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 for three times with The same efficiency

Keywords: bis(indolyl)methanes, *N,N'*-alkylidene bisamides, mild conditions, silzic

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, synthesis of this class of molecules under mild conditions have been reported, with promoters such as Montmorillonite clay K-10[1,2], trichloro-1,3,5-triazine[3], $AlPW_{12}O_{40}$[4], sodium dodecyl sulfate (SDS)[5], $ZrCl_4$[6], I_2 [7], $In(OTf)_3$/ionic liquid [8], $CuBr_2$ [9], MW/Lewis acids ($FeCl_3$, $BiCl_3$, $InCl_3$, $ZnCl_2$, $CoCl_2$)[10], $NaHSO_4$ and Amberlyst-15 [11], silica sulfuric acid (SSA) [12], metal hydrogen sulfates [13], $NaHSO_4$/ionic liquid [14], CAN [15], NBS [16], and Ph_3CCl [17]. Amides and bisamides are functionalized groups represent important biological and medicinal scaffolds. that 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 synthesis symmetrical *N,N'*-alkylidene bisamides by the reaction of aldehydes with nitriles in the presence of sulfamic acid, however the yields are moderate. Milenkovic*et al.*[23] have synthesized activated imines and aminal derivatives as potential precursors for the synthesis of amino acid using Dean-Stark water trap. Zav'yalov*et al.*[24] have reported the condensation of amides with carbonyl compounds in the presence of DMF-Chlorotrimethylsilane as a catalyst system. Bhatnagar *et al.*[25,26] have reported the synthesis of benzylidene bisamides from direct condensation of benzaldehyde and different amide derivatives. However, most of the existing methods involve toxic metal ions and solvents, have high costs, use corrosive reagents and have cumbersome work-up procedures. Synthetic methodologies based on green chemistry processes are of increasing interest in organic synthesis. Recently, silica supported zinc chloride (Silzic) has been used as a solid acid catalyst in many organic transformations[27-29]. 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

Typical procedure for the synthesis of bisindolylmenthane

To a stirred mixture of aldehyde, or ketone (5 mmol), and indole (10 mmol), was added Silzic (0.2g, 20 mol %) and the mixture was allowed to stir at 100 ℃ for the total recorded time. After completion (the reaction was monitored by TLC), was added EtOAc (20 mL) to the reaction mixture. Then, the mixture was filtered off, the extract was vaporized, 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[30-32].

General procedure for Synthesis of N,N'-alkylidene bisamides

To a stirred mixture of aldehyde (5 mmol), and actamide (10 mmol), was added Silzic (0.2g, 20 mol%) and the mixture was allowed to stir at 100°C for the recorded time. After completion (the reaction was monitored by TLC), was added EtOH (20 mL) to the reaction mixture. Then, the mixture was filtered off, the extract was vaporized, and the solid residue was washed with diethyl ether to gave 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.

Data for a representative example are showed:

N,N'-((4-methoxyphenyl)methylene)diacetamide, **4b**: Mp = 230 ℃;

IR (KBr, plate): ν 3276, 3030, 2933, 2838, 1671, 1567, 1513, 1367, 1249, 1183,1090, 820, 596 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO) δ = 8.03 (d, *J* =7.3 Hz, 2H, 2NH), 7.33 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.80 (d, *J* = 8.1Hz, 2H, Ar-H), 6.54 (t, *J* =7.5 Hz, 1H, CH),3.81 (s, 3H, OCH_3), 1.79 (s, 6H, $2CH_3$); ^{13}C-NMR (75 MHz, DMSO) δ =170.25, 158.5, 141.3, 127.2, 114.2, 68, 55, 23.2; MS: *m/z* (%) = 236.12 (M^+, 100.0), 237.12 (M^++1, 13.3); Analysis, calcd: C, 61.00; H, 6.83; N, 11.86, found: C, 60.86; H, 6.43; N, 11.56.

N,N'-(p-methylphenyl)methylene)diacetamide, **4d**: Mp = 236 ℃;

IR (KBr, plate): ν 3275, 3031, 2951, 2854, 1670, 1566,1541,1394, 1280, 1092, 859,809, 630 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO) δ = 8.28 (d, *J* =7.6 Hz, 2H, 2NH), 7.14 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.11 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.53 (t, *J* =7.7Hz, 1H, CH), 2.43 (s, 3H, CH_3) 1.84 (s, 6H, $2CH_3$) ppm ; ^{13}C-NMR (75

MHz, DMSO) δ = 170.25, 140.3, 136.5, 128.2, 124.2, 68, 23.2, 21.2; MS: *m/z* (%) = 220.12 (M^+, 100.0), 221.12 (M^++1, 13.7)

Analysis, calcd: C, 65.43; H, 7.32; N, 12.72, found: C, 65.43; H, 7.22; N, 12.52.

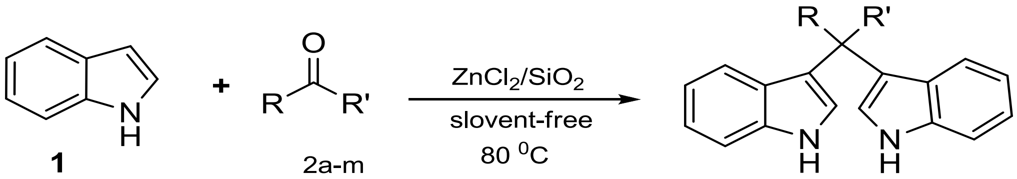
3. Results and discussion

The synthesis of bis (indolyl)methane **(3a-m)** in an efficient yield, 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 reactions, we studied the efficacy of the amount of catalyst at different temperature using indole (10 mmol) and bezldehyde (5 mmol) as a modle. The obtained results are summarized in Table 1.

Table 1. optimization of the reaction conditions

Entry	Amount of reagent	Temperature	Time	Yield %
1	0	Room temp	5 hr	0
2	0.1 mg	Room temp	5hr	20
3	0.2 mg	50^oC	4hr	45
4	0.2 mg	80^oC	35 min.	93
5	0.3 mg	100^oC	35 min.	93

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



1

2a-m

3a-m

2a,3a; R=Ph, R'= H
2b,3b; R=4-OMePh, R'= H
2c,3c; R=4-ClPh, R'= H
2d,3d; R=4-MePh, R'=H
2e,3e; R=4-NO_2Ph, R'=H
2f, 3f; R=4-BrPh, R'=H
2g,3g; R=2,4-diOMePh, R'=H
2h,3h; R=3,5-diOMePh, R'=H
2i, 3i; R=3,4-diClPh, R'=H
2j, 3j, R,R'=cyclohexane
2k,3k;R,R'=cyclopentane
2l, 3l; R,R'=cyclheptane
2m,3m;R=Ph, R'=Me

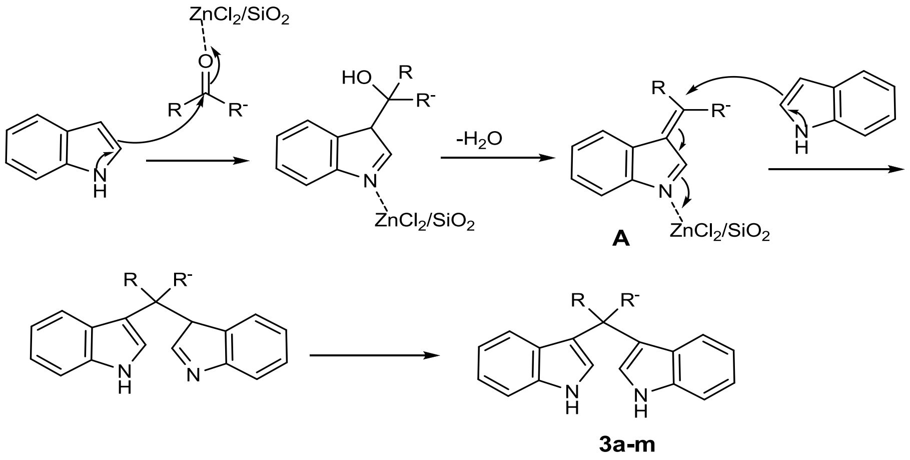
Scheme 1. Synthesis of bis(indolyl)methane.

To investigate the scope and the generality of this new protocol, the reaction was extended towards a variety of aldehydes as well as ketones with indole and the results are summarized in Table-1. Though the reactions of indole with various aldehydes were fast, the reaction with ketones took relatively longer time (Entry 10-13, Table 2). 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 3,5,6) react faster than aldehydes having electron-donating groups (Table 2, entries 2,4,7,8).

Table (2): Synthesis of bis(indolyl)methanes using $SiO_2/ZnCl_2$ (silzic)

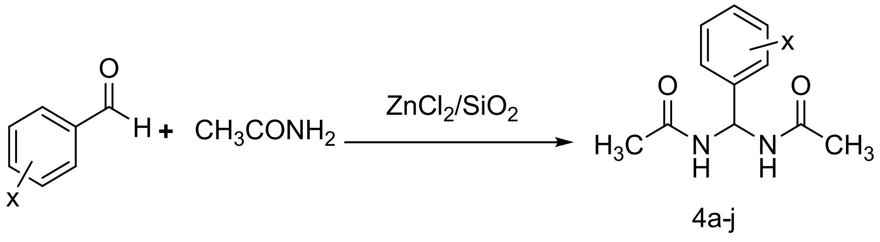
Entry	Aldehyde or ketone (2)	Product (3)	Time (min.)	Yield %
1	Benzaldehyde	**3a**	35	93
2	4-Methoxybenzalde Hyde	**3b**	33	92
3	4-Chlorobenzaldehy De	**3c**	27	93
4	4-Methylbenzalde Hyde	**3d**	35	91
5	4-Nitrobenzalde Hyde	**3e**	25	95
6	4-Bromobenzalde Hyde	**3f**	25	94
7	2,4Dimethoxybenzal dehyde	**3g**	30	90
8	3,5-Dimethoxybenza Ldehyde	**3h**	28	91
9	3,4-Dichlorobenzald Ehyde	**3i**	30	89
10	Cyclohexanone	**3j**	40	70
11	Cyclopentanone	**3k**	42	65
12	Cycloheptanone	**3l**	44	55
13	Acetophenone	**3m**	53	35

The structure elucidation of bis(indolyl)methane derivatives was assigned on the basis of melting point and spectral analyses[30-32] First, in the IR spectra of these compounds, the absorption at 3400-3460 cm^{-1} attributed for NH group, and 1335 for C-N. The ^1H-NMR spectra of **3** showed singlet at 5.83-5.91 ppm for the proton of C-H, another singlet for two N-H protons has appeared at 7.85-7.94 ppm, and the aromatic protons appeared at 6.36-7.45 ppm. For example, the ^1H-NMR of **3d** displayed a singlet at 5.87 ppm for C-H proton, and singlet at 7.89 ppm for two N-H protons which disappeared with D_2O exchange, in addition to the signal of methyl group at 2.34 ppm. In addition, ^1H-NMR of **3j** showed one doublet at 2.58 and one multiblet at 1.69 ppm. These were assigned to the cyclohexane protons. The C-H proton of **3j** disappeared. The mechanism of to the silzic- catalyzed synthesis of bisindolylmenthane is proposed as 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 bisindolylmenthane (**3a-m)**.



Scheme 2. A plausible mechanism for the formation of bis(indolyl)methane.

New, mild and convenient protocol for the synthesis of symmetrical bisamides by condensing aryl aldehydes and acetamide using silzic as catalyst (**4a-j**) (Scheme 3, table3).



4a, x = H, 4b, x= 4-OMe,
4c, x= 4-Cl, 4d, x= 4-Me,
4e, x= 4-NO_2, 4f, x= 4-Br,
4g, x=2,4-diOMe, 4h, x= 4-($(CH_3)_2N$),
4i, x= 3,4-(O-CH_2-O)-, 4j,x=2,3-$(CH=CH)_2$-

Scheme 3. Synthesis of *N,N'*-Alkylidene Bisamides.

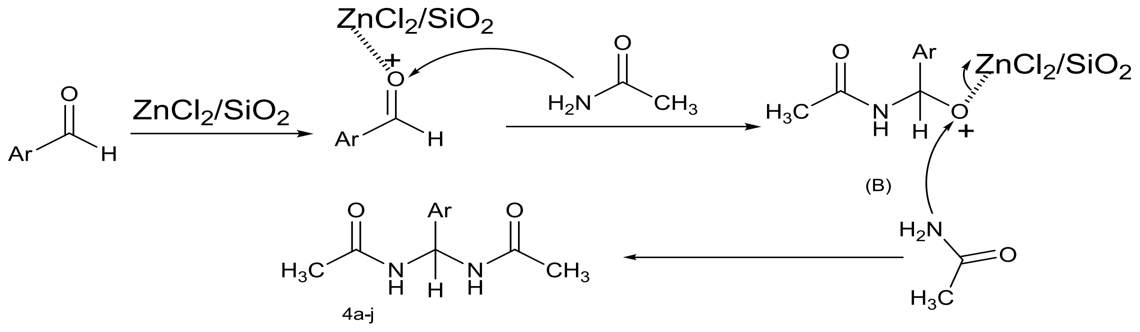
The experimental results (which summarized in **table 3**) illustrate the efficiency of the present method. The reactions are preceded well with various aromatic aldehydes and acetamide to provide symmetrical *N,N'*-alkylidene bisamides. aromatic aldehydes containing electron-withdrawing groups (such as nitro-) gave shorter time and high yield than that with electron- donating groups (such as methoxy-). In addition, the present procedure works well with satirically hindered aldehydes, e.g., 2,4-Dimethoxy benzaldehyde**,** benzo[d][1,3]dioxole-5-carbaldehyde, and 1-Naphthaldehyde and give good yields (table 3, entries 7,9,10).

Table 3. Synthesis of *N,N′*-Alkylidene Bisamides Using Silzic under solvent –free conditions

Entry	Aldehyde	Product (4)	Time min	Yield%
1	Benzaldehyde	**4a**	35	83
2	4-Methoxybenzalde Hyde	**4b**	33	75
3	4-Chlorobenzalde hyde	**4c**	27	82
4	4-Methylbenzalde hyde	**4d**	35	77
5	4-Nitrobenzalde hyde	**4e**	25	85
6	4-Bromobenzalde Hyde	**4f**	25	81
7	2,4-Dimethoxybenzald ehyde	**4g**	30	73
8	4-(Dimethyl amino)benzaldehyde	**4h**	28	82
9	benzo[d][1,3]dioxole -5-carbaldehyde	**4i**	30	89
10	1-Naphthaldehyde	**4j**	40	70

The structures of the products were assigned based on the analysis of spectroscopic data analysis such as IR, and ^{1}H-NMR which found to be in agreement with the literature values[22, 33-35]. The IR spectral showed characteristic absorption bands at 3319 -3265and 1671- 1654cm^{-1} for –NH group, and carbonyl group respectively. The ^{1}H-NMR showed a triplet at 6.52-6.59 ppm with J = 7.8 Hz for CH proton (which converted to singlet with D_2O exchange), a multiplet at 6.78-7.65 ppm for the aromatic protons, and at 8.19-8.72 ppm with J = 7.8 Hz a doublet was observed for the NH proton (which disappeared with D_2O exchange). On the observations recorded above, NH proton makes coupling with CH proton with J = 7.8 Hz.

To explain the formation of bisamides *via* the one-pot multi-component reaction, we have proposed a plausible reaction mechanism, which is illustrated in Scheme 4. Firstly, the activation of aldehyde by π empty orbital of Lewis acid was occurred to form a cation intermediate (**B**). The second molecule of amide is added to **(B)** and converted into the product.



Scheme 4. A plausible mechanism for the formation of bisamide.

To check the reusability of catalyst, the catalyst was filtered off and washed with chloroform repeatedly, dried and reused. It was found that catalyst can be recycled for at least three cycles without any change in activity.

4. Conclusions

In conclusion, silzic has been successfully used as effective catalyst for the synthesis of symmetrical *N,N'*-alkylidene bisamides for the first time. This procedure has advantages in competition with the previously reported methods, in terms of yield, green catalyst, mild reaction condition, simple procedure, lack of toxicity, low cost, and the use of a commercially available catalyst and simplicity of workup.

Acknowledgments

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