sciences

2-(4-Arylbuta-1,3-dien- or 1-en-3-yn-1-yl)chromones as synthons for the synthesis of other nitrogen and oxygen heterocyclic compounds

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Abstract

It is well known the great biological relevance of oxygen and nitrogen heterocycles. Herein, the reactivity of 2-(4-aryl-1,3-dien- and 1-en-3-yn-1-yl)chromones are explored in order to establish new synthetic routes towards the preparation of new heterocyclic compounds such as xanthones and triazoles. The reactive sites of the starting chromone derivatives (the double and triple bonds) allow them to be involved in reactions such as Diels-Alder and Huisgen cycloadditions. These reactions are used separately or subsequently in order to prepare new biologically active compounds emphasizing the synthetic potential of the referred chromone derivatives. Using these new synthetic routes we were able to develop new compounds, such xanthones bearing triazole moiety, which are expected to enclosure interesting biological properties.

Acknowledgements

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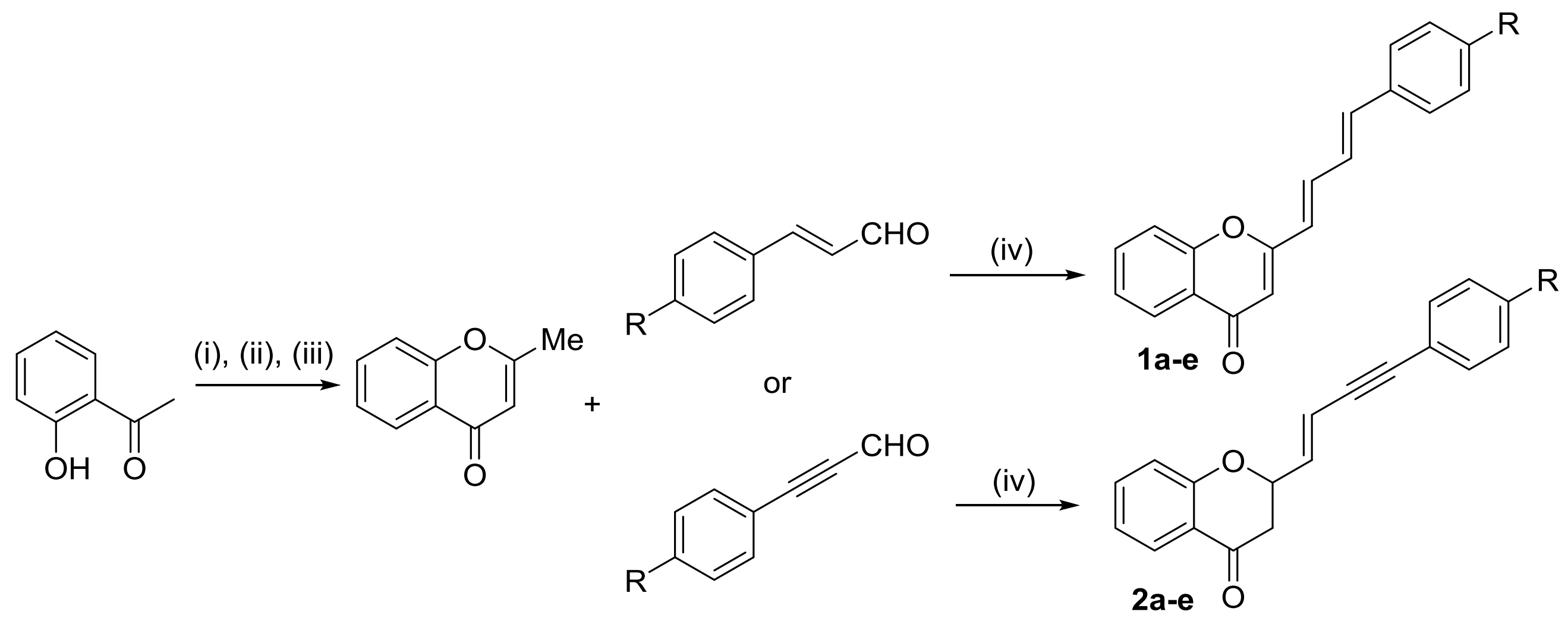
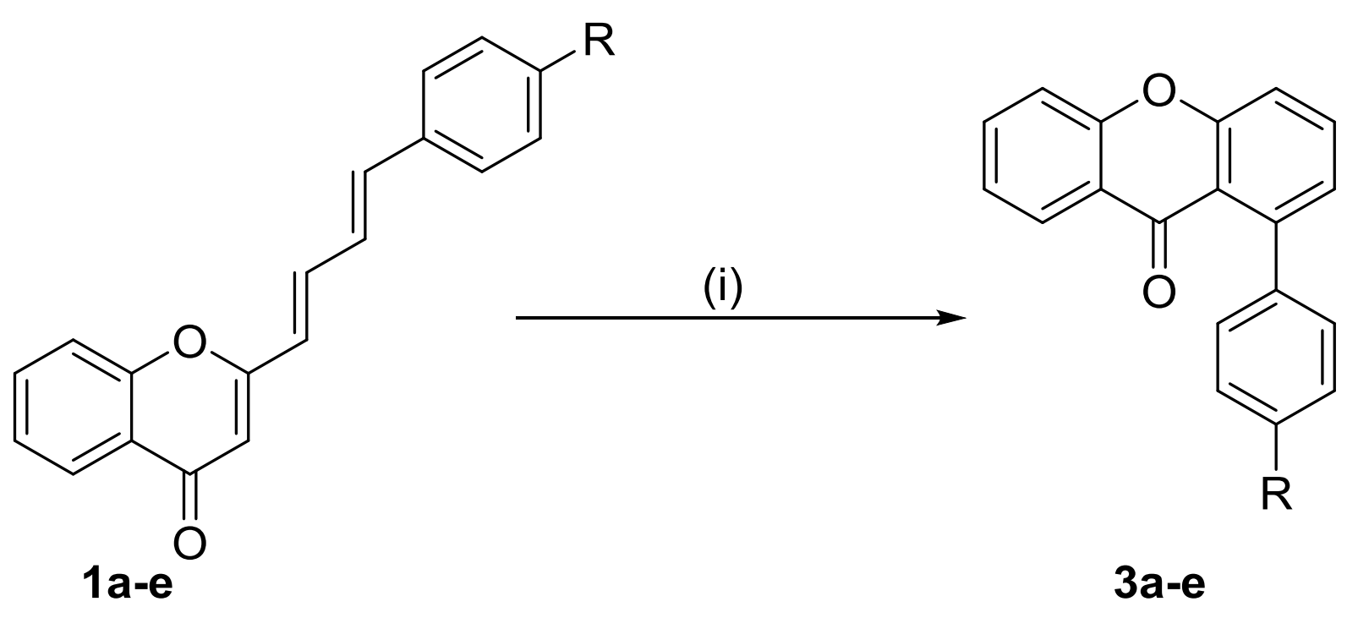
Oxygen and nitrogen heterocyclic compounds, such as xanthones and triazoles, have great importance in life and science because of their numerous applications. Xanthones are very appellative compounds to medicinal chemists because of their pronounced biological activity within a notably broad spectrum of disease states, as a result of their interaction with a correspondingly diverse range of target biomolecules. Regarding the triazoles, its substituted derivatives are best known as antifungals. Actually, the most common antifungals in the market are indeed triazole derivatives. As consequence of this remarkable potential, new synthetic strategies are being developed in order to synthesize new xanthone and triazole derivatives. Herein, we are presenting two versatile molecules which can be used as synthons towards the synthesis of xanthone and/or triazole derivatives.

Chromone derivatives **1a-e** and **2a-e** are useful synthons to synthesize other heterocyclic compounds, and are prepared through the aldol condensation of methylchromone with the appropriate α,β-unsaturated aldehydes (Scheme 1).



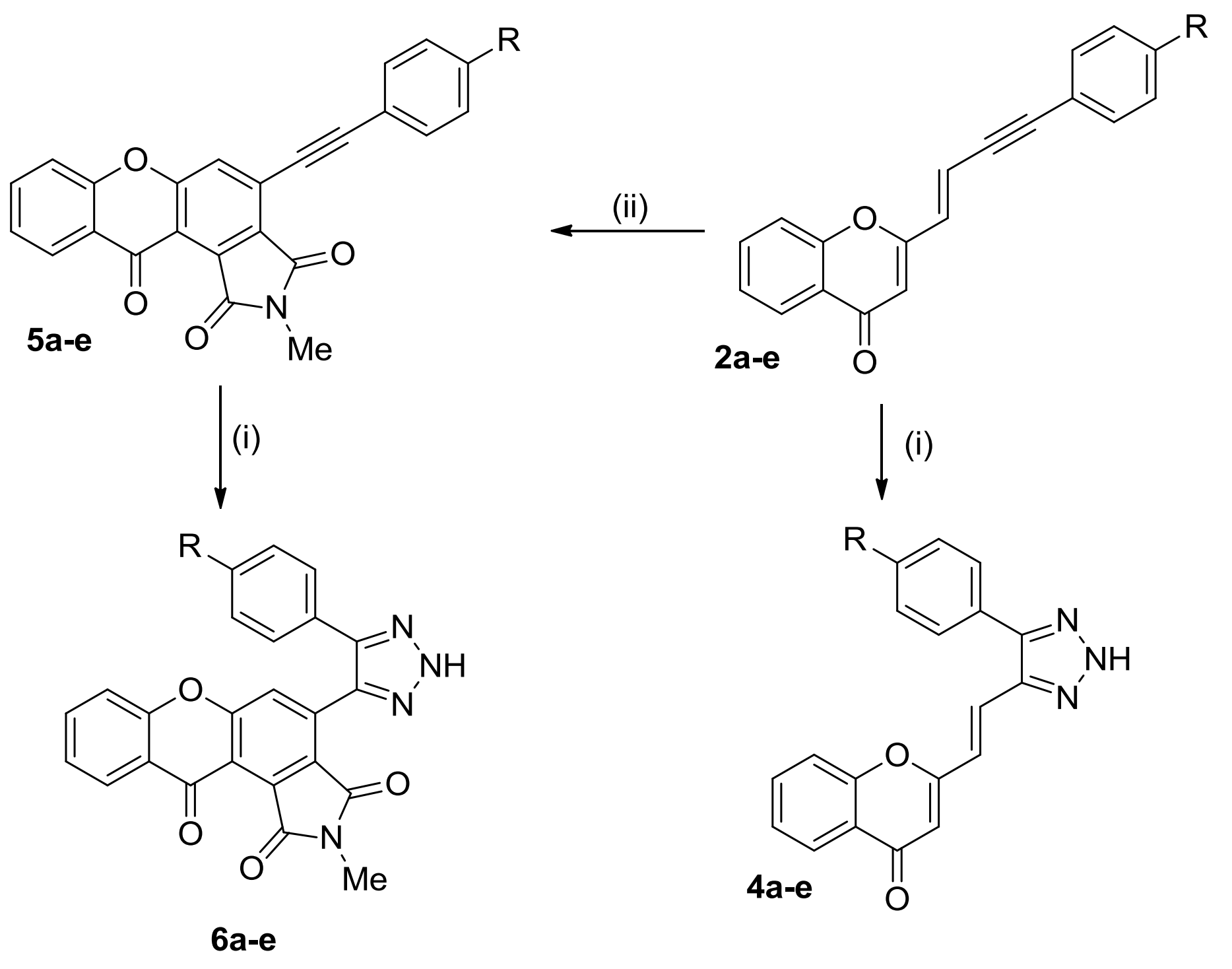
Scheme 1: Synthesis of chromone derivatives **1** and **2**; Conditions: (i) CH_3COCl, pyridine, rt, 1h; (ii) NaH, THF, reflux, 2h; (iii) *p*-TSA, DMSO, 100ºC, 2h; (iv) Na, EtOH, rt, 4h; a) R=H, b) R=OMe; c) R=Me; d) R=Br; e) $R=NO_2$

2-(4-Arylbuta-1,3-diene)chromones **1a-e** are transformed in 1-arylxanthones **3a-e** by refluxing them in 1,2,4-trichlorobenzene. The single bonds of the conjugated double bond system of 2-(4-arylbuta-1,3-diene)chromones **1a-e** are able to rotate under strongly energetic conditions (high temperature), and undergo electrocyclization and oxidation processes to afford the desired 1-arylxanthone derivatives **3a-e** (Scheme 2). The yields were worst in the cases of derivatives with electron-withdrawing substituents.



Scheme 2: Synthesis of xanthone derivatives **3**; Conditions: (i) I_2, 1,2,4-TCB, reflux, 48h; a) R=H, b) R=OMe; c) R=Me; d) R=Br; e) $R=NO_2$

2-(4-Arylbuta-1-en-3-yn-1-yl)chromones **2a-e**, have two important reactive sites (the diene system and the triple bond), which can be used separately to synthesize xanthones, 1,2,3-triazoles and xanthones bearing a 1,2,3-triazole moiety. Taking advantage of the triple bond and exploring the Huisgen cycloaddition reaction with sodium azide we are able to synthesize triazole derivatives **4a-e** (Scheme 3) bearing aryl and chromone substituents, in almost quantitative yields. Once again, the derivatives with electron-withdrawing substituents gave worst results. The Diels-Alder reaction of *N*-methylmaleimide and the dienic system of chromones **2a-e** afforded tetrahydroxanthones, which under further oxidation provided the xanthone derivatives **5a-e** (Scheme 3). Contrary to the previous reactions, the effect of electron-withdrawing substituents did not has particular relevance in this reaction.



Scheme 3: Synthesis of xanthone and triazole derivatives **4-6**; Conditions: (i) NaN_3, DMF, reflux, 2h; (ii) *N*-methylmaleimide, DMF, MW, 170ºC, 40min; a) R=H, b) R=OMe; c) R=Me; d) R=Br; e) $R=NO_2$

In chromones **2a-e**, it is possible to explore two different reactions (Diels-Alder and Huisgen cycloaddition) towards the synthesis of xanthones and 1,2,3-triazoles. Therefore, if we use the two reactions subsequently, in order words, Diels-Alder reactions to prepare xanthones **5a-e** and Huisgen cycloadditions to obtain triazoles **4a-e**, we can obtain pyrroloxanthones bearing a 1,2,3-triazole moiety **6a-e** (Scheme 3). The structures of the obtained compounds were elucidated by using 1D and 2D NMR techniques.

Conclusion

In this work we established new synthetic routes towards the synthesis of new heterocyclic compounds, emphasising the synthetic potential of the previous mentioned chromone derivatives **1** and **2**. We observed an electron-withdrawing substituent effect in the electrocyclization reaction and in Huisgen cycloaddition, however, this effect was not detected in Diels-Alder reactions. The newly complex synthesized structures evidence the synthetic potential of the referred chromone derivatives.

References

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