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Original Article

Synthesis of thiazolo- and benzothiazolo[3,2-a]pyrimidine derivatives using onion peel as natural catalyst

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Abstract

In this work, a facile, metal-free and efficient protocol for the synthesis of thiazolo- and benzothiazolo[3,2-a]pyrimidine-6-carboxylate derivatives using onion peel as catalyst is described. For the first time, the onion peels are used for the synthesis of thiazolo- and benzothiazolo[3,2-a]pyrimidine-6-carboxylate derivatives. The current protocol has numerous advantages, including cost-effectiveness, avoiding the use of external acids and bases, and the high porosity of the natural catalyst has led to the desired products in good to excellent yields. We anticipate that this environmental friendly catalyst presented here will be of great utility in both research institution and industry.

Keywords: onion peel, thiazolo and benzothiazolo-[3,2-a]pyrimidine, metal-free synthesis, heterocyclic compounds

1. Introduction

Multi-component reactions (MCRs) have emerged as one of the powerful and efficient strategies for organic synthesis (Domling, Wang, & Wang, 2012; Molla, Hossain, & Hussain, 2013). Complex molecules such as heterocyclic compounds are easily assessable using the MCRs, which offer fast and experimentally simple methods. In MCR, three or more starting materials are reacted together in a single-pot reaction to form new compounds that consists of all reactants (Dekamin, Mehdipoor, & Yaghoubi, 2017; Simon & Li, 2012). From the perspective of green chemistry, MCR is a valuable tool as it is known for high atom economy, high synthetic efficiency and it provides environmental benefits in the synthesis of structurally diverse therapeutic compounds (Cioc, Ruijter, & Orru, 2014; Zheng *et al.*, 2015). In this respect, the thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives have been the therapeutic target of intense research due to their broad spectra of important biological activities such as anticancer (Hassan, El-Messery, & Abbas, 2017), anti-inflammatory activity (Alam, Khan, Siddiqui, & Ahsan, 2010), antibacterial activity (Sahi & Paul, 2016), analgesic activity (Moty, Hussein, Aziz, & Abou-Salim, 2016), anti-oxidant (Banothu *et al.*, 2014), anti-acetylcholinesterase activity (Zhi *et al.*, 2013), anti-viral property (Babu *et al.*, 2012) and others. Besides having therapeutic elements,

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thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives can also be used as insecticide (Sherif, Youssef, Mobarak, & Abdel-Fattah, 1993).

Owing to their significant biological activities, various methods for the synthesis of thiazolo[3,2-a]pyrimidine derivatives have been reported. Literature surveys reveal the use of energy input, Lewis acid and inorganic catalysts for the synthesis of benzothiazo- and thiazolo[3,2-a]pyrimidine derivatives including the use of K_2CO_3 (Darehkordi, Fazli-Zafarani, & Kamali, 2017), potassium fluoride/alumina catalyst (Singh *et al.*, 2013), strontium chloride hexahydrate (Kotaiah *et al.*, 2012), MgO in the presence of tungstophosphoric acid (Sheibani & Babaie, 2013), L-proline (Sahu, Sahu, Samadhiya, Sahu, & Agarwal, 2016) and ultrasound irradiation (Tan, Chuah, & Chia, 2016). Unfortunately, most of these methods have had several drawbacks, such as the use of harmful reagents, harsh reaction conditions, metals and external acids and bases.

Every month, mankind has generated million tons of bio-waste, and the sources are mainly from house-holds, food stalls, restaurants and food processing factories (Choi, Cho, Moon, & Bae, 2015). With the boom in human population, the generation of bio-waste has greatly escalated in recent years as a result of an increasing demand on agricultural production (Marshall & Farahbakhsh, 2013). For years, most of the bio-waste is directed to land-fills, which may lead to adverse effects on our ecosystem, wild life and human health (Gao, Li, Geng, Wei, & Zhang, 2015). Onion (Allium Cepa L.) is one of the most cultivated crops grown globally for therapeutic, nutritional and other functional properties and its by-product, namely the onion peel is produced as bio-waste annually (Nile & Park, 2013). To that end, surveys show that human consumption and food processing industries in some countries, such as the US and the European countries have generated more than 100,000 tons of onion waste annually (Manousaki, Jancheva, Grigorakis, & Makris, 2016; Roldán, Sánchez-Moreno, de Ancos, & Cano, 2008; Sharma, Mahato, Nile, Lee, & Lee, 2016).

Recently, efforts have intensified on developing environmentally friendly and cheaper chemical reagents and catalysts that can be substituted for the toxic and expensive one. Some of these notable examples were exhibited by the use of water extract of banana (Boruah, Ali, Saikia, & Sarma, 2015) and rice straw ash (Boruah & Ali, 2015) to catalyze Suzuki-Miyaura cross-coupling reactions, without the use of an external base. In addition, this base catalyzed media has avoided the use of toxic ligands and has emerged as a feasible method of synthesis, which is of industrial relevance and academic importance. In view of the growing demand to develop a simple, highly economic and environmental sustainable route of synthesizing diverse heterocyclic privileged compounds, herein, we would like to report the use of the onion peel as natural catalyst to synthesize an important privileged scaffold in pharmaceuticals, namely the thiazolopyrimidine derivatives (Schneider & Schneider, 2017). Previously, we have reported the use of water extract of burned-ash of onion peel waste (ash-water extract) for the synthesis of bisenols (Chia, Lim, Yong, Poh, & Kan, 2018) and water extract of onion peel for the synthesis of bisindolylmethanes (Chia, Lim, Tan, Yong, & Kan, 2018). Further research on the waste onion peel in our research group shows that it can be used as a natural catalyst to facilitate the formation of thiazolo and benzothiazolo-[3,2-a]pyrimidines and the yield of the end-products were obtained in good to moderate yields. Significant advantages of this protocol include simple operation, cost-effective and avoiding the use of external acids and bases in performing MCR reaction that would be of industrial interest in the near future.

2. Experimental

2.1 Materials and methods

All the chemicals and solvents (technical grade) utilized in this experiment were purchased from Sigma-Aldrich (Malaysia) and were used without further purification unless stated. Chemicals and reagents used include the *n*-hexane, ethyl acetate, benzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzldehyde, 4-chlorobenzaldehyde, 2-bromobenzal-dehyde, 3-bromobenzaldehyde, 3-fluorobenzaldehyde, 4-isoporpylbenzaldehyde, 4-methoxybenzaldehyde and silica gel 60 (0.063-0.200 mm). The characterization of samples on the ^{1}H and ^{13}C-NMR analysis performed on Bruker Avance III 400 spectrometer, were recorded using $CDCl_3$ as solvent. The normal phase of GC-MS spectra were recorded using Shimadzu QP2010SE equipped with a Supelco fused silica capillary column (30 m × 0.25 mm i.d., 0.25 mm film thickness). The aliquot samples were dissolved in methanol and injected directly into GCMS (EI mode). The oven was held at 50 °C for 5 min and heated at a gradient of 20 °C/min to 150 °C, 280 °C injector temperature; 100:1 split ratio and 1.0 mL/min flow. LCMS-IT-TOF (Shimadzu, Kyoto, Japan) separation was performed using a Shim-pack XR-ODS II C18 column 2.0 mmi.d. x 150 mm (Shimadzu, USA) at a constant flow rate of 0.2 ml/min. After injection of 1 µl of sample, samples were eluted using gradients of 10-100% solvent B (ACN) for 25 minutes. LCMS-IT-TOF was operated with the heated capillary temperature set at 200°C. Data were collected at scan ranges of 142-1000 for MS (ESI positive and negative modes). The total carbon, hydrogen, nitrogen and sulfur (CHNS) analysis was performed using CHNS Analyzer Flashea 1112 series. The Infrared analysis was performed using Perkin Elmer Spectrum 100 FTIR Spectrometer. The metal content analysis of onion peel was performed using Varian Vista Pro Inductive Coupled Plasma-Optical Emission Spectroscopy (ICP-OES). The ICP-OES analysis of onion peel was conducted in triplicate and data were shown as mean value ± standard deviation (SD). The morphology of the recovered onion peel was studied using Scanning Electron Microscope (SEM) JEOL 6360 LA.

2.2 Preparation of onion peel powder

In this experiment, the onion waste was collected in a nearby local restaurant. The onion peel was separated from bulb and washed with distilled water. Subsequently, the onion peel was air-dried for four days. The dried onion peel was sliced into small pieces and ground into powder using mortar and pestle.

2.3 General procedure for preparation of thiazolo- and benzothiazolopyrimidine 5a-5s

The powdered onion peel was added into a 50 mL round-bottom flask containing 2-aminobenzothiazole or 2-aminothiazole (1.00 mmol), benzaldehydes (1.00 mmol) and ethyl acetoacetate (1.00 mmol) under solvent-less condition. The mixture was then stirred magnetically and heated at 120 °C. The progress of the reaction was monitored using Thin-Layer Chromatography (TLC) with mobile phase (ethyl acetate: *n*-hexane, 2: 8). After the complete of the reaction as indicated by the TLC, the catalyst was filtered off and the reaction mixture was subjected over silica-gel column purification and ethyl acetate/n-hexane (1: 9) as eluent. All pure products were characterized by NMR (^{1}H and ^{13}C) and were further supported by GC-MS analysis.

2.4 Selected Spectra data for thiazolo- and benzothiazolopyrimidines

7-Methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **(5a)**; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.36 (m, 5H), 6.55 (d, 1H, *J* = 4.7 Hz), 6.26 (d, 1H, *J* = 4.7 Hz), 6.19 (s, 1H), 4.06 (m, 2H), 2.44 (s, 3H), 1.16 (t, *J* = 7.19 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.46, 163.47, 141.29, 137.91, 132.90, 129.97, 128.61, 127.18, 126.60, 123.97, 111.78, 103.05, 60.09, 57.75, 23.42, 14.33; GC-MS calcd for $C_{16}H_{16}N_2SO_2$ $[M]^+$, 300.09; Found 300.09.

5-(2-Fluoro-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **(5b)**; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.01 (m, 4H), 6.71 (d, *J* = 4.76 Hz, 1H), 6.60 (s, 1H), 6.29 (d, *J* = 4.76 Hz, 1H), 4.02 (m, 2H), 2.50 (s, 3H), 1.10 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.10, 164.93, 159.85, 157.31, 130.38, 129.59, 126.41, 125.15, 115.33, 115.11, 105.90, 97.62, 59.67, 52.76, 23.43, 14.03; GC-MS calcd for $C_{16}H_{15}N_2SFO_2$ $[M]^+$, 318.08; Found 318.08

5-(3-Fluoro-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **(5c)**; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-6.94 (m, 4H), 6.60 (d, *J* = 4.76 Hz, 1H), 6.33 (d, *J* = 4.76 Hz, 1H), 6.20 (s, 1H), 4.10 (m, 2H), 2.44 (s, 3H), 1.18 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 165.15, 164.19, 156.44, 145.30, 130.36, 126.46, 122.45, 115.41, 113.94, 105.85, 99.06, 60.34, 59.86, 23.68, 14.20; GC-MS calcd for $C_{16}H_{15}N_2SFO_2$ $[M]^+$, 318.08; Found 318.08.

5-(4-Fluoro-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **(5d)**; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-6.99 (m, 4H), 6.61 (d, *J* = 4.60 Hz, 1H), 6.40 (d, *J* = 3.84 Hz, 1H), 6.20 (s, 1H), 4.08 (m, 2H), 2.47 (s, 3H), 1.18 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.59, 166.58, 160.1, 156.15, 138.58, 128.66, 126.47, 115.83, 115.61, 108.39, 105.79, 99.54, 60.41, 59.84, 23.74, 14.25; GC-MS calcd for $C_{16}H_{15}N_2SFO_2$ $[M]^+$, 318.08; Found 318.08.

5-(2-Chloro-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **(5e)**; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.19 (m, 4H), 6.82 (d, *J* = 4.80 Hz, 1H), 6.79 (s, 1H), 6.26 (d, *J* = 4.76 Hz, 1H), 4.01 (m, 2H), 2.51 (s, 3H), 1.09 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.12, 164.93, 157.25, 140.47, 131.09, 130.24, 129.80, 129.25, 128.28, 126.20, 105.66, 98.73, 59.64, 55.96, 23.50, 14.07; GC-MS calcd for $C_{16}H_{15}N_2SClO_2$ $[M]^+$, 334.05; Found 334.04.

5-(3-Chloro-phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester **(5f)**; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (m, 4H), 6.57 (d, *J* = 4.72 Hz, 1H), 6.34 (d, *J* = 4.72 Hz, 1H), 6.16 (s, 1H), 4.08 (m, 2H), 2.45 (s, 3H), 1.19 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.19, 164.73, 155.49, 144.51, 134.79, 130.26, 128.83, 127.12, 126.45, 125.12, 106.61, 99.30, 60.27, 59.95, 23.36, 14.24; GC-MS calcd for $C_{16}H_{15}N_2SClO_2$ $[M]^+$, 334.05; Found 334.04.

5-(o-toluphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid ethyl ester (**5n**); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.11 (m, 1H), 7.20-7.11 (m, 3H), 6.46 (s, 1H), 6.44 (d, *J* = 5.08 Hz, 1H), 6.23 (d, *J* = 5.08 Hz, 1H), 4.03 (m, 2H), 2.52 (s, 3H), 2.45 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.60, 164.95, 155.83, 141.66, 134.26, 130.55, 129.15, 128.34, 127.10, 126.32, 105.40, 99.71, 59.61, 57.17, 23.67, 19.11, 14.22; GC-MS calcd for $C_{17}H_{18}N_2SO_2$ $[M]^+$, 314.11; Found 314.11.

Ethyl 2-methyl-4-(phenyl)-4*H*-pyrimido-[2,1-*b*][1, 3]benzothiazole-3-carboxylate (**5o**); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.41 (m, 3H), 7.23-7.19 (m, 4H), 7.13-7.10 (t, 2H), 6.40 (s, 1H), 4.17 (m, 2H), 2.47 (s, 3H), 1.28 (t, *J* = 7.19 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.50, 154.49, 146.0, 144.20, 142.4, 137.91, 132.90, 131.10, 129.97, 128.61, 127.18, 126.60, 123.97, 122.13, 111.78, 103.05, 60.09, 57.75, 23.42, 14.33; GC-MS calcd for $C_{20}H_{18}N_2SO_2$ $[M]^+$, 350.11; Found 350.11.

3. Results and Discussion

The onion peels sampling from a local waste disposal site was compared to those onion peels purchased from a local grocery shop. As shown in the FTIR analysis (Figure 1), the broad signal at 3,393 cm^{-1} is attributed to the stretching vibration of hydroxyl groups, while the signal at 1637 cm^{-1} can be assigned to the stretching vibration of carbonyl groups. Based on the IR spectra of Figure 1b, the relative intensity, shapes and the stretching frequencies of all signals were well preserved as compared to that of Figure 1a. Thus, the result indicated that there was no considerable changes, in terms of the chemical structure (functional groups and hydrogen bonding network) observed on the onion peels sampled from a local waste disposal site (Figure 1b) as compared to that of onion peel purchased from a local grocery shop (Figure 1a).

Next, the morphology of the recovered onion peel was studied using Scanning Electron Microscopy (SEM). In Figure 2a, a smooth surface of onion peel was shown before the onion peel was ground. After grinding it, the onion peel shows high porosity as shown in the SEM (Figure 2b) as compared to the non-powdered onion peel. The high porosity of powdered onion peel could serves for catalytic purpose, as a result of providing adequate morphology for the adsorption of various organic materials. In this case, it has promoted the multicomponent reaction of thiazolo- and benzothiazolo[3,2-

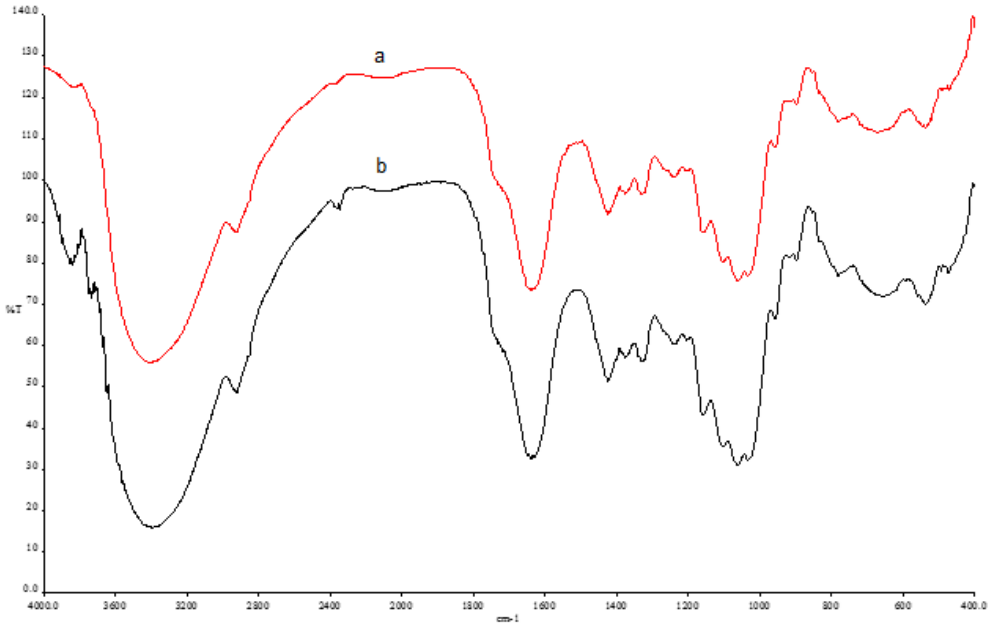


Figure 1. FTIR spectra of (a) onion peels purchased from a local grocery shop, and (b) onion peels sampled from a local waste disposal site.

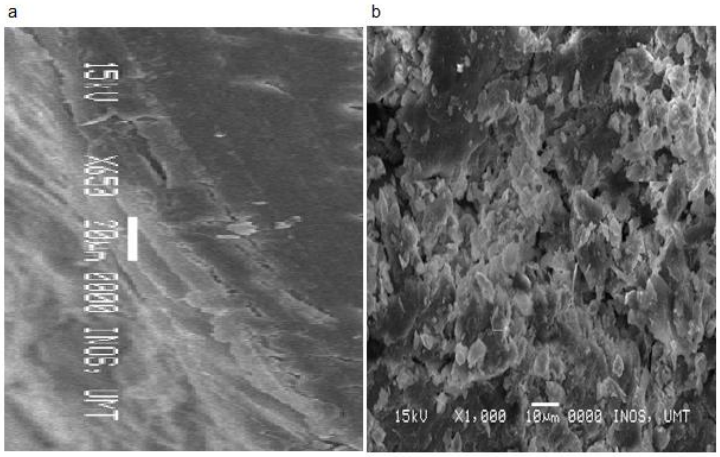


Figure 2. SEM images of (a) non-powdered onion peel, (b) powdered onion peel.

a]pyrimidine in solvent-less condition. Additionally, the surface area of the powdered onion peel were analyzed using the Brunauer-Emmett-Teller (BET) method and the specific surface area of the powdered onion peel is 58.10 m^2/g. The metal content of onion peel was also characterized with Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) and the metals that were recorded were shown as follows: K (22927.00 ± 0.47 ppm), Na (14930.00 ± 0.21 ppm), Mg (7896.00 ± 6.26 ppm), S (2225.00 ± 1.44 ppm), P (2172.00 ± 2.13 ppm), Fe (1815.00 ± 1.03 ppm), Al (1366.00 ± 1.07 ppm), Sr (300.00 ± 2.52 ppm), Mn (216.00 ± 2.18 ppm), B (107.00 ± 0.09 ppm), Ba (53.00 ± 0.23 ppm), Zn (52.00 ± 0.11 ppm), Rb (35.00 ± 0.02 ppm), La (15.00 ± 0.31 ppm), Ga (15.00 ± 0.12 ppm), Cu (13.00 ± 0.17 ppm), Pb (9.80 ± 0.23 ppm).

The LC-MS analysis was also performed on the water extract of onion peel before studying the catalytic activity of onion peel in the synthesis of thiazo- and benzothiazolo[3,2-a]pyrimidine derivatives. The LC-MS result shows that most of the chemical constituents in the onion peel extract are water-soluble compounds, namely the caffeic acid, ferullic acid, sinapinic acid, tannic acid, along with other organic acids (Figure 3). The result of the LCMS was in agreement with a previous study, which reported that the onion peel contains flavanols, flavones, anthocyanidines, tannic acid and other minor constituents (Gawish, Helmy, Ramadan, Farouk, & Mashaly, 2016). However, the chemical constituents of the onion peel vary according to the location grown and seasonal harvesting and processing.

In the search for optimized reaction condition, 2-aminothiazole (1.00 mmol), benzaldehyde (1.00 mmol) and ethyl acetoacetate (1.00 mmol) were employed as model starting materials for this study. Various parameters, such as the amount of catalysts required, solvents and reaction temperature were studied as shown in Table 1. In the absence of onion peel catalyst, the desired product was produced in 20

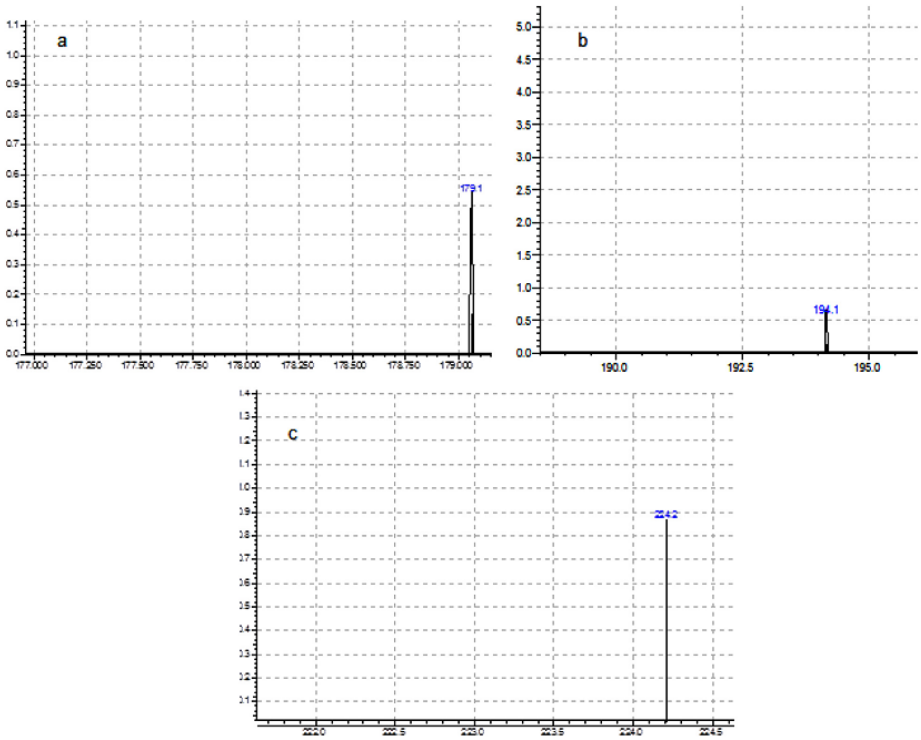


Figure 3. Selected spectra of the chemical constituents on the onion peel analyzed with LCMS. a) m/z: 179.1, $[M-H]^-$ of caffeic acid, b) m/z: 194.1, $[M]^+$ of ferullic acid, and c) m/z: 224.2, $[M]^+$ of sinapinic acid.

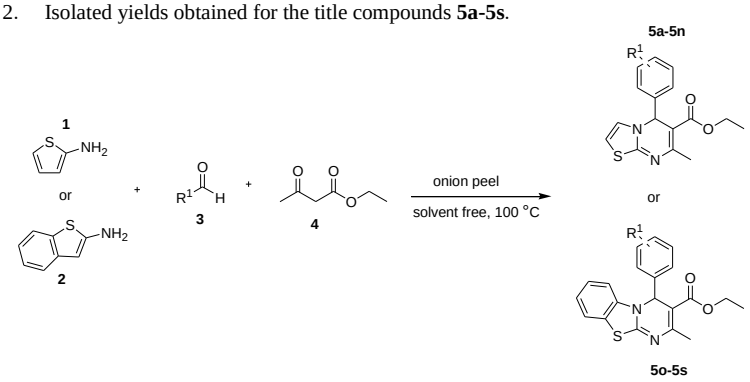
Table 1. Optimization of model reaction catalyzed by onion peel catalyst.

Entry	Catalyst (g)	Time (h)	Solvent	Temperature (°C)	Yield[a] (%)
1	-	1	Solvent-less	120	20
2	0.03	1	Solvent-less	120	81
3	0.05	1	Solvent-less	120	91
4	0.05	1	Solvent-less	100	85
5	0.07	1	Solvent-less	120	91
6	0.05	1	H_2O	reflux	55
7	0.05	1	EtOH	reflux	62
8	0.05	1	CH_2Cl_2	reflux	32
9	0.05	1	Toluene	reflux	28
10	0.05	1	THF	reflux	30

% yield under solvent-less condition at 120 °C (Table 1, entry 1). The desired product was produced, when the same condition was applied with onion peel added as catalyst and this time 91 % yield was recorded after 60 min (Table 1, entry 3). The effect of different solvent towards the synthesis of **5a** was evaluated. Different solvents employed, such as H_2O, EtOH, CH_2Cl_2, toluene and THF were added as solvent in the synthesis of **5a** in the presence of onion peel (Table 1, entries 6-10). Based on the experimental result, the yield of **5a** was found to be decreased as compared to that of solvent-free condition. The high reaction rate in solvent-less condition can be explained by the fact that high concentration of starting materials in dry media reaction that has facilitated the formation of the desired compounds. In order to optimize the catalyst amount, the synthesis of **5a** was carried out using different amounts of catalyst (0.03, 0.05 and 0.07 g). The result revealed that there was no significant increase in reaction yields when the amount of catalyst loaded increased (Table 1, entries 2, 3 and 5). With all these results in hand, the solvent-less condition loaded with 0.05 g of catalyst at 120 °C was found to be the optimized condition and this condition was employed for other scope of study in the synthesis of other thiazolo[3,2-a]pyrimidine derivatives.

Next, we have examined the scope of the functional-group compatibility of the current protocol using various benzaldehydes bearing electron-withdrawing and electron-donating groups. As indicated in Table 2, the condensation reaction of 2-aminothiazole **1,** benzaldehyde with different electron-withdrawing and donating groups and ethyl acetoacetate has afforded thiazolo[3,2-a] derivatives in moderate to good yields (Table 2, entries 1-14). In particular, the benzaldehydes bearing electron withdrawing groups (Table 2, entries 1-12) afforded the desired products of **5** in good yields compared to that of benzaldehydes bearing electron-donating groups (Table 2, entries 13-14). The result also showed that the current protocol is efficient, when

Table 2. Isolated yields obtained for the title compounds **5a-5s**.



Entry	Starting materials	R_1	Compound	Isolated yield (%)
1	1	H	5a	88
2	1	2-F	5b	85
3	1	3-F	5c	74
4	1	4-F	5d	86
5	1	2-Cl	5e	89
6	1	3-Cl	5f	72
7	1	4-Cl	5g	75
8	1	2-Br	5h	81
9	1	3-Br	5i	73
10	1	4-Br	5j	70
11	1	3-NO_2	5k	69
12	1	4-NO_2	5l	73
13	1	$CH(CH_3)_2$	5m	68
14	1	2-CH_3	5n	63
15	2	H	5o	78
16	2	3-F	5p	85
17	2	3-Cl	5q	78
18	2	3-Br	5r	79
19	2	2-NO_2	5s	81

substituting the 2-aminothiazole **1** with 2-aminobenzothiazole **2,** the corresponding products **5o**-**5s** were afforded in satisfactory yields (Table 2, entries 15-19).

A plausible mechanism for the formation of thiazolo- and benzothiazolo[3,2-a]pyrimidine in the presence of onion peel was proposed as shown in Figure 4. Prior to that, we have carried out the pH measurement for the water extract of onion peel and the media shows a pH value of 3.68. Based on the LCMS result and previous literature (Chavan, Nagore, Mane, & Bangale, 2015; Shitole, Shitole, Kakde, & Shingare, 2013; Singh & Duvedi, 2014), onion peel contain phenolic acids and other minor constituents, which act as Lewis acid that protonate the carbonyl group of an aldehyde followed by Michael addition by 2-aminothiazole, provides intermediate A. Subsequently, cyclodehydration of intermediate B and dehydration led to the desired product. The same mechanism was also proposed for the synthesis of benzothiazolo[3,2-a]pyrimidine derivatives under the identical reaction condition.

4. Conclusions

In summary, we have described a facile and metal-free synthesis of thiazolo- and benzothiazolo[3,2-a]pyrimidine derivatives with onion peel as natural catalyst. The current catalytic system offers many advantages including efficient catalytic system, simple work-up, avoid the use of external

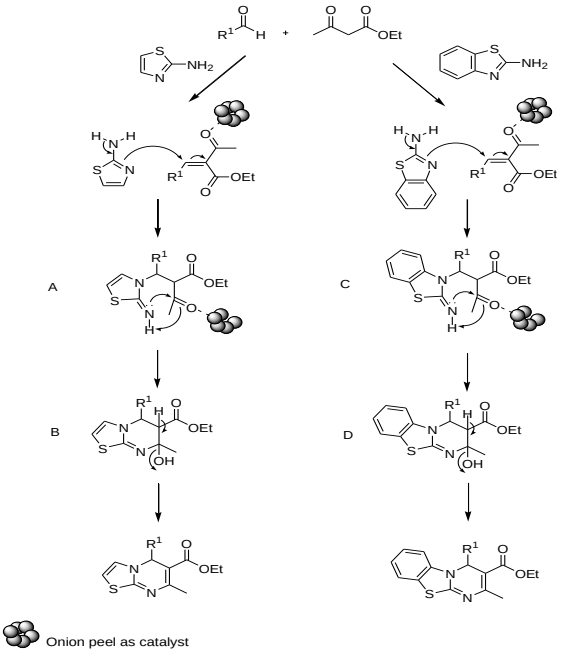


Figure 4. Plausible mechanism pathway for the synthesis of thiazolo- and benzothiazolo[3,2-a]pyrimidine derivatives catalyzed by onion peel.

acids and base, cheap and the desired products were recovered in moderate to good yields. The current study enforces on the concept of the usefulness of by-products derived from agriculture in the synthesis of bioactive heterocyclic compounds, which are of great interest to researchers who work in the same field.

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