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An expedient access to chromanols via an arginine-mediated cascade cyclisation in water

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ABSTRACT

A mild and efficient protocol for the synthesis of chromanols has been elaborated via an arginine-mediated cascade cyclisation reaction between salicylaldehyde and methyl vinyl ketone in water. Various substituted salicylaldehydes were successfully used in the aqueous based reaction, affording the chromanol adducts in very good yields. Mechanistically, the reaction presumably proceeds via an oxa-Michael addition followed by an intramolecular aldol addition pathway; the lack of stereoselectivity in the formation of the chromanols alludes to a non-covalent interaction of the amino acid with the substrates as the most plausible interpretation for the activation.

The importance of molecules possessing the unsaturated 1-benzopyran scaffold, popularly known as the chromene scaffold, needs no elaboration. In fact, both the isomeric forms – 2*H*- and 4*H*-chromenes (Fig. 1) – are considered privileged structures in the medicinal chemistry world due to their ubiquity in therapeutic agents.[1] Needless to mention, synthetic access to the scaffold continues to attract a fair share of research attention.[2] Extensive research has revealed a Michael addition-aldol condensation cascade involving salicylic aldehyde and activated olefinic systems as the simplest strategy for the construction of the chromene scaffold,[3] although a Baylis-Hillman-oxa-Michael addition cascade has also been invoked under appropriate conditions;[4] the former strategy has been amply demonstrated by Brase and co-workers in the synthesis of numerous natural products bearing the chromene unit.[3d–g] The closely related chroman-4-ol scaffold (Fig. 1) also forms the core of many biologically active molecules[5] and several elegant methods have been developed over the years to access molecules bearing the framework. Not surprisingly, similar to the synthesis of the chromenes, strategies for the construction of chromanols have revolved around the use of a salicylic aldehyde derivative as the precursor, with its phenolic moiety suitably functionalized to bring about the desired cyclisation either through a radical pathway or a metal-mediated coupling reaction.[6] An early example of the strategy was demonstrated by Wu & co-workers who used a bromo-substituted alkenyl chain hooked to the phenolic oxygen of salicylaldehyde to promote a tin-mediated intramolecular allylation.[6a] Other illustrations of the carbonyl-olefin cyclisation method include a titanium promoted radical cyclisation of *O*-propargyl and *O*-allyl substituted salicylic aldehydes developed by Roy & Jana[6b] and a tin hydride catalysed radical cyclisation of similar substrates reported by Parsons & co-workers.[6c] Furthering the idea, Rueping & co-workers recently provided an excellent demonstration of a visible light photoredox-catalysed ketyl-olefin coupling for the synthesis of chromanol derivatives in very good yields.[6d] The chromanol scaffold can evidently get decorated with one or more stereoegenic centres depending on the substitution on the pyran ring, giving rise to some elegant stereoselective strategies. Notable examples include Ho's elegant Ni(0)-NHC-Et_2AlCN mediated alkene-aldehyde coupling to synthesise chromanols at room temperature,[7a] Maruoka & co-workers' enantioselective organotin hydride catalysed radical cyclisation[7b] and a catalytic enantioselective protocol described by Trost and Toste much earlier.[7c] Apart from the popular strategy of utilising a suitably functionalised salicylaldehyde derivative, worthy approaches to construct chromanols also include an intramolecular [3+2] cycloaddition of *O*-allyl salicylaldoxime[8] and a Pd-mediated intramolecular coupling of aryl iodides with aldehydes,[9] among several other reports. Pertinent to the present work, a one-step protocol was recently revealed by Menon and co-workers involving a base-mediated cyclocondensation of salicylaldehyde with 2-bromoallyl sulfones.[10] However, the focus of this work was more on the synthesis of the corresponding 3-sulfonyl chromene

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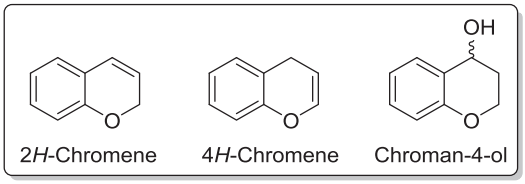


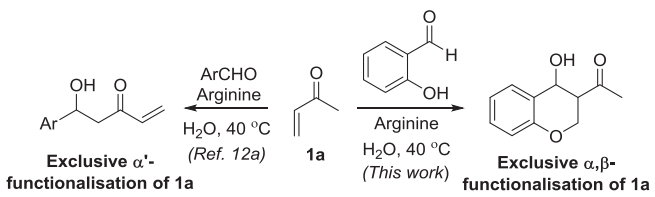
Fig. 1. The chromene and chromanol scaffolds.

derivatives rather than the corresponding chromanol. In fact, as mentioned earlier, investigations by Shi, Brase and others have established the cyclocondensation of salicylaldehyde with α,β-unsaturated carbonyl compounds as the most versatile method for accessing chromenes.[3] To our knowledge, the intermediate chromanol adduct in a domino oxa-Michael-aldol reaction of this kind has proved elusive to isolate; apparently, the spontaneous dehydration of the intermediate adduct has been difficult to control under the conditions of the protocol, leading invariably to the cyclocondensed chromene product. This is a significant issue, since a controlled reaction would enable access to the chromanol scaffold that possesses two chiral centres, and the substrates involved provide ample scope for the elaboration of a suitable asymmetric protocol, particularly involving an organocatalytic activation.

On a parallel note, there has been a concerted effort worldwide towards the development of more sustainable synthetic protocols in the domain of organocatalysis.[11] Its resemblance to natural processes has given rise to a spate of aqueous based methods, arguably the most direct method to address the toxic organic waste problem. Our group has been endeavouring in this direction, utilising simple and inexpensive organocatalysts – especially the naturally available amino acids – to bring about important C—C and C-hetero atom bond forming transformations under aqueous or solvent-free conditions.[12] In light of the above discussion, we herein report an expedient access to chromanols via a facile arginine-mediated cascade cyclisation of salicylaldehydes with alkyl vinyl ketones. The reaction worked smoothly in water, affording very good yields of the chromanol adducts without formation of the corresponding chromenes.

We had recently reported an arginine-mediated aldolisation of methyl vinyl ketone (**1a**) under aqueous conditions.[12a] The result was noteworthy since methyl vinyl ketone has historically proved difficult to aldolise, and a general aldol addition protocol was deemed valuable to the synthetic community. The reaction had proceeded quite swiftly and cleanly in water especially with isatin as the electrophilic partner to provide the corresponding aldol adducts in generally excellent yields. Looking to further expand the scope of the reaction, we were curious to test other aldehydes, chiefly those that bore additional functional groups, e.g., salicylaldehyde. A clean reaction ensued upon subjecting salicylaldehyde (**2a**), **1a** and arginine to conditions identical to those used in our previous work, resulting in a single product; characterisation of the product revealed it to be a chromanol – formed presumably from an oxa-Michael-aldol cascade cyclisation involving both the functional groups of salicylaldehyde – rather than the simple aldol adduct. Although we were a little surprised by the outcome at first glance, we realised that it was certainly not an implausible one; nevertheless, we were intrigued by two principal features that could be inferred from the result: (i) the α′-C of **1a**, the original intended target of functionalisation, was left untouched by the reaction; an α,β-functionalisation of **1a** had occurred instead. When considered in totality, the present reaction accomplishes an electrophilic activation of **1a**, leading to the observed α,β-functionalisation, whereas our previous work involved **1a** as the nucleophilic partner, resulting in an α′- functionalisation. Scheme 1 illustrates this exciting mutually exclusive activation of methyl vinyl ketone by arginine under near identical conditions; (ii) exclusive formation of the chromanol had taken place, with no accompanying formation of the dehydrated chromene product; this is worth noting, not just due to the history of the reaction in delivering the chromene but also because the present conditions involve a highly basic catalyst and elevated temperatures that might be expected to favour a condensed product.

Excited by these features, we embarked on a full-fledged study of the reaction. A short survey of other potential mediating agents such as imidazole, N-methyl imidazole, guanidine derivatives and proline showed them to be ineffective for the desired transformation, as did a reaction without any catalyst (Table 1, entries 1–6). Much like our previous experience using arginine, the presence of water as a solvent was essential, since the catalyst otherwise presumably remained largely out of solution to be effective (entry 7). A quick study varying the other parameters (entries 8–11) allowed us to settle upon a reaction carried out at 40 °C using 30 mol% of arginine and 5 eq. of **1a** in 250 μL of H_2O (entry 9) as the optimised conditions for further expansion. Nonetheless, it was pleasing to observe that the reaction could be carried out at room temperature as well, albeit understandably requiring a longer duration to achieve a high degree of conversion (entry 12). It was disappointing that the reaction did not exhibit any stereoselectivity of either kind – diastereo- or enantio- – and the product was obtained as a 1:1 mixture of diastereomers. The lack of enantioselectivity suggested that the reaction perhaps did not proceed via an iminium ion that might be expected from a covalent interaction of arginine with **1a** (Fig. 2, **I**). Oxa-Michael addition of **2a** to this iminium would have in turn generated a chiral enamine, which could then be expected to offer a certain degree of stereocontrol in the subsequent intramolecular addition to the aldehyde in typical enamine-mediated aldol fashion to complete the cascade process. However, the lack of stereoselectivity, particularly enantioselectivity, suggests that this is perhaps not the case; it may be surmised therefore that the interaction of arginine with **1a** – and also **2a** – is only in terms of a non-covalent activation that facilitates the cascade cyclisation (Fig. 2, **II**). It must be emphasised that such a mechanism is only speculative at this stage and there could be several other factors – the intriguing role of water for e.g. – that could be controlling the eventual shape of the transition state. It is worth reiterating at this juncture that, in complete contrast to the present situation, the arginine catalysed reaction of **1a** with 'simple' aromatic aldehydes results in the exclusive activation of the former as an enolate. On a different note regarding the mechanism, an alternative pathway involving an initial Baylis-Hillman reaction between the activated olefin and the aldehyde followed by an intramolecular oxa-Michael addition to complete the cyclisation may also be considered. In fact, such a mechanism has been invoked by Kaye & Nocanda in a DABCO mediated reaction of similar substrates.[4] However, Brase and co-workers in an independent investigation have confirmed the oxa-Michael-aldol cascade as the more plausible reaction pathway under general



Scheme 1. Difference in reactivity of methyl vinyl ketone with salicylaldehyde and other aromatic aldehydes.