

## Original article

# An efficient synthesis of bis(indolyl) methanes and *N,N'*-alkylidene bisamides by Silzic under solvent free conditions



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## ABSTRACT

An operationally simple and green method for the synthesis of a wide range of bis(indolyl)methanes, and *N,N'*-alkylidene bisamides under mild conditions, with excellent yields using Silzic, has been developed. This improved method furnishes in good yields bis(indolyl)methanes derivatives starting from indole and aldehydes, or ketones, and *N,N'*-alkylidene bisamides derivatives starting from acetamide and aldehydes. The catalytic system was reused up to three times with the same efficiency.

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## 1. Introduction

Bis(indolyl)alkanes have important biological, industrial, and synthetic applications. Thus, their preparation is of considerable interest for the researchers in the development of new protocols. In recent years, syntheses of this class of molecules under mild conditions have been reported, with promoters such as Montmorillonite clay K-10 [1] in solid state reactions [2], trichloro-1,3,5-triazine [3], AIPW<sub>12</sub>O<sub>40</sub> [4], sodium dodecyl sulfate (SDS) [5], ZrCl<sub>4</sub> [6], I<sub>2</sub> [7], In(OTf)<sub>3</sub>/ionic liquid [8], CuBr<sub>2</sub> [9], MW/Lewis acids (FeCl<sub>3</sub>, BiCl<sub>3</sub>, InCl<sub>3</sub>, ZnCl<sub>2</sub>, CoCl<sub>2</sub>) [10], NaHSO<sub>4</sub> and Amberlyst-15 [11], silica sulfuric acid (SSA) [12], metal hydrogen sulfates [13], NaHSO<sub>4</sub>/ionic liquid [14], CAN [15], NBS [16], and Ph<sub>3</sub>CCl [17].

Amides and bisamides are functionalized groups represent important biological and medicinal scaffolds, which play a major role in the development and composition of biological and pharmacological systems [18,19]. In particular, symmetrical and unsymmetrical *N,N'*-alkylidene bisamides and their derivatives are found as key structural subunits for the construction of peptidomimetic frameworks [20,21]. Recently, Perumal *et al.* [22] have reported an alternative approach to synthesize symmetrical *N,N'*-alkylidene bisamides by a reaction of aldehydes with nitriles in the

presence of sulfamic acid. However, the yields were moderate. Milenkovic *et al.* [23] have synthesized activated imines and amination derivatives as potential precursors for the synthesis of amino acid under Dean-Stark water trapping conditions. Zhu *et al.* [24] have reported the synthesis of fluorine-containing *N,N'*-alkylidenebisamides in the presence of fluoroalkanesulfonic acids. Bhatnagar *et al.* [25,26] have reported the synthesis of benzylidene bisamides from the direct condensation of benzaldehyde and different amide derivatives. However, most of these existing methods involve toxic metal ions and solvents, carry high costs, use corrosive reagents and require cumbersome work-up procedures. Synthetic methodologies based on green chemistry processes are of increasing interest in organic syntheses. Recently, silica supported zinc chloride (Silzic) has been used as a solid acid catalyst in many organic transformations [27–29] and this is consistent with our interest in using silicon-based reagents in organic syntheses [30]. Herein we wish to report the use of Silzic as a reusable solid acid catalyst for the synthesis of bis(indolyl)methanes and *N,N'*-alkylidene bisamides.

## 2. Experimental

### 2.1. Typical procedure for the synthesis of bisindolylmethanes

To a stirred mixture of aldehyde, or ketone (5 mmol), and indole (10 mmol), Silzic (0.2 g, 20 mol%) was added and the mixture was allowed to stir at 100 °C for the total recorded time. After the

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completion (the reaction was monitored by TLC analysis) of the reaction, EtOAc (20 mL) was added to the reaction mixture. Then, the solid was filtered off, the filtrate was concentrated, and the residue was subjected to short column chromatography using pet.ether-EtOAc (8:2) to give pure **3a–m**. The bisindolylmethane **3** are known compounds and all spectroscopic data were in agreement with literature reports [31–33].

## 2.2. General procedure for synthesis of *N,N'*-alkylidene bisamides

To a stirred mixture of aldehyde (5 mmol), and acetamide (10 mmol), was added Silzic (0.2 g, 20 mol%) and the mixture was allowed to stir at 100 °C for the recorded time. After the completion of the reaction (the reaction was monitored by TLC analysis), EtOH (20 mL) was added to the reaction mixture. Then, the solid was filtered off, the filtrate was concentrated, and the solid residue was washed with diethyl ether to give the pure products (**4a–j**). Some of the *N,N'*-alkylidene bisamides **4** are known compounds and all spectroscopic data were in agreement with literature reports.

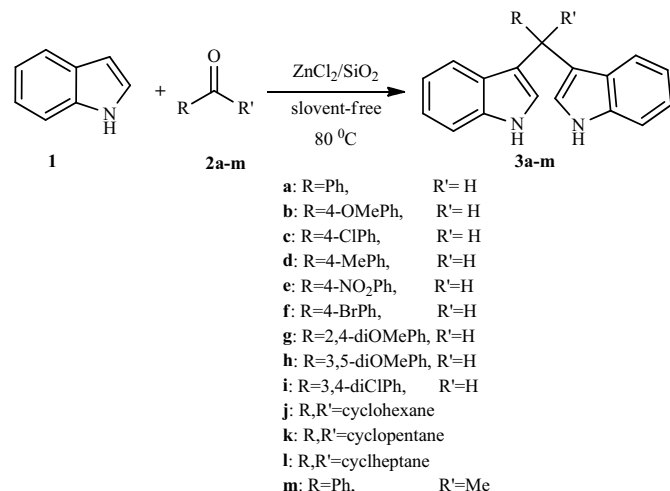
Data for a representative example are showed:

*N,N'*-(4-Methoxyphenyl)methylene)diacetamide (**4b**): Mp 230 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  3276, 3030, 2933, 2838, 1671, 1567, 1513, 1367, 1249, 1183, 1090, 820, 596; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.03 (d, 2H, *J* = 7.3 Hz, 2NH), 7.33 (d, 1H, *J* = 8.1 Hz, Ar-H), 6.80 (d, 2H, *J* = 8.1 Hz, Ar-H), 6.54 (t, 1H, *J* = 7.5 Hz, CH), 3.81 (s, 3H, OCH<sub>3</sub>), 1.79 (s, 6H, 2CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  170.25, 158.5, 141.3, 127.2, 114.2, 68, 55, 23.2; MS: *m/z* (%) 236.12 (M<sup>+</sup>, 100.0), 237.12 (M<sup>+</sup> + 1, 13.3); Anal. calcd. C, 61.00; H, 6.83; N, 11.86, found: C, 60.86; H, 6.43; N, 11.56.

*N,N'*-(4-Methylphenyl)methylene)diacetamide (**4d**): Mp 236 °C; IR (KBr, cm<sup>-1</sup>):  $\nu$  3275, 3031, 2951, 2854, 1670, 1566, 1541, 1394, 1280, 1092, 859, 809, 630; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.28 (d, 2H, *J* = 7.6 Hz, 2NH), 7.14 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.11 (d, 2H, *J* = 8.6 Hz, Ar-H), 6.53 (t, 1H, *J* = 7.7 Hz, CH), 2.43 (s, 3H, CH<sub>3</sub>) 1.84 (s, 6H, 2CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  170.25, 140.3, 136.5, 128.2, 124.2, 68, 23.2, 21.2; MS: *m/z* (%) = 220.12 (M<sup>+</sup>, 100.0), 221.12 (M<sup>+</sup> + 1, 13.7); Anal. calcd. C, 65.43; H, 7.32; N, 12.72, found: C, 65.43; H, 7.22; N, 12.52.

## 3. Results and discussion

The synthesis of bis(indolyl)methanes (**3a–m**) in high yields, was achieved through a reaction of indole (**1**) and aldehydes or ketones (**2**) using Silzic as depicted in Scheme 1. As a part of an ongoing study to investigate the optimum conditions for these



Scheme 1. Synthesis of bis(indolyl)methane.

Table 1  
Optimization of the reaction conditions.

Entry	Amount of Silzic	Temp (°C)	Time	Yield (%)
1	0	r.t.	5 h	0
2	0.1 mg	r.t.	5 h	20
3	0.2 mg	50	4 h	45
4	0.2 mg	80	35 min	93
5	0.3 mg	100	35 min	93

reactions, we studied the effect of the catalyst loading at different temperatures using indole (10 mmol) and benzaldehyde (5 mmol) as a model reaction. The obtained results are summarized in Table 1.

It is found that the use of 0.2 g, 20 mol% of Silzic at 80 °C resulted in the highest yield, and the increase of the catalyst or temperature does not lead to increased output.

To investigate the scope and the generality of this new protocol, the reaction was extended to a variety of aldehydes as well as ketones with indole and the results are summarized in Table 2. Though the reactions of indole with various aldehydes were fast, the reaction with ketones took longer time (Table 2, entries 10–13). The electron deficiency and nature of the substituent on the aromatic ring affect the conversion rate, As expected the aldehydes having electron-withdrawing groups on the aromatic ring (Table 2, entries 3,5 and 6) react faster than aldehydes having electron-donating groups (Table 2, entries 2,4,7 and 8).

The structural elucidation of bis(indolyl)methane derivatives was assigned on the basis of melting point and spectral analyses. First, in the IR spectra of these compounds, the absorption at 3400–3460 cm<sup>-1</sup> attributed for the NH group, and 1335 for C–N. The <sup>1</sup>H NMR spectrum of **3** showed a singlet at 5.83–5.91 ppm for the proton of C–H, another singlet for two N–H protons appeared at 7.85–7.94 ppm, and the aromatic protons appeared at 6.36–7.45 ppm. For example, the <sup>1</sup>H NMR of **3d** displayed a singlet at 5.87 ppm for C–H proton, and a singlet at 7.89 ppm for two N–H protons, which disappeared with D<sub>2</sub>O exchange, in addition to the signal of a methyl group at 2.34 ppm. In addition, <sup>1</sup>H NMR of **3j** showed one doublet at 2.58 and one multiplet at 1.69 ppm. These were assigned to the cyclohexane protons. The mechanism of the Silzic-catalyzed synthesis of bisindolylmethane is proposed as shown in Scheme 2. First, an aldehyde or ketone was activated by the Silzic and underwent an electrophilic substitution reaction at the 3-position of the indole. After dehydration, intermediate (A) was formed and was further activated by Silzic to become an electrophile, which was attacked by a second molecule of indole, to form bisindolylmethane (**3a–m**).

The present study has established a new, mild and convenient protocol for the synthesis of symmetrical bisamides by condensing

Table 2  
Synthesis of bis(indolyl)methanes using Silzic.

Entry	Aldehyde/ketone	Time (min)	Product	Yield (%)
1	Benzaldehyde	35	<b>3a</b>	93
2	4-Methoxybenzaldehyde	33	<b>3b</b>	92
3	4-Chlorobenzaldehyde	27	<b>3c</b>	93
4	4-Methylbenzaldehyde	35	<b>3d</b>	91
5	4-Nitrobenzaldehyde	25	<b>3e</b>	95
6	4-Bromobenzaldehyde	25	<b>3f</b>	94
7	2,4-Dimethoxybenzaldehyde	30	<b>3g</b>	90
8	3,5-Dimethoxybenzaldehyde	28	<b>3h</b>	91
9	3,4-Dichlorobenzaldehyde	30	<b>3i</b>	89
10	Cyclohexanone	40	<b>3j</b>	70
11	Cyclopentanone	42	<b>3k</b>	65
12	Cycloheptanone	44	<b>3l</b>	55
13	Acetophenone	53	<b>3m</b>	35

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