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New chemical access for pyran core embedded derivatives from bisalkenylated 1,3-diketones and 1,3-diketoesters via tandem C-dealkenylation and cyclization ☆

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ABSTRACT

New chemical access has been developed for the synthesis of pyran core embedded derivatives from 1,3-diketones and 1,3-diketoesters, in which the active methylene group of 1,3-diketone or 1,3-diketoester was alkenylated with three equivalents of alkenyl bromides in presence NaH to give bisalkenyl 1,3-diketones or 1,3-diketoesters and the resultant bisalkenyl 1,3-diketones or 1,3-diketoesters were reacted with $AlCl_3$ at room temperature to furnish pyran core embedded derivatives in good to excellent yields.

Pyran core is embedded in several natural products of biological importance such as coumarins (**I**),[1] terpenoids (**II**),[2] flavonoids (**III**),[3] anthraquinones (**IV**),[4] alkaloids (**V**),[5] (Fig. 1). Several groups described synthesis of these pyran intermediates using α,β-unsaturated aldehydes and 1,3-diketones by formal [3+3] cyclo-addition in presence of Lewis acid as catalyst,[6] or a reaction between an activated α,β-unsaturated iminium salt and 1,3-diketones,[7] or palladium catalyzed tandom Stille-oxo-electrocyclization reaction between 2-iodenones and 4-cis-stannylenones.[8–11] Recently Moreau et al. synthesized 3,4-dihydro-2*H*-pyran derivatives by addition of enolizable β-diketones to α,β-unsaturated aldehydes and subsequent selective hydrogentation of resultant dihydro-2*H*-chromenones using chiral phosphoric acid catalysts.[12] Enolizable 1,3-diketones are important building blocks and their usefulness in heterocyclic preparations,[13] pyrazole,[14] isoxazole,[15] triazole[16] and benzopyran-4-ones[17] has been largely illustrated. These 1,3-diketeones are also key structural units in many chelating ligands for lanthanide and transition metals.[18] Rich synthetic potential of 1,3-dicarbonyl compounds (1,3-DCC) is due to variety of chemical reactions with participation of ketone-methelene (polyketide) fragment and their ability to incorporate electrophilic or nucleophilic functionalities.

In continuation of our program on the synthesis of bioactive natural products, we were interested in preparing 3,4-dihydro-2*H*-pyran derivatives from enolizable β-diketones. The general method for the synthesis of 3,4-dihydro-2*H*-pyran derivatives from 1,3-diketones involves the C-alkenylation of enolizable β-diketones and subsequent cyclization in presence of acids such as H_2SO_4, HCl, P_2O_5, acetic acid, Lewis acids etc.[19] We therefore carried out a prenylation reaction on cyclohexa-1,3-dione (**1a**) and obtained mixture of C-2-prenyl-1,3-cyclohexadione (**2a**) and C-2-bisprenyl-1,3-cyclohexadione (**3a**).[20] Similar reaction was attempted on bisprenylated 1,3-cyclohexadione **3a** with different Lewis acids to obtain dipyran system **5a** (Scheme 1). None of them

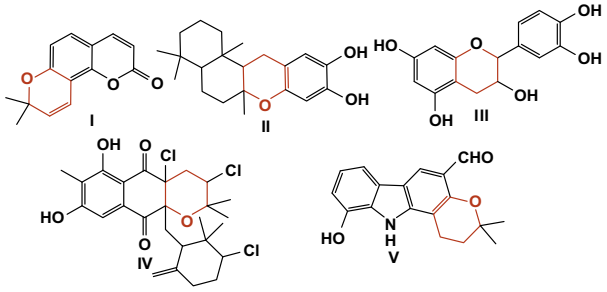

Figure 1. Pyran core embedded natural products (**I**–**V**).

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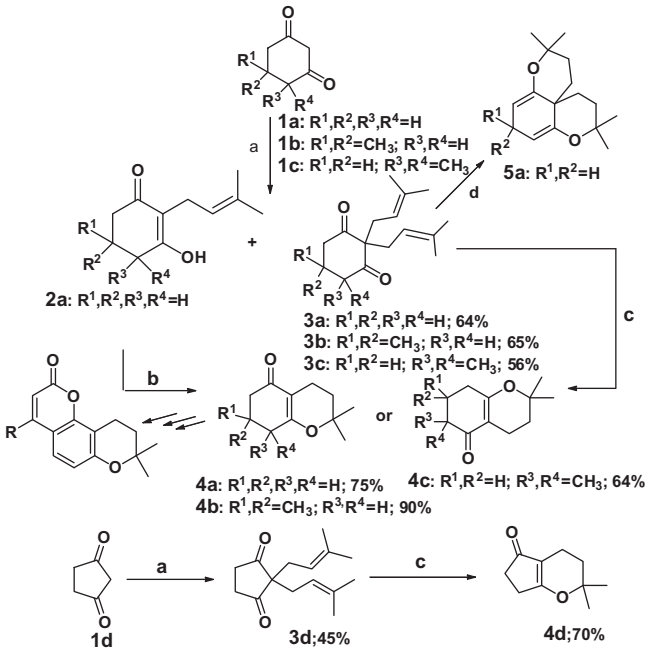
provided the anticipated dipyran **5a**, however $AlCl_3$ surprisingly provided the 2-methyl-2,3,4,6,7,8-hexahydro-chromen-5-one (**4a**) in reasonably good yields (Scheme 1).[21] To best of our knowledge, this unusual reaction (tandem dealkenylation and cyclization) with $AlCl_3$ was not reported earlier in the literature. To confirm the formation of **4a** from **3a**, a similar reaction was carried out with other bisprenylated diketones such as 5,5-dimethyl 2,2-diprenyl 1,3-diketone (**3b**), 4,4-dimethyl-2,2-diprenyl-1,3-cyclohexadione (**3c**) and bisprenylated 1,3-cyclopentadione (**3d**) which also gave respective pyran derivatives (**4b–d**) under the same conditions in reasonably good yields (Scheme 1). In case of **3c** the corresponding cyclized product **4c** exclusively formed, might be due to steric effect.



Scheme 1. Synthesis of pyran derivatives (**4a–d**) from bisalkenylated 1,3-cyclohexadione (**3a–d**). Reagents and conditions: (a) NaH in DMF at −20 °C, prenylbromide **b** and **d**, $AlCl_3$ and other Lewis acids in dry dioxane at rt for 3–5 h; (c) only $AlCl_3$ in dry dioxane at rt for 3–5 h.

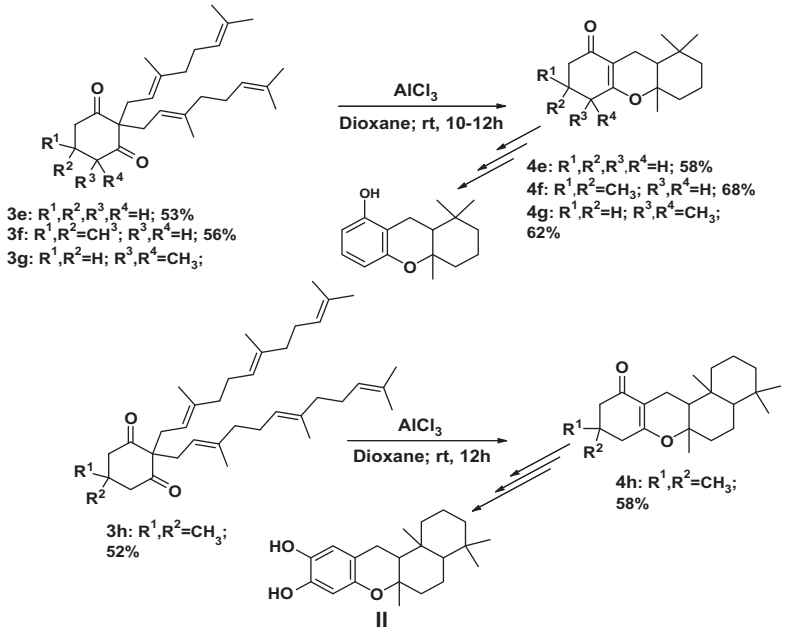
To explore the generality of the reaction, we focused to change the alkenyl groups on 1,3-diketones. Bisgeranylated 1,3-cyclohexadione (**3e**), 4,4-dimethyl-1,3-cyclohexadione (**3f**) and 5,5-dimethyl-cyclohexadiones (**3g**) and bisfarnesylated 4,4-dimethyl-1,3-cyclohexadione (**3h**) were prepared from **1a–c** and subjected to further reaction with $AlCl_3$, which again provided the respective pyran derivatives **4e–h** (Scheme 2) by tandem dealkenylation followed by cyclization. It is noteworthy to mention here that in addition to formation of pyran system the side chain of geranyl and farnasyl units further cyclized to give tricyclic (**4e–g**) and tetracyclic compound (**4h**) due to double and triple cyclization reactions, respectively.

To demonstrate the applicability of this procedure to prepare naturally occurring flavonoid derivatives **III** (Scheme 3) we synthesized **3i** from **1b** and carried out cyclization with $AlCl_3$ which resulted in the synthesis of 7,7-dimethyl-2-phenyl-2,3,4,6,7,8-hexahydro-chromen-5-one (**4i**).

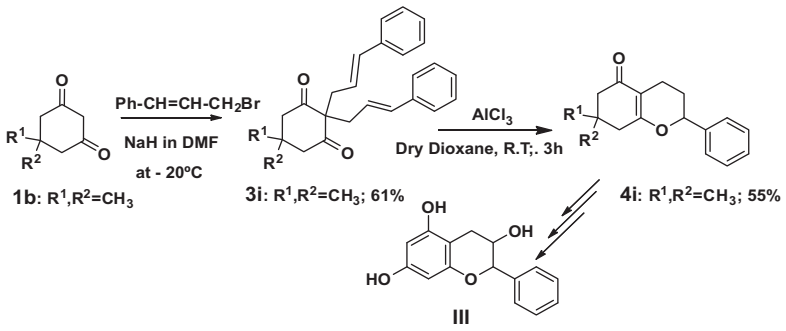
Few mixed alkenylated 1,3-diketones such as **3j**, **3k**, **3l,** and **3m** were prepared and subsequently reacted with $AlCl_3$ to give **4a** and **4b**, respectively (Scheme 4). This indicates that $AlCl_3$ preferentially dealkenylates the bulky groups only.

To broaden the reaction utility, 1,3-diketoesters were chosen for alkenylation (Scheme 5). Compounds **3n** and **3o** were synthesized from 3-oxo-butyric acid ethyl ester (**1e**) and subsequently reacted with $AlCl_3$, which surprisingly provided 2,2,6-trimethyl-3,4-dihydro-2*H*-pyran (**4j**) and 2,5,5,8-tetramethyl-4,5,6,7,8,8a-hexahydro-4*H*-chromene (**4k**), respectively, instead of **6a** or **6b** and **6c** or **6d**. Interestingly the decarboxylation reaction appears to be taking place before or after tandem dealkenylation and cyclization steps (Scheme 5).

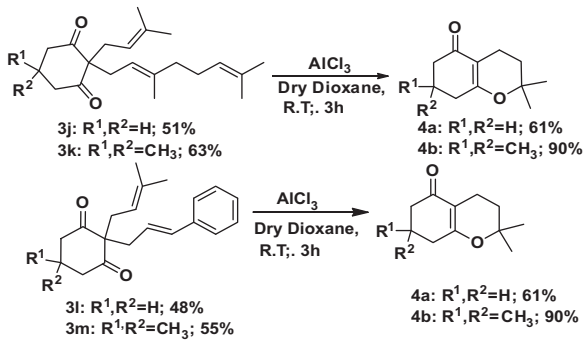
The reaction mechanism in the formation of pyran system appears to be the retro-Claisen rearrangement of one of the alkenyl group of **3a** to give intermediate **VI** and subsequent tandem dealkenylation and cyclization of second alkenyl group with enolic hy-



Scheme 2. Synthesis of tricyclic (**4e–g**) and tetracyclic pyran core system (**4h**).



Scheme 3. Synthesis of natural products like molecules (**4i**).



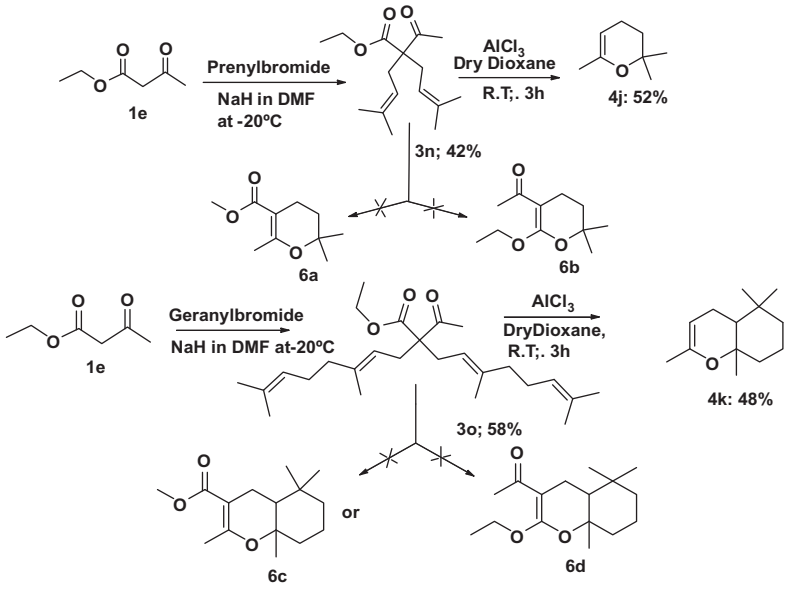
Scheme 4. Synthesis of pyrans **4a** and **4b** from mixed alkenylated 1,3-diketones.

droxyl provides the desired pyran **4a** and isoprene (**7**). The formation of **7** was confirmed by authentic sample of isoperene on TLC and GC (Fig. 2).

The reaction with **8** did not provide the pyran **4c** under similar conditions, The attempts to synthesize 3,4-dihydro-*2H*-pyran derivatives from bisallylated 1,3-diones (**3p**) also failed to provide the pyran core (**4l**), might be due to formation of O-alkenylated intermediate (**VIII**) via 3,3-retro-Claisen rearrangement, (Scheme 6). It appears to be that breakage of C–O bond in **8** generates primary carbocation on the alkenyl group might not be feasible, where as in the intermediate **VI** and **VII** breakage of C–O bond leads to the formation of tertiary and secondary carbocation, respectively. Further studies however are required to confirm the exact reaction mechanism.

To determine the role of the solvents in the reaction time and yields various solvents such as DMF, DMSO, H_2O, THF, dioxane, benzene, AcCN, EtOH, AcOH were used. Best results were obtained only in presence of dioxane, EtOH and AcOH.

In conclusion a new chemical access has been developed for the synthesis of pyrans and pyran core embedded derivatives from 1,3-diketone derivatives such as bisalkenyl cyclohexa-1,3-diketone, 4,4-dimethyl-1,3-diketone, 5,5-dimethyl-1,3-diketone (dimedone), cyclopenta-1,3-diketone and also 1,3-diketoesters in one step for the first time using $AlCl_3$. During this process we have prepared several natural products like building blocks such as tricyclic (**4e**–**g**), tetracyclic (**4h**) and flavonoid like intermediates (**4i**), which can be utilized for the total synthesis of natural products **I**–**III** of biological importance (Fig. 1; Schemes 1–3). Further work is in progress in our laboratory in this direction.



Scheme 5. Synthesis of pyran derivatives (**4j** and **4k**) from 1,3-dikentoester (**1e**).

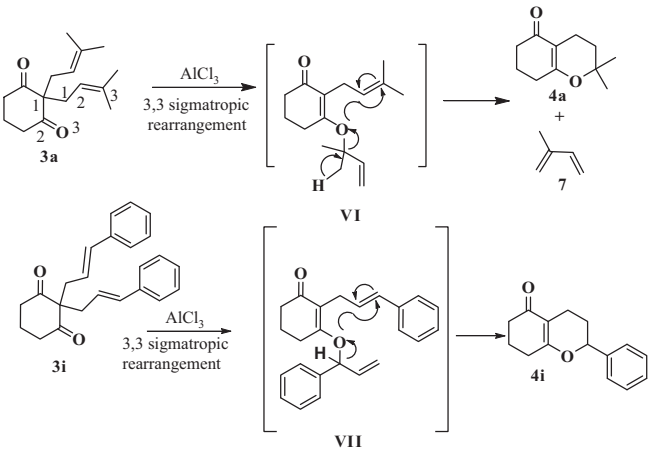
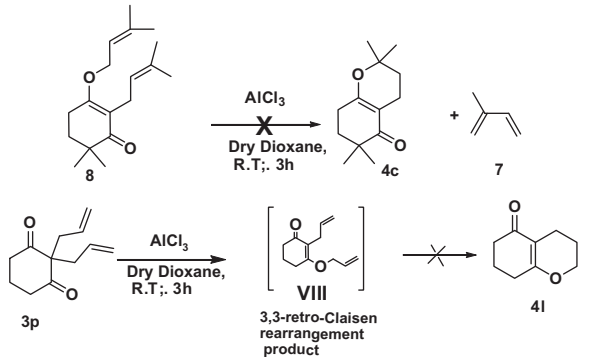


Figure 2. Possible reaction mechanisms in the formation of pyran core.



Scheme 6. Cyclization attempt on C and O-prenylated dione (**8**) and bisallylated 1,3-diketone (**3p**).

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Supplementary data

Supplementary data(Spectroscopic characterization of all new compounds along with their ^{1}H and ^{13}C spectra and 2D NMR spectra, mass) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.030.

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20. *Representative procedure for the preparation of* **3a**: 1,3-diketone **1**a (0.5 g, 5 mmol, 1.0 equiv) was added drop wise by syringe to a stirred solution of sodium hydride (0.3 g, 13.4 mmol, 3 equiv) in dimethyl formamide (10 mL) at −20 °C. The resulting pale-yellow solution was stirred for 20 min at −20 °C, then prenyl bromide (1.6 mL, 13.4 mmol, 3 equiv) was added drop wise by syringe. The reaction mixture was stirred for 20 min at this temperature, then the reaction flask was removed from the cooling bath and was allowed to reach to room temperature. The reaction mixture was stirred for 1 h at room temperature. Then reaction was quenched by adding ice-cold water and extracted three times with ether. Ether part was concentrated by rotary evaporation. The pale-yellow oily residue was purified by flash-column chromatography (hexanes) to provide a colorless oil of **3a** Yield: 64%; TLC (10% ethyl acetate–hexanes) R_f = 0.60%; IR (Neat) 3441, 2932, 2365, 1720, 1609, 1455, 1391, 1220, 1131, 925, 840, 753, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83–4.77 (m, 2H), 2.46–2.41 (m, 8H), 1.88–1.79 (m, 2H), 1.57 (s, 6H), 1.50 (s, 6H); ^{13}C NMR (75 MHz): 212.1 (2C), 135.7 (2C), 118.9 (2C), 68.1, 40.7 (2C), 36.6 (2C), 26.2 (2C), 18.1 (2c), **1**6.9; MS (ESI) *m/z* 181.1 $(M+H)^+$.
21. *Representative procedure for* **4a**: To a stirred solution of **3a** (0.5 g) in dry dioxane (5 mL) was added catalytic amount of $AlCl_3$ at room temperature and stirred for 3–4 h. After dilution with moist ether (100 mL), the solution was washed with water (3 × 50 mL) to discharge the color. The combined ethereal solution obtained after extraction was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude mixture was isolated on column-chromatography to afford desired compound **4a**; yield: 75%; TLC (10% ethyl acetate–hexanes) R_f = 0.35; IR (Neat) 3753, 3679, 3493, 3020, 2928, 2856, 2401, 1719, 1611, 1523, 1393, 1216, 1156, 1115, 1014, 928, 761, 670, 532 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36–2.30 (m, 2H), 2.26–2.21 (m, 2H), 1.97–1.88 (m, 2H), 1.65 (t, *J* = 6.60 Hz, 2H), 1.57(t, *J* = 7.66 Hz, 2H), 1.26 (s, 6H); ^{13}C NMR (75 MHz): 198.8, 171.1, 110.2, 83.1, 36.9, 32.4, 29.4, 26.8 (2C), 21.2, 15.8; MS (ESI) *m/z* 181.1 $(M+H)^+$.