

Zirconyl(IV) Chloride - Catalysed Reaction of Indoles: An Expeditious Synthesis of Bis(indolyl)Methanes

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Abstract

Zirconyl(IV) chloride is found to be an efficient catalyst for the electrophilic substitution reaction of indole with aldehydes / ketones to afford the corresponding bis(indolyl)methanes in good yields. The remarkable features of this new procedure are high conversions, shorter reaction times, cleaner reaction profiles and simple experimental and work-up procedures.

Keywords: Zirconyl(IV) chloride, aldehydes, ketones, bis(indolyl)methanes, indole

Introduction

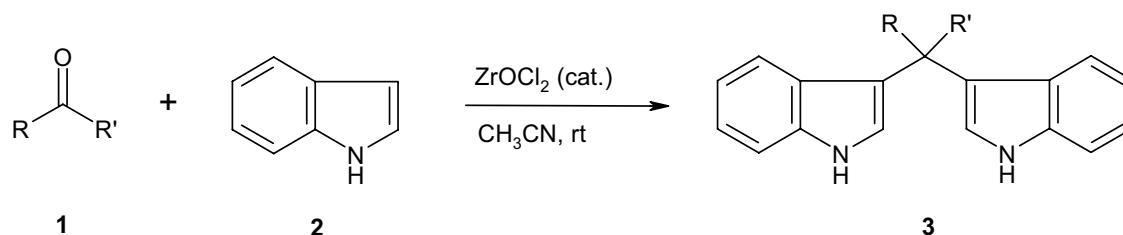
Development of bis(indolyl)alkane synthesis has been of considerable interest in organic synthesis because of their wide occurrence in various natural products possessing biological activity¹ and usefulness for drug design.² Bis(indolyl)methanes are most active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells.³ Consequently, numerous methods have been reported for the synthesis of bis(indolyl)methanes.⁴ Of these methods, the acid-catalysed electrophilic substitution reaction of indoles with aldehydes is one of the most simple and straightforward approaches for the synthesis of bis(indolyl)methanes. A variety of reagents such as acetic acid,⁵ InCl₃,⁶ In(OTf)₃,⁷ InF₃,⁸ Dy(OTf)₃,⁹ Ln(OTf)₃,¹⁰ LiClO₄,¹¹ FeCl₃,¹² I₂,¹³ NBS,¹⁴ KHSO₄,¹⁵ NaHSO₄, SiO₂,¹⁶ PPh₃·HClO₄ (TPP),¹⁷ CAN,¹⁸ zeolites,¹⁹ clay,²⁰ H₃PMo₁₂O₄₀·xH₂O,²¹ and 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquids²² have been employed to accomplish this transformation. Recently, rare-earth perfluorooxanoates [RE(PFO)₃],²³ trichloro-1,3,5-triazine,²⁴ hexamethylenetetramine-bromine,²⁵ ion-exchange resin²⁶ and ionic liquids in conjugation with In(OTf)₃ or FeCl₃·6H₂O²⁷ were also found to promote this reaction. However, some of the reported methods have the following drawbacks: for example, use of expensive reagents,^{7,9,10} longer reaction times,^{5,6,8,22} low yields of products^{5, 20b} and use of an additional microwave oven.¹² Because of their wide range of biological, industrial and synthetic applications,

the preparation of bis(indolyl)methanes has received renewed interest of researchers for the discovery of improved protocols and still awaits further development of milder and high-yielding processes.

Due to their easy availability and low toxicity, Zr(IV) salts have recently attracted much attention. Zirconyl(IV) chloride is moisture stable, readily available and inexpensive oxy-salt of zirconium, and until now has not been explored in synthetic organic chemistry as a mild and versatile Lewis acid catalyst. Compared to conventional Lewis acids, particularly zirconyl(IV) chloride has advantages of low catalyst loading, moisture stability and catalyst recycling. However, there are no examples of the use of zirconyl(IV) chloride as a catalyst for the preparation of bis(indolyl)methanes.

Results and discussion

Herein, we wish to disclose a novel protocol for the rapid synthesis of a variety of biologically important bis(indolyl)methanes using a catalytic amount of zirconyl(IV) chloride under extremely mild conditions (**Scheme 1**). Firstly, 4-chlorobenzaldehyde (**1a**) was chosen as a model for the reaction with indole. Compound **1a** was treated with 2.0 equivalents of indole in the presence of 5 mol % ZrOCl₂ (based on the amount of indole) at room temperature in various solvents (**Table 1**, entries 1-7). In CH₃CN, the reaction completed within 20 minutes to give bis(indolyl)methane **3a** in 90 % yield. The reactions in CH₂Cl₂, AcOEt, MeOH, EtOH, DMF and THF required longer reaction



Scheme 1

times, and unreacted **1a** and indole remained. Lower catalyst loading can be used with only a marginal drop in reaction rate (Table 1, entry 8).

Table 1. Screening of reaction conditions for the synthesis of **3a**:

Entry	Solvent	Catalyst	Time(hr.)	Yield (%) ^a
1	CH ₃ CN	5% ZrOCl ₂	0.35	90
2	AcOEt	5% ZrOCl ₂	2	84
3	CH ₂ Cl ₂	5% ZrOCl ₂	3	82
4	MeOH	5% ZrOCl ₂	3	76
5	EtOH	5% ZrOCl ₂	2	74
6	THF	5% ZrOCl ₂	5	72
7	DMF	5% ZrOCl ₂	7	53
8	CH ₃ CN	1% ZrOCl ₂	0.75	83

^a isolated yields

Having established the reaction conditions, various aldehydes **1** were treated with indole **2** to investigate the reaction scope, and several representative examples are summarized in Table 2. Aromatic, aliphatic (entry b) and a heterocyclic aldehyde (entry j) underwent smooth transformation to the corresponding bis(indolyl)methanes in high to excellent yield in relatively shorter reaction times. It has been observed that the electronic properties of the aromatic ring have an effect on the rate of this electrophilic substitution reaction. The rate is accelerated if an electron withdrawing group is present on the

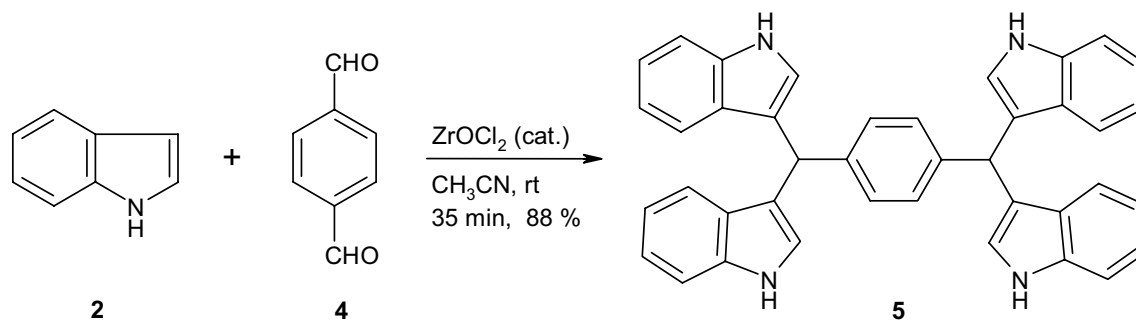
aromatic ring. The reaction of ketones with indole took longer time when compared with aldehydes, and unreacted ketone and indole remained. It is also found that the reaction of terephthalaldehyde **4** with 4 equivalents of indole proceeded rapidly to give *p*-di(bis-indolylmethyl)benzene **5** in similar conditions in high yield (Scheme 2).

Conclusions

In summary, the electrophilic substitution reaction of indole with aldehydes was successfully carried out in the presence of catalytic amount of ZrOCl₂ at room temperature. This method offers several significant advantages, such as high conversions, easy handling, cleaner reaction profile and shorter reaction times, which makes it an useful and attractive process for the rapid synthesis of substituted bis(indolyl)methanes.

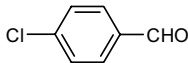
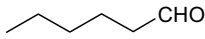
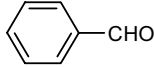
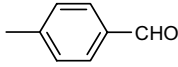
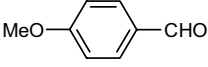
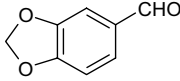
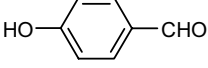
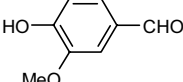
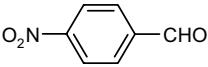
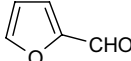
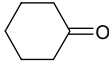
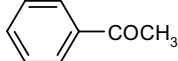
Experimental

Melting points are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Electron-spray ionization mass spectra (ES-MS) were recorded on a Water-Micromass Quattro-II spectrometer. IR spectra were recorded on a Varian spectrometer. All reagents were of AR grade and were used without further purification. Column chromatography employed silica gel of 60-120 mesh.



Scheme 2

Table 2. ZrOCl₂ - Promoted synthesis of bis(indolyl)methane derivatives

Entry	Substrate	Time (min)	Yield %	M.P.(°C)	
				Found	Reported
a		20	90	76-77	77-81 ²
b		65	84	68-70	70-72 ²⁶
c		35	89	123-125	125-127 ^{20b}
d		40	93	96-98	94-96 ^{27b}
e		45	88	190-192	187-189 ^{27b}
f		35	86	100-102	97-99 ¹¹
g		40	84	124-125	122-124 ¹⁸
h		45	90	111-112	110-112 ^{19b}
i		15	88	221-223	220-222 ²⁶
j		40	87	320-323	322 ²⁵
k		310	69	118-120	118-120 ¹¹
l		325	54	189-190	190-192 ¹⁸

General Procedure

A mixture of indole (2 mmol), aldehyde or ketone (1 mmol) and ZrOCl₂ (0.1 mmol) in acetonitrile was stirred at room temperature for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (3x10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to afford the crude compound. The crude compounds were purified by silica gel column chromatography using ethyl acetate / hexane as eluent, to afford the desired compound in pure form. All the synthesized compounds were characterized by ¹H NMR,

¹³C NMR, mass spectrometry (ES-MS), elemental analysis and melting point.

4-Chlorophenyl-3,3'-bis(indolyl)methane (3a):

Yield 90 %, mp 76-77 °C, IR (KBr): 3411, 3055, 2923, 2848, 1617, 1417, 1337, 1089, 1013, 743 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 5.86 (s, 1H, Ar-CH), 6.65 (s, 2H), 7.02 (t, 2H, *J*=7.6 Hz), 7.18 (t, 2H, *J*=7.6 Hz), 7.26-7.38 (m, 8H), 7.93 (br, s, 2H, NH). ¹³C NMR (50 MHz, CDCl₃): δ 46.5, 100.6, 110.1, 118.0, 119.1, 121.2, 127.0, 127.8, 129.5, 130.3, 134.2, 135.2, 135.6. Mass (ES/MS): *m/z* 357 (M+H, 100 %). Anal. Calcd. for C₂₃H₁₇ClN₂: C 77.41, H 4.80, N 7.85. Found: C 77.55, H 4.73, N 7.90

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Povzetek

Cirkonil(IV) klorid (ZrOCl₂) je bil uporabljen kot učinkovit katalizator pri elektrofilni substituciji indola z aldehidi in ketoni. Pri tem nastanejo ustrezni bis(indolil)metani z dobrimi izkoristki. Pomembne odlike novega postopka so velik delež pretvorbe, krajši reakcijski časi, čistejše reakcijske poti ter enostavnejši postopek priprave in izolacije produkta.