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A convenient and biogenetic type synthesis of few naturally occurring chromeno dihydrochalcones and their in vitro antileishmanial activity ☆

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Abstract—2′,2′-Dimethyl chromeno dihydrochalcones are very rare in nature as plant secondary metabolites. Recently we have reported three such compounds from the plant *Crotalaria ramosissima*. Chromeno dihydrochalcones contain a 2′,2′-dimethyl benzopyran system, which are frequently encountered in many natural products and exhibit a variety of biological activities. We here report the strategy to conveniently synthesize naturally occurring chromeno dihydrochalcones by biogenetic type pyridine or Amberlyst-15 catalyzed chromenylation of dihydrochalcones and in vitro antileishmanial activity of chromeno dihydrochalcones and their intermediates.

1. Introduction

In continuation of our programme on the isolation of bioactive compounds from the *Crotalaria* genus,[1] Leguminosae family, we have isolated several chalcones, chromeno chalcones and chromeno dihydrochalcones. Recently we have reported three such 2′,2′-dimethyl chromeno dihydrochalcones **1**–**3** (Fig. 1) from *Crotalaria ramosissima*, which are very rare as plant secondary metabolites. So far no such natural products exist except our compounds. Few synthetic dihydrochalcones possessing chromenyl moiety has been prepared by solid state method.[2] Chromeno dihydrochalcones, contain 2′,2′-dimethyl benzopyran system, frequently encountered in many natural products and some of them exhibit significant bioactivities[3] that is anti HIV, insecticidal, antiinflammatory and antifeedant activity. We therefore, wanted to get sufficient material for testing the biological activity of these compounds.

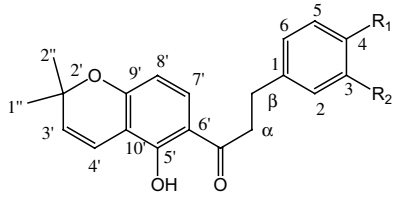

Figure 1. Naturally occurring chromeno dihydro chalcones isolated from *C. ramosissima*.

2. Synthesis

The general synthesis of dihydrochalcones involves the Claisen–Schmidt condensation of acetophenone with appropriate aldehyde and subsequent Pd/C reduction of chalcone double bond. In case of chromeno dihydrochalcones that contain a sensitive functionality that is olefinic site in chromene, reduction of the corresponding chalcone double bond cannot be used. Initially we have attempted to synthesize these compounds from respective chromeno chalcones (**9**/**10**) by reducing α–β unsaturated double bond selectively.

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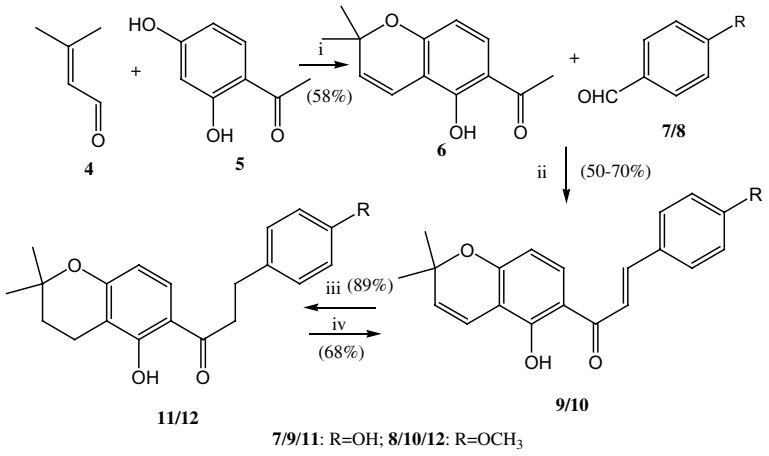


Scheme 1. Reagents and conditions: (i) pyridine, reflux at 150 °C; (ii) KOH/EtOH rt; (iii) Pd/C, H_2; (iv) DDQ/benzene.

Several reducing agents such as Pd/C in aprotic solvents, $NaBH_4/NiCl_2$[4] and enzymatic reaction with *Saccaromices cerevisiae*[5] have failed to reduce the α–β unsaturated double bond selectively without affecting the chromene double bond in **9/10**[6,7] and ultimately we have ended up with fully saturated product **11/12**. When we tried to selectively dehydrogenate the fully saturated product **11/12** using DDQ, dehydrogenation took both the places to give starting diene **9/10** (Scheme 1).

Recently Krohn et al.[8] synthesized these compounds by a different method (Scheme 2). In their attempt to alkylate the acylchromene enolate **6** with the corresponding benzyl halide **14** in presence of LDA at −80 °C also failed except the benzyl iodide **13**, which was very unstable.

In view of the failure to reduce the chalcone double bond selectively and to avoid the preparation of unstable benzyl iodide and also reaction conditions to condense the acylchromene enolate with the benzyl iodide, we have changed our strategy. In our approach, we have prepared the chalcones (**16**–**18**)[9] by condensation of resacetophenone (**5**) with respective substituted aldehydes (**7**,**8**,**15**) using Claisen–Schmidt method. The resultant chalcones were converted into dihydrochalcones (**19**–**22**)[10] using Pd/C in methanol and thus the readily available dihydrochalcones were used for chromenylation using 3-methyl-2-butenal in presence of pyridine[11] (Table 1) or 3-hydroxy-3-methyl but-1-yn in presence of Amberlyst-15 cation exchange resin,[12] to give 2′,2′-dimethyl chromeno dihydrochalcones **1**–**3** and **23** (Scheme 3).

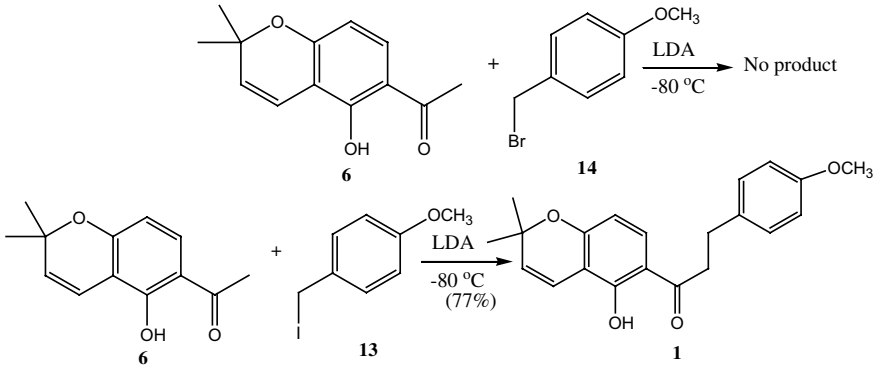
Table 1. Pyridine catalyzed chromenylation of dihydrochalcones

Entry	Substrate	Product	Isolated yield (%)
1	**19**	**1**	59
2	**20**	**2**	55
3	**21**	**3**	48
4	**22**	**23**	50

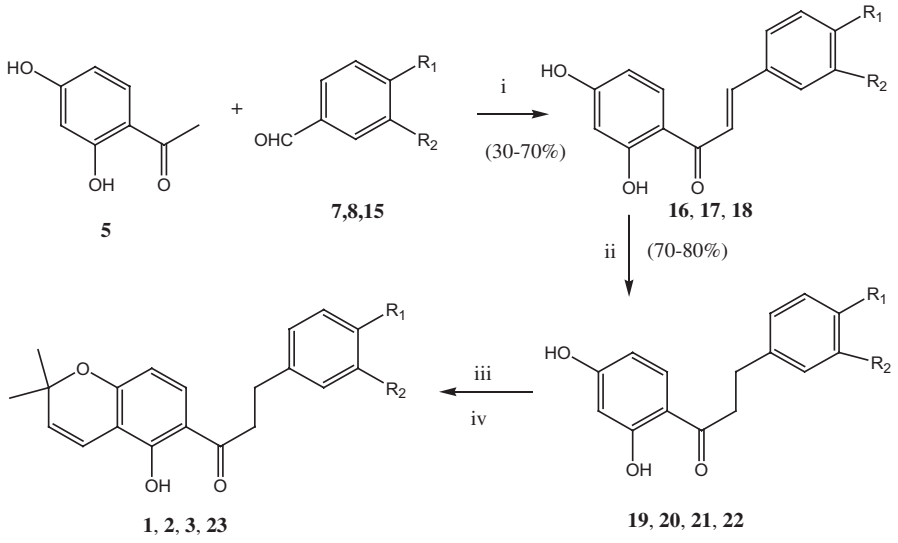
The yield, however, was very poor (∼10%) when we used Amberlyst-15.

2.1. In-vitro antileishmanial activity

Licochalcone-A[13] isolated from Chinese licorice roots and subsequently a large number of synthetic chalcones have been reported for their antileishmanial activity and prompted us to screen our compounds activity. Chromeno dihydrochalcones and their intermediates were tested against extracellular promastigotes of *Leishmania donovani*[14] and intracellular amastigotes[15] residing within murine macrophages (Table 2). Our compounds



Scheme 2. Preparation of chromeno dihydrochalcones by alklyating the acylenolates.



1/7/16/19: R_1=OCH_3; R_2=H; **2/8/17/20**: R_1=OH; R_2=H
3/22: R_1=OH; R_2=OH; **15/18/21/23**: R_1=OCH_3; R_2=OCH_3

Scheme 3. Reagents and conditions: (i) KOH/EtOH, rt; (ii) Pd/C, H_2; (iii) 3-methyl-2-butenal/pyridine reflux at 150 °C; (iv) 3-hydroxy-3-methyl-1-butyne/Amberlyte-15 resin in benzene at 100 °C.

Table 2. In-vitro antileishmanial activity of naturally occurring chalcones at 50 μg/mL dose (inhibition in percentage)

Compound	Motility of promastigotes	Promastigotes (% inhibition)	MQ amastigotes (% inhibition)
1	Nonmotile	78	47
2	Nonmotile	89	Toxic
3	Active	30	Inactive
9	Nonmotile	84	74
10	Nonmotile	85	53
16	Nonmotile	60	15
21	Nonmotile	79	Toxic
23	Active	Inactive	22
Pentamidine 5 μg/mL	Nonmotile and vacuolated	97	50
Stibanate 50 μg/mL	Active	Inactive	85

have shown 30–89% inhibition in viability of promastigotes and 22–74% inhibition in amastigotes multiplication at 50 μg/mL dose. The most potent compound that is chromeno chalcone **9**, which has hydroxyl group on 4-position in ring A, shown 84% inhibition against promastigotes and 74% inhibition against amastigotes, where as its methylated compound **10**, has good promastigotes inhibition (85%) but comparatively less amastigotes inhibition (53%). The compound **9** also has better antileishmanial activity than the 2′,4′-hydroxy,4-methoxy chalcone **16**. Comparisons of the above in vitro activity results (Table 2) disclose that hydroxyl group at 4-position in ring-A is essential for the antileishmanial activity in chromeno chalcones. Chromeno dihydrochalcone **1**, which has methoxy substitution similar to compound **10** shown 78 and 47% inhibition against promastigotes and amastigotes, respectively. The 2′,2′-dimethyl chromeno dihydrochalcone **2** has 89% promastigotes inhibition and toxic to amastigotes at 50 and 25 μg/mL doses and at a further low dose of 12.5 μg/mL the compound has low promastigotes inhibition (15%). The chromeno chalcone **10** and its dimethylated compound **9** have good antileishmanial activity than chromeno dihydrochalcone **1** and its dimethylated derivative **2** indicating that the α–β unsaturated double bond also contributing towards more antileishmanial activity. In compounds **9/10** and **1/2** the 4′-hydroxyl group is involved in the chromene formation and these are more potent than 4′-hydroxy,4-methoxy chalcone **16**, which support the substitution at 4′ position by a large group also important for their antileishmanial activity. Orthodihydric or orthodimethoxy substitution pattern in ring-A (**3**,**21**) decreased the antileishmanial activity.

3. Conclusion

In summary we developed operationally simplified method for the synthesis of chromeno dihydrochalcones, which contain a sensitive functional group. We have also obtained few naturally occurring chalcones, dihydrochalcones and chromeno chalcones as intermediates in the process of synthesis of chromeno dihydrochalcones and investigated their antileishmanial activity to provide a scientific rational for the antiprotozoal potency of plants used in ethnomedicine in the search of new antiprotozoal drugs. Our results shows that the chalcones, which contain 2′,2′-dimethyl benzopyran system are potent antileishmanial agents than the simple chalcones.

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