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Research note

Green procedure for the synthesis of bis(indolyl)methanes in water

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KEYWORDS

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Squaric acid;
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Abstract A green and environmentally benign protocol for squaric acid catalyst electrophilic substitution reactions of indole derivatives, with various aldehydes in water, in good to excellent yields, is developed. The advantages of low sensitivity towards moisture and oxygen, high tolerance of different functional groups, green reaction media and efficient recyclability make this organocatalyst suitable for both laboratory and industrial scale synthesis of bis(indolyl)methanes under very mild conditions.

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1. Introduction

Nowadays, reactions in unconventional media for sustainable organic synthesis, like aqueous media, supercritical media, fluoruous biphasic catalysis, ionic liquids and biphasic combination, allow intensified separation technologies by selective recovery of the desired products, by-products and catalysts in different phases, thus avoiding tedious and costly procedures which involve high volumes of organic solvents. In this context, designing organic reactions in aqueous media is another attractive area in green chemistry. Water is the most abundant molecule on earth, and an environmentally benign universal solvent in which the chemistry of life-processes mostly occurs. As a reaction medium, it offers several benefits, including control over exothermic reactions, salting in and salting out, and variation of pH. Work up and purification can be carried out by simple phase separation techniques [1,2].

The indole ring system is the most ubiquitous heterocycle in many biological systems commonly found in nature [3,4], as well as in many compounds that show pharmacological and biological activity [5,6]. The bis(indolyl)alkane moiety is present in various natural products possessing important

biological activity [7,8]. Therefore, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives have been reported in the literature, using the reaction of indole with various aldehydes and ketones in the presence of either a Lewis acid or a protic acid [9–30].

However, there are various limitations, such as long reaction times, use of organic solvents, high temperatures, moderate yields and limited substrate. Therefore, the development of a suitable alternative reaction methodology that uses the highly simple organocatalyst in water still remains an important reaction methodology challenge for the indole condensation reaction.

2. Results and discussion

As a part of our research, aimed at developing green chemistry by using water as the reaction medium or by performing organic transformations under solvent-free conditions [31–34], we describe the use of novel small organic catalysts capable of promoting electrophilic substitution reactions of indole derivatives with various aldehydes and ketones in water.

As a model reaction, benzaldehyde was reacted with indole with different loadings of starting material, solvent and catalyst. It was found that by simple mixing of benzaldehyde (1 mmol) and indole (2 mmol), in the presence of squaric acid (10 mg) in water (2 mL), the desired product was obtained at 90% yield (Scheme 1).

Encouraged by these successful results, we studied various aldehydes and ketones under optimized conditions to better

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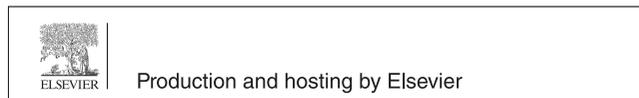


Table 1: Simple synthesis of bisindol methane derivatives in water.

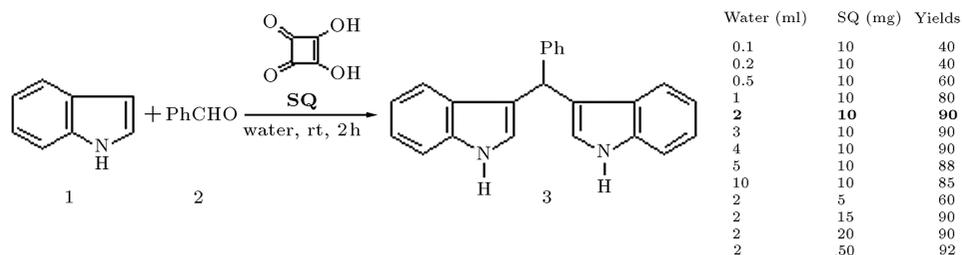
1a: R=H, R1 = H, X = H
1b: R=CH₃, R1 = H, X = H
1c: R=H, R1 = H, X = Br
1d: R=H, R1 = CH₃, X = H

Entry	Carbonyl compounds	Indole	Products	Yields	M.p. (°C)		Ref.
					Founds	Reported	
1		1a	3a	90	125–127	125–126	[25]
2		1b	3b	90	184–186	185–187	[25]
3		1d	3c	95	180–183	182–185	[28]
4		1a	3d	74	90–92	93–94	[24]
5		1b	3e	86	145–148	146–148	[28]
6		1d	3f	80	172–176	174–175	[24]
7		1a	3g	82	76–78	74–75	[11]
8		1b	3h	88	142–145	162–168	[14]
9		1d	3i	76	180–184	186–188	[25]
10		1a	3j	78	103–106	103–105	[22]
11		1b	3k	84	120–123	128–130	[26]
12		1c	3l	72	144–147	152–153	[14]
13		1a	3m	80	220–224	217–219	[11]
14		1b	3n	85	264–268	266–270	[21]
15		1c	3o	70	290–294	-	[21]
16		1a	3p	80	221–224	220–222	[11]
17		1b	3q	85	156–158	157–159	[28]
18		1a	3r	84	140–143	142–144	[11]
19		1b	3s	90	120–124	-	-
20		1d	3t	84	198–202	-	-
21		1a	3u	84	184–186	185–187	[11]
22		1a	3v	84	258–261	-	-
23		1a	3w	84	148–150	146	[11]
24		1a	3x	84	128–131	128–130	[11]

understand the scope and generality of this simple procedure (Table 1).

A series of aromatic and heterocyclic aldehydes and simple ketones underwent an electrophilic substitution reaction

with indole, 1-methyl indole and 5-bromo indole, smoothly, to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. This method is equally effective for aldehydes bearing electron withdrawing or donating



Scheme 1: Optimization of reaction condition.

Table 2: Comparison of the catalytic efficiency of various catalysts reported in the literature.

Entry	Catalyst	Condition	Yields
1	ZrCl ₄	CH ₃ CN/rt	91
2	ZrOCl ₂	CH ₃ CN/rt	89
3	LiClO ₄	CH ₃ CN/rt	90
4	ILIS-SO ₂ Cl	CH ₃ CN/rt	93
5	H ₃ PW ₁₂ O ₄₀	Water	84
6	H ₃ PMo ₁₂ O ₄₀	Water	86
7	[bnmim][HSO ₄]	Neat/MW	93
8	AlPW ₁₂ O ₄₀	CH ₃ CN	92
9	Sb ₂ (SO ₄) ₃	MeOH	96
10	Al(HSO ₄) ₃	EtOH	92
11	P ₂ O ₅ /SiO ₂	Neat	94
12	(CO ₂ H) ₂ /CTAB	H ₂ O	98
14	LiClO ₄	Neat	92
15	Dy(OTf) ₃	IL	98
16	NbCl ₅	MeOH	98
17	HBFe ₄ -SiO ₂	Neat/rt	94
18	SQ	H ₂ O	90

groups in the aromatic rings. Furthermore, acid sensitive aldehydes worked well without any decomposition or polymerization under these reaction conditions. 1-methyl indole provided a better yield of products in comparison with indole and 5-bromoindole under the same reaction conditions. Furthermore, simple ketones, like cyclohexanone and 2-butanone, reacted under the same reaction condition, albeit with a longer reaction time.

Finally, the recyclability of the organocatalyst was also examined; the squaric acid catalyst is insoluble in most organic solvents and could be readily recovered using a simple workup. Upon completion of the reaction, the addition of water and diethyl ether to the reaction mixture, and after a simple workup, the aqueous phase was collected and the water was evaporated under reduced pressure to give squaric acid, completely, which was analyzed by ¹H NMR in D₂O as solvent.

In addition, this procedure is superior, compared to literature data (Table 2), with respect to the catalyst, solvent and ecofriendliness.

3. Conclusion

In summary, an operationally simple and green method for the synthesis of a wide range of bis(1H-indol-3-yl)methans, under mild conditions, with good yields, has been developed. This simple protocol has the advantages of environmental friendliness, higher yields, shorter reaction times and convenient operation, which only requires stirring the reaction mixture at ambient temperature, without the use of any additional energy source like heating or sonication.

4. Experimental

4.1. General

¹H NMR spectra were recorded on a 500 MHz NMR Bruker spectrometer, and ¹³C NMR spectra were recorded on a 125 MHz NMR Bruker spectrometer, respectively, using CDCl₃ or DMSO-d₆ as solvent at ambient temperature. Chemical shifts are given in ppm. All aldehydes and other reagents and catalysts are commercially available, and were purchased and used without further purification; water and other solvents were distilled before use. Silica gel (Merck, 230–400 mesh, 60 Å) for column chromatography was used as received. Melting points were determined using a Buchi 535 melting point apparatus and are uncorrected. Squaric acid is commercially available and was purchased and used without further purification; water and other solvents were distilled before use. Although squaric acid has been known as a commercially available strong acid, squaric acid itself has attracted little attention from the synthetic community, mainly due to its extremely poor solubility in organic solvents. Recently, some groups have developed a new chiral Brønsted acid from the squaric acid scaffold, which has been successfully used in organic synthesis [35,36].

4.2. General procedure for preparation of bis-indolylmethanes

To a mixture of indole (2 mmol), aldehydes or ketones (1 mmol) and water (2 mL), squaric acid (10 mg) was added and stirred vigorously at room temperature until the disappearance of the starting indole, checked by TLC (2–4 h). When the reaction was completed, the reaction mixture was filtrated and washed with water. Then, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, using ethyl acetate and petroleum ether (1:3), to yield the corresponding product. In the case of indole, the crude product was recrystallized using ethanol.

4.2.1. Selected data

3, 3'-Bis-indolyl phenylmethane (3a)

solid, mp: 125–127 °C ¹H-NMR (CDCl₃): δ 7.82 (s, 2H, N-H), 7.43 (d, J = 7.9 Hz, 2H, Ar-H), 7.40–7.36 (m, 3H, Ar-H), 7.35–7.29 (m, 3H, Ar-H), 7.28–7.24 (m, 1H, Ar-H), 7.21 (dt, J = 0.8, 7.9 Hz, 2H, Ar-H), 7.05 (dt, J = 0.8, 7.9 Hz, 2H, Ar-H), 6.61 (d, J = 1.5 Hz, 2H, Ar-H), 5.92 (s, 1H). ¹³C-NMR (CDCl₃): δ 144.0, 136.7, 128.8, 128.3, 127.1, 126.2, 123.7, 121.9, 120.0, 119.7, 119.2, 111.1, 40.2. MS (EI, 70 eV): m/z = 322 (M+, 20), 245 (75), 206 (100), 77 (10).

3, 3'-Bis-(N-methylindolyl)phenylmethane (3b)

solid, mp: 185–187 °C ¹H-NMR (CDCl₃): δ 7.43 (d, J = 7.8 Hz, 2H, Ar-H), 7.38 (d, J = 8.4 Hz, 2H, Ar-H), 7.33–7.28 (m, 4H, Ar-H), 7.24–7.20 (m, 3H, Ar-H), 7.02 (dt, J = 0.9, 7.8 Hz, 2H, Ar-H), 6.52 (s, 2H, Ar-H), 5.90 (s, 1H), 3.70 (s, 6H, 2 × CH₃). ¹³C-NMR (CDCl₃) δ 143.1, 138.1, 128.8, 128.4, 128.1, 127.1, 125.2, 120.1, 119.2, 117.4, 116.1, 108.4, 41.0, 31.9.

3, 3'-Bis-indolyl-(4-methylphenyl)methane (3d)

mp: 93–95 °C ¹H NMR (CDCl₃) δ 7.88 (s, 2H, N-H), 7.40 (d, J = 7.4 Hz, 2H, Ar-H), 7.31 (d, J = 7.8 Hz, 2H, Ar-H), 7.18 (d, J = 8.3 Hz, 2H, Ar-H), 7.16 (dt, J = 1.2, 9.1 Hz, 2H, Ar-H), 7.01 (d, J = 7.1 Hz, 2H, Ar-H), 6.08 (dt, J = 1.2, 8.2 Hz, 2H, Ar-H), 6.61 (dd, J = 2.1, 0.9 Hz, 2H, Ar-H), 5.81 (s, 1H), 2.30 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ 140.9, 135.6, 135.1, 127.8, 128.1, 126.9, 122.1, 121.1, 120.0, 118.2, 118.0, 110.1, 38.1, 20.4.

3, 3'-Bis-(N-methylindolyl)-(4-methylphenyl)methane (3e)

mp: 146–148 °C ¹H NMR (CDCl₃) δ 7.41 (d, J = 7.4 Hz, 2H, Ar-H), 7.22 (d, J = 7.3 Hz, 2H, Ar-H), 7.20–7.01 (m, 4H, Ar-H), 7.00 (d, J = 7.2 Hz, 2H, Ar-H), 6.08 (dt, J = 1.1, 7.8 Hz, 2H, Ar-H), 6.51 (s, 2H, Ar-H), 5.79 (s, 1H), 3.67 (s, 6H, 2 × CH₃), 2.30 (s, 3H, CH₃).

¹³C NMR (CDCl₃) δ 140.1, 136.1, 134.9, 127.6, 127.1, 126.9, 126.5, 120.9, 119.4, 117.2, 116.1, 108.1, 38.1, 31.3, 20.9.

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