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Nitromethane conjugate addition to 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones

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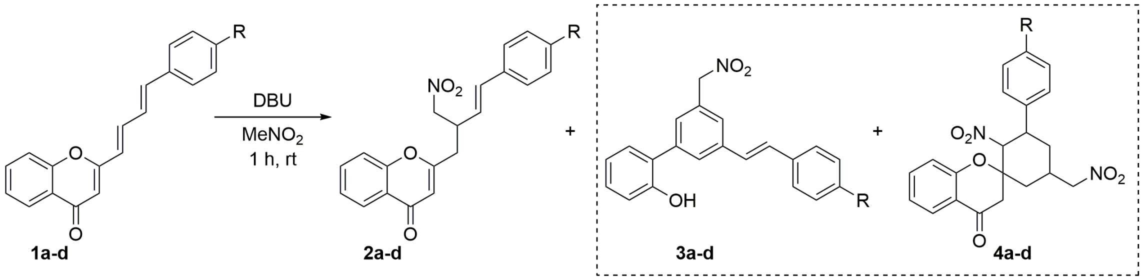
Chromone are a group of oxygen-containing heterocycles, which are often associated to important biological activities.[1] Chromone derivatives are also seen as interesting scaffolds to input further functionalizations,[2] most of them through chemical transformations such as oxidation, condensation, Diels-Alder or conjugate addition. Conjugate addition of carbon nucleophiles to electron-deficient alkenes is one of the most important methods available for carbon–carbon bond-forming reactions. A wide range of carbon nucleophiles easily undergo conjugate addition with various substrates such as chalcones, cinnamylideneacetophenones or styrylchromones.

Following previous work of our research group involving the 1,6-conjugate addition of nitromethane to (*E*)-2-styrylchromones,[3] herein we report the first reactivity studies in the nitromethane conjugate addition to the extended unsaturated π-system of 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **1** (Scheme 1). The DBU catalyzed nitromethane addition reaction afforded the corresponding β-(nitromethyl)chromones **2** (1,6-conjugate addition) as major products. (*E*)-5'-(Nitromethyl)-3'-styryl-[1,1'-biphenyl]-2-ol **3** and 3'-aryl-2'-nitro-5'-(nitromethyl)spiro [chromane-2,1'-cyclohexan]-4-one **4** derivatives were also isolated as minor products, which result from the addition of two nitromethane molecules, through tandem processes.



a) R = H, **b)** R = Cl, **c)** R = OMe, **d)** R = Me

Scheme 1: Nitromethane conjugate addition to 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **1**.

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NITROMETHANE CONJUGATE ADDITION TO 2-[(1*E*,3*E*)-4-ARYLBUTA-1,3-DIEN-1-YL]-4*H*-CHROMEN-4-ONES

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Abstract

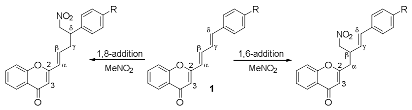
Conjugate addition reaction of nitromethane to the extended π-conjugated system of several chromone derivatives afforded the 1,6-conjugate addition products, together with structure complex oxygen heterocycles through *tandem* processes.

Acknowledgements

Thanks are due to FCT/MEC for the financial support of the QOPNA research unit (FCT UID/QUI/00062/2013) through national founds and, where applicable, co-financed by the FEDER, within the PT2020 Partnership Agreement, and to the Portuguese NMR Network. H.M.T.A. is grateful to FCT for his PhD grant (SFRH/BD/86277/2012).

Introduction

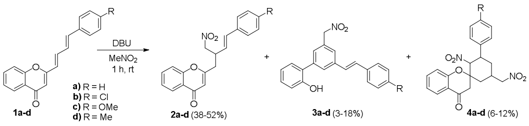
Following previous work of our research group,[1-3] herein, the reactivity of the extended 3,2:α,β:γ,δ-triunsaturated system of chromones **1** in conjugate addition reactions with nitromethane was addressed. In comparison with 2-styrylchromones, the presence of a third unsaturation extends the π-conjugated system on chromones **1** and allows δ-position to become a novel site for nucleophilic attack (possible 1,8-conjugate addition) (Scheme 1). This feature enables the synthesis of multisubstituted heterocyclic derivatives with new stereocenters.



Scheme 1. Possible sites of conjugate addition to chromones **1**.

Nitromethane conjugate additions

The DBU-catalyzed addition reaction of nitromethane, under neat conditions, to chromones **1** afforded the β-(nitromethyl)chromones **2** (1,6-conjugate addition) as major products (higher R_f), together with (*E*)-5'-(nitromethyl)-3'-styryl-[1,1'-biphenyl]-2-ol and 3'-aryl-2'-nitro-5'-(nitromethyl)spiro[chromane-2,1'-cyclohexan]-4-one (lower R_f) derivatives **3** and **4**, respectively, as minor products. These byproducts result from the addition of a second molecule of nitromethane, in *tandem* processes (Scheme 2). The structural elucidation of all compounds was accomplished by NMR (Figures 1-3).



Scheme 2. Nitromethane conjugate addition to chromones **1**.

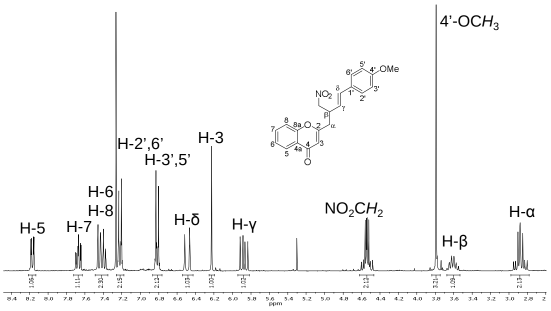
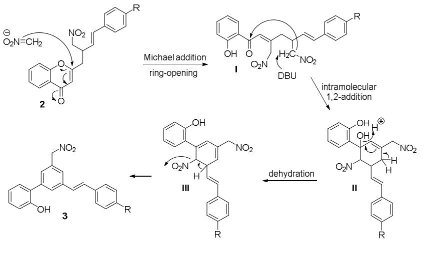


Figure 1. ^1H NMR spectrum of β-(nitromethyl)chromone **2c**.

The formation of derivatives **3** could be explained based on the Michael addition of a nitromethane anion to C-2 of β-(nitromethyl)chromones **2** along with chromone ring opening to give intermediates **I**. A DBU-catalyzed intramolecular 1,2-addition led to intermediates **II**, which upon dehydration affords intermediates **III**, that affords derivatives **3** after HNO_2 elimination (Scheme 3).



Scheme 3. Proposed mechanism towards the formation of compounds **3**.

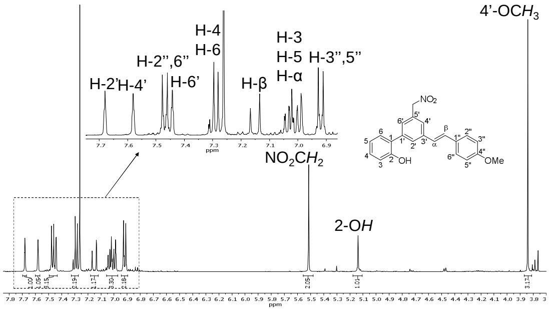
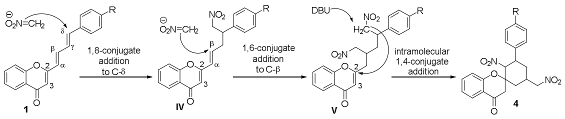


Figure 2. ^1H NMR spectrum of (*E*)-3'-(4-methoxystyryl)-5'-(nitromethyl)-[1,1'-biphenyl]-2-ol (**3c**).

The plausible mechanism for the formation of derivatives **4** involves the 1,8-conjugate addition of a nitromethane anion to C-δ of chromones **1**, affording intermediates **IV**. Then, the 1,6-conjugate addition of another nitromethane anion to C-β of **IV** gives intermediates **V**, which undergoes DBU-catalyzed intramolecular 1,4-conjugate addition to C-2 leading to the formation of the spiro trisubstituted cyclohexanes **4** (Scheme 4).



Scheme 4. Proposed mechanism towards the formation of compounds **4**.

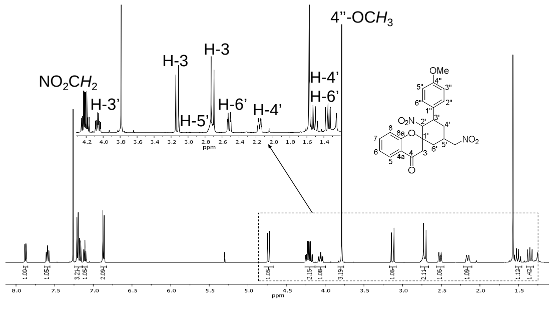


Figure 3. ^1H NMR spectrum of 3'-(4-methoxyphenyl)-2'-nitro-5'-(nitromethyl)spiro[chromane-2,1'-cyclohexan]-4-one (**4c**).

Conclusion

The conjugate addition reaction of nitromethane to chromones **1** afforded β-(nitromethyl)chromones **2** as major products, as well as compounds **3** and **4** as minor ones, which are formed through *tandem* processes, due to the competition of 1,6 and 1,8 addition reactions.

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