http://www.e-journals.net

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2012, **9(1),** 301-307

$B(HSO_4)_3$ as an Efficient Catalyst for the Syntheses of Bis(1*H*-Indol-3-yl)ethanones and Bis(benzotriazol-1-yl)ethanones

MOHAMMAD HOSSEIN MOSSLEMIN* and ABOLFAZL ESHGHI MOVAHHED

Department of Chemistry, Islamic Azad University
Yazd Branch, P.O. Box 89195-155, Yazd, Iran
mhmosslemin@yahoo.com

Received 12 May 2011; Accepted 15 July 2011

Abstract: Efficient syntheses of bis (1*H*-indol-3-yl)ethanones and bis (benzotriazolyl)ethanones via reaction of phenylglyoxals with indole or 1,*H*-benzotriazole in the presence $B(HSO_4)_3$ in solvent-free thermal and in aqueous media conditions are discribed. The syntheses have several advantages such as: generality, short reaction time, simple experiment and work-up procedures, excellent isolated yields.

Keywords: $B(HSO_4)_3$, Indole, Bis(1*H*-indol-3-yl)ethanones, Solvent-free condition, Phenylglyoxal

Introduction

Indole and its derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry. These compounds exhibit various physiological properties and pharmacological activities[1] such as: beneficial estrogen metabolism promoter[2], inhibitor for human prostate cancer cells[3] and radical scavengers[4]. Therefore, there is a great deal of interest in the synthesis of these classes of compounds.

On the other hand there have been a few reports for the reaction of indole with the phenyglyoxals[5] but numerous methods have been reported for the reaction of indole with aromatic or aliphatic aldehydes or ketones with a variety of reagents[6-15].

Our group decided to investigate the reaction of indole with various phenyglyoxals in the presence $B(HSO_4)_3$. This catalyst is safe, easy to handle, environmentally benign and presents fewer disposal problems. Boron sulfonic acid was easily prepared by addition of

chlorosulfonic acid to boric acid under N_2 atmosphere at room temperature. This reaction was easy and clean, because HCl gas was evolved from the reaction vessel immediately[16]. Now, we are reporting mild, simple and efficient methods for the syntheses of bis (1*H*-indol-3-yl)ethanones and bis(benzotriazol-1-yl)ethanones in the presence of $B(HSO_4)_3$ in solvent-free thermal and in aqueous media conditions.

Experimental

All chemicals were purchased from Merck, Fluka and Aldrich and used without further purification. The products were characterized by their melting point and spectral data. All yields refer to isolated products. ^{1}H NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX-400 in DMSO-d6 relative to TMS as an internal standard. IR spectra were run on a Shimadzu IR- 470 spectrometer. Elemental analyses were performed of using a Heraeus CHN-O-Rapid analyzer.

Preparation of boron sulfonic acid

A 50 mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25 mmol) was charged in the flask and chlorosulfonic acid (8.74 g, *ca.* 5 mL, 75 mmol) was added drop wise over a period of 1 h at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 1 h, while the residual HCl was eliminated by suction. Then the mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid. Finally, a grayish solid material was obtained in 93% yield (7.0 g)[16].

General procedure for preparation of compounds 3a-h

Method A

Indole or 1 *H*-benzotriazol (10 mmol) and boron sulfonic acid (0.2 g) were added to the phenylglyoxal (5 mmol), the mixture was pulverized in a mortar then the mixture was kept on an oil bath, heated to 110 °C and was stirred by a magnetic stirrer for 10 min. Completion of the reaction was indicated by TLC. After completion, the reaction mass was cooled to 25 °C, then warm pure EtOAc was added and the mixture was stirred until a solid crude product was dissolved. The boron sulfonic acid was filtered. In continuation of work up, the filtrate solution was concentrated then the aqueous ethanol 15% was added to the solution, the precipitate was separated and then recrystallized using aqueous ethanol 15%.

Method B

Indole or 1 *H*-Benzotriazol (2 mmol), boron sulfonic acid (0.04 g) and water (10 mL as solvent) were added to the phenylglyoxal (1 mmol) and the mixture was refluxed for 40 min. Completion of the reaction was indicated by TLC. After completion, the reaction was extracted by ethyl acetate (2×10 mL) and then the organic phase was concentrated. The solid product was purified via a recrystallization procedure in aqueous EtOH (15%).

*1-(4-Chlorophenyl)-2, 2- di(1H-indol-3-yl)ethanone (**3a**)*

Brown solid; mp 195-197 °C. IR (ν_{max}, cm^{-1}): 3400, 1677, 1586, 1433, 1080; ^{1}H NMR (DMSO) (400 MHz): δ = 6.58 (s,1H), 6.9 (t, *J* = 7.2 Hz, 2H), 7.01 (t, *J* =7.2 Hz, 2H), 7.15(d, *J* = 2 Hz,2H), 7.3(d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 2H), 10.89(2H,NH). ^{13}C NMR (DMSO): δ= 42.2, 112, 113.1, 118.98, 119.43, 121.51, 124.93, 126.91, 129.24, 130.91, 135.72, 136.81, 138.24, 197.38; Anal. Calcd for $C_{24}H_{17}ClN_2O$ (384.86): C, 74.90; H, 4.45; N, 7.28%, Found: C, 75.03; H, 4.41; N, 7.16%.

*1-(4-Bromophenyl)-2, 2- di(1H-indol-3-yl)ethanone (**3b**)*

Brown solid; mp 229-231 °C. IR (ν_{max}, cm^{-1}): 3400, 1676, 1583, 1452, 1004; ^1H NMR (DMSO) (400 MHz): δ= 6.32(s,1H), 6.83(s,2H), 6.94 (t, *J* =7.2 Hz, 2H), 7.04 (t, *J* =7.2 Hz, 2H), 7.25(d, *J* = 8 Hz, 2H), 7.42 (d, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 9.23(2H,NH). ^{13}C NMR (DMSO): δ= 42.81, 111.99, 113.69, 119.11, 119.69, 122.19, 124.69, 126.93, 128.11, 130.71, 132.18, 136.1, 137.08, 197.9; Anal. Calcd for $C_{24}H_{17}BrN_2O$ (429.31): C, 67.14; H, 3.99; N, 6.53%, Found: C, 67.02; H, 4.07; N, 6.63%.

*1-(4-Nitrophenyl)-2, 2- di(1H-indol-3-yl)ethanone (**3c**)*

Brown solid; mp 225-227 °C. IR (ν_{max}, cm^{-1}): 3400, 1676, 1527, 1342; ^1H NMR (DMSO) (400 MHz): δ= 6.7(s,1H), 6.94 (t, *J* =7.2 Hz, 2H), 7.04 (t, *J* =7.2 Hz, 2H), 7.18(d, *J*= 2 Hz, 2H), 7.33(d, *J*= 8 Hz, 2H), 7.55(d, *J* = 8 Hz, 2H), 8.25 (d, *J*= 8.4 Hz, 2H), 8.35(d, *J*= 8.4 Hz, 2H), 10.94(2H,NH). ^{13}C NMR (DMSO): δ= 42.85, 112.05, 112.53, 119.07, 121.59, 124.22, 125.11, 126.86, 136.83, 130.28, 136.83, 142.05, 150.09, 197.43.; Anal. Calcd for $C_{24}H_{17}N_3O_3$ (395.41): C, 72.90; H, 4.33; N, 6=10.63%, Found: C, 73.02; H, 4.41; N, 10.69%.

*1-(Phenyl)-2, 2- di(1H-indol-3-yl)ethanone (**3d**)*

Brown solid; mp 205-206 °C. IR (ν_{max}, cm^{-1}): 3390, 1675, 1453, 1339, 1006, ^1H NMR (DMSO) (400 MHz) : δ= 6.64(s,1H), 6.93 (t, *J* =7.2 Hz, 2H), 7.04 (t, *J* =7.2 Hz, 2H), 7.17(s,2H), 7.33(d, *J* = 7.6 Hz, 2H), 7.46(d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 3H), 8.16(d, *J* = 7.6 Hz, 2H), 10.91(2H,NH). ^{13}C NMR (DMSO): δ = 42.13, 112, 113.29, 118.97, 119.45, 121.5, 124.8, 126.98, 129.01, 129.15, 133.33, 136.83, 137.07, 198.3; Anal. Calcd for $C_{24}H_{18}N_2O$ (350.41): C, 82.26; H, 5.18; N, 7.99%, Found: C, 82.32; H, 5.13; N, 7.84%.

*1-(4-Chlorophenyl)-2, 2- di(benzotriazol-1-yl)ethanone (**3e**)*

Brown solid; mp 185-187 °C, IR (ν_{max}, cm^{-1}): 1694, 1588, 1281, 1073; ^1H NMR (DMSO) (400 MHz) : δ = 7.41(1H), 7.42 (t, *J* =7.2 Hz, 2H), 7.59 (2H), 7.59(d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8 Hz, 2H). ^{13}C NMR (DMSO): δ = 81.81, 112.07, 119.79, 124.88, 128.34, 129.44, 131.29, 132.54, 132.84, 139.43, 145.94, 191.82; Anal. Calcd for $C_{20}H_{13}ClN_6O$ (388.81): C, 61.78; H, 3.37; N, 21.61%, Found: C, 61.89; H, 3.42; N, 21.67%.

*1-(4-Bromophenyl)-2, 2- di(benzotriazol-1-yl)ethanone (**3f**)*

Brown solid; mp 222-224 °C. IR (ν_{max}, cm^{-1}): 1694, 1587, 1274, 1008; ^1H NMR (DMSO) (400 MHz) : δ= 7.38(1H), 7.38(t, *J* =7.2 Hz, 2H), 7.48(d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* =7.2 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8 Hz, 2H), 8.01 (d, *J* = 8 Hz, 2H). ^{13}C NMR (DMSO): δ= 82.35, 112.55, 120.25, 124.98, 128.05, 129.1, 131.15, 132.25, 132.54, 133.32, 146.2, 192.2; Anal. Calcd for $C_{20}H_{13}BrN_6O$ (433.26): C, 55.44; H, 3.02; N, 19.40%, Found: C, 55.49; H, 3.07; N, 19.32%.

*1-(4-Nitrophenyl)-2, 2- di(benzotriazol-1-yl)ethanone (**3g**)*

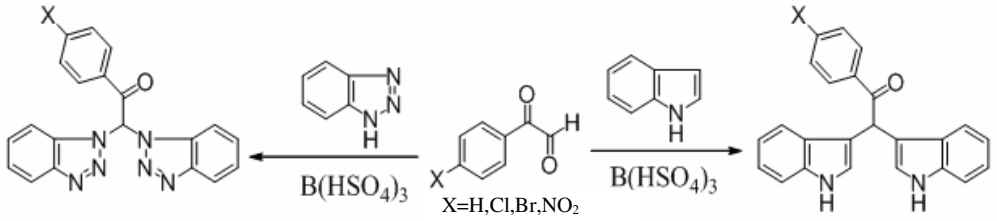
Brown solid; mp 217-219 °C. IR (ν_{max}, cm^{-1}): 1692, 1532, 1351; ^1H NMR (DMSO) (400 MHz) : δ = 7.44(1H), 7.44 (t, *J* =7.2 Hz, 2H), 7.59 (t, *J* =7.2 Hz, 2H), 7.85(d, *J* = 8 Hz, 2H), 8.07 (d, *J* = 8 Hz, 2H), 8.23 (d, *J* = 8.4 Hz, 2H), 8.32 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (DMSO): δ = 82.38, 112.18, 119.77, 124.92, 127.62, 125.11, 130.65, 132.48, 139.8, 145.95, 151.12, 191.8; Anal. Calcd for $C_{20}H_{13}N_7O_3$ (399.36): C, 60.15; H, 3.28; N, 24.55%, Found: C, 60.02; H, 3.32; N, 24.67%.

*1-(Phenyl)-2, 2- di(benzotriazol-1-yl)ethanone (**3h**)*

Brown solid; mp 195-197 °C. IR (ν_{max}, cm^{-1}): 1686, 1458, 1342, 1009; ^{1}H NMR (DMSO) (400 MHz) : δ= 7.43(1H),7.43 (t, *J* =7.2 Hz, 2H), 7.59 (t, *J* =7.2 Hz, 2H), 7.61(d, *J* =7.6 Hz, 3H), 7.82(d, *J* =7.2 Hz,2H), 8.01 (2H), 8.01 (d, *J* =7.6 Hz, 2H). ^{13}C NMR (DMSO): δ= 81.72, 112.12, 119.8, 124.94, 128.33, 129.25, 129.6, 132.72, 134.2, 134.6, 146.12, 192.8; Anal. Calcd for $C_{20}H_{14}N_6O$ (354.36): C, 67.79; H, 3.98; N, 23.72%, Found: C, 67.66; H, 4.04; N, 23.80%.

Results and Discussion

Now, we are reporting mild, simple and efficient methods for the syntheses of bis(1*H*-indol-3-yl)ethanones and the bis(benzotriazol-1-yl)ethanones in the presence of $B(HSO_4)_3$ in solvent-free thermal and in aqueous media conditions. Figure 1



Method A: Thermal solvent-free, Method B: Solvent

Figure 1. Reaction of the phenylglyoxals with indole or 1 *H*-benzotriazol

At first, the reaction of indole (2 mmol) with phenylglyoxal (1 mmol) was examined in the presence of different amounts of $B(HSO_4)_3$ at range of 25-120 ºC under thermal solvent-free conditions (Method A) in order to optimize the reaction conditions with respect to amount of the catalyst and temperature. The results are summarized in Table 1.

Table 1. Effect of amount of $B(HSO_4)_3$ and temperature on the reaction of indole and *p*-nitro phenylglyoxal

Amount of $B(HSO_4)_3$, g	Temperature, °C	Time, min	Yield[a], %
0.01	110	20	60
0.02	110	18	74
0.03	110	15	85
0.04	110	10	92
0.05	110	8	89
0.04	r.t	120	Trace
0.04	80	25	75
0.04	100	15	86
0.04	120	8	88

[a]*Isolated yield*

As it can be seen from Table 1, the reasonable results were obtained when the reaction was carried out using 0.04 g $B(HSO_4)_3$ at 110 ºC. Phenylglyoxals were synthesized by oxidation of acetophenones with selenium dioxide in the presence of dioxane or ethyl alcohol as solvent[17].

We also investigated the effect of some solid acids on the yields of bis (1*H*-indol-3-yl) ethanones. As shown in the Table 2, $B(HSO_4)_3$ is a more suitable solid acid catalyst for this condensation reaction.

Table 2. Investigation of the ability of various catalysts on the condensation of indole and *p*-nitrophenylglyoxal under thermal solvent-free conditions

Catalyst	Amount of catalyst	Time, min	Yield[a], %
$B(HSO_4)_3$	0.04	10	92
$Ca(HSO_4)_2$	0.04	20	78
$Ca(HSO_4)_2$	0.05	15	82
$Mg(HSO_4)_2$	0.05	15	85
$Fe(HSO_4)_3$	0.04	20	82
$Fe(HSO_4)_3$	0.05	15	84
$Zn(HSO_4)_2$	0.05	20	82
$NaHSO_4$	0.1	20	48
$KHSO_4$	0.1	20	53

[a]*Isolated yield*

In another study, the reaction was checked in several solvents to recognize the efficiency of the solvent-free procedure in comparison to solution conditions. For this purpose, a mixture of indole (2 mmol), phenylglyoxal (1 mmol) and $B(HSO_4)_3$ (0.04 g) was stirred in different solvents (10 mL) at under reflux conditions (Table 3). As Table 1 indicates, the solvent-free method afforded the product in higher yield and shorter reaction time.

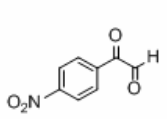
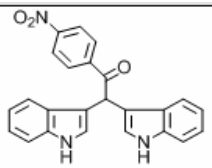
Table 3. Comparative the reaction between indole and *p*-nitrophenylglyoxal using $B(HSO_4)_3$ in solutions condition versus the solvent-free method

Solvent	Temperature, °C	Time, min	Yield[a], %
MeOH	Reflux	40	42
EtOH	Reflux	40	40
CH_3CN	Reflux	40	57
THF	Reflux	40	42
CH_2Cl_2	Reflux	40	55
$CHCl_3$	Reflux	40	52
H_2O	Reflux	40	80
Solvent-free	110	10	92

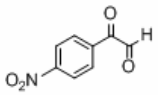
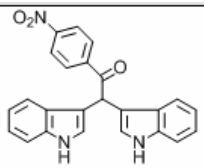
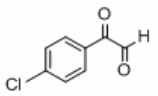
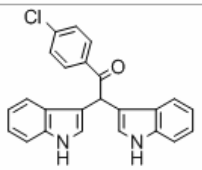
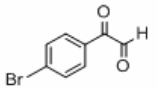
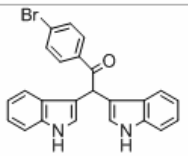
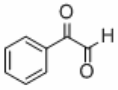
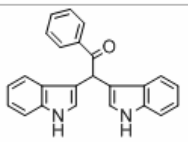
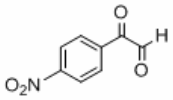
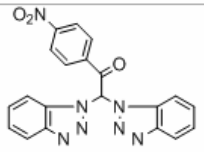
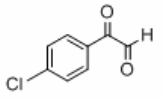
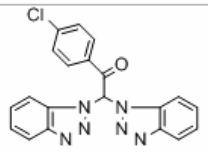
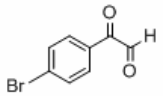
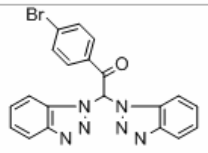
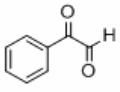
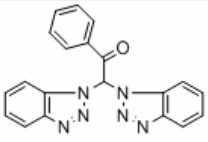
[a]*Isolated yield*

Thus, we prepared the bis(1*H*-indol-3-yl)ethanones and the bis(benzotriazol-1-yl) ethanones under the optimized reaction conditions of the 2 methods. The results are presented in Table 4.

Table 4. Syntheses of bis(1*H*-indol-3-yl)ethanones and bis(benzotriazol-1-yl)ethanones in the presence of $B(HSO_4)_3$

Entry	X,phenylglyoxal	Product	Method A or B, Time, min/ Yield, %[a,b], [Ref]
3a	**2a** 		10/92, 40/80

Contd...

3a	**2a** 		10/92, 40/80
3b	**2b** 		10/90, 40/77, [73]
3c	**2c** 		10/88, 40/75
3d	**2d** 		10/90, 40/79, [77]
3e	**2a** 		10/91, 40/78
3f	**2b** 		10/88, 40/77
3g	**2c** 		10/86, 40/74
3h	**2d** 		10/90, 40/76

Yields refers to isolated products.[a] *Method A.*[b] *Method B.*[d] *Reference [5]*

Conclusion

Efficient protocols for the syntheses of the bis(1*H*-indol-3-yl)ethanones and the bis(benzotriazol-1-yl) ethanones via the reactions of indole or 1, *H*-benzotriazole and the

phenylglyoxals under solvent-free thermal and solvent in the presence of $B(HSO_4)_3$, as an easily available catalyst, were described. The catalyst was easily separated in simple work-up. Moreover, the procedure offers several advantages, including high yields, operational simplicity, cleaner reactions and minimal environmental impact, which makes it a useful and attractive process for the synthesis of these compounds.

Acknowledgment

We gratefully acknowledge financial support from the Research Council of Islamic Azad University, Yazd branch and the Islamic Azad University, Zahedan branch.

References

1. Sundberg R J, The Chemistry of Indoles, Academic Press, New York, 1970, 1-3.
2. (a) Zeligs M A, *J Med Food*., 1998, **67;** (b) Cang Y C, Riby J, Chang G H, Peng B, Firestone G and Bjeldanes L F, *Biochem Pharmacol.*, 1999, **58**, 825.
3. Grubbs C J, Steele V E, Casebolt T, Juliana M M and Eto I, Whitaker L M, Dragnev K H, Kelloff G J and Lubet R L**,** *Anticancer Res.,* 1995, **15(3)**, 709-716.
4. Benabadji S H, Wen R, Zheng J and Dong X, *Acta Pharmacol Sin.,* 2004**, 25**, 666.
5. (a) Zhungietu G I and Chukhrii F N, *Chem Heterocycl Compounds*, 1969, **5(5)**, 952. (b) Ivonin S P and Lapandin A V, *Chem Heterocycl Compounds,* 2005, **41,** 1390-1393.
6. Sharma G V M, Reddy J J, Lakshmi P S and Krishna P R, *Tetrahedron Lett.,* 2004, **45**, 7729-7732.
7. Firouzabadi H, Iranpoor N and Jafari A A, *J Mol Catal A: Chem.,* 2005, **244**, 168.
8. Deb M L and Bhuyan P J, *Tetrahedron Lett*., 2006, **47(79)**, 1441-1443.
9. Rahul R, Nagawade R R and Shinde D B, *Bull Korean Chem Soc*., 2005, **26(12),** 1962.
10. Bandgar B P and Shaikh K A, *Tetrahedron Lett.,* 2003, **44**, 1959.
11. Ramesh C, Banerjee J, Pal R and Das B, *Adv Synth Catal.,* 2003, **345**, 557-559.
12. Hagiwara H, Sekifuji M, Hoshi T, Qiao K and Yokoyama C, *Synlett.,* 2007, 1320.
13. Azizi N, Torkian L and Saidi M R, *J Mol Catal A: Chem.,* 2007, **275**, 109-112.
14. Mehrazma S, Azizi N and Saidi M R, *Lett Org Chem.,* 2006, **3**, 161-164.
15. Zolfigol M A, Salehi P, Shiri M and Tanbakouchian Z, *Catal Commun.,* 2007, **8**, 173.
16. Kiasat A R, Fallah-Mehrjardi M. *J Braz Chem Soc.,* 2008, **19(8)**, 1595-1599.
17. Furniss B S, Hannaford A J, Smith P W G and Tatchell A R, Vogel's Textbook of Practical Organic Chemistry, 5th Edn., Wiley: New York, 1989, p. 629.