Asian Journal of Chemistry; *Vol. 24, No. 11 (2012), 5302-5304*

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Cobalt(II) Sulfamate as An Efficient Catalyst for Synthesis of *Bis*(1*H*-Indol-3-yl)methanes

YANAN ZHANG* and QING LIU

College of Chemistry & Chemical Engineering, Taishan University, 271021 Tai'an, P.R. China

*Corresponding author: Fax: +86 538 6715536; Tel: +86 538 6715546; E-mail: nn8210@126.com

(*Received*: 31 October 2011; *Accepted*: 16 June 2012) AJC-11622

The catalytic activity of eleven metal sulfamates for synthesis of *bis*(1*H*-indol-3-yl)methanes was compared under the same condition, cobalt(II) sulfamate proved to be the best. Cobalt sulfamate catalyzing the electrophilic substitution reactions of indole with aromatic, heterocyclic and unsaturated aldehydes as well as alicyclic and aromatic ketones were carried out in 90.6-99.2 % yield at room temperature in ethanol through conventional stirring or under ultrasound irradiation. More significant improvements were observed by carrying out the reactions under lower frequencies of ultrasound irradiation.

Key Words: *Bis*(1*H*-indol-3-yl)methanes, Cobalt sulfamate, Ultrasound, Catalysis.

INTRODUCTION

Bis(1*H*-indol-3-yl)methanes (BIMs), which contain two indole or substituted indole units in a molecule, feature widely in bioactive metabolites of terrestrial and marine origin[1]. Recent studies have shown that *bis*(1*H*-indol-3-yl)methanes can act as highly selective fluorescent molecular sensors for Cu^{2+} cations[2] and also as colon cancer cell and tumor growth inhibitors[3]. Because of their versatile biological activities, in particular the pharma-cological activity, various methods are mentioned for the preparation of *bis*(1*H*-indol-3-yl)methanes.

Ultrasonication, based on cavitation effects leading to mass transfer improvement, is an important technique that is widely used today in organic synthesis and has a profound impact on the way chemists approach organic and parallel synthesis[4]. Recently, the ultrasound-assisted synthesis of *bis*(1*H*-indol-3-yl)methanes has been reported[5], but all these methods have some drawbacks like the long reaction time[5a], strictly reactive condition (N_2 atmosphere)[5b], noxious solvent[5c] and large excess of catalyst (150 mol %)[5b] or carbonyl compounds (4 equiv.)[5d]. Therefore, the development of an efficient and green protocol is of interest.

We have reported that chromic sulfamate was efficient for synthesis of BIMs[6]. Continuing our investigations in sonocatalysis organic transformations[7], we wish to disclose a new and efficient protocol for synthesis of BIMs in the presence of metal sulfamates through conventional stirring (method A) or under ultrasound irradiation (method B).

EXPERIMENTAL

All reagents were purchased and used without further purification. Melting points were determined by using XT-4 micromelting point apparatus. GC analyses were carried out on a Shanghai GC-7890II gas chromatograph. Ultrasonication was performed in a KQ-300VDE ultrasound cleaner with a frequency of 45, 80 and 100 kHz and an output power 300W.

General procedure for synthesis of *bis*(1*H*-indol-3-yl)methanes through method A: To a mixture of indole (20 mmol) and carbonyl compound (10 mmol), ethanol (5 mL), was added cobalt sulfamate tetrahydrate (0.2 mmol) at room temperature under magnetic stirring. After completion of the reaction (monitored by GC), H_2O (10 mL) was added to the reaction mixture. Then, ethyl acetate (3 × 10 mL) was added and the upper organic phase was dried with Na_2SO_4 and evaporated under vacuum to give a crude product which was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:9 as the eluent) to furnish the product. All products were identified by comparing their spectral and physical data with those for authentic samples.

General procedure for synthesis of *bis*(1*H*-indol-3-yl)methanes through method B: Carbonyl compound (10 mmol), indole (20 mmol), ethanol (5 mL) and 0.2 mmol of cobalt sulfamate tetrahydrate were put in a flask. The flask was located at the maximum energy area in the ultrasonic cleaner and addition or removal of water was used to control the temperature of the water bath at room temperature (25-

30 ºC). After completion of the reaction, the subsequent steps were the same as in method A.

All products were identified by comparing their spectral and physical data with those for authentic samples.

RESULTS AND DISCUSSION

At the begining, we investigated the catalytic activity of different metal sulfamates in a model reaction of benzaldehyde with indole through method A. As shown in Table-1, most of the metal sulfamates screened were effective on catalyzing the reaction and cobalt sulfamate was found to be the best since it resulted in the highest yield to the desired product in the shortest time. However, the influence of central metal on the activity was hard to explain through either electronegativity or ionic radius, the reason for this is not yet clear. Then the influence of the amount of cobalt sulfamate on the reaction yield was studied in the same reaction time. When the amount of cobalt sulfamate was increased from 1 mol % to 3 mol % (Table-1, entries 1, 12-15), the yield of *bis*(1*H*-indol-3-yl)phenylmethane firstly increased to a maximum and then gradually decreased and the highest yield was obtained using 2 mol % of the catalyst (Table-1, entry 13).

TABLE-1
EFFECT OF CATALYST ON THE SYNTHESIS OF *BIS*(1*H*-INDOL-3-YL)PHENYLMETHANE[a]

Entry	Catalyst	Amount (mol %)	Time (h)	Yield[b] (%)
1	$Co(NH_2SO_3)_2$	2.0	0.67	98.2
2	$Fe(NH_2SO_3)_3$	2.0	0.75	90.1
3	$Cr(NH_2SO_3)_3$	2.0	1.5	97.6
4	$Cu(NH_2SO_3)_2$	2.0	3	96.5
5	$Ca(NH_2SO_3)_2$	2.0	3	89.4
6	$Zn(NH_2SO_3)_2$	2.0	4	97.5
7	$Cd(NH_2SO_3)_2$	2.0	16	52.1
8	$Ni(NH_2SO_3)_2$	2.0	17	85.7
9	$Ce(NH_2SO_3)_3$	2.0	72	94.8
10	$Pb(NH_2SO_3)_2$	2.0	72	NR[c]
11	$Bi(NH_2SO_3)_3$	2.0	72	NR[c]
12	$Co(NH_2SO_3)_2$	1.0	0.67	88.3
13	$Co(NH_2SO_3)_2$	1.5	0.67	96.9
14	$Co(NH_2SO_3)_2$	2.5	0.67	98.0
15	$Co(NH_2SO_3)_2$	3.0	0.67	95.7

[a]Reaction conditions: benzaldehyde (10 mmol), indole (20 mmol), ethanol (10 mL), at room temperature; [b]Isolated yields; [c]No reaction was observed.

The solvent effect on the yield of *bis*(1*H*-indol-3-yl)methane is given in Table-2. We carried out the reaction of benzaldehyde with indole in the presence of 2 mol % of cobalt sulfamate in different solvents at room temperature for 40 min. Among the solvents examined, ethanol was found to be the most effective, whereas the desired reaction proceeded slowly in other solvents. Furthermore, the influence of the amount of ethanol on the reaction yield was also investigated. The yield was up to 98.7 % in 5 mL ethanol (Table-2, entry 7). The reaction proceeded difficultly when the amount of solvent was too little (Table-2, entry 5), while there was a little decrease in the yield when more solvent was added because of the dilution of the solvent (Table-2, entries 4, 8).

TABLE-2
SYNTHESIS OF *BIS*(1*H*-INDOL-3-YL)PHENYLMETHANE CATALYZED BY COBALT(II) SULFAMATE TETRAHYDRATE[a]

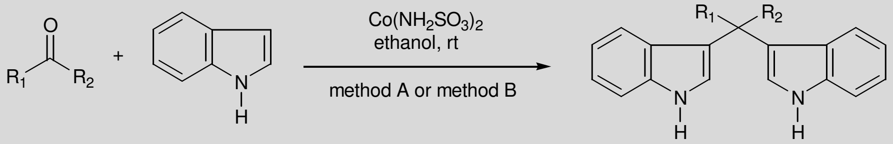
Entry	Solvent	Volume (mL)	Ultrasound (kHz)	Time (min)	Yield[b] (%)
1	Dichloromethane	10	–	40	35.8
2	Acetonitrile	10	–	40	80.8
3	Acetone	10	–	40	70.8
4	Ethanol	10	–	40	98.2
5	Ethanol	1	–	40	51.2
6	Ethanol	3	–	40	82.7
7	Ethanol	5	–	40	98.7
8	Ethanol	15	–	40	94.8
9	Ethanol	5	45	15	98.8
10	Ethanol	5	80	28	97.5
11	Ethanol	5	100	35	96.2

[a]Reaction conditions: benzaldehyde (10 mmol), indole (20 mmol), cobalt sulfamate tetrahydrate (0.2 mmol), at room temperature; [b]Isolated yields.

We also observed the effect of frequency of ultrasound irradiation. The reactions were compared at 45, 80 and 100 kHz with the same output power of 300 W. Compared to the reaction without ultrasound irradiation (Table-2, entry 7), the yield was 98.8 % only after 15 minutes with ultrasound 45 kHz (Table-2, entry 9). Experiments performed with variable frequency (80 and 100 kHz) showed the similar trends. These facts mean that ultrasound could enhance this reaction catalyzed by CoSM and there was an optimum frequency of 45 kHz for synthesis of *bis*(1*H*-indol-3-yl)methanes. We all know the driving energy of ultrasound is provided by cavitations. The formation and collapse of bubbles, liberates considerable energy in short time. While the critical size and life time of the cavitations bubbles depend on the liquid and the frequency of ultrasound. On account of longer ultrasonic periods, the implosion time and the size of the cavitation bubbles and the mechanical mixing effects in the liquid increase with decreasing frequencies, so lower frequencies are preferred for the synthesis of *bis*(1*H*-indol-3-yl)methanes. The similar frequency effect was observed for several other reactions[8]. As a result, further experiments were carried out with 45 kHz ultrasound irradiation.

The reactions were carried out in the presence of cobalt sulfamate through both method A and B at room temperature. As shown in Table-3, the reaction time was reduced and most of the yields were improved under ultrasound irradiation. The methodology was found to be general as the reactions of a variety of substituted aromatic aldehydes (Table-3, entries 3-8), α,β-unsaturated aldehydes (Table-3, entries 9-10), as well as alicyclic and aromatic ketones (Table-3, entries 11-12) with indoles had furnished the corresponding BIMs in excellent yields. The nature and electronic properties of the substituents on the aromatic ring affected the reaction rate and aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table-3, entries 3-4, 8) reacted faster than electron-donating groups (Table-3, entries 6-7). It was important to note that heterocyclic aldehyde (Table-3, entry 2) underwent smoothly with indole giving excellent yields of the corresponding BIMs. Furthermore, ketones required longer reaction time, which was most probably due to the electron-donating and steric effects of the methyl group.

TABLE-3
SYNTHESIS OF *BIS*(INDOLYL)METHANES BY THE REACTION OF INDOLE WITH ALDEHYDES AND KETONES IN THE PRESENCE OF COBALT SULFAMATE TETRAHYDRATE IN ETHANOL



Entry	Carbonyl compound	Method A[a]		Method B[b]		m.p. (ºC)	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)	Found	Reported
1	Benzaldehyde	40	98.7	15	98.8	125-126	124-125[10]
2	Furfural	40	99.2	12	97.5	321-323	322-324[9]
3	2-Chlorobenzaldehyde	20	96.6	10	97.3	73-74	72-74[10]
4	4-Methoxybenzaldehyde	20	96.8	15	96.2	191-193	190-192[10]
5	Vanillin	20	97.8	25	97.2	99-101	99-100[9]
6	Salicylal	60	93.5	45	91.2	345-348	348-349[9]
7	4-Hydroxybenzaldehyde	40	95.1	25	96.7	119-121	120-121[10]
8	2, 4-Dichlorobenzaldehyde	20	97.0	20	97.5	103-105	103-106[10]
9	Cinnamaldehyde	50	96.3	31	92.4	96-99	95-97[10]
10	Crotonaldehyde	65	96.0	50	94.5	124-126	123-126[11]
11	Cyclohexanone	60	92.5	45	95.7	115-117	115-116[10]
12	Hypnone	80	91.3	40	90.6	188-191	188-191[10]

[a]Method A: without ultrasound irradiation; [b]Method B: under ultrasound irradiation; [c]Isolated yield.

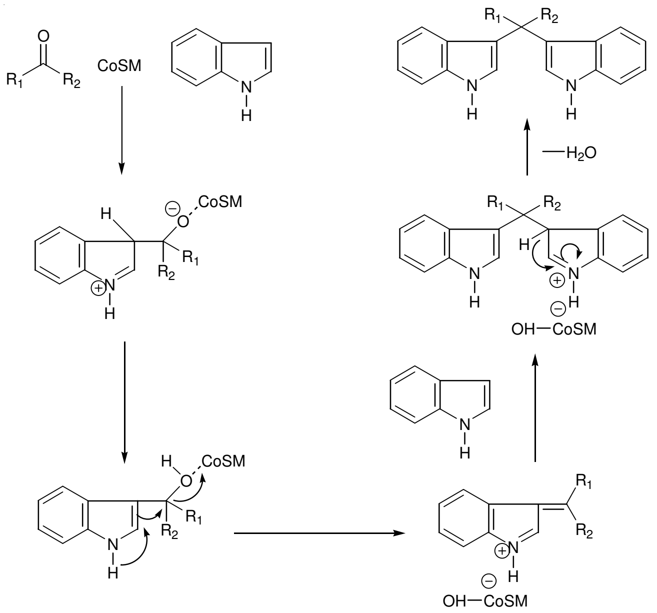


Fig. 1. Feasible mechanism for the reaction

We proposed a feasible mechanism for the reaction between indole and carbonyl compounds catalyzed by cobalt sulfamate (Fig. 1). The reaction was likely to proceed *via* the formation of an azafulvenium salt which in turn underwent further addition with a second indole molecule leading to the formation of *bis*(1*H*-indol-3-yl)methanes.

Conclusion

In summary, cobalt sulfamate was found to be an efficient catalyst for the electophilic substitution reactions of indoles with a variety of aldehydes and ketones giving *bis*(1*H*-indol-3-yl)methanes in excellent yields in short time through conventional stirring or under ultrasound irradiation. Improvements were observed by carring the reactions under ultrasound irradiation. The use of this inexpensive and easily available catalyst, the simple work-up procedure and the cleaner reaction made this protocol practical and economically attractive.

REFERENCES

1. (a) R.J. Sundberg, The Chemistry of Indoles, Academic Press, New York (1996); (b) A. Casapullo, G. Bifulco, I. Bruno and R. Riccio, *J. Nat. Prod.*, **63**, 447 (2000); (c) T.R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa and H. Yukawa, *J. Nat. Prod.*, **63**, 596 (2000); (d) B. Bao, Q. Sun, X. Yao, J. Hong, C.O. Lee, C.J. Sim, K.S. Im and J.H. Jung, *J. Nat. Prod.*, **68**, 711 (2005).
2. R. Martínez, A. Espinosa, A. Tárraga and P. Molina, *Tetrahedron*, **64**, 2184 (2008).
3. (a) P. Lei, M. Abdelrahim, S.D. Cho, S. Liu, S. Chintharlapalli and S. Safe, *Carcinogenesis*, **29**, 1139 (2008); (b) P. Diana, A. Carbone, P. Baraja, A. Montalbano, A. Martorana, G. Dattolo, O. Gia, L.D. Via and G. Cirrincione, *Bioorg. Med. Chem. Lett.*, **17**, 2342 (2007); (c) H.C. Zhang, L.V.R. Bonaga, H. Ye, C.K. Derian, B.P. Damiano and B.E. Maryanoff, *Bioorg. Med. Chem. Lett.*, **17**, 2863 (2007).
4. (a) M. Nikpassand, M. Mamaghani, F. Shirini and K.H. Tabatabaeian, *Ultrason. Sonochem.*, **17**, 301 (2010); (b) T.J. Mason, *Ultrason. Sonochem.*, **14**, 476 (2007); (c) N.M.A. Rahman, T.S. Saleh and M.F. Mady, *Ultrason. Sonochem.*, **16**, 70 (2009); (d) E.K. Goharshadi, Y. Ding, N.M. Jorabachi and P. Nancarrow, *Ultrason. Sonochem.*, **16**, 120 (2009); (e) J.L. Luche, Synthetic Organic Sonochemistry, Plenum, New York (1998).
5. (a) S.Y. Wang, S.J. Ji and X.M. Su, *Chin. J. Chem.*, **26**, 22 (2008); (b) J.T. Li, H.G. Dai, W.Z. Xu and T.S. Li, *Ultrason. Sonochem.*, **13**, 24 (2006); (c) I. Mohammadpoor-Baltork, H.R. Memarian, A.R. Khosropour and K. Nikoofar, *Lett. Org. Chem.*, **3**, 768 (2006); (d) R.S. Joshi, P.G. Mandhane, S.D. Diwakar and C.H. Gill, *Ultrason. Sonochem.*, **17**, 298 (2010); (e) J.T. Li, M.X. Sun, G.Y. He and X.Y. Xu, *Ultrason. Sonochem.*, **18**, 412 (2011).
6. Q. Liu and Zhen Li, *Asian J. Chem.*, **23**, 3208 (2011)
7. Q. Liu, H.M. Ai and Z. Li, *Ultrason. Sonochem.*, **18**, 477 (2011).
8. (a) S. Koda, A. Suzuki and H. Nomura, *Polymer*, **27**, 1144 (1995); (b) Y. Kojima, S. Koda and H. Nomura, *Ultrason. Sonochem.*, **8**, 75 (2001).
9. K.D. Deepak, R.P. Bhat and S.D. Samant, *Indian J. Chem.*, **46B**, 1455 (2007).
10. R. Ghorbani-Vaghei, H. Veisi, H. Keypour and A.A. Dehghani-Firouzabadi, *Mol. Divers.*, **14**, 87 (2010).
11. M.L. Deb and P.J. Bhuyan, *Tetrahedron Lett.*, **47**, 1441 (2006).