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Original article

Water extract of onion peel for the synthesis of bisindolylmethanes

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ABSTRACT

An efficient catalytic system for the synthesis of bisindolylmethanes (BIMs) using Water Extract of Onion Peel (WEOP) is described in this study. The advantages of this protocol include avoid the use of acids and bases, reusability of the WEOP catalytic system, good to excellent yield and reduce the use of toxic reagents. This is the first report of using WEOP catalytic system in the preparation of BIMs. We anticipate the method presented here will find great utility in the field of synthetic chemistry and the synthesis of other heterocyclic compounds in the near future.

1. Introduction

Lately there has been an increasing trend towards substituting toxic, polluting and expensive chemical reagents and catalysts with more eco-friendly ones. The organic reactions performed in water have exhibited many desirable characteristics such as environmental friendly, benign, inexpensive and a readily-available medium (Kiyani and Ghorbani, 2017, Heravi et al., 2015). In addition, numerous studies reported that chemical reaction rates were enhanced by using water as solvent (Bhowmick et al., 2015, Eymur et al., 2014, He et al., 2013, Jimeno, 2016, Miklós and Fülöp, 2016). In the development of new synthetic and catalytic protocols, the use of water as a reaction medium is worthwhile to be explored and is still an active field of research devoted to accomplish greener chemical processes.

In parallel to the use of clean water as solvent, continuous efforts were also made by using waste water, and water extracts of fruits and vegetables juices as biocatalysts and solvents in catalyzing organic reactions. Current examples of using such system to accomplish organic reactions include the Suzuki–Miyaura reaction (Boruah et al., 2015), synthesis of coumarin-3-carboxylic acid and cinnamic acids (Fiorito et al., 2016), Sonogashira reaction (Dewan et al., 2016), Henry reaction (Surneni et al., 2016), peptide coupling (Konwar et al., 2016), Dakin reaction (Saikia and Borah, 2015) and several other examples. Water extract of bio-wastes is a better alternative to pure water and has become an emerging field of research in organic synthesis (Sarmah et al., 2017). Bio-wastes are waste disposed from household, food stalls, restaurants and food processing factories and mankind generates million tons of bio-wastes every month (Choi et al., 2015). With the increasing demand on agricultural products as a result of the booming human population, the generation of bio-wastes has greatly escalated in recent years (Marshall and Farahbakhsh, 2013). In the past, most of the bio-wastes are destined for disposal in landfills and this has a considerable effect towards our ecosystem, wildlife and human health (Gao et al., 2015). In contrast, if used wisely, such bio-wastes may in turn act as an effective catalytic system to mediate organic reactions that was hard to be achieved conventionally or mostly achieved by using hazardous chemical reagents. One of the notable examples of bio-wastes produced is the waste generated from onion (*Allium cepa* L.) processing. Onion is considered as one of the valuable crops grown globally for its pharmaceutical, nutritional and other functional properties (Nile and Park, 2013). Human consumption and food processing industries have generated huge amount of onion waste. Statistics showed that the US and European countries alone dispose of 100,000 to 500,000 tonnes of onion waste annually (Sharma et al., 2016).

Indoles are important chemical scaffold and are found in abundance in biologically active natural products, pharmaceuticals and also embedded in biological systems (Ruiz-Sanchis et al., 2011,

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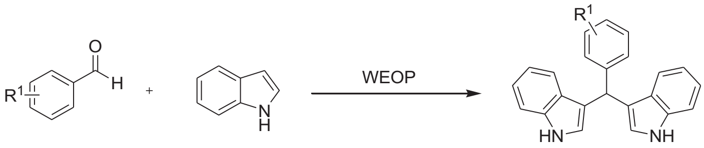


Scheme 1. Synthetic route towards the preparation of bisindolylmethanes (BIMs).

Vicente, 2011). The bisindolylmethanes (BIMs) which consist of indoles as its core units, were mainly isolated from both terrestrial and marine sources (Shiri et al., 2010). BIMs are an appealing class of heterocyclic compounds which exhibit a wide range of biological activities which include anti-cancer (Safe et al., 2008), anti-leishmanial (Bharate et al., 2013), anti-viral (Liu et al., 2015), anti-inflammatory (Qu et al., 2013) activities and others. Among the synthetic protocols that had been employed in the synthesis of BIMs include ionic liquid (Kalantari, 2012), NaNO TiO_2/SiO_2 (Haghighi and Nikoofar, 2016), ammonium niobium oxalate (Mendes et al., 2015), tetrabutylammonium hydrogen sulphate (Siadatifard et al., 2016) or $ZnCl_2$/Urea (Seyedi et al., 2015) and others. In view of the wide scope of biological activities of BIMs and the growing demand to develop a simple and environmental benign method of synthesizing diverse heterocyclic privileged compounds, herein, we disclosed the synthesis of BIMs via the Water Extract of Onion Peel (WEOP) catalytic system (Scheme 1). The significant advantages of this protocol are free of external acids and bases, reusability of the WEOP catalytic system, good to excellent product yield, reduction in the use of toxic reagents and a simple and effective catalytic system for the synthesis of BIMs.

2. Experimental

2.1. Materials and methods

In this experiment, the chemicals and solvents utilized were of technical grade and were used without further purification unless stated. The fine chemicals used including ethyl acetate, benzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzldehyde, 4-chlorobenzaldehyde, 2-bromobenzaldehyde, 3-bromobenzaldehyde, 3-fluorobenzaldehyde, 4-isopropylbenzaldehyde, 4-methoxybenzaldehyde and silica gel 60 (0.063–0.200 mm). The ^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent on Bruker Avance III 400 spectrometer. The CHNS analysis was performed using CHNS Analyzer Flashea 1112 series.

2.2. Preparation of the Water Extract of Onion Peel (WEOP)

The onion peel waste was collected from a local restaurant. The outer layer of the onion was separated from bulb and washed thoroughly with distilled water. The onion peel was then left for air drying for three days. The WEOP was prepared according to a known literature (Bhuyan and Saikia, 2005). Firstly, the dried onion peels (1.0 g) were cut into small pieces and were put into a 100 mL conical flask. Subsequently, 20 mL distilled water was added into the same conical flask and the mixture was heated at 70 °C for 3 h. The aqueous medium was then filtered using Whatman filter paper No.1 and the filtrate was termed as WEOP (Fig. 1). The filtrate was then stored at 4 °C in a sample vial.

2.3. Synthesis procedure for bisindole *3a-3 k*

To a 25 mL round-bottom flask containing indole (2.00 mmol) and benzaldehydes (1.00 mmol) was added with the WEOP (1 mL). The reaction mixture was stirred magnetically at 50 °C. The formation of bisindole was monitored using Think-Layer Chromatography (TLC). After the completion of reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was then separated from the aqueous layer and concentrated under reduced pressure. The crude product was subjected over silica gel column purification and ethyl acetate/hexane (9:1) as eluent. All the pure products were characterized by NMR (^{1}H and ^{13}C) and were further supported by CHNS analysis.

2.4. Spectroscopic data of bisindoles

2.4.1. 3,3′-(Phenylmethylene)bis(1H-indole) *(3a)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.85 (s, 1H), 6.63 (s, 2H), 7.01 (t, J = 6.7 Hz, 2H), 7.12–7.21 (m, 3H), 7.24–7.31 (m, 2H), 7.32–7.41 (m, 6H), 7.92 (brs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.2, 111.1, 119.2, 119.4, 119.7, 121.7, 123.5, 126.0, 126.9, 128.0, 128.6, 135.6, 143.9 ppm; GC–MS: $C_{23}H_{18}N_2$, m/z 322.15 $(M)^+$. Anal. calcd for $C_{23}H_{18}N_2$: C 85.68, H 5.63, N, 8.69; found C 85.54, H 5.57, N 8.76.

2.4.2. 3,3′-(2-Chlorophenylmethylene)bis(1H-indole) *(3b)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.33 (s, 1H), 6.64 (s, 2H), 7.03 (t, J = 8.0 Hz, 2H), 7.12–7.22 (m, 6H), 7.35–7.42 (m, 4H), 7.95 (brs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.6, 112.0, 117.0, 118.4, 119.8, 122.0, 123.8, 127.0, 127.3, 128.0, 129.4, 130.5, 133.2, 136.7, 141.3 ppm; GC–MS: $C_{23}H_{17}ClN_2$, m/z 356.11 $(M)^+$. Anal. calcd for $C_{23}H_{17}ClN_2$: C 77.41, H 4.80, N, 7.85; found C 77.39, H 4.77, N 7.81.

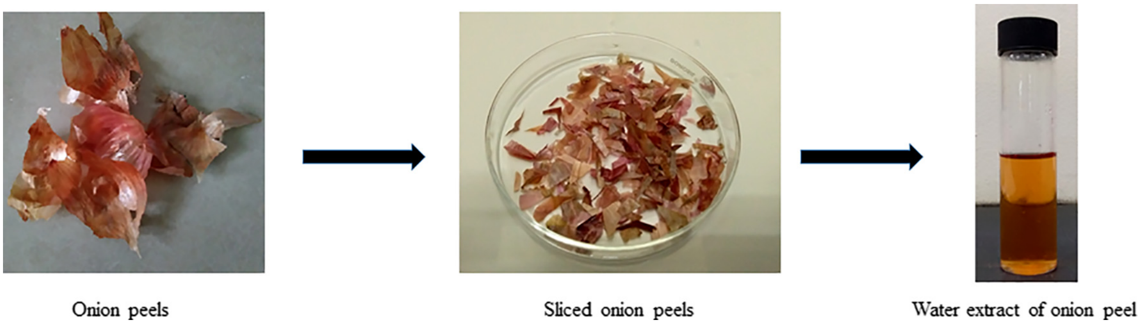


Fig. 1. Preparation of WEOP for the synthesis of Bisindolylmethanes.

2.4.3. *3,3′-(3-Chlorophenylmethylene)bis(1H-indole)* ***(3c)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.87 (s, 1H), 6.55 (d, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 2H), 7.23 (m, 5H), 7.35 (t, 3H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.80 (brs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.8, 111.3, 118.7, 119.3, 119.7, 122.2, 123.7, 126.8, 127.1, 128.7, 129.3, 134.1, 136.5, 146.1 ppm; GC–MS: $C_{23}H_{17}ClN_2$, m/z 356.11 $(M)^+$. Anal. calcd for $C_{23}H_{17}ClN_2$: C 77.41, H 4.80, N, 7.85; found C 77.38, H 4.79, N 7.83.

2.4.4. *3,3′-((4-Chlorophenyl)methylene)bis(1H-indole)* ***(3d)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.85 (s, 1H), 6.63 (s, 2H), 7.01 (t, *J* = 8.1 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.21–7.27 (m, 4H), 7.33 (d, *J* = 7.1 Hz, 4H), 7.95 (br s, 2H) ppm. Anal. calcd for $C_{23}H_{17}ClN_2$: C 77.41, H 4.80, N 7.85; found C 77.37, H 4.79, N 7.80 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.7, 111.8, 118.3, 119.4, 121.3, 124.0, 126.7, 128.5, 130.3, 130.6, 137.3, 144.4 ppm; GC–MS: $C_{23}H_{17}ClN_2$, m/z 356.11 $(M)^+$. Anal. calcd for $C_{23}H_{17}ClN_2$: C 77.41, H 4.80, N, 7.85; found C 77.37, H 4.78, N 7.82.

2.4.5. *3,3′-((2-Fluorophenyl)methylene)bis(1H-indole)* ***(3e)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.16 (s, 1H), 6.63 (s, 2H), 6.90 – 7.34 (12H), 7.88 (brs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.8, 111.1, 118.3, 119.3, 119.8, 123.6, 123.9, 126.9, 127.8, 127.9, 130.7, 130.4 136.7 ppm; GC–MS: $C_{23}H_{17}FN_2$, m/z 340.14 $(M)^+$. Anal. calcd for $C_{23}H_{17}FN_2$: C 81.16, H 5.03, N 8.23; found C 81.14, H 4.99, N 8.18.

2.4.6. *3,3′-((3-Fluorophenyl)methylene)bis(1H-indole)* ***(3f)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.80 (s, 1H), 6.58 (s, 2H), 6.80 – 7.31 (12H), 7.86 (brs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.7, 111.1, 119.0, 119.3, 119.7, 122.1, 124.4, 126.9, 129.5, 129.6, 136.7, 144.6 ppm; GC–MS: $C_{23}H_{17}FN_2$, m/z 340.14 $(M)^+$. Anal. calcd for $C_{23}H_{17}FN_2$: C 81.16, H 5.03, N 8.23; found C 81.15, H 5.01, N 8.19.

2.4.7. *3,3′-((4-Fluorophenyl)methylene)bis(1H-indole)* ***(3g)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.86 (s, 1H), 6.61 (s, 2H), 6.95 (t, *J* = 7.9 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.26–7.30 (m, 2H), 7.35 (t, *J* = 7.3 Hz, 4H), 7.88 (br s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.7, 111.1, 115.1, 119.3, 119.6, 119.9, 122.0, 123.6, 126.9, 130.0, 130.1, 136.7, 139.7 ppm; GC–MS: $C_{23}H_{17}FN_2$, m/z 340.14 $(M)^+$. Anal. calcd for $C_{23}H_{17}FN_2$: C 81.16, H 5.03, N 8.23; found C 81.13, H 4.98, N 8.19.

2.4.8. *3,3′-((2-Bromophenyl)methylene)bis(1H-indole)* ***(3h)***

^{1}H NMR($CDCl_3$, 400 MHz): δ: 6.35 (s, 1H), 6.60 (s, 2H), 6.95–7.46 (m, 12H), 7.97 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.7, 111.7, 118.4, 119.3, 120.2, 122.1, 123.7, 126.7, 127.6, 129.2, 130.2, 133.4, 136.3, 141.6 ppm; GC–MS: $C_{23}H_{17}BrN_2$, m/z 400.06 $(M)^+$. Anal. calcd for $C_{23}H_{17}BrN_2$: C 68.84, H 4.27, N, 6.98; found C 68.79, H 4.22, N 6.95.

2.4.9. *3,3′-((3-Bromophenyl)methylene)bis(1H-indole)* ***(3i)***

^{1}H NMR($CDCl_3$, 400 MHz): δ: 5.95 (s, 1H), 6.55 (s, 2H), 7.94–6.98 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.7, 111.6, 118.5, 119.5, 120.1, 122.2, 123.5, 126.7, 127.8, 129.1, 131.2, 136.4, 138.3, 146.6 ppm; GC–MS: $C_{23}H_{17}BrN_2$, m/z 400.06 $(M)^+$. Anal. calcd for $C_{23}H_{17}BrN_2$: C 68.84, H 4.27, N, 6.98; found C 68.80, H 4.23, N 6.94.

2.4.10. *3,3′-[(4-Methoxyphenyl)methylene]bis(1H-indole)* ***(3j)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.67 (s, 3H), 5.85 (s, 1H), 6.63 (s, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.97 (t, *J* = 7.2 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.90 (br s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.6, 55.6, 111.4, 113.5, 119.4, 120.4, 121.8, 123.4, 126.6, 129.8, 132.2, 135.8, 137.3, 158.5 ppm; GC–MS: $C_{24}H_{20}N_2O$, m/z 352.16 $(M)^+$. Anal. calcd for $C_{24}H_{20}N_2O$: C 81.79, H 5.72, N 7.95; found C 81.76, H 5.68, N 7.91.

2.4.11. *3,3′-[(4-Isopropylyphenyl)methylene]bis(1H-indole)* ***(3k)***

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (d, *J* = 7.0 Hz, 6H), 2.84 (sept, *J* = 7.00 Hz, 1H), 5.74 (s, 1H), 6.71 (s, 2H), 7.05 (t, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.90 (br s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6, 34.2, 39.8, 111.4, 113.5, 119.5, 120.4, 120.5, 122.4, 124.1, 126.7, 127.5, 128.9, 137.2, 141.6, 146.9 ppm; GC–MS: $C_{24}H_{24}N_2$, m/z 364.19 $(M)^+$. Anal. calcd for $C_{24}H_{20}N_2$: C 85.68, H 6.64, N 7.69; found C 85.62, H 6.60, N 7.67.

3. Results and discussion

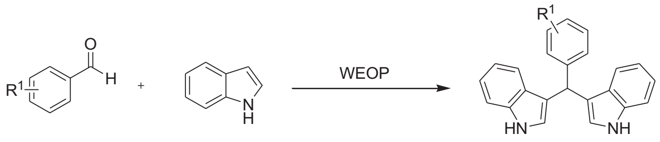
For the reaction optimization process, the optimized reaction condition was determined by using benzaldehyde (1 mmol) and indole (2 mmol) as the model starting materials. Both compounds were added into a 25 mL round bottom flask suspended with WEOP and the reaction mixture was stirred under magnetic stirring at 50 °C. The progress of the reaction was monitored by TLC analysis using hexane/ethyl acetate (8:2) solvent mixture. The influence of WEOP and temperature were studied (Table 1, entries 1–9). Initially, a 0.2 mL of WEOP was used as solvent for the model reaction and was heated at 50 °C. The yield of the required product was found to be at 50% (Table 1, entry 2). Further increment of the amount of WEOP used increased the yield to 65% (Table 1, entry 3). The complete conversion of the **3a** (≥90% yield) was observed with

Table 1
The optimization of reaction condition for **3a.**

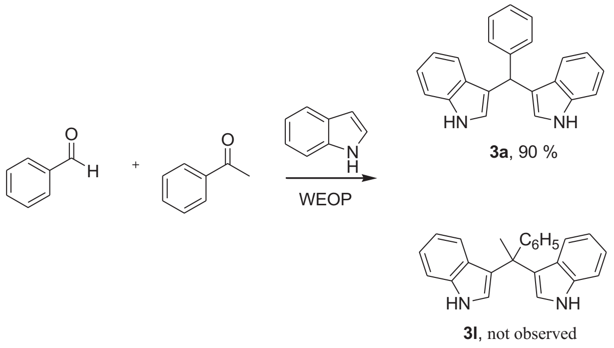
Entry	Solvent (mL)	Time (h)	Temperature (°C)	Yield[a] (%)
1	H_2O (1.0)	5	50	20
2	WEOP (0.2)	1	50	50
3	WEOP (0.5)	2	50	65
4	WEOP (0.5)	3	50	75
5	WEOP (1.0)	5	50	90
6	WEOP (2.0)	5	50	89
7	WEOP (1.0)	12	50	86
8	WEOP (1.0)	5	80	85
9	WEOP (1.0)	5	40	76

[a] Isolated yield of product **3a**.

Table 2
Isolated yields and the catalytic synthesis of BIMs 3.



Entry	R_1	Product	Reaction Time (h)	Isolated yield (%)
1	H	3a	5	90
2	2-Cl	3b	5	84
3	3-Cl	3c	5	88
4	4-Cl	3d	5	87
5	2-F	3e	5	89
6	3-F	3f	5	78
7	4-F	3 g	5	75
8	2-Br	3 h	5	76
9	3-Br	3i	5	72
10	4-OCH_3	3j	12	62
11	4-$(CH_3)_2CH$	3 k	12	65



Scheme 2. The chemoselectivity study using the WEOP catalytic system.

the use of 1.0 mL of WEOP and the reaction mixture was heated at 50 °C for 5 h (Table 1, entry 5). In contrast, we observed no change in the yield of the desired product, even in a prolonged reaction time (Table 1, entry 7) and increment of reaction temperature (Table 1, entry 8). The temperature that rendered the best yield of **3a** was found to be at 50 °C, whereas at lower temperature (Table 1, entry 9) the reaction yield was decreased. With these results in mind, subsequent study was proceeded with 1.0 mL of WEOP as reaction medium at 50 °C for 5 h (Table 1, entry 5) as the optimized reaction condition. A controlled experiment was also carried out by subjecting the model starting materials to pure water as the solvent. Under the identical temperature and reaction time, the conversion of model starting materials to **3a** was found to be in poor yield (20%) as compared to that of WEOP as solvent (Table 1, entry 5).

To widen the scope of our study on the WEOP, commercially available aldehydes were selected to synthesize a variety of different substituted **3.** In all of the cases, the pure BIMs were purified over a short silica column chromatography (62–90%). As shown in Table 2, high yields were achieved for the synthesis of different substituted bisindoles **3** within a reasonable time (Table 2, entries 1–11). Benzaldehydes substituted with electron-withdrawing groups (Table 2, entries 1–9) afforded the bisindoles of **3** in good to excellent yields in 5 h. In contrast, the benzaldehydes substituted with electron-donating groups (Table 2, entries 10–11) required a longer reaction time to accomplish good conversion.

The chemoselectivity of the WEOP catalytic system was also investigated (Scheme 2). In order to explore this, acetophenone **3 l** (1 mmol) and benzaldehyde **3a** (1 mmol) were added into a 100 mL round bottom flask containing indole (4 mmol) and WEOP (1.0 mL). The reaction mixture was magnetically stirred at 50 °C for 5 h. It was found that **3a** was the sole isolated product after heating for 5 h resulting in a 90% yield, while **3 l** remained unchanged. This result indicated the high chemoselectivity of the WEOP catalytic system.

Prior to the reusability study of the WEOP catalyst system, a LC-MS analysis was carried out on the WEOP catalytic system before condensation of indole and benzaldehyde and compared to that of the WEOP which was recovered after five successive usages.

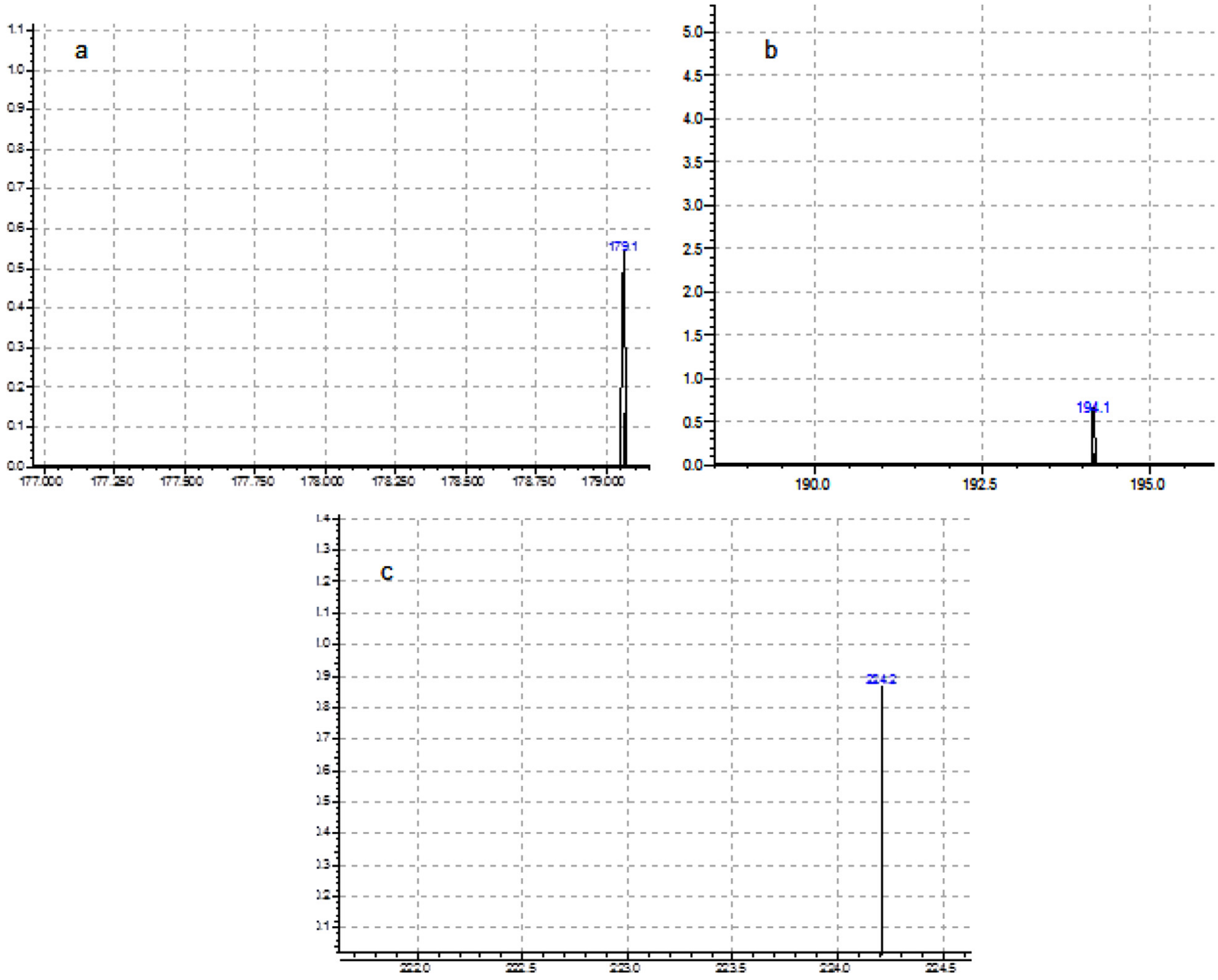


Fig. 2. Selected spectra of LC-MS analysis on the WEOP. a) [M-H]$^-$ of caffeic acid, b) [M]$^+$ of ferullic acid, and c) [M]$^+$ of sinapinic acid.

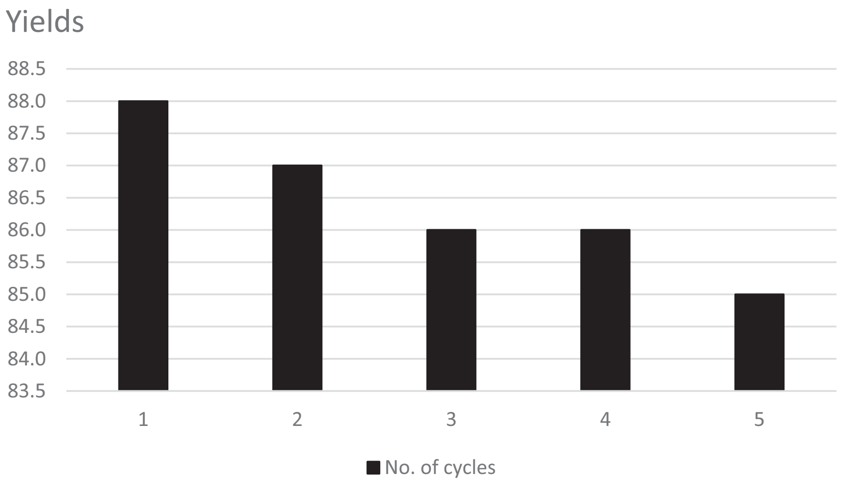


Fig. 3. Recycling of WEOP for synthesis of **3a**. Reaction condition: 1 mmol of benzaldehyde, 2 mmol of indole, 1 mL of WEOP, 50 °C.

Table 3
Yields of bisindoles in the reusability study.

Entry	R_1	Product	Isolated yield (%)					
1	H	3a	90	88	87	86	86	85
2	2-Cl	3b	84	83	82	81	80	78
3	3-Cl	3c	88	85	84	83	82	80
4	4-Cl	3d	87	86	85	83	82	79
5	2-F	3e	89	85	84	83	81	78
6	3-F	3f	78	76	75	72	71	71
7	4-F	3 g	75	74	73	70	69	68
8	2-Br	3 h	76	73	72	70	68	67
9	3-Br	3i	72	71	70	69	65	64
10	4-OCH_3	3j	62	60	58	58	57	55
11	4-$(CH_3)_2CH$	3 k	65	63	61	59	58	54

The LC-MS revealed that most of the phytochemicals in the WEOP are water-soluble compounds, such as caffeic acid, ferullic acid, sinapinic acid, cyanidin, tannic acid and other organic acids (Fig. 2). These organic acids were still detectable in the aqueous system of WEOP after being reused for five successive cycles for the synthesis of **3a** with good yields (85–88%) (Fig. 3). These organic acids were believed to serve as catalysts in the formation of **3a**. Though there was a slight decrease in terms of product yield that might be due to the use of ethyl acetate in extraction of crude product after each subsequent cycle of using reused WEOP, the reusability test showed that the overall yield of **3a** and other bisindoles were still satisfactory, as shown in Table 3.

The dramatic promotion of the synthesis of BIMs by using the WEOP catalytic system is currently not well understood. Literature report revealed that onion peels contain phenolic acids as major constituent, along with other minor chemical constituents such as flavanols, flavones and anthocyanidines (Benkeblia, 2007). pH measurement for the WEOP media revealed a pH value of 3.68 that are due to the presence of water soluble phytochemicals- caffeic acid, ferullic acid, sinapinic acid, cyanidin, tannic acid and other organic acids. These organic acids were still detectable in the recovered WEOP after five successive usages. Therefore, we propose that the organic acids present in the WEOP served to protonate the oxygen atom on the carbonyl group of aldehydes, thereby facilitating the nucleophilic attack on indole and promoting the synthesis of BIMs, in a way similar way to that reported in a previous literature (Fiorito et al., 2016). In order to show the merit of the WEOP protocol, the previous methods and their yields for synthesising **3a** were summarised in Table 4. To date, many efficient catalytic system have been reported for this reaction, however, most of the previous methods encompassed the use of harsh condition, high temperature, expensive and non-recyclable catalysts for the synthesis of bisindolylmethanes.

Table 4
Synthesis of **3a** mediated by different catalysts.

Entry	Catalyst	Yield (%)	Reference
1	WEOP	90	
2	Ammonium niobium oxalate	99	(Mendes et al., 2015)
3	Tetrabutylammonium hydrogen sulphate	91	(Siadatifard et al., 2016)
4	$ZnCl_2$/Urea	92	(Seyedi et al., 2015)
5	Squaric acid/water	90	(Azizi et al., 2012)
6	[bnmim][HSO_4]/microwave irradiation	93	(Sadaphal et al., 2008)
7	$ZrOCl_2.8H_2O$	89	(Mishra and Ghosh, 2011)
8	Glacial acetic acid	90	(El-Sayed et al., 2014)
9	Oleic acid	98	(Ganesan et al., 2015)

4. Conclusions

In summary, we have demonstrated the synthesis of BIMs in the presence of WEOP. The current protocol offers many advantages including a simple and effective catalytic system, simple work-up, benign reagents, cheap but good to excellent yields and the reusability of the WEOP catalytic system. Further application of the WEOP in the synthesis of other bioactive heterocyclic compounds is currently ongoing in our laboratory and the results will be reported in due course.

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