



Glycerin and CeCl₃·7H₂O: a new and efficient recyclable medium for the synthesis of bis(indolyl)methanes

Claudio C. Silveira^{a,*}, Samuel R. Mendes^a, Francieli M. Líbero^a, Eder J. Lenardão^b, Gelson Perin^b

^aDepartamento de Química, Universidade Federal de Santa Maria, UFSM, 97105-900 Santa Maria, RS, Brazil

^bInstituto de Química e Geociências, LASOL, Universidade Federal de Pelotas, UFPel, P.O. Box 354, 96010-900 Pelotas, RS, Brazil

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ABSTRACT

Glycerin and CeCl₃·7H₂O were successfully used in recyclable catalytic system for the synthesis of several bis(indolyl)methanes in good to excellent yields through the reaction of indoles with aldehydes. The method is applicable to aliphatic and aromatic aldehydes, and the mixture of glycerin and CeCl₃·7H₂O can be reused up to five times without special treatment and with comparable yields.

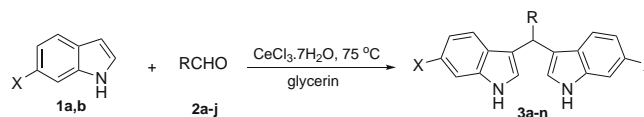
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Indoles and their derivatives are widely present in bioactive metabolites of compounds of both terrestrial and marine origin.¹ Recent studies have shown that bis(indolyl)methanes can act as highly selective fluorescent molecular sensors for Cu²⁺ cations² and also as colon cancer cell and tumor growth inhibitors.³ Because of their versatile biological activities, in particular the pharmacological activity, various methods are mentioned for the preparation of bis(indolyl)methanes. The most common protocol involves the Lewis or protic acid-promoted electrophilic substitution reaction of indoles with carbonyl compounds.⁴ Despite the high atomic efficiency of these reactions, a drawback of most of the described methods is the use of expensive and toxic reagents and volatile solvents. Recently, some improvements on the preparation of bis(indolyl)methanes have been described.⁵ These comprise the use of I₂,^{5a} modified zirconia,^{5b} HBF₄–SiO₂,^{5c} ZnO,^{5d} oxalic acid,^{5e} trityl chloride,^{5f} and CeCl₃·7H₂O–NaI–SiO₂^{5g} under solvent-free conditions, dodecylsulfonic acid in the presence of water,^{5h} PEG-supported sulfonic acid,⁵ⁱ catalytic [bmim][MeSO₄],^{5j} or ionic liquid in the absence of any catalyst.^{5k} In general, these reactions occur under mild conditions, are simple and clean, and give yields comparable to the conventional methods. In spite of these advantages, the direct reuse of the catalytic system is not possible in most of the described methods.

Recently, glycerin, which is easily available as a co-product in the biodiesel production, has attracted attention as it is a versatile, cheap, and renewable feedstock in synthetic organic chemistry.⁶ Because of our interest in the use of glycerin as a solvent,⁷ and in new applications of cerium(III) in organic synthesis,⁸ we decided

to study the electrophilic substitution reaction of indoles **1** with carbonyl compounds **2** to obtain bis(indolyl)methanes **3** (Scheme 1, Tables 1 and 2).

Initially, we chose indole (**1a**, 1 mmol) and benzaldehyde (**2a**, 0.5 mmol) as standard starting materials to establish the best conditions for the reaction. We examined the temperature, amount of CeCl₃·7H₂O, and reaction time using glycerin as a recyclable solvent (Table 1). It was found that by using 0.5 equiv of CeCl₃·7H₂O and 2.0 mL of glycerin at room temperature, the reaction proceeded slowly and in 95% yield after stirring for 24 h (Table 1, entry 1). However, when the mixture was heated at 60 and 75 °C, the desired product **3a** was obtained in similar yields, after 3 and 1.5 h, respectively (entries 2 and 3). At higher temperatures no products were isolated, even after stirring for several hours (entry 4). The effect of the amount of the catalyst was also evaluated. When only 0.1 equiv of CeCl₃·7H₂O was used, **3a** was obtained in excellent yield after stirring at 75 °C for 1.5 h (entry 5). On the other hand, by using 1.0 equiv of CeCl₃·7H₂O, no increase in yield or reduction in time was observed (entry 6).



1 X = (a) H, (b) Br

2 R = (a) C₆H₅, (b) 4-NO₂C₆H₄, (c) 4-ClC₆H₄, (d) 4-CH₃OC₆H₄, (e) 2-ClC₆H₄, (f) 2-CH₃C₆H₄, (g) C₆H₅CH=CH, (h) 3,4-OCH₂O-C₆H₃, (i) 2-furyl, (j) C₄H₉.

Scheme 1.

* Corresponding author. Tel./fax: +11 55 55 220 8754.

E-mail address: silveira@quimica.ufsm.br (C.C. Silveira).

Table 1
Optimization of the synthesis of bis(indolyl)methanes according to Scheme 1^a

Entry	Solvent	CeCl ₃ ·7H ₂ O (equiv)	Temp. (°C)	Time (h)	Yield (%)
1	Glycerin	0.5	rt	24	95
2	Glycerin	0.5	60	3	95
3	Glycerin	0.5	75	1.5	94
4	Glycerin	0.5	100	24	— ^b
5	Glycerin	0.1	75	1.5	96
6	Glycerin	1.0	75	1.5	94
7	Glycerin	0	rt	24	31
8	Glycerin	0	75	24	32
9	CH ₃ CN	0.5	rt	24	N.R. ^c
10	PEG-400	0.5	rt	24	30
11	PEG-400	0	rt	24	N.R. ^c
12	ⁱ C ₃ H ₇ OH	0.5	rt	24	N.R. ^c
13	CH ₃ NO ₂	0.5	rt	24	N.R. ^c

^a Reaction conditions: indole (**1a**, 1.0 mmol); benzaldehyde (**2a**, 0.5 mmol).^b A complex mixture was obtained.^c No reaction.

When the reaction was performed in glycerin, without CeCl₃·7H₂O, at room temperature or by heating (75 °C), incomplete consumption of the starting materials and poor yields were observed (entries 7 and 8). We also used other solvents instead of glycerin, such as CH₃CN, CH₃NO₂, ⁱPrOH, and PEG-400. However, only PEG-400 afforded the product, but in modest yield (30%), even after 24 h (Table 1, entry 10).

Since the best conditions were established (Table 1, entry 5), the protocol was extended to other aromatic and aliphatic aldehydes, reacting with indole and 6-bromoindole (Table 2, Scheme 1).⁹

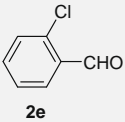
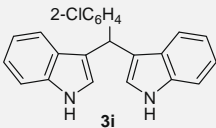
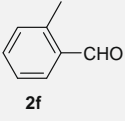
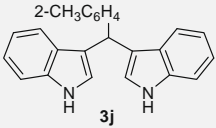
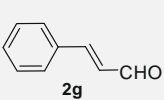
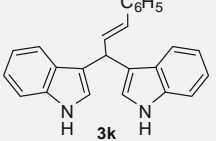
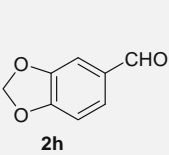
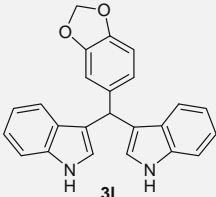
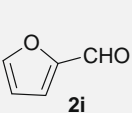
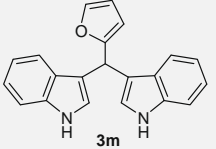
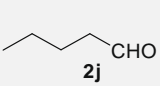
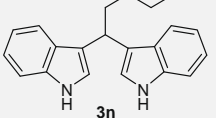
For all the tested examples, the bis(indolyl)methanes **3** were obtained in good to excellent yields after stirring at 75 °C for 1.5–5 h, except for *p*-chlorobenzaldehyde (**2c**), which needed 8–10 h of reaction (Table 2). When 6-bromo-1*H*-indole (**1b**) was used, the respective brominated products were obtained in slightly lower yields, compared to **1a** (entries 2, 4, 6 and 8, Table 2). For substituted benzaldehydes containing either NO₂ (**2b**, entries 3 and 4) or

Table 2
Synthesis of bis(indolyl)methanes **3** using the mixture of glycerin/CeCl₃·7H₂O

Entry	Indoles 1	Aldehydes 2	Product 3	Time (h)	Yield ^a (%)
1				1.5	96
2		2a		1.5	85
3	1a			5	79
4	1b	2b		5	73
5	1a			8	88
6	1b	2c		10	77
7	1a			2	87
8	1b	2d		4	73

(continued on next page)

Table 2 (continued)

Entry	Indoles 1	Aldehydes 2	Product 3	Time (h)	Yield ^a (%)
9	1a	 2e	 3i	5	84
10	1a	 2f	 3j	2	96
11	1a	 2g	 3k	2	75
12	1a	 2h	 3l	5	72
13	1a	 2i	 3m	2	86
14	1a	 2j	 3n	5	75

^a Yields of pure products isolated by column chromatography (hexanes/AcOEt) and identified by mass spectrometry, ¹H and ¹³C NMR, Refs. 4 and 5.

Cl (**2c**, entries 5 and 6; and **2e**, entry 9), longer reaction times were needed to completely consume the starting materials. The aliphatic aldehyde pentanal (**2j**) reacted with indole **1a** under our conditions to afford, after 5 h, 3,3'-pentane-1,1-diylbis-1*H*-indole (**3n**) in 75% (entry 14).

The glycerin/CeCl₃·7H₂O mixture can be successfully reused up to five times without any treatment with excellent results. Thus, for example, after the completion of the reaction of indole **1a** and benzaldehyde **2a** (Table 2, entry 1), the product **3a** was simply extracted with ethyl acetate (3 × 5 mL) and the glycerin/catalyst mixture was reused in a new electrophilic substitution. The product was obtained in 95%, 94%, 96%, 94%, and 95% yields after successive cycles.

In conclusion, the mixture of glycerin/CeCl₃·7H₂O has proved to be an effective, recyclable catalytic system for the synthesis of bis(indolyl)methanes. The method is simple, clean, and general for the reaction of aromatic and aliphatic aldehydes with indole. The use of low-cost, renewable feedstock glycerin as a solvent and of a small amount of the catalyst, together with the possibility of their direct reuse for several cycles, is particularly relevant to the green chemistry concept.

Acknowledgments

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9. *General procedure for the synthesis of bis(indolyl)methanes*: To a mixture of glycerin (2 mL), indole (**1a**, 0.117 g, 1.0 mmol), and benzaldehyde (**2a**, 0.053 g, 0.5 mmol) was added 0.1 equiv of CeCl₃·7H₂O (0.0186 g, 0.05 mmol) at room temperature. The temperature was slowly raised to 75 °C, under magnetic stirring. The reaction progress was followed by TLC, and after 1.5 h (see Table 2) the oil bath was removed. Then, at room temperature, ethyl acetate (3 × 5 mL) was added and the upper organic phase was separated from the glycerin/catalyst mixture, dried with MgSO₄, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (ethyl acetate:hexanes, 1:9) yielding **3a** as a light pink solid (0.155 g, 96%). Mp 123–125 °C (Lit.^{4a} 124–125 °C); ¹H NMR (200 MHz, CDCl₃) δ (ppm) 7.89 (br s, 2H); 7.40–7.30 (m, 6H); 7.28–7.23 (m, 2H); 7.23–7.12 (m, 3H); 6.98 (t, *J* = 6.8 Hz, 2H); 6.64 (s, 2H); 5.87 (s, 1H).