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Vegetable oil as a highly effective 100% bio-based alternative solvent for the one-pot multicomponent Biginelli reaction⁺

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Multicomponent one-pot Biginelli reactions have been successfully performed using vegetable oil as biobased, non-toxic, and environmentally friendly solvents. Palm oil was demonstrated to be a highly effective greener solvent as compared to petroleum-based solvents such as cyclohexane, with comparable yields for the Biginelli reaction of urea, benzaldehyde, and methyl 3-oxobutanoate, of 74% and 73%, respectively. Moreover, palm oil was easily recovered from the reaction mixture and reused for at least 4 additional reactions with a consistent yield of 60%, which was in stark contrast with cyclohexane that was unable to recovered and reused in this reaction. Virgin palm oil exhibited clear solvent effects including enhanced solubility of substrates and promotion of the keto-enol tautomerisation leading to an increased reaction productivity when compared to previous published bio-based solvents such as p-cymene and ethyl lactate. Green metrics evaluation using process mass intensity (PMI), E-factor, solvent intensity (SI), and water intensity (WI) for the Biginelli reaction using palm oil was found to be more sustainable and safer than cyclohexane, p-cymene and ethyl lactate. Moreover, waste palm oil could be utilised with comparable yields to p-cymene and ethyl lactate, but importantly has a lower associated environmental impact. If sustainably sourced, vegetable oils can create new opportunities for chemists to improve the green credentials of multicomponent reactions with a safer and cheaper renewable alternative to petroleum derived solvents.

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Introduction

Traditional petrochemically derived solvents are typically volatile organic compounds that can suffer from environmental or toxicity issues.^{1–4} Several of these commonly utilised solvents are now facing stricter regulations on their use worldwide.^{5,6} As such, considerable attention has been placed on the development of greener, bio-derived, and renewable solvents for application in all aspects of synthetic chemistry.⁷ In multicomponent reactions (MCRs), the utilisation of greener solvents for replacing conventional solvents provides not only an important enhancement of sustainability but also synthetic efficiency. Moreover, the utilisation of unconventional greener solvents has been successfully conducted in several one-pot MCRs.⁸

The Biginelli reaction is one of the most recognised multicomponent reaction that involves the condensation of urea, aldehyde, and β -keto ester to give dihydropyrimidinones (DHPMs) which displays a wide range of biological activities such as antitumor, antiviral, antibacterial, anti-inflammatory and antimalarial.9-12 The classical Biginelli protocol involving the reaction under strong acidic conditions using hydrochloric acid in ethanol as the solvent.¹³ Although ethanol is a green and bio-based solvent, the major drawback of using it in the Biginelli reaction is the low product yield, when using substituted aromatic or aliphatic aldehydes.^{14,15} Previously, a number of conventional solvents have been used for synthesis of DHPMs such as THF, dioxane, toluene, hexane, MeCN, and DMF.16-20 These non-renewable petroleum-based solvents are usually toxic, flammable, volatile and are frequently non-biodegradable in nature. In the case of dioxane, toluene, hexane, MeCN, and DMF these have been recognised as hazardous air pollutants by the US EPA.²¹ To overcome these issues, numerous research studies have aimed to discover green and efficient methodologies for the synthesis of DHPMs. Several reports on catalyst systems for the Biginelli reaction have been conducted using some greener reaction media such as water, ionic

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liquids and solventless systems.^{22–27} Moreover, few examples of using bio-based solvent for the Biginelli reaction are reported in the literature. Xu *et al.* reported the synthesis of DHPMs in a biomass-derived solvent, ethyl lactate with the catalysis of trimethylsilyl chloride in good to excellent yields.²⁸ Surprisingly, there has been limited report on the role of solvents in the Biginelli reaction. Clark *et al.* did demonstrate that the efficiency of the Biginelli reaction depends on the solvent ability to promote tautomerisation equilibrium of β -keto ester to the enol form which is required for the reaction. They found that the use of *p*-cymene encourage the enol form of β -keto ester and gave the product in good yield.²⁹ As such, the search for greener bio-based and renewable solvents is of paramount importance in the modern Biginelli reaction.

Importantly, non-polar solvents are more likely to promote the keto-enol tautomerisation equilibrium, thereby enhancing production of the Biginelli product. Vegetable oils could be promising greener and eco-friendly bio-based non-polar solvent candidates. Vegetable oils can be derived from several renewable feedstocks such as rape, sunflower, soybeans, oil palm fruit and kernels. These are non-toxic, have high biodegradability, low-volatility, flammability, and are renewable.³⁰ They are promising as low cost widely available bioresource that require relatively simple processing technologies.³¹ However, the use of food grade vegetable oils as solvents does raise discussions over foods verses chemicals. As such, it is important to utilise waste oils or sustainably sourced non-food grade vegetable oils, whenever practically possible. Few research studies have been reported on the utilisation of vegetable oils as green solvents for synthesis of polymeric capsules.^{32,33} Musyanovych et al. reported the use of bio-inert oil miglyol 812N (caprylic/capric triglycerides) in the synthesis of DNA-loaded nanocapsules via the interfacial anionic polymerisation.³² Ishizuka and co-workers reported the synthesis of polymeric microcapsules via RAFT photopolymerisation in vegetable oil as a green solvent.³³ Although several studies have on the use of vegetable oils to replace conventional solvents in chemical extraction,³⁴⁻⁴⁵ it has not been utilised in multicomponent reaction.

Herein, this research demonstrates that vegetable oils are promising solvents for synthesising several DHPMs in good yields through a more sustainable method. Waste vegetable oils from palm and soy were investigated alongside virgin oils to compare against petroleum-based solvents in the one pot multi component Biginelli reaction. The recovery and reusability of vegetable oils was also investigated. The utilisation of vegetable oil could crucially broaden the scope of multicomponent moving forward providing a sustainable, ecologic, and economic alternative to hazardous petroleum-based solvents in organic synthesis.

Results and discussion

Initial solvent screening of castor oil, jojoba oil, CPME, cyclohexane, DMF, *n*-heptane, linseed oil, neem oil, palm oil, palm

kernel oil, soybean oil, TMO, and waste palm and soybean oils was undertaken for the Biginelli reaction of urea, benzaldehyde, and methyl 3-oxobutanoate (Scheme 1). Palm, palm kernel and soybean oils are edible vegetable oils that are nonpolar lipophilic, non-toxic, biodegradable, and renewable feedstock and are compost of main triglycerides (>90%).^{30,54} In addition to triglyceride components in vegetable oil, there are other minor components that can be divide into two classes including glycerolipids (mono- and diglycerides, phospholipids) and non-glycerolipids (sterols, tocopherols, tocotrienols, free fatty acids, vitamins, pigments, proteins, phenolic compounds, water, etc.).³⁰ Castor, jojoba, linseed, and neem oils are inedible plant oils that are not suitable for human consumption and in some cases they contain some toxic components.^{55,56} Castor oil contains ricinolein, the triglyceride of ricinoleic acid which has a hydroxy group in fatty acid chain, while the main composition of jojoba oil are straight chain monoester (wax esters).⁵⁶ The fatty acid composition of all oils is reported in Table S2 (ESI[†]).

The aprotic solvents were selected to cover a wide polarity range, as identify by the Kamlet–Taft solvent parameters descriptors of hydrogen bond acidity (α), hydrogen bond basicity (β), and a combined measure of polarity and polarizability (π^*) (Table 1). Table 1 also included the solvent parameters of other bio-based solvents from previous reports for the comparison of their polarity.^{28,29} The β values of oils were high due to the structure of triglyceride consist with the presence of oxygen atoms, which can promote their hydrogen-bond accepting ability, while their α values are low (or negative) because of the strongly basic triglyceride on the probe molecule and/or hydrogen-bonding between the free fatty acid and the triglyceride.⁵²

From the results of solvent screening, reaction productivity was plotted against tautomerisation equilibrium (Fig. 1A). The observed solvent trend is consistent with previously reported studies.²⁹ The reaction productivity was quantified in terms of the natural logarithm of the molar ratio of isolated product to the yield-limiting agent (unincorporated urea). The productivity of the Biginelli reaction was impacted by the solvent ability to promote the tautomerisation equilibrium of β -keto ester which showed the relationship with the Kamlet–Taft parameter of a combined measure of dipolarity and polarizability (π^*) (Fig. 1B). In solution, the enol form of β -keto ester is needed for the C–C bond formation. As such, solvents that can encourage the enol form of β -keto ester are these with low hydrogen bond acidity (α) and little polarity and polarizability (π^*).



Scheme 1 Model Biginelli reaction used to determine the reaction yield in different solvents.

 Table 1
 Polarity data and the tautomerisation equilibrium constants of solvents

| Solvent | α | β | π^* | $\ln(K_{\rm T})$ |
|-------------------|-------------|-------------|--------------|------------------|
| Acetic acid | 1.12^{46} | 0.45^{46} | 0.64^{46} | -2.92^{29} |
| Castor oil | -0.40 | 0.64 | 0.59 | -1.98 |
| CPME | 0.00^{47} | 0.52^{47} | 0.43^{47} | -1.48 |
| <i>p</i> -Cymene | 0.00^{48} | 0.13^{48} | 0.39^{48} | -1.33^{29} |
| c-Hexane | 0.00^{49} | 0.00^{49} | 0.00^{49} | -0.09^{29} |
| DMF | 0.00^{50} | 0.69^{50} | 0.88^{50} | -2.91^{29} |
| Ethanol | 0.83^{46} | 0.75^{46} | 0.54^{46} | -1.91^{29} |
| Ethyl acetate | 0.00^{46} | 0.45^{46} | 0.45^{46} | -2.00^{29} |
| Ethylene glycol | 0.90^{51} | 0.52^{51} | 0.92^{51} | -3.21^{29} |
| Ethyl lactate | 0.69^{52} | 0.52^{52} | 0.82^{52} | -2.70 |
| Jojoba oil | -0.24 | 0.42 | 0.37 | -1.30 |
| Lactic acid | n/a | 0.40^{53} | 1.09^{53} | -3.48^{29} |
| Linseed oil | -0.27 | 0.80 | 0.42 | -1.43 |
| <i>n</i> -Heptane | 0.00^{52} | 0.00^{52} | -0.08^{52} | 0.12 |
| Palm oil | -0.12 | 1.22 | 0.21 | -0.79 |
| Palm kernel oil | n/a | 0.58 | 0.30 | -1.07 |
| Propanoic acid | n/a | n/a | n/a | -2.35^{29} |
| Soybean oil | -0.14 | 1.04 | 0.24 | -0.90 |
| TMO | 0.00^{49} | 0.77^{49} | 0.35^{49} | -1.23 |
| Waste palm oil | -0.26 | 1.32 | 0.40 | -1.37 |
| Waste soybean oil | -0.37 | 1.22 | 0.54 | -1.82 |

To this end, petroleum-based solvents, cyclohexane, and *n*-heptane as well as bio-derived solvents, palm and soybean oils gave good yields of 73% ± 1.02, 68% ± 0.78, 74% ± 0.87 and $65\% \pm 5.17$, respectively. Cyclohexane and *n*-heptane are produced from non-renewable feedstocks, but have marginally less harmful health, safety, and environmental profiles compared to other low polarity hydrocarbons such as pentane and hexane. However, the environmental impact can still be significant in the case of *n*-heptane.⁵⁷ Although *n*-heptane has a high ability to promote tautomerisation equilibrium (Table 1), making it a potential suitable solvent for Biginelli reaction, the yields obtained are lower than expected. This might be due to solubility problems often associated with a solvent of such low polarity. Palm and soybean oils provided marginally improved yield over the predicted yield (Fig. 1A) and palm oil demonstrated comparable yields to petrochemical solvents like cyclohexane. This due to the solubility of the starting materials, which depends on many factors including the solvents supramolecular complexity and their compositions.³⁰ Yara-Varón et al. showed various polarity products from lipophilic to hydrophilic were more soluble in sunflower oil than *n*-hexane by using the simulation of COSMO-RS.³⁰ Moreover, Li et al. reported a significant difference on the extraction yield of phenolic compounds from olive leaves using various refined and unrefined oils, which confirmed the solvation properties were dependent on oil composition.58

To investigate the greenness of palm oil, a larger scale (10-fold) reaction was also investigated, and this resulted in yields of $72\% \pm 0.06$ on the larger scale compared to $74\% \pm 0.87$ at the lab scale. These results demonstrate significant promise for the use of palm oil as a solvent for the Biginelli reaction at scale.

Comparing all virgin oils, the productivity of the reaction with soybean and palm kernel oils, as well as inedible oils



Fig. 1 (A) The relationship between reaction productivity and $ln(K_T)$ to give **4** by HCl catalysis. (B) Solvent dependent of the tautomerization equilibrium of **3**. AcOH = acetic acid; CO = castor oil; CPME = cyclopentyl methyl ether; DMF = *N*,*N*-dimethylformamide; EG = ethylene glycol; EtOAc = ethyl acetate; EtOH = ethanol; JO = jojoba oil; LcOH = lactic acid; LO = linseed oil; PcOH = propanoic acid; PKO = palm kernel oil; PO = palm oil; SO = soybean oil; TMO = 2,2,5,5-tetramethyloxolane; WPO = waste palm oil; WSO = waste soybean oil. Blue dots = this work, black dots = Clark *et al.*²⁹

were lower than those from palm oil due to their composition (Table S2[†]).⁵⁹⁻⁶⁴ Palm kernel oil consists of over 80% of saturated fatty acids but gave a much lower yield $(51\% \pm 1.81)$ than those from palm oil which contains about 50% saturated fatty acid due to most of fatty acid components of palm kernel oil are short-chain saturated fatty acids such as lauric and myristic acids that exhibit marginally greater polarity compared to palmitic acid of palm oil.59,65 Moreover, Soybean oil and the inedible oils contain more unsaturated fatty acids,60-65 which results in a higher dipolarity/polarizability (π^*) and lower yields than palm oil (Table S1, ESI[†]). In the case of castor oil, the productivity of the reaction was much lower than the predicted yield because the major constituent of its fatty acid profile is ricinoleic acid (approximately 90%), which is hydroxy monosaturated fatty acid. Castor oil was also highly viscous leading to poor mixing and potential diffusion limitations. The difference between the diketo and enol tautomers depends on π^* of solvents (Fig. 1B and Scheme S1 of the ESI[†]).²⁹ As such, this could be assumed that the best oil

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solvent for Biginelli reaction should contain less polar triglycerides with long-chain saturated fatty acids structures.

An increasing world population leads to greater demand for food. To overcome these challenges and avoid the "food vs. chemicals" debate, non-edible waste vegetable oils could be used as a sustainable solvent. The use of waste oils as reaction media for the Biginelli reaction demonstrated only moderate reaction yields for waste palm and soybean oils of $57\% \pm 0.74$ and $46\% \pm 0.32$, respectively. These yields were significantly lower than those from virgin oils but were in good agreement with that prediction based on the tautomerisation equilibrium relationship (Fig. 1A). The decomposition or contamination of vegetable oils is via complex series of reactions such as hydrolysis, oxidation, polymerisation, isomerisation, and cyclisation during frying which might affect their efficiency.^{54,66} To test if contaminants have a negative influence on yield in the Biginelli reaction, palm oil was spiked with 0.5 mmol of hydrolysis product *i.e.* glycerol and free fatty, acrylamide which forms during the frying of food,⁶⁷ and ethanol which can contaminate the oil during product recovery (Table S3, ESI[†]). All tested contaminants caused a change in polarity and thus resulted in lower yields. Waste soybean oil showed much lower productivity than waste palm oil due to its higher degradation rate during frying which affects its composition for use as a reaction medium. During frying, soybean oil was degraded at a much higher rate than palm oil due to its lower content of antioxidants and probably to the lack of tocotrienols.⁶⁸ Although waste vegetable oil has advantages in terms of food security and cheaper price compare to the virgin oil, virgin oil still proved to be a more suitable solvent for the Biginelli reaction.

The green credentials of the bio-based solvents and conventional solvents were assessed using the CHEM21 solvent selec-

 Table 2
 Simplified version of safety, health, and environmental scores, and overall ranking of solvents according to the CHEM21 solvent selection guide⁶⁹



^{*a*} Scores are based on the order of hazard statement: low hazard (1–3, green); medium hazard (4–6, yellow); high hazard (7–10, red). ^{*b*} Key ranking: Hazardous (one score of 8 or higher, or two scores between 7 and 10); Problematic (one score equal to 7, or two scores between 4 and 6); Recommended (all other solvents).

tion guide.⁶⁹ These were compared to bio-based solvents previously reported (*p*-cymene and ethyl lactate).^{28,29} The solvents were categorised by a three-tiered assessment of safety, health, and environmental impact (SH&E), each scored from 1-10, representing the ascending order of hazard (Table 2). Several bio-based solvents such as TMO, virgin oils and waste oils were not been listed by the original CHEM21 report, but they could be assigned the SH&E scores by applying the physical data and hazard statements extracted from Safety Data Sheets.⁶⁹ Overall, most of the solvents represent a problematic ranking except for DMF which is ranked as hazardous. In addition, p-cymene, TMO, and waste oils have a health score of 5 by default as they are yet to be REACH registered. In case of virgin vegetable oils they have been exempted for registration according to REACH Annex V.⁷⁰ They are better than the case of ethyl lactate which has a problematic health score based on the hazard statements in the GHS/CLP system (H318 and H335).⁶⁹ Vegetable oils have a better safety score than petroleum-based solvents such as cyclohexane and *n*-heptane, as well as bio-based solvent *p*-cymene due to the high flash point of vegetable oils that represents their less flammable. However, vegetable oils are ranked as problematic due to the high boiling point (received a red shaded environmental score of at least 7). This is for the perspective of the pharmaceutical industry that the need for an energy-intensive consumption for solvent removal or product drying for non-volatile solvents.⁶⁹ However, proposed method in this work avoids the need for evaporation of the oil, thereby reducing the environmental impact and energy demand of the process.

Unlike other solvents, vegetable oil was easily recovered in high yields from the reaction mixture with no significant changes to the chemical composition or solvent properties after the first reuse (Table S4, ESI[†]). Palm oil was simply separated from the aqueous washing due to its insolubility and removing trace amount of water by anhydrous Na₂SO₄. The recover palm oil was reused in another four consecutive reac-



Fig. 2 Reusability study for palm oil. Reaction conditions: the reactions were carried out with urea (1, 5 mmol), benzaldehyde (2, 5 mmol), methyl 3-oxobutanoate (3, 7.5 mmol) and HCl (10 mol%) in palm oil at 75 °C for 3 h.

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tions (Fig. 2). Interestingly, the results shows that the yields of the product slightly decreased from the first to the third cycles then remained consistent until the fifth cycle but demonstrated good yields (57%) that were comparable to the yields from waste palm oil. The decrease in the yield may be due to the increase of some minor polar compounds or small traces of ethanol (NMR spectrum and Table S3, ESI[†]) during the washing process that increase the polarity of palm oil, which affects the ability to promote the tautomerisation equilibrium. The yields maintained from the third cycle due to no further increase in polar compounds. This trend is comparable with the previous experiments where the total amount of polar compounds slightly increased from the first to the third consecutive frying cycles and then retained until the sixth consecutive cycle.⁷¹ As such, further work needs to focus on improving the recycling method. In addition, cyclohexane presented high product yields, however the solvent was crucially unable to be recovered and recycled in this reaction due to the solvent forming a single phase during aqueous washing, that could not be separated. This is potentially due to ethanol and unreacted starting materials enhance the solubility of cyclohexane in the aqueous phase. They could interact with water by hydrogen-bonding which interrupts the hydrogen-bonded network of water and allows water structural more freedom that enhances the solubility of hydrocarbon such as cyclohexane.⁷² Moreover, previous studies of bio-based solvents such as *p*-cymene and ethyl lactate did not demonstrate any recycling of the solvents.28,29

To evaluate the greenness of utilisation of palm oil in the one-pot multicomponent Biginelli reaction and comparison with two literature bio-based solvents (*p*-cymene and ethyl lactate) shown in Scheme 2, the green metrics calculations



Scheme 2 Processes A-C for green metrics evaluation.

Table 3 Green metrics (PMI, E-factor, SI, and WI) for processes A-C



were conducted which included process mass intensity (PMI), E-factor (E), solvent intensity (SI), and water intensity (WI) (Table 3) (see ESI[†] for the definition of metrics and calculations).^{73,74} Calculations of these green metrics enable us to simply compare the environmental effect of each synthetic methodology. Overall, processes A and C (Scheme 2 and Table 3) exhibit significantly better PMI, E-factor, SI and WI than process B (ethyl lactate). Process C1 (palm oil) was the best for all calculated green metrics. PMI and E-factor of process A (42 and 41), C1 (35 and 34), C2 (44 and 43), and C3 (38 and 37) are much better compared to process B (1758 and 1757). The evaluation of solvent intensity (SI) and water intensity (SI) showed that large excess of solvent and water were used in process B (1591 and 164) compared to process A (31 and 8), C1 (25 and 9), C2 (31 and 10), and C3 (28 and 8). Surprisingly, process C2 that using waste palm oil that gave a lower yield (57%) than process A using p-cymene (66%) but exhibits comparable results in all green metrics. The utilisation of cyclohexane as a solvent in process C3 shows comparable green metrics to process C1 that using palm oil as a solvent but still faces the problem as it is a non-renewable petroleum-based solvent that cannot be reused or recycled utilising the current work-up methods. Although process A (p-cymene) exhibits comparable metrics to process C1 (palm oil), it suffers in terms of large-scale availability and cost as there are insufficient sources to meet global demand.^{75,76}

To further explore the scope and possible limitations of palm oil as renewable alternative solvents, additional Biginelli reactions were carried out using a range of different substrates (Fig. 3). The solvent cyclohexane and *p*-cymene were tested alongside the palm oil to give a benchmark for yields achieved using a petroleum-based solvent and bio-based solvent from



Fig. 3 Substrate scope of the Biginelli reaction in palm oil and cyclohexane. Reaction conditions: the reactions were carried out with (thio) urea (1, 5 mmol), aromatic aldehydes (2, 5 mmol), β -keto esters (3, 7.5 mmol) and HCl (10 mol%) in palm oil or *p*-cymene or cyclohexane at 75 °C for 3 h. ^a NMR yields.

previous reported in the literature. In the case of using urea in palm oil, the electronic effect of the aromatic ring substitute 2 influence on the reaction yield. The substrate of aromatic aldehydes with strong electron-withdrawing groups (**4c** and **4f**) afforded high yields (69 and 85%) due to their more reactivity. The aromatic with no substitute (**4a** and **4d**) slightly reduced the reaction yields (73% and 69%). While the substrate with electron-donating groups (**4b** and **4e**) was found to be less reac-

tive and provided lower yields (50% and 62%). These results contradicted with those of Xu and co-workers who demonstrated that the aromatic aldehyde substrates with strong electron-withdrawing groups were less reactive, however this was due to the steric effect with the hindered chiral primary amine catalyst.¹⁸ In the case of thiourea, the results showed a similar trends to the urea and previous reports that electron-withdrawing groups in aldehyde (4i and 4l) promote the formation of products with good yield (85% and 57%), while aldehyde with the electron-donating groups (4h and 4k) afforded lower yields (32%).²⁸ The productivity of using thiourea was lower than urea and is in agreement with the previous experiments.⁷⁷ However, in the case of the use of thiourea and 4-nitrobenzaldehyde, the products were obtained as orange viscous oil that unable to purify by simple crystallisation, so other purification techniques were needed to obtain pure product such as column chromatography. Interestingly, the performance of palm oil was comparable to cyclohexane under the conditions tested. In many cases, results showed comparable (4a, 4b, 4f, 4g, 4i, and 4k) or even superior (4c, 4d, 4e, and 4j) reaction yields using palm oil as a solvent compared to cyclohexane. Compared to the bio-based solvent, p-cymene, palm oil demonstrated superior reaction yields for all substrates. These encouraging results suggest that vegetable oils and in particular, palm oil is suitable for one-pot multicomponent Biginelli reaction. Virgin oil and even waste oils have proven to be a better solvent for the Biginelli reaction compared to other biobased solvents such as ethyl lactate.

Although palm oil has shown to be a promising alternative solvent, there is controversy regarding palm oil plantations and their environmental impacts, such as deforestation, loss of habitat, water and air pollutions, and forest fires due to the rapidly increasing global demand.78-81 However, comparing with other oil crops, palm oil is a highly productive crop which has the highest production yield enabling optimum utilisation of land to supply the highest amount of oil for food and nonfood applications.^{78,82} Moreover, there are many sustainable developments being implemented on palm oil plantations resolving issues around this crop including establishment of the Roundtable on Sustainable Palm Oil (RSPO) to promote the encourage companies to use Certified Sustainable Palm products Oil (CSPO) in their for environmental protection.^{78,79,83-89} and some NGOs are promoting the elimination of incentives for palm oil production employing unsustainable methods and practices.⁸³ Recently, several possible solutions to improve existing palm oil industry processes with Industry 4.0 technologies.78

Conclusions

This work reports the first application of vegetable oil as a highly effective solvent for one-pot multicomponent Biginelli reactions. The bio-based oils offer several advantages over petrochemical counterparts including biodegradability, worldwide availability, low cost, renewability, and great ecological

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aspects (i.e., low ecotoxicity and low toxicity toward humans). Palm oil can deliver comparable reaction yields in Biginelli reactions to those obtained in a petroleum-based solvent such as cyclohexane and is also better than those previous biobased solvents such as p-cymene. Palm oil can be used as an efficient and practical alternative to petroleum-based solvent to promote the quantity of available enol in the reaction mixture and its dissolving power. In addition, palm oil could be used as a more sustainable solvent due to its easy recovery and reusability. Scope of the substrate has been also performed, demonstrating the broader capacity and limitation of palm oil as a solvent in the Biginelli reaction. The results described herein open a new possibility for chemists to improve the green credentials of multicomponent reactions with a safer and cheaper renewable alternative to petroleum derived solvents. In terms of green chemistry metrics analysis, the utilisation of palm oil as reaction media for the Biginelli reaction showed to be favourable compared with cyclohexane and two previous reports using bio-based solvents, p-cymene and ethyl lactate, for its high synthetic efficiency and low waste generation.

Experimental

Unless otherwise stated, all reagents and solvents were used as obtained from commercial sources without purification. Palm and soybean oils were obtained locally. Waste cooking oils were collected from a local kitchen household. 2,2,5,5-tetramethyloxolane (TMO) was synthesised and purified as previously reported.⁴⁹ NMR spectra were recorded on a Bruker Avance Neo 400 MHz in DMSO- d_6 . UV vis. Spectra were recorded on a Cary 60 UV-Vis spectrophotometer in quartz cuvettes at 25 °C.

Determination of the Kamlet-Taft parameters

The determination of the π^* Kamlet–Taft parameter was performed in the same manner as previously described with *N*,*N*diethyl-4-nitroaniline.⁴⁹ Similarly, values of β were obtained by calculation from the maxima wavelengths of 4-nitroaniline.⁵² Calculation of α values require spectroscopic data from Dimroth-Reichardt's betaine dye and the contributions of π^* .⁹⁰

Representative experimental procedure for biginelli reaction

Compound 4 was prepared by the method previously reported by Clark *et al.*²⁹ Briefly, in a 50 mL round bottom flask located with urea (0.3 g, 5.0 mmol) and the chosen solvent (4 mL) was added. Waste cooking oil was collected from local households in Khon Kaen. After filtering to remove crude solid impurities, waste cooking oils were used without any further treatment. The mixture was heated to 75 °C until reaching thermal equilibrium. Then, benzaldehyde (0.51 mL, 5.0 mmol), methyl 3-oxobutanoate (0.81 mL, 7.5 mmol), and finally concentrated hydrochloric acid (10 mol%) were added to the mixture. The reaction was stirred at 300 rpm for a duration of 3 h and then was cooled to ambient temperature slowly. Finally, the resultant solid was separated from the reaction mixture by filtration, washed with 50% aqueous ethanol, and recrystallised from ethanol to give a white crystalline solid. Palm oil was recovered by separating out the aqueous ethanol layer using separatory funnel. The oil was washed a further two time with an equal quantity of distilled water, prior to being dried with anhydrous Na_2SO_4 .

Conflicts of interest

There are no conflicts to declare.

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