantioselection. The best enantioselection (54%) was observed in the reaction of 3, 4-dimethoxy benzaldehyde with acetone. In all other reactions only poor enantioselction was observed.



R= H, 4-NO_2, 2-NO_2, 4-Br, 3,4-di-OMe, 3,4,5-tri-OMe

Scheme 3

Table 3: Aldol reaction of acetone with different aromatic aldehydes in presence of 10 mol % D-glucosamine at room temperature

Entry	Aromatic aldehyde, R	Time (hr)	% Yield	% ee[a]
1	H	6	50	<10
2	4-NO_2	12	56	<10
3	2-NO_2	14	35	<10
4	4-Br	19	50	<10
5	3,4-*di*-OMe	9	70	54
6	3,4,5- *tri*-OMe	9	65	24

[a] Determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min)

Conclusion: In summary, we have demonstrated that D-glucosamine, a naturally occurring amino sugar acts as organocatalyst for direct aldol reaction of ketones and aromatic aldehydes affording good yields of the aldol product. The reaction being run in water only and use of molar quantities of aromatic aldehydes and ketones make this process simple, economical and eco-friendly. Application of D-glucosamine and its simple derivatives as organocatalyst is being investigated for other C-C bond forming reactions.

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General procedure for direct aldol reaction of ketones with aromatic aldehydes

A mixture of aromatic aldehyde (1.0 mmol), ketone (1.0 mmol) and aqueous solution of D-glucosamine (10 mol% 2ml, prepared by neutralization of D-glucosamine hydrochloride solution in water with 1 equivalent of $NaHCO_3$) was stirred at ambient temperature for 11-19 hrs. Ethyl acetate was added to the reaction mixture and the organic layer washed with water, dried (anh. Na_2SO_4) and concentrated in vacuo to give a gummy mass. The latter was chromatographed over SiO_2 using a gradient hexane: EtOAc (9:1) as eluent to afford the pure products. The physical data of the selected compounds are shown below.

2-[(4- Nitrophenyl)-hydroxymethyl]- cyclohexanone

A mixture of 4-nitrobenzaldehyde (1.0g, 6.62 mmol), cyclohexanone (0.7mL, 6.62 mmol) and aqueous solution of D-glucosamine (10 mol% 2ml, prepared by neutralization of D-glucosamine hydrochloride solution in water with 1 equivalent of $NaHCO_3$) was

stirred at ambient temperature for 11 hrs. Ethyl acetate was added to the reaction mixture and the organic layer washed with water, dried (anh. Na_2SO_4) and concentrated in vacuo to give a gummy mass. The latter was chromatographed over SiO_2 using a gradient hexane: EtOAc (9:1) as eluent to afford the pure products (0.989g, 75% Yield[a]).

2-[(4- Nitrophenyl)-hydroxy-methyl]-cyclohexanone

Yellow solid, m.p.: 160˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 8.23-7.47(m, 4*H*, Ar-H), [5.49 (s, -CH[b], *syn* isomer) and 4.90 (d, J = 8 Hz, -CH[b], *anti* isomer), 1*H*], [4.10 and 3.21 (bs, 1*H*, -OH, *anti* and *syn* isomers), 2.62-2.59(m, 3*H*, $-CH_2$ and –CH[a] of *syn* and *anti* isomers), 1.84-1.65 (m,4*H*, $-CH_2$), 1.60-1.52(m,2*H*, $-CH_2$), IR(KBr): ν_{max} = 3475, 1599, 1447 cm^{-1}, ESMS: *m*/*z* 250

2-[(4- Bromophenyl)-hydroxy-methyl]-cyclohexanone

A mixture of 4-bromobenzaldehyde (1.0g, 5.4mmol), cyclohexanone (0.6mL, 5.4mmol) and aqueous solution of D-glucosamine (10 mol% 2ml, prepared by neutralization of D-glucosamine hydrochloride solution in water with 1 equivalent of $NaHCO_3$) was stirred at ambient temperature for 17 hrs. Ethyl acetate was added to the reaction mixture and the organic layer washed with water, dried (anh. Na_2SO_4) and concentrated in vacuo to give a gummy mass. The latter was chromatographed over SiO_2 using a gradient hexane: EtOAc (9:1) as eluent to afford the pure products (0.745g, 65% Yield).

Pale yellow solid, m.p.: 130˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.49-7.16(m, 4*H*, Ar-H), [5.34(s, -CH^b, syn isomer), 4.74(d, J=8.76 Hz, -CH^b, *anti* isomer), 1*H*], 4.00 and 3.07(bs, 1*H*, –OH anti- and syn-isomers), 2.55-2.41(m, 3*H*, -CH_2 and -CH^a), 2.17-1.60(m, 6*H*, -CH_2), IR(KBr): ν_{max} = 3447, 1602, 1459 cm^{-1}, ESMS: *m*/*z* 284

4-(3,4-Dimethoxyphenyl)-4-hydroxy-butan-2-one

Yellow solid, m.p.: 94˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 6.90-6.81(m, 3*H*, Ar-H), 5.05 (dd, J=3.94 and 4.47, 1*H*, -CH), 3.88 and 3.86 (two s, 6*H*, –OCH_3), 3.21(bs, 1*H*, –OH), 2.85-2.78(m, 2*H*, -CH_2), 2.17(s, 3*H*, -CH_3), IR(KBr): ν_{max} = 3480, 1705, 1450 cm^{-1}, ESMS: *m*/*z* 225

4-(4-Nitrophenyl)-4-hydroxy-butan-2-one

Yellow viscous mass, ^{1}H NMR (200MHz, $CDCl_3$): δ = 8.23-7.26(m, 4*H*, Ar-H), 5.27(m, -1*H*, CH), 3.60(bs, 1*H*, –OH), 2.87-2.84(m, 2*H*, -CH_2), 2.22(s, 3H, -CH_3) IR(KBr): ν_{max} = 3475, 1599, 1447 cm^{-1}, ESMS: *m*/*z* 211

4-(2-Nitrophenyl)-4-hydroxy-butan-2-one

Yellow viscous mass, ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.97-7.40(m, 4*H*, Ar-H), 5.69-5.64(m, 1*H*, -CH), 3.8(s, 1*H*, –OH), 2.81-2.67(m, 2*H*, -CH_2), 2.22(s, 3*H*, -CH_3): IR (KBr) v_{max} = 3409, 1710, 1350 cm^{-1}, (ESMS): *m*/*z* 210

4-(3,4, 5-Trimethoxyphenyl)-4-hydroxy-butan-2-one

Yellow solid, m.p.: 62˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 6.54(s, 2*H*, Ar-H), 5.05(m, 1*H*, -CH), 3.86-3.80(m, 9*H*, –OCH_3), 3.26(bs, 1*H*, –OH), 2.84-2.79(m, 2*H*, -CH_2), 2.20(s, 3*H*, -CH_3), IR(KBr): v = 3482, 1701, 1459 cm^{-1}, ESMS: *m*/*z* 255

4-Hydroxy-4-phenyl-butan-2-one

Yellow solid, m.p.:61˚C,, ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.29-7.19(m, 5*H*, Ar-H), 5.09-5.03(m, -1*H*, CH), 3.4(bs, 1*H*, –OH), 2.79-2.74(m, 2*H*, -CH_2), 2.14(s, 3H, -CH_3) IR(KBr): v_{max} = 3475, 1599, 1447 cm^{-1}, ESMS: *m*/*z* 165

General procedure for direct aldol reaction of ketones with aromatic aldehydes

A mixture of aromatic aldehyde (1.0 mmol), ketone (1.0 mmol) and aqueous solution of D-glucosamine (10 mol% 2ml, prepared by neutralization of D-glucosamine hydrochloride solution in water with 1 equivalent of $NaHCO_3$) was stirred at ambient temperature for 11-19 hrs. Ethyl acetate was added to the reaction mixture and the

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2-[(3- Nitrophenyl)-hydroxy-methyl]-cyclohexanone

Yellow solid, m.p.: 99 ˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 8.19-7.47(m, 4*H*, Ar-H), [5.46(s, -CH^b, *syn* isomer), 4.88(d, J=8.43 Hz, -CH^b, *anti* isomer), 1*H*], 4.09 and 3.21(bs, 1*H*, –OH syn- and anti-isomers), 2.61-2.38(m, 3*H*, -CH_2 and -CH^a), 1.85-1.54(m, 6*H*, -CH_2), IR(KBr): ν_{max}= 3428, 1530, 1456 cm^{-1}, ESMS: *m*/*z* 250

2-[(2- Nitrophenyl)-hydroxy-methyl]-cyclohexanone

Yellow solid, m.p.: 91˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 8.19-7.48(m, 4*H*, Ar-H), [5.46(s, -CH^b, *syn* isomer), 4.87(d, J=8.4 Hz, -CH^b *anti* isomer), 1*H*], 4.10, 3.22(bs, 1*H*, -OH, *syn* and *anti*-isomers), 2.61-2.45(m, 3*H*, -CH_2 and -CH^a), 1.85-1.55(m, 6*H*, -CH_2), IR(KBr): ν_{max} = 3424, 1654, 1460 cm^{-1}, ESMS: *m*/*z* 250

2-[Hydroxy-(3,4,5-trimethoxyphenyl)-methyl]-cyclohexanone

Pale yellow solid, m.p.:112 ˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 6.50-6.48(m, 2*H*, Ar-H), [5.30(s, -CH^b, *syn* isomer), 4.65(d, J=8 Hz, -CH^b *anti* isomer), 1*H*], 4.00, 3.10 (bs, 1*H*, OH *anti* and *syn* isomers), 3.85(s, 9*H*, -OCH_3), 2.43-1.59(m, 8*H*, -CH_2 and 1*H*, -CH^a), IR(KBr): ν_{max} = 3424, 1654, 1460 cm^{-1}, ESMS: *m*/*z* 295

2-[(3,4-Dimethoxyphenyl)- hydroxy methyl]-cyclohexanone

Yellow viscous mass, ^{1}H NMR (200MHz, $CDCl_3$): δ = 6.86-6.78(m, 3*H*, Ar-H), [5.23(s, -CH, syn isomer), 4.70(d, J=8.8 Hz, -CH *anti* isomer), 1*H*], 4.15 and 3.15 (bs, 1*H*, –OH

anti and *syn* isomers), 3.89 (s, 6*H*, -OCH_3), 2.55-1.59(m, 8*H*, -CH_2 and 1*H*, -CH^a), IR(KBr): ν_{max} = 3424, 1654, 1460 cm^{-1}, ESMS: *m*/*z* 265

2-(Hydroxyphenyl-methyl)-cyclohexanone

Yellow solid, m.p.: 85 ˚C, ^1H NMR (200MHz, $CDCl_3$): δ = 8.19-7.48(m, 4*H*, Ar-H), [5.46(s, -CH, syn isomer), 4.87(d, J=8.4, -CH *anti* isomer),1*H*], 4.10 and 3.22(bs, 1*H*, –OH *syn* and *anti* isomers), 2.61-2.45(m, 3*H*, -CH_2 and -CH^a), 1.85-1.55(m, 6*H*, -CH_2), IR(KBr): ν_{max} = 3424, 1654, 1460 cm^{-1}, ESMS: *m*/*z* 250

4-(3,4-Dimethoxyphenyl)-4-hydroxy-butan-2-one

Yellow solid, m.p.: 94˚C, ^1H NMR (200MHz, $CDCl_3$): δ = 6.90-6.81(m, 3*H*, Ar-H), 5.05 (dd, J=3.94 and 4.47, 1*H*, -CH), 3.88 and 3.86 (two s, 6*H*, –OCH_3), 3.21(bs, 1*H*, –OH), 2.85-2.78(m, 2*H*, -CH_2), 2.17(s, 3*H*, -CH_3), IR(KBr): ν_{max} = 3480, 1705, 1450 cm^{-1}, ESMS: *m*/*z* 225

4-(4-Nitrophenyl)-4-hydroxy-butan-2-one

Yellow viscous mass, ^1H NMR (200MHz, $CDCl_3$): δ = 8.23-7.26(m, 4*H*, Ar-H), 5.27(m, -1*H*, CH), 3.60(bs, 1*H*, –OH), 2.87-2.84(m, 2*H*, -CH_2), 2.22(s, 3H, -CH_3) IR(KBr): ν_{max} = 3475, 1599, 1447 cm^{-1}, ESMS: *m*/*z* 211

4-(4-Bromophenyl)-4-hydroxy-butan-2-one

Brown viscous mass, ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.72-7.20(m, 4*H*, Ar-H), 5.13-5.07 (m, 1*H,* -CH), 3.50(bs*,* 1*H*, –OH), 2.83-2.79(*m,* 2*H*, -CH_2), 2.19(s, 3*H*, -CH_3): IR (KBr) v_{max} = 3441, 1708, 1362 cm^{-1}, (ESMS): *m*/*z* 245

4-(2-Nitrophenyl)-4-hydroxy-butan-2-one

Yellow viscous mass, ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.97-7.40(m, 4*H*, Ar-H), 5.69-5.64(m*,* 1*H*, -CH), 3.8(bs, 1*H*, –OH), 2.81-2.67(m*,* 2*H*, -CH_2), 2.22(s, 3*H*, -CH_3): IR (KBr) v_{max} = 3409, 1710, 1350 cm^{-1}, (ESMS): *m*/*z* 210

4-(3,4, 5-Trimethoxyphenyl)-4-hydroxy-butan-2-one

Yellow solid, m.p.: 62˚C, ^{1}H NMR (200MHz, $CDCl_3$): δ = 6.54(s, 2*H*, Ar-H), 5.05(m, 1*H*, -CH), 3.86-3.80(m, 9*H*, –OCH_3), 3.26(bs, 1*H*, –OH), 2.84-2.79(m*,* 2*H*, -CH_2), 2.20(s, 3*H*, -CH_3), IR(KBr): v = 3482, 1701, 1459 cm^{-1}, ESMS: *m*/*z* 255

4-Hydroxy-4-phenyl-butan-2-one

Yellow solid, m.p.:61˚C,, ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.29-7.19(m, 5*H*, Ar-H), 5.09-5.03(m*,* -1*H*, CH), 3.4(bs, 1*H*, –OH), 2.79-2.74(m*,* 2*H*, -CH_2), 2.14(s, 3H, -CH_3) IR(KBr): v_{max} = 3475, 1599, 1447 cm^{-1}, ESMS: *m*/*z* 165

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