Synthesis of 4\textit{H}-chromene-3,4-dicarboxylate derivatives via an isocyanide-based one-pot three component reaction

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Received 18 January 2016; accepted (revised) 28 June 2016

An efficient one pot three-component reaction method has been developed for the synthesis of dialkyl-5,8-dihydro-6-hydroxy-5,8-dioxo-2-(alkyl/arylamino)-7-undecyl-4\textit{H}-chromene-3,4-dicarboxylate derivatives by the reaction of embelin, dialkylacetylenedicarboxylates and alkyl/aryl isocyanides. The method when applied to the synthesis of the title compounds give good yields at room temperature with easy reaction work-up. All the synthesized compounds are well characterized by physical and analytical spectral data (IR, \textit{\textsuperscript{1}H} and \textit{\textsuperscript{13}C} NMR, mass and elemental analyses).

Keywords: Embelin (2,5-dihydroxy-6-undecyl-1,4-benzoquinone), dialkylacetylenedicarboxylate, isocyanide

Embelin is a natural hydroxyl benzoquinone with alkyl substitution that is one of the main constituents of plant \textit{Embeliaribes} (family: Myrsinaceae). Embelin is reported to possess various biological activities including antimicrobial\textsuperscript{1,2}, hepatoprotective\textsuperscript{3}, analgesic, anti-inflammatory\textsuperscript{4}, anticonvulsant\textsuperscript{5}, cytotoxicity\textsuperscript{6}, anxiolytic\textsuperscript{7}, antifertility\textsuperscript{8}, etc. Embelin is also known for anti-tumor activity via inhibition of X-linked inhibitor of apoptosis protein (XIAP)\textsuperscript{9,10}. 2\textit{H}-Pyran-2-ones and their fused derivatives are well-represented structural units found in a variety of natural products\textsuperscript{11}, their synthetic analogs and many other compounds not having natural counterparts, but nevertheless in many cases exhibiting important biological activity. Furthermore, due to their multifunctional character they display a plethora of potential applications in organic synthesis\textsuperscript{12}. For example, a recent report by Lee \textit{et al.}\textsuperscript{13} shows a promising \textit{in vitro} anticancer activity for 6-substituted-4-amino-2\textit{H}-pyran-2-ones (APO) representing a simplified version of the tanshinactones, which were shown to be even more potent against the ER+ human breast cancer cell lines than tamoxifen citrate. In 2009 Cardellina II and coworkers isolated\textsuperscript{14} (\textit{R})-rugulactone from the plant \textit{Cryptocarya rugulosa}, possessing 5, 6-dihydropyran-2-one skeleton and inhibiting the nuclear factor \textit{\textalpha}B activation pathway that is found to be active in many types of cancers.

Results and Discussion
In continuation of our earlier work on embelin\textsuperscript{15-18} we wish to report a novel MCR approach for the preparation of highly functionalized 4\textit{H}-chromene derivatives. In our approach, three-component condensation reaction between 2,5-dihydroxy-6-undecyl-1,4-benzoquinone, diethylacetylenedicarboxylates and isocyanides led to the formation of dialkyl-5,8-dihydro-6-hydroxy-5,8-dioxo-2-(alkyl/arylamino)-7-undecyl-4\textit{H}-chromene-3,4-dicarboxylates \textit{4}. The structures of these compounds were identified by elemental analyses, IR, \textit{\textsuperscript{1}H} and \textit{\textsuperscript{13}C} NMR and mass spectra.

The one-pot three-component condensation reaction between 2,5-dihydroxy-6-undecyl-1,4-benzoquinone \textit{1}, diethylacetylenedicarboxylates \textit{2} and isocyanides \textit{3} in acetonitrile at RT resulted in the formation of dialkyl-5,8-dihydro-6-hydroxy-5,8-dioxo-2-(alkyl/arylamino)-7-undecyl-4\textit{H}-chromene-3,4-dicarboxylates \textit{4}, in moderate to good yields (Scheme I).

A plausible mechanism for the formation of the products is proposed in Scheme II. The initial Michael type of reaction between isocyanide and dialkylacetylenedicarboxylate led to the formation of intermediate \textit{5}. The intermediate \textit{5} on reaction with 2,5-dihydroxy-6-undecyl-1,4-benzoquinone \textit{1} leads to formation of another intermediate keteneimine \textit{6}. The intermediate \textit{6} on intramolecular cyclization gave the desired product \textit{4}. The \textit{\textsuperscript{1}H} NMR spectrum of \textit{4a} exhibited a triplet for CH\textsubscript{3} at \(\delta\) 0.85, a multiplet for-(CH\textsubscript{2})\textsubscript{9} at \(\delta\) 1.23-1.26, a multiplet for the
cyclohexyl ring at δ 1.33-1.90, a triplet for allylic CH₂ at δ 2.30, two singlets for two methoxy groups at δ 3.57 and 3.63, a singlet for CH-NH of cyclohexyrlring at δ 3.73, a singlet for CH-CO₂Me at δ 4.45 and a broad singlet for NH group at δ 11.15. The proton-decoupled ¹³C NMR spectrum of 4a showed 26 distinct signals which confirm the proposed structure. The quinone carbonyl appeared down field at δ 178.9 and 181.0 respectively. In the mass spectra of these compounds the molecular ion peaks have been observed at appropriate m/z values.

**Experimental Section**

**General procedure for the synthesis of 14-aryl-14H-7-oxa-benzo[a]naphthacene-8,13-dione, 4**

A mixture of 2,5-dihydroxy-6-undecyl-1,4-benzoquinone (1 mmol), diethyacetylene dicarboxylate (1 mmol) and isocyanides (1 mmol) was stirred in
CH$_3$CN (5 mL) at RT for 24 h. The progress of the reaction was monitored by TLC (20% methanol in chloroform). After completion of the reaction, the separated solid was filtered off and washed with hexane. The crude product was purified by recrystallization from ethanol to give 4.

**Diethyl-2-(cyclohexylamino)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3,4-dicarboxylate, 4a:** Yield 90%. m.p.108-109°C. IR (KBr): 3268 (N-H), 2952 (C-H), 1750 (C=O), 1678 (s, 1H, CH-NH), 4.15 (m, 6H, 2CH$_2$). 4.23 (m, 4H, 2OCH$_2$), 4.44 (s, 1H, CH-COOEt), 11.30 (bs, 1H, NH). Anal. Calcd for C$_{32}$H$_{47}$NO$_5$: C, 66.99; H, 8.26; N, 2.44. Found: C, 66.92; H, 8.23; N, 2.40%.

**Diethyl-2-(tert-butylamino)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3,4-dicarboxylate, 4b:** Yield 88%. m.p.120-121°C. IR (KBr): 3440 (N-H), 2952 (C-H), 1750 (C=O), 1672 cm$^{-1}$ (C=O); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 0.85 (t, 3H, CH$_3$), 1.25-1.29 (m, 18H, -(CH$_2$)$_{17}$), 1.32 (s, 9H, t-Bu), 11.15 (bs, 1H, NH). Anal. Calcd for C$_{32}$H$_{47}$NO$_5$: C, 64.72; H, 2.7; N, 7.95. Found: C, 64.70; H, 2.65; N, 2.64%.

**Diethyl-2-(cyclohexylamino)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3,4-dicarboxylate, 4c:** Yield 92%. m.p.129-30°C. IR (KBr): 3316 (N-H), 2952 (C-H), 1750 (C=O), 1678 cm$^{-1}$ (C=O); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 0.85 (t, 3H, CH$_3$), 1.25-1.29 (m, 18H, -(CH$_2$)$_{17}$), 2.12 (s, 6H, 2CH$_3$), 2.44 (t, 2H, Allylic CH$_2$), 3.68 (s, 3H, OCH$_3$), 3.72 (s, 3H, OCH$_3$), 4.64 (s, 1H, CH-COOOMe), 7.14 (m, 3H, Aromatic). Anal. Calcd for C$_{32}$H$_{47}$NO$_5$: C, 67.71; H, 7.28; N, 2.47. Found: C, 67.74; H, 7.23; N, 2.44%.

**Diethyl-2-(cyclohexylamino)-5,8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3,4-dicarboxylate, 4d:** Yield 92%. m.p.116-17°C. IR (KBr): 3419 (N-H), 2931 (C-H), 1726 (C=O), 1676 cm$^{-1}$ (C=O); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 0.86 (t, 3H, CH$_3$), 1.25-1.29 (m, 18H, -(CH$_2$)$_{17}$), 1.32-1.95 (m, 10H, 5CH$_2$ of cyclohexyl), 2.38 (t, 2H, Allylic CH$_2$), 3.75 (s, 1H, CH-NH), 4.15 (m, 6H, 2CH$_2$), 4.23 (m, 4H, 2OCH$_2$), 4.44 (s, 1H, CH-COOEt), 11.30 (bs, 1H, NH). Anal. Calcd for C$_{32}$H$_{47}$NO$_5$: C, 67.63; H, 8.85; N, 2.32. Found: C, 67.67; H, 8.81; N, 2.28%.
Di-tert-butyl-2-(2,6-dimethylphenylamino)-5, 8-dihydro-6-hydroxy-5,8-dioxo-7-undecyl-4H-chromene-3,4-dicarboxylate, 4i: Yield 89%. m.p. 113-14°C. IR (KBr): 3435 (N-H), 2926 (C-H), 1740 (C=O), 1668 cm$^{-1}$ (C=O); $^{1}H$ NMR (400 MHz, DMSO-$d_{6}$): δ 0.85 (t, 3H, CH$_{3}$), 1.23-1.27 (m, 18H, -(CH$_{2}$)$_{9}$-), 1.40 (s, 9H, -C(CH$_{3}$)$_{3}$), 1.48 (s, 9H, -C(CH$_{3}$)$_{3}$), 2.06 (s, 6H, 2CH$_{3}$), 2.34 (t, 2H, Allylic CH$_{2}$), 4.55 (s, 1H, CH-COO$_{t}$Bu), 7.26 (m, 3H, Aromatic), 10.82 (bs, 1H, NH). Anal. Calcd for C$_{38}$H$_{53}$NO$_{8}$: C, 70.02; H, 8.20; N, 2.15. Found: C, 69.96; H, 8.16; N, 2.10%.

Conclusion
An efficient three component one-pot method for the synthesis of dialkyl-5,8-dihydro-6-hydroxy-5,8-dioxo-2-(alkyl/arylamino)-7-undecyl-4H-chromene-3,4-dicarboxylates derivatives has been achieved via cyclocondensation of embelin, diethyl acetylene dicarboxylate and isocyanide in acetonitrile. This method has the advantage of being single-step, having easy work-up, milder reaction conditions, and good yields.

Acknowledgments
The authors acknowledge financial assistance from the Science and Engineering Research Board (SERB) and the Department of Science and Technology (DST), New Delhi.

References