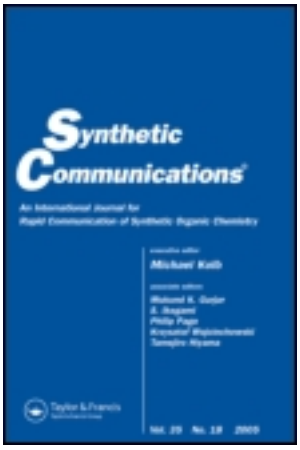
This article was downloaded by: [Brown University]
On: 21 February 2013, At: 05:19
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient Synthesis of Bis(indol)alkanes by Niobium(V) Chloride

Majid M. Heravi [a], Fatemeh Nahavandi [a], Samaheh Sadjadi [a], Hosien A. Oskooie [a] & Mahmood Tajbakhsh [b]

[a] Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

[b] Department of Chemistry, University of Mazandaran, Babolsar, Iran

Version of record first published: 12 Aug 2009.

To cite this article: Majid M. Heravi , Fatemeh Nahavandi , Samaheh Sadjadi , Hosien A. Oskooie & Mahmood Tajbakhsh (2009): Convenient Synthesis of Bis(indol)alkanes by Niobium(V) Chloride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:18, 3285-3292

To link to this article: http://dx.doi.org/10.1080/00397910902752246

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan,

sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Downloaded by [Brown University] at 05:19 21 February 2013

Synthetic Communications®, 39: 3285–3292, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902752246

Taylor & Francis
Taylor & Francis Group

Convenient Synthesis of Bis(indol) alkanes by Niobium(V) Chloride

Majid M. Heravi,[1] Fatemeh Nahavandi,[1] Samaheh Sadjadi,[1] Hosien A. Oskooie,[1] and Mahmood Tajbakhsh[2]
[1]Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran
[2]Department of Chemistry, University of Mazandaran, Babolsar, Iran

Downloaded by [Brown University] at 05:19 21 February 2013

Abstract: Bis(indolyl)alkanes have been synthesized in excellent yields in the presence of a catalytic amount of niobium(V) chloride under solvent-free conditions.

Keywords: Bis(indolyl)alkanes, niobium(V) chloride, solvent-free conditions

INTRODUCTION

The synthesis of bis(indolyl)alkane has been of considerable interest in organic synthesis because of its wide occurrence in various natural products possessing biological activity and its usefulness for drug design.[1]

Bis(indolyl)alkane is known to promote estrogen metabolism in both women and men and is expected to have an application in the prevention of breast cancer.[2] Several catalysts have been used for the preparation of these compounds, such as lanthanide triflate,[3] $FeCl_3$,[4] HOAc,[5] molecular iodine,[6] indium trichloride,[7] trifluoroacetic acid,[8] triphenyl phosphonium perchlorate,[9] copper(II) bromide,[10] molibdatophosphoric-acid,[11] and trichloro-1,3,5-triazine.[12]

Received October 26, 2008.
Address correspondence to Majid M. Heravi, Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran. E-mail: mmh1331@yahoo.com

Niobium(V) chloride, known as niobium pentachloride, is a yellow crystalline solid often used as a starting material in niobium chemistry.[13]

Recently, it has been shown that niobium chloride is an efficient Lewis acid catalyst in various organic transformations.[14,15] For example, the Diels–Alder reaction,[16] ring opening of epoxides,[17] allylation of aldehydes,[18] and N-acyliminium ions[19] have been catalyzed in the presence of this catalyst. Some of the advantages of application of this catalyst are ease of handling and low catalyst loading.[20]

Herein, we describe the electrophilic substitution reaction of indoles with aldehydes in the presence of a catalytic amount of niobium(V) chloride under solvent-free conditions (Scheme 1).

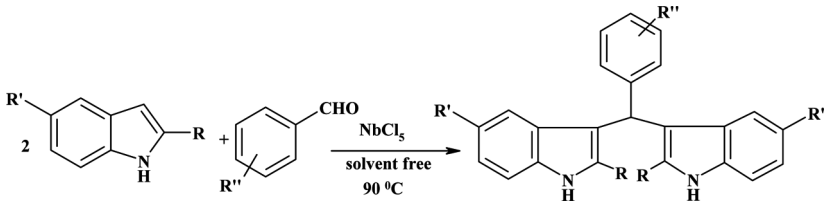
According to previous work using $NbCl_5$ as catalyst in organic reactions,[20] the proposed mechanism may involve the activation of the carbonyl group through coordination with Nb(V) and subsequent reaction of indoles with this activated aldehydes (Scheme 2).

To optimize the reaction conditions, the reaction of indole and benzaldehyde was selected as the model reaction.

To find the optimum amount of catalyst, the yields of the model reaction using various amounts of catalysts (0.5, 1, and 1.5 mol%) were obtained and compared. The results are summarized in Table 1. From these results, it can be concluded that the yields of reaction with very small amounts of catalyst are very high and the optimum amount of catalyst is 0.5 mol%.

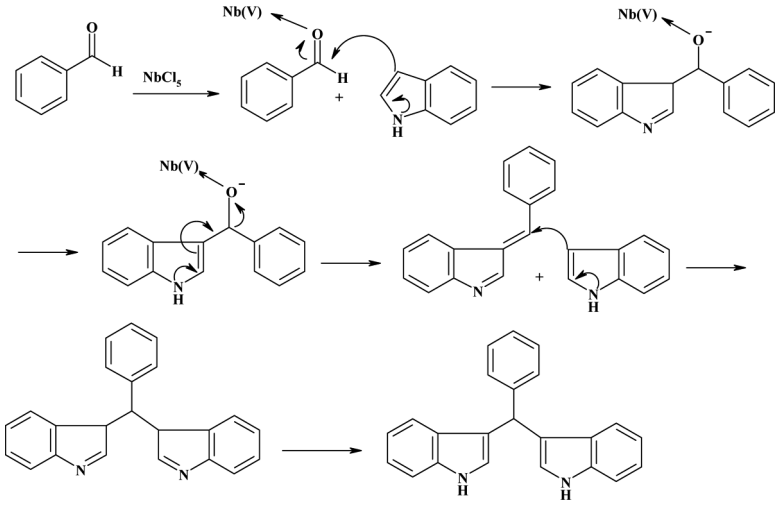
To investigate the effect of solvent on the yields of reactions, the model reaction was performed in various solvents including methanol (MeOH), H_2O, CH_2Cl_2, and ethanol (EtOH) and without solvent. The results are shown in Table 2. Considering these results, the solvent-free condition was selected as the best condition for all reactions.

It is known that $NbCl_5$ is very hygroscopic and readily hydrolyzes to niobic acid. To check the active catalyst in the case of using water as solvent, the infrared (IR) spectrum of the recovered catalyst was compared with that of $NbCl_5$. The results show that $NbCl_5$ in water will be hydrolyzed to niobic acid. From this observation, it can be concluded



Scheme 1. Synthesis of bis(indolyl)alkanes.

Downloaded by [Brown University] at 05:19 21 February 2013



Scheme 2. The proposed mechanism for the synthesis of bis(indolyl)alkanes.

Table 1. Effect of amount of catalyst on the yield of the reaction

Entry	Time (min)	Catalyst amount (mol%)	Yield (%)[a]
1	10	1.5	96
2	15	1	94
3	10	0.5	93

[a]Yields refer to isolated products.

Table 2. Effect of kind of solvent on the reaction of indole with benzaldehyde

Entry	Solvent	Time (min)	Yield (%)[a]
1	MeOH	10	96
2	EtOH	15	94
3	CH_2Cl_2	10	93
4	H_2O	30	97
5	Solvent-free	5	98

[a]Yields refer to isolated products.

Downloaded by [Brown University] at 05:19 21 February 2013

Table 3. Solvent-free synthesis of bis(indolyl)alkanes derivatives catalyzed by niobium(V) chloride

						Mp(°C)	
Entry	R	R′	R″	Time (min)	Yield (%)[a]	Found	Reported
1	H	H	H	5	96	125	125–127[21]
2	H	H	4-OH	10	98	123	122–124[22]
3	H	H	4-Cl	12	97	77	77–81[21]
4	H	H	3-NO_2	12	98	263	265–266[21]
5	Me	H	OMe	10	96	112	112–114[23]
6	Me	H	3-NO_2	3	95	254	257–259[23]
7	H	Br	OH	16	94	72	—
8	H	Br	OMe	12	92	208	—

[a]Yields refer to isolated products.

Downloaded by [Brown University] at 05:19 21 February 2013

that in water $NbCl_5$ is not an active catalyst and should not be selected as a suitable and appropriate solvent for this reaction.

The results of synthesis of bis(indolyl)alkanes in the presence of catalytic amounts of $NbCl_5$ are shown in Table 3.

To show the merits of this method, the yield of the model reaction in the presence of $NbCl_5$ was compared with various catalysts as reported in previous works. This comparison is shown in Table 4. As is shown in this table, $NbCl_5$ can catalyze the synthesis of bis(indol)alkanes in good yields and short reaction times with no solvent.

In conclusion, we have found a simple, efficient, and convenient procedure for the synthesis of bis(indolyl)alkanes under solvent-free conditions. Some advantages of this procedure are good yields, absence of volatile and hazardous solvents, short reaction times, and good conversions.

EXPERIMENTAL

Chemicals and Apparatus

Melting points were measured using the capillary tube method with an electrothermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQC Avance 300-MHz spectrometer using tetramethylsilane (TMS) as an internal standard ($CDCl_3$ and dimethyl sulfoxide [DMSO] solution). IR spectra were recorded from KBr disk on the Fourier transform (FT)–IR Bruker Tensor 27. Mass spectra (MS) were recorded on a 5973 network mass selective detector. Known products were

Table 4. Comparison between $NbCl_5$ and various catalysts used in synthesis of bis(indolyl)alkanes

Entry	Condition	Time (min)	Catalyst	Yield (%)
1	Solvent-free condition	5	$NbCl_5$	96
2	Solvent-free condition at room temperature	10	I_2	72[6]
3	30–38°C in EtOH aqueous solution under ultrasound irradiation	30	H_2NSO_3H	93–95[23]
4	Stirring at 60°C	30	TPA-ZrO_2	90[24]
5	Stirring at room temperature	720	—	70[25]
6	Stirring at 90°C, Solvent-free condition	120	NH_4Cl	96[26]
7	Stirring at room temperature	15	Trichloro-1, 3,5-triazine	92[12]
8	Stirring at 50°C	40	$ZrOCl_2 \cdot 8H_2O$	84[27]
9	Solvent-free condition	40	$H_6P_2W_{18}O_{62}$	96[21]
10	Stirring in ethanol at room temperature	180	$Zn(HSO_4)_2$	91[22]
11	Stirring in ethanol at room temperature	360	$Mg(HSO_4)_2$	89[22]
12	Stirring in ethanol at room temperature	210	$Ca(HSO_4)_2$	91[22]
13	Stirring in ethanol at room temperature	150	$Al(HSO_4)_3$	92[22]
14	Stirring in ethanol at room temperature	120	Silica sulfuric acid	No reaction[22]

Downloaded by [Brown University] at 05:19 21 February 2013

characterized by ^1H NMR, FT-IR, and comparison of their melting points with authentic samples.

General Procedure

A mixture of benzaldehyde (1 mmol), indole (2 mmol), and niobium(V) chloride (0.5 mol%) was magnetically stirred in a round-bottomed flask at 90°C. The progress of the reaction was monitored by thin-layer chromatography (TLC) using n-hexane–ethylacetate (4:1) as eluents. After completion of the reaction, the product was solved in the dichloromethane (DCM), and the catalyst was separated from the reaction mixture by simple filtration. After evaporating the solvent, the crude

product was obtained. For further purification, the product was recrystallized from n-hexane–dichloromethane 4:96.

Spectral Data for New Compounds

Entry **7**

Mp: 72°C, IR (KBr): 3480, 3385, 3128, 2917, 2855, 1457, 1196, 782, 470 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 10.90 (s, 2H, NH), 9.11 (s, 1H), 7.30–7.42 (m, 2H), 7.20–7.32 (m, 2H), 6.80 (d, 2H), 6.61–6.70 (d, 2H), 5.70 (s, 1H); ^{13}C NMR (300 MHz, DMSO, d, δ): 156.35, 136.14, 135.37, 129.93, 129.26, 125.96, 124.21, 122.12, 119.10, 115.81, 115.60, 114.40, 111.67, 38.98; MS (m/z): 496, 479, 323, 89.

Entry **8**

Mp: 208°C, IR (KBr): 3455, 3429, 3128, 2956, 2928, 1508, 1456, 1247, 1096, 792 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 11.22 (s, 2H, NH), 7.10–7.30 (m, 8H), 6.80–6.91 (m, 4H), 5.83 (s, 1H), 3.80 (s, 1H); ^{13}CNMR (300 MHz, DMSO, d, δ): 158.35, 137.12, 136.14, 129.97, 129.22, 125.99, 124.26, 122.08, 118.88, 114.44, 111.70, 55.81, 38.90; MS (m/z): 510, 479, 429, 403, 107.

ACKNOWLEDGMENT

The authors are thankful to Azzahra Research Council for partial financial support.

REFERENCES

1. Osawa, T.; Namiki, M. Structure elucidation of streptindole, a novel genotoxic metabolite isolated from intestinal bacteria. *Tetrahedron Lett.* **1983**, *24*, 4719.
2. Karthik, M.; Tripathi, A. K.; Gupta, N. M.; Palanichamy, M.; Murugeson, V. Zeolite-catalyzed electrophilic substitution reaction of indoles with aldehydes: Synthesis of bis(indolyl)methanes. *Catal. Commun.* **2004**, *5*, 371.
3. Xia, M.; Wang, S.; Yuan, W. Lewis acid–catalyzed electrophilic substitution of indole with aldehydes and Schiff's bases under microwave solvent-free irradiation. *Synth. Commun.* **2004**, *34*, 3175.
4. Vigmond, S. J.; Chang, M. C.; Kallury, K. M. R.; Thompson, M. Direct synthesis of aryldipyrromethanes. *Tetrahedron Lett.* **1994**, *35*, 2455.
5. Kamal, A.; Qureshi, A. A. Syntheses of some substituted di-indolylmethanes in aqueous medium at room temperature. *Tetrahedron* **1963**, *19*, 513.

Downloaded by [Brown University] at 05:19 21 February 2013

6. Ji, S. J.; Wang, S. Y.; Zhang, Y.; Loh, T.-P. Facile synthesis of bis(indolyl)-methanes using catalytic amount of iodine at room temperature under solvent-free conditions. *Tetrahedron* **2004**, *60*, 2051.
7. Babu, G.; Sridhar, N.; Perumal, P. T. A convenient method of synthesis of bis-indolylmethanes: Indium trichloride–catalyzed reactions of indole with aldehydes and Schiff's bases. *Synth. Commun.* **2000**, *30*, 1609.
8. Lee, C. H.; Lindsey, J. S. One-flask synthesis of *meso*-substituted dipyrromethanes and their application in the synthesis of *trans*-substituted porphyrin building blocks. *Tetrahedron* **1994**, *50*, 11427.
9. Nagarajan, R.; Perumal, P. T. Electrophilic substitution of indoles catalyzed by triphenyl phosphonium perchlorate: Synthesis of 3-acetyl indoles and bis-indolylmethane derivatives. *Synth. Commun.* **2002**, *32*, 105.
10. Mo, L. P.; Ma, Z. C.; Zhang, Z. H. $CuBr_2$-catalyzed synthesis of bis(indolyl)-methanes. *Synth. Commun.* **2005**, *35*, 1997.
11. Zolfigol, M. A.; Salehi, P.; Shiri, M. An efficient procedure for the preparation of mono- and di- bis-indolyl methanes catalyzed by molibdatophosphoric acid. *Phosphorus Sulfur Silicon Relat. Elem.* **2004**, *179*, 2273.
12. Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. A versatile and practical synthesis of bis(indolyl)methanes/bis(indolyl)glycoconjugates catalyzed by trichloro-1,3,5-triazine. *Tetrahedron Lett.* **2004**, *45*, 7729.
13. Cotton, F. A.; Kibala, P. A.; Matusz, M.; Sandor, R. B. W. Structure of the second polymorph of niobium pentachloride. *Acta Cryst.* **1991**, *47*, 2435.
14. Kleber, C.; Andrade, Z. Niobium pentachloride in organic synthesis: Applications and perspectives. *Curr. Org. Synth.* **2004**, *1*, 333.
15. Kleber, C.; Andrade, Z.; Rocha, R. O. Recent applications of niobium catalysts in organic synthesis. *Mini-Rev. Org. Chem.* **2006**, *3*, 271.
16. Howarth, J.; Gillespie, K. Lewis acid catalysis of the Diels–Alder reaction using niobium and tantalum chlorides in the presence of coordinating ligands. *Molecules* **2000**, *5*, 993.
17. Constantino, M. G.; Lacerda, Jr., V.; Aragao, V. Niobium pentachloride–catalysed ring opening of epoxides. *Molecules* **2001**, *6*, 770.
18. Andrade, C. K. Z.; Azevedo, N. R. Niobium(V) chloride–mediated allylation of aldehydes: Scope and stereoselectivity. *Tetrahedron Lett.* **2001**, *42*, 6473.
19. Wang, R.; Li, B. G.; Huang, T. K.; Shi, L.; Lu, X. X. $NbCl_5$-catalyzed one-pot Mannich-type reaction: Three-component synthesis of b-amino carbonyl compounds. *Tetrahedron Lett.* **2007**, *48*, 2071.
20. Yadav, J. S.; Bhunia, D. C.; Krishna, K. V.; Srihari, P. Niobium(V) pentachloride: An efficient catalyst for C, N, O, and S-nucleophilic substitution reactions of benzylic alcohols. *Tetrahedron Lett.* **2007**, *48*, 8306.
21. Heravi, M. M.; Bakhtiari, K.; Fatehi, A.; Bamoharram, F. F. A convenient synthesis of bis(indolyl)methanes catalyzed by diphosphooctadecatungstic acid. *Catal. Commun.* **2008**, *9*, 289.
22. Niknam, K.; Zolfigol, M. A.; Sadabadi, T.; Nejati, A. Preparation of indolylmethanes catalyzed by metal hydrogen sulfates. *J. Iranian Chem. Soc.* **2006**, *3*, 318.

Downloaded by [Brown University] at 05:19 21 February 2013

23. Li, J. T.; Dai, H. G.; Xu, W. Z.; Li, T. S. An efficient and practical synthesis of bis(indolyl)methanes catalyzed by aminosulfonic acid under ultrasound. *Ultrasonics Sonochem.* **2006**, *13*, 24.
24. Satam, J. R.; Parghi, K. D.; Jayaram, R. V. 12-Tungstophosphoric acid supported on zirconia as an efficient and heterogeneous catalyst for the synthesis of bis(indolyl)methanes and tris(indolyl)methanes. *Catal. Commun.* **2008**, *9*, 1071.
25. Deb, M. L.; Bhuyan, P. J. An efficient and clean synthesis of bis(indolyl)-methanes in a protic solvent at room temperature. *Tetrahedron Lett.* **2006**, *47*, 1441.
26. Azizian, J.; Teimouri, F.; Mohammadizadeh, M. R. Ammonium chloride–catalyzed one-pot synthesis of diindolylmethanes under solvent-free conditions. *Catal. Commun.* **2007**, *8*, 1117.
27. Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. $ZrOCl_2 \cdot 8H_2O$/silica gel as a new, efficient, and a highly water-tolerant catalyst system for facile condensation of indoles with carbonyl compounds under solvent-free conditions. *J. Mol. Catal. A: Chem.* **2006**, *253*, 249.

Downloaded by [Brown University] at 05:19 21 February 2013