Chapter VI

Synthesis of some cinnamic ester derivatives from Oxalis pes-caprae (Bermuda Buttercup) using immobilized Bronsted dual acidic ionic liquid and microwaves along with other conventional methodologies

Introduction and Literature Review:

Cinnamic ester derivatives are widely distributed in plant kingdom and are known to exhibit a wide range of pharmacological activities such as anti-oxidative, cytotoxic, antimicrobial and antiviral. Besides the biological activity, cinnamates have been used as intermediates for a large variety of heterocyclic compounds, such as benzofuran, 2-styryl chromones, styryl pyrazoles, stilbenes, synthesis of aziridins, dihydrocoumarin, coumarin, chalcones, β-truxinic acid, ducarmycin, etc.

(E)-Cinnamic esters are immensely important organic compounds due to their application in a wide range of industrial products such as plasticizers, graphics, lubricants, flavours, perfumes and cosmetics. For example; (E)-2-ethylhexyl-4-methoxycinnamate is a UV absorbing sunscreen agent and a common ingredient in most of the new sunscreen lotions and many other cosmetic formulations.

\[
\text{(E)-2-Ethylhexyl 4-methoxycinnamate}
\]

Lignin is the second most abundant natural product on the earth which consists of vast array of cinnamates. There are many cinnamate derivatives present in nature which are used for the inhibitions of germination of the plants, serve both as an antioxidant as well as flavouring agent, are reported to possess anti-inflammatory, anti-cancer, antifungal and plant growth inhibitor activity as well as used as anti-rheumatic drug for relieving lumbago and pain in the knees, potent inhibitor of the 17 β-hydroxysteroid dehydrogenase enzymes involved in diseases such as prostatic and breast cancer, Alzheimer disease and benign prostatic hyperplasia.

Bermuda buttercup, also known as Oxalis pes-caprae L. (Oxalidaceae), a native plant of South Africa, is a very successful aggressive colonized invasive weed and can maintain high level of allelopathy. One of the most useful aspects of allelopathy in manipulated
ecosystems is its role in agriculture. In the search for new potential allelochemicals from plants, recent studies made by DellaGreca et al. have led to the isolation of some new aryl and benzyl cinnamic ester derivatives (I-VII), from leaves and twigs of Bermuda buttercup.

\[
\begin{align*}
I, R = R^3 = CH_3; & \quad II, R = CH_3, R^1 = H; \quad III, R = R^3 = H; \\
IV, R = R^3 = CH_3, R^1 = H, R^2 = OCH_3; & \quad V, R = R^3 = H, R^2 = OCH_3, R^1 = CH_3; \\
VI, R = R^3 = CH_3, R^1 = COCH_3, R^2 = OCII, & \quad VII, R = R^1 = R^2 = R^3 = H.
\end{align*}
\]

There is a wide range of methods available for ester synthesis such as Knoevenagel-Doebner reaction, microwave assisted synthesis, PASP synthesis, carbene mediated extended umpolung reaction, Pd-catalysed Heck reaction, Ru-catalysed oxidation-Wittig reaction, Bronsted acid catalysed, Wittig reaction, Transesterification, using o-nitrophenyl sulfoxides as a precursor, the oxidative esterification of activated alcohols and aldehyde in presence of cyanide and MnO\textsubscript{2} or Ag\textsubscript{2}O, redox esterification, esterification using water tolerant ZrOCl\textsubscript{2}.8H\textsubscript{2}O, HfOCl\textsubscript{2}.8H\textsubscript{2}O as catalyst & Heteropolyacid, etc. Consequently, a great variety of powerful methods for their preparation have been developed, mostly being E-stereoselective, and many use aldehydes as precursors.

But only a few procedures are known which have been used to prepare aryl cinnamates. However, most of the reported methods require strong acids like sulfuric acid, hydrochloric acid, and toxic chemicals such as dimethyl sulfate, methyl iodide and diazomethane, which are environmentally hazardous, mostly non catalytic, lacking atom economy, require harsh reaction conditions and hence unacceptable. Therefore, it is still a challenge to improve known methods and develop new procedures which provide good yield, ensure operational simplicity and mild conditions that will allow the use of sensitive substrates.

Although, Rao et al. have described the synthesis of most of these cinnamate derivatives using DCC/DMAP for the esterification reaction. But their procedure resulted into very poor yields of the final products (45-65%).
Recently, Waghmare et al.\textsuperscript{[49]} also prepared a few such aryl and benzyl cinnamates using water mediated Wittig reaction of various $\alpha$-bromoesters with aldehydes. Major drawback of this method lies in the use of $\alpha$-bromoesters which are well known to be the lachrymatory chemicals and are highly toxic in nature.

Herein we report a novel, simple, safe and highly efficient synthesis of a few cinnamates (Figure 27) utilizing immobilised Brønsted dual acidic ionic liquid SiO$_2$-\textsuperscript{[PimSO$_3$H]H$_2$SO$_4$} (15) as a reusable catalyst for esterification reaction, under MWI conditions.

These have been stated to show high inhibitory effect on germination of seeds, greater phytotoxic activities on the root length and reduction in the shoot length of \textit{Lactuca sativa}, even greater than standard herbicide pendimethalin. To the best of our knowledge no such
Results and Discussion:

Retrosynthetic analysis of these cinnamate derivatives has been shown in Scheme 27. Detailed study of the described scheme revealed that 3,4,5-trimethoxybenzaldehyde (155) could well act as the common starting material for preparing all the three compounds.

To start with the synthesis of compound 159, modified Wittig reaction via a known procedure\textsuperscript{150} was carried out taking 3,4,5-trimethoxybenzaldehyde (155) as the starting material to give (E)-ethyl 3,4,5-trimethoxycinnamate (157) in 90% yield with high $E$-selectivity (Scheme 28). The $^1$H NMR of the compound 157 showed appearance of a peaks at $\delta$ 1.27 (t, 3H, $J = 7.2$ Hz, -OCH$_2$CH$_3$), 3.77 (s, 3H, -OCOCH$_3$), 3.80 (s, 6H, 2x-OCH$_3$), 4.17 (q, 2x-H) and 7.27 (s, 6H, -OCH$_3$), 7.30 (s, 6H, -OCH$_3$).
2H, J = 7.2 Hz, -OCH2CH3), 6.20 (d, 1H, -CH=CH-C=O, J = 15.9 Hz.), 6.64 (s, 2H, ArH), 7.48 (d, 1H, -CH=CH-C=O, J = 15.9 Hz). Higher values of coupling constant (J values) confirm the E-selectivity obtained during the course of the reaction. Also, a peak corresponding to aldehydic proton disappears in the product. Similarly, in 13C NMR spectrum peaks corresponding to –C=C– as well as –C=O of ester group appear hence confirming the formation of the compound 157.

![Scheme 28](image)

Scheme 28. (a) K2CO3, H2O, 70 °C, 4 h; (b) EtOH, aqueous KOH, reflux, 2.5 h; (c) 1,2-Ethane diol (34), catalyst 15, MWI, 70-75 °C, 6 min.

Further, the compound 157 prepared above was hydrolysed by refluxing the ethanolic solution of ester with aqueous KOH to give compound 158 in 98% yield.\[51] Formation of 3,4,5-trimethoxycinnamic acid (158) was confirmed through the spectroscopic studies. The 1H NMR of the compound showed appearance of a peak at $\delta$ 3.83 (s, 9H, 3×-OCH3), 6.29 (d, 1H, -CH=CH-C=O, J = 15.9 Hz.), 6.71 (s, 2H, ArH), 7.64 (d, 1H, -CH=CH-C=O, J = 15.9 Hz). Similarly, in 13C NMR spectrum a peak at $\delta$ 171.8 corresponding to –COOH appears hence confirming the formation of the acid 158.

Finally, the compound 158 (2 mmol) was esterified with 1,2-ethane diol (34, 2.2 mmol) using immobilized Bronsted dual acidic ionic liquid SiO2-[PimSO3H]HSO4 (15), under MWI conditions to obtain (E)-2-hydroxyethyl 3,4,5-trimethoxycinnamate (159) in 81% yield. Successful formation of cinnamate 159 was confirmed through the spectroscopic studies. The 1H NMR of the compound showed appearance of a peak at $\delta$ 3.77 (s, 3H, -OCH3), 3.80 (s, 6H, 2×-OCH3), 4.05 (t, 2H, J = 7.2 Hz, -OCH2CH2O-), 4.17 (t, 2H, J = 7.2 Hz, -OCH2CH3).
Hz, -OCH₂CH₂O-), 6.20 (d, 1H, -CH=CH-C=O, J = 15.9 Hz.), 6.64 (s, 2H, ArH), 7.48 (d, 1H, -CH=CH-C=O, J = 15.9 Hz). Similarly, in ¹³C NMR spectrum a peak at δ 67.5 corresponding to -OCH₂CH₂O- appears hence confirming the formation of the cinnamate 5.

Cinnamate 160 was prepared by acylation of compound 159 using immobilized Bronsted dual acidic ionic liquid 15, under MWI conditions in 92% yield (Scheme 29). The ¹H NMR of the compound 160 showed appearance of a peak at δ 2.10 (s, 3H, -COCH₃), 3.83 (s, 9H, 3x-OC₃H₃), 4.52-4.75 (m, 4H, -OCH₂CH₂O-), 6.29 (d, 1H, -CH=CH-C=O, J = 15.9 Hz.), 6.71 (s, 2H, ArH), 7.64 (d, 1H, -CH=CH-C=O, J = 15.9 Hz). Similarly, in ¹³C NMR spectrum an additional peak at δ 170.0 along with 166.4 appears corresponding to newly incorporated carbonyl carbon from acyl group.

Scheme 29. (d) Ac₂O, catalyst 15, MWI, 70-75 °C, 4 min.

Cinnamic acid derivative 158 was converted to acid chloride 161 by treatment with SOCl₂ in 97% yield,¹⁵² which was further esterified with resorcinol to obtain cinnamate 162 in 84% yield (Scheme 30).

Scheme 30. (e) SOCl₂, reflux; (f) Resorcinol, catalyst 15, MWI, 70-75 °C, 9 min.
Formation of acid chloride 161 was confirmed through its $^{13}$C NMR spectrum as the peak corresponding to the $\text{--COOH}$ at $\delta$ 171.8 disappears in the product and a new peak corresponding to $\text{--COCl}$ at $\delta$ 163.8 appears. Otherwise, the $^1$H NMR spectrum could not clearly differentiate between compound 158 and 161.

Then, esterification of the above formed acid chloride 161 (1 mmol) was carried out with resorcinol (1.1 mmol) using immobilized Bronsted dual acidic ionic liquid 15, under MWI conditions to give the final product ($E$)-3-hydroxyphenyl 3,4,5-trimethoxycinnamate (162). Its $^1$H NMR spectrum showed peaks at $\delta$ 3.83 (s, 9H, $3\times$-OCH$_3$), 6.29 (d, 1H, $-\text{CH=CH-C=O}$, $J$ = 15.9 Hz.), 6.66-6.79 (m, 3H, ArH), 6.81 (s, 2H, ArH), 7.18 (m, 1H, ArH), 7.64 (d, 1H, $-\text{CH=CH-C=O}$, $J$ = 15.9 Hz). Similarly, in $^{13}$C NMR spectrum additional peaks in the aromatic region are seen which confirm the successful conversion of compound 161 to cinnamate 162 in 84% yield.

In conclusion, we have achieved an efficient and mild synthesis of three naturally occurring cinnamic ester derivatives (159, 160 and 162) isolated from methanol extract of leaves and twigs of Oxalis pes-caprae, which show inhibitory effects on the germination and growth of Lactuca sativa. 3,4,5-Trimethoxybenzaldehyde (155) has been used as the starting material. The key step in the synthesis involved the microwave induced esterification reaction using immobilized Bronsted dual acidic ionic liquid SiO$_2$-[PimSO$_3$H]HSO$_4$ (15) to afford the final compounds (159, 160 and 162).

**EXPERIMENTAL:**

($E$)-Ethyl 3,4,5-trimethoxycinnamate (157):
A mixture of 3,4,5-trimethoxybenzaldehyde (155, 4.0 g, 20.4 mmol), anhydrous K$_2$CO$_3$ (5.52 g, 40 mmol), triethyl phosphonoacetate (156, 4.8 ml, 24 mmol) and water (4 ml) was stirred at 70 °C for 4 h. The reaction mixture was poured into water (20 ml) and extracted with DCM (3×20 ml). The organic layer was washed with water and brine, dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. Recrystallization of the residue from n-hexane yielded the product 157 as colourless needles in 90% yield (4.90 g). M.pt. = 68-69 °C.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.27 (t, 3H, $J$ = 7.2 Hz, $\text{-OCH$_2$CH$_3$}$), 3.77 (s, 3H, $\text{-OCH$_3$}$), 3.80 (s, 6H, $2\times$-$\text{OCH$_3$}$), 4.17 (q, 2H, $J$ = 7.2 Hz, $\text{-OCH$_2$CH$_3$}$), 6.20 (d, 1H, $\text{-CH=CH-C=O}$, $J$ = 15.9 Hz.), 6.64 (s, 2H, ArH), 7.48 (d, 1H, $\text{-CH=CH-C=O}$, $J$ = 15.9 Hz).
\(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 14.5, 56.0, 60.2, 60.7, 105.4, 117.5, 129.9, 144.5, 153.5, 166.4.

IR (cm\(^{-1}\), neat): \(v\) 1117, 1242, 1450, 1580, 1631, 1700.

\((E)-3,4,5\)-Trimethoxycinnamic acid (158):
To a solution of ester (157, 2.55 g, 9.6 mmol) in ethanol (90 ml) was added drop wise a solution of KOH (1.14 g, 12.8 mmol) in water (12 ml). The reaction mixture was refluxed for 2.5 h, cooled and solvent was evaporated under vacuum. The crude material thus obtained was taken up in diethyl ether (120 ml), washed with 10% HCl (2 \(\times\) 20 ml), brine and then dried over anhydrous Na\(_2\)SO\(_4\). Solvent was evaporated under vacuum to obtain the pure product 158 in 98% yield (2.23 g). Colourless solid. M.pt. = 125-127 °C.

\(^{1}\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 3.83 (s, 9H, 3\(\times\)-OCH\(_3\)), 6.29 (d, 1H, -CH=CH-C=O, \(J\) = 15.9 Hz), 6.71 (s, 2H, ArH), 7.64 (d, 1H, -C//=CH-C=O, \(J\) = 15.9 Hz).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 56.2, 60.9, 105.6, 116.3, 129.4, 147.0, 153.5, 171.8.

IR (cm\(^{-1}\), neat): \(v\) 1114, 1243, 1452, 1580, 1695, 3200.

\((E)-2\)-Hydroxyethyl 3,4,5-trimethoxycinnamate (159):
A mixture of acid (158, 0.476 g, 2.0 mmol), 1,2-ethanediol (34, 0.136 g, 2.2 mmol) and catalyst [SiO\(_2\)-PimSO\(_3\)H][HSO\(_4\)] (15, 0.220 g, 5 mol%, 0.1 mmol) was taken in an open Erlenmeyer flask (50 ml) and covered with clinching foil. It was then exposed to microwave radiations in a commercial microwave oven having 50:10 sec heating:cooking cycle each at 70-75 °C (80% power level) for 6 min. The completion of reaction was monitored using TLC. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (3\(\times\)20 ml), filtered, washed with sodium bicarbonate, brine and dried over anhydrous Na\(_2\)SO\(_4\). Solvent was evaporated under reduced pressure to yield the crude product which was chromatographed using hexane:EtOAc (70:30) as the eluent to yield corresponding ester 159 in 81% yield (0.45 g). Colourless solid. M.pt. = 94-96 °C.

\(^{1}\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 3.77 (s, 3H, -OCH\(_3\)), 3.80 (s, 6H, 2\(\times\)-OCH\(_3\)), 4.05 (t, 2H, \(J\) = 7.2 Hz, -OCH\(_2\)CH\(_2\)O-), 4.17 (t, 2H, \(J\) = 7.2 Hz, -OCH\(_2\)CH\(_2\)OH), 6.20 (d, 1H, -CH=CH-C=O, \(J\) = 15.9 Hz), 6.64 (s, 2H, ArH), 7.48 (d, 1H, -CH=CH-C=O, \(J\) = 15.9 Hz).

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 56.0, 60.2, 60.7, 67.5, 105.4, 117.5, 129.9, 144.5, 153.5, 166.4.
Chapter VI

IR (cm\(^{-1}\), neat): \(v\) 1123, 1284, 1419, 1585, 1626, 3492.

MS m/z: \([M+1]^+ 283.1, [M+2]^+ 284.1\) (Calculated for C\(_{14}H_{18}O_6\) 282.1100).

(E)-2-Acetyylethyl 3,4,5-trimethoxycinnamate (160):
A mixture of (E)-2-hydroxyethyl 3,4,5-trimethoxycinnamate (159, 0.282 g, 1 mmol), acetic anhydride (61, 0.102 g, 1 mmol) and catalyst \([\text{SiO}_2-\text{PimS}_3\text{H}]\text{[HSO}_4\text{]}\) (15, 0.110 g, 5 mol%, 0.1 mmol) was taken in an open Erlenmeyer flask (50 ml) and covered with clinching foil. It was then exposed to microwave radiations in a commercial microwave oven having 50:10 sec heating:cooling cycle each at 70-75 °C (80% power level) for 4 min. The completion of reaction was monitored using TLC. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (3 x 10 ml), filtered, washed with sodium bicarbonate, brine and dried over anhydrous Na\(_2\)SO\(_4\). Evaporation of the solvent under reduced pressure gave the crude product which was chromatographed using hexane:EtOAc (70:30) as the eluent to yield corresponding ester 160 in 92% yield (0.29 g). Colourless solid. M.pt. = 94-96 °C.

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 2.10 (s, 3H, -CO\(\text{CH}_3\)), 3.83 (s, 9H, 3\times-OC\(\text{H}_3\)), 4.52-4.75 (m, 4H, -OCH\(_2\)CH\(_2\text{O}-\)), 6.29 (d, 1H, -CH=CH-C=O, \(J = 15.9\) Hz), 6.71 (s, 2H, ArH), 7.64 (d, 1H, -CH=CH-C=O, \(J = 15.9\) Hz).

\(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 20.5, 56.0, 60.2, 62.5, 67.5, 105.4, 117.5, 129.9, 144.5, 153.5, 166.4, 170.0.

IR (cm\(^{-1}\), neat): \(v\) 1120, 1244, 1503, 1580, 1690, 1739.

MS m/z: \([M+1]^+ 325.2, [M+2]^+ 326.2, [M+3]^+ 327.2\) (Calculated for C\(_{16}H_{20}O_7\) 324.1205).

(E)-3,4,5-Trimethoxycinnamoyl chloride (161):
A mixture of acid (158, 0.60 g, 2.5 mmol) and thionyl chloride (0.42 g, 3.5 mmol) was taken in a round-bottomed flask (50 ml) equipped with a stir bar. Bubbles evolved out from the light yellow solution immediately. The mixture was stirred at room temperature for 10 min and then heated under reflux for 30 min, during which time the mixture turned brown. Then the solution was heated up to 80 °C and stirred for 3 h. The excess thionyl chloride was removed by distillation to give the pure product 161 in 97% yield (0.62 g). Dark brown oil.
B.pt. = 375 °C.
(E)-3-Hydroxyphenyl 3,4,5-trimethoxy cinnamate (162):
A mixture of acid chloride (161, 0.256 g, 1 mmol), resorcinol (0.121 g, 1.1 mmol) and catalyst [SiO2-PimSO3H][HSO4] (15, 0.110 g, 5 mol%, 0.1 mmol) was taken in an open Erlenmeyer flask (50 ml) and covered with clinching foil. It was then exposed to microwave radiations in a commercial microwave oven having 50:10 sec heating:cooling cycle each at 70-75 °C (80% power level) for 9 min. The completion of reaction was monitored using TLC. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (3×10 ml), filtered, washed with sodium bicarbonate, brine and dried over anhydrous Na2SO4. Evaporation of the solvent under reduced pressure gave the crude product which was chromatographed using hexane:EtOAc (70:30) as the eluent to yield corresponding ester 162 in 84% yield (0.27 g). Colourless solid. M.pt = 118-120 °C.

\(^1\)H NMR (CDCl₃, 300 MHz): δ 3.83 (s, 9H, 3×-OCH₃), 6.29 (d, 1H, -CH=CH-C=O, J = 15.9 Hz.), 6.71 (s, 2H, ArH), 7.64 (d, 1H, -CH=CH-C=O, J = 15.9 Hz).

\(^13\)C NMR (CDCl₃, 75 MHz): δ 56.2, 60.9, 105.6, 116.3, 129.4, 147.0, 153.5, 163.8.

IR (cm⁻¹, neat): ν 1114, 1243, 1452, 1580, 1705, 2944.

SPECTROSCOPIC DATA:

(E)-2-Hydroxyethyl 3,4,5-trimethoxycinnamate (159):
Chapter VI

(E)-2-Acetyethyl 3,4,5-trimethoxycinnamate (160):
(E)-3-Hydroxyphenyl 3,4,5-trimethoxycinnamate (162):

![Chemical Structure Diagram]
Chapter VI
Chapter VI

REFERENCES:


