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MW-ASSISTED SYNTHESIS OF CHROMENO[3,4-*b*]XANTHONES AND (BENZO[*c*]CHROMENYL)CHROMONES

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Abstract

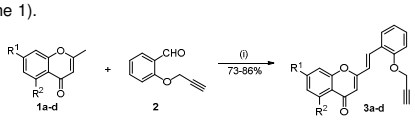
Two series of novel propargyloxychromones were designed and synthesized. Both chromone derivatives were used as substrates in MW-assisted intramolecular Diels-Alder reactions, affording chromeno[3,4-*b*]xanthones and (benzo[*c*]chromenyl)chromones. This is the first report involving chromone derivatives in intramolecular Diels-Alder reactions for the synthesis of new oxygen heterocycles, namely xanthones and flavones.

Introduction

Chromones are a natural occurring class of oxygen heterocycles, known for their manifoldness of biological activities[1]. Simple chromones and its derivatives are often considered interesting substrates to further functionalization through many chemical transformations such as oxidation, condensation, conjugate addition or Diels-Alder (DA) reactions[2]. Particularly, intramolecular DA reactions are well-recognized and can be employed in one or more steps in the total synthesis of several polycyclic natural products. However, to the best of our knowledge, there are no reports in the literature involving chromone derivatives in intramolecular DA reactions. Thus, following our previous studies dealing with the reactivity of chromones substituted with different unsaturated systems in DA reactions[3,4], herein we aimed to prepare propargyloxychromones to be used as substrates in intramolecular DA reactions.

Synthesis of propargyloxychromones

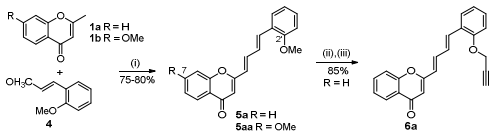
The (*E*)-2'-propargyloxy-2-styrylchromone derivatives **3a-d** were prepared (η 73-86%) through base-catalyzed aldol condensation of the appropriate 2-methylchromones **1a-d** with the *ortho*-propargyloxybenzaldehyde **2** (Scheme 1).



a) $R^1 = R^2 = H$; b) $R^1 = OMe$, $R^2 = H$; c) $R^1 = H$, $R^2 = OMe$; d) $R^1 = R^2 = OMe$

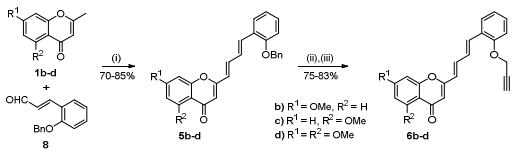
Scheme 1. Synthesis of (*E*)-2'-propargyloxy-2-styrylchromones **4a-d**. *Reagents and conditions*: (i) Na, EtOH, r.t., 3-6 h.

The synthesis of 2-{(1*E*,3*E*)-4-[2-(prop-2-yn-1-yloxy)phenyl]buta-1,3-dien-1-yl}chromones was not straightforward. The initial strategy involved the base-catalyzed aldol condensation of the 2-methylchromone **1a** with the commercially available *ortho*-methoxycinnamaldehyde **4**, affording the methoxy-substituted chromone **5a** in good yield [Scheme 2, (i)]. Then, the methyl group was cleaved with BBr_3 and the propargylation was accomplished with propargyl bromide, in the presence of K_2CO_3 as base, giving the desired *O*-propargyl-2-butadienylchromone **6a** [Scheme 2, (ii) and (iii)]. This strategy was applied to the 2-methylchromone derivative **1b**, however, the demethylation step lead to the undesired cleavage of both methyl groups (2'-OMe and 7-OMe).



Scheme 2. Synthesis of chromones **5a**, **5aa** and **6a**. *Reagents and conditions*: (i) Na, EtOH, r.t., 2-3 h; (ii) BBr_3, CH_2Cl_2, r.t., 2 h; (iii) K_2CO_3, propargyl bromide, acetone, reflux, 5 h.

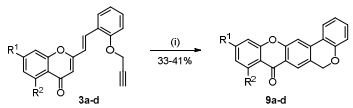
The new strategy relied on the preparation of a specific cinnamaldehyde **8**, through palladium-catalyzed cross-coupling reaction, with an appropriate *ortho*-benzyl group, which could be selectively cleaved using mild conditions. The base-catalyzed aldol condensation of 2-methylchromones **1b-d** with cinnamaldehyde **8** afforded the desired chromones **5b-d** in good yields [Scheme 3, (i)]. The next step of this strategy involved the selective cleavage of the benzyl group using a mixture of AcOH/HCl (37%) (10% v/v), followed by propargylation with propargyl bromide, which afforded the desired chromones **6b-d** in good overall yields [Scheme 3, (ii), (iii)].



Scheme 3. Synthesis of chromones **6b-d**. *Reagents and conditions*: (i) Na, EtOH, r.t., 4-6 h; (ii) AcOH/HCl (10% v/v), 100 °C, 16 h; (iii) K_2CO_3, propargyl bromide, acetone, reflux, 5 h.

Intramolecular Diels-Alder reactions

The (*E*)-2'-propargyloxy-2-styrylchromones **3a-d** were used as substrates in the synthesis of chromeno[3,4-*b*]xanthone derivatives through MW-assisted intramolecular DA reaction. The preliminary optimization led to the synthesis of chromeno[3,4-*b*]xanthones **9a-d** (see Figure 1 for ^{1}H NMR of **9a**) in low yields (Scheme 4). Further optimization by changing the solvent, temperature, reaction time and Lewis acid catalysis are still needed.



a) $R^1 = R^2 = H$; b) $R^1 = OMe$, $R^2 = H$; c) $R^1 = H$, $R^2 = OMe$; d) $R^1 = R^2 = OMe$

Scheme 4. MW-assisted synthesis of chromeno[3,4-*b*]xanthones **9a-d**. *Reagents and conditions*: (i) DMF, MW, 200 °C, 80 min.

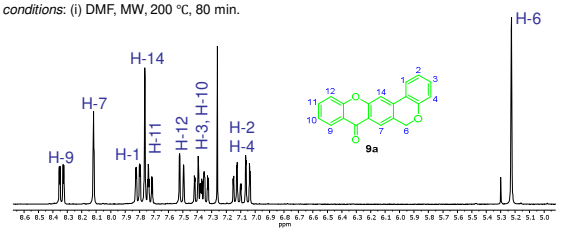
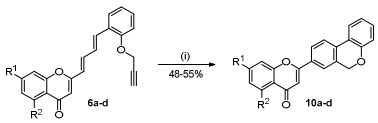


Figure 1. ^{1}H NMR of 6*H*,8*H*-chromeno[3,4-*b*]xanthen-8-one (**9a**).

In the case of chromones **6a-d**, the best reaction conditions achieved so far, afforded the desired (benzo[*c*]chromenyl)chromones **10a-d** (see Figure 2 for ^{1}H NMR of **10a**) in fair yields in the presence of $Sc(OTf)_3$ as Lewis acid (Scheme 5). Once again further optimization of the reaction conditions is necessary.



a) $R^1 = R^2 = H$; b) $R^1 = OMe$, $R^2 = H$; c) $R^1 = H$, $R^2 = OMe$; d) $R^1 = R^2 = OMe$

Scheme 5. MW-assisted synthesis of 2-(benzo[*c*]chromenyl)chromones **10a-d**. *Reagents and conditions*: (i) $Sc(OTf)_3$, DMF, MW, 200 °C, 30 min.

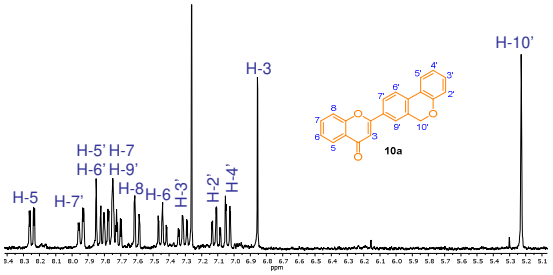


Figure 2. ^{1}H NMR of 2-(6*H*-benzo[*c*]chromen-8-yl)-4*H*-chromen-4-one (**10a**).

Conclusions

2'-Propargyloxy-2-styrylchromones and 2'-propargyloxy-2-(4-arylbuta-1,3-dien-1-yl)chromones were prepared and further used as substrates in intramolecular DA reactions. Chromeno[3,4-*b*]xanthones and 2-(benzo[*c*]chromenyl)chromones were obtained *via* MW-assisted intramolecular DA reaction, followed by *in situ* dehydrogenation.

References

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Acknowledgements

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