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Chromones as versatile building blocks in cycloaddition reactions

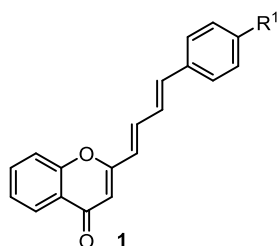
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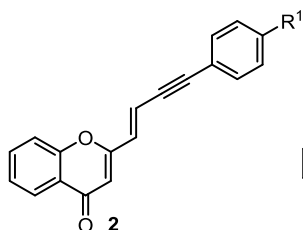
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4*H*-Chromen-4-ones commonly referred as chromones are a class of naturally occurring heterocyclic compounds implicated in a series of biological and pharmacological properties.[1] It is also an interesting scaffold involved in a range of chemical transformations for the preparation of novel and more complex oxygen-containing heterocyclic derivatives.[2]

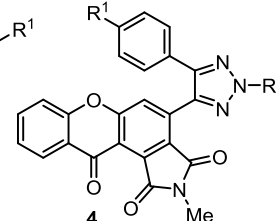
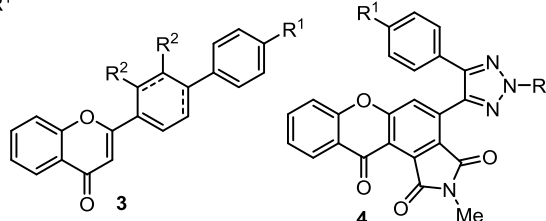
Following our interest in the chemistry of chromones, we design two different building blocks, 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **1** and (*E*)-2-(4-arylbut-1-en-3-yn-1-yl)-4*H*-chromen-4-ones **2**, and explore the reactivity of the unsaturated systems in cycloaddition reactions. In the former case, chromones **1** were used as dienes in microwave-assisted Diels–Alder (DA) reactions with various electron-poor and electron-rich dienophiles to provide flavone-type compounds **3**. [3] In the latter case, the diene system of chromones **2** was involved in DA reactions with *N*-methylmaleimide whereas the acetylene moiety react with sodium azide, via 1,3-dipolar cycloaddition reaction, to afford xanthene-1,2,3-triazole dyads **4**. [4] In this communication, we will present and discuss the synthetic details and spectroscopic characterization of the main products and some interesting byproducts, as well as the intermediate compounds isolated in each case.



Diels-Alder reaction with electron-poor and electron-rich dienophiles



Diels-Alder reaction with *N*-methylmaleimide and 1,3-dipolar reaction with sodium azide



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

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- [2] a) M.A. Ibrahim, T.E. Ali, Y.A. Alnamer, Y.A. Gabr, *Arkivoc* **2010**, (i), 98. b) C.M.M. Santos, A.M.S. Silva, *Eur. J. Org. Chem.* **2017**, *in press*.
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CHROMONES AS VERSATILE BUILDING BLOCKS IN CYCLOADDITION REACTIONS

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INTRODUCTION

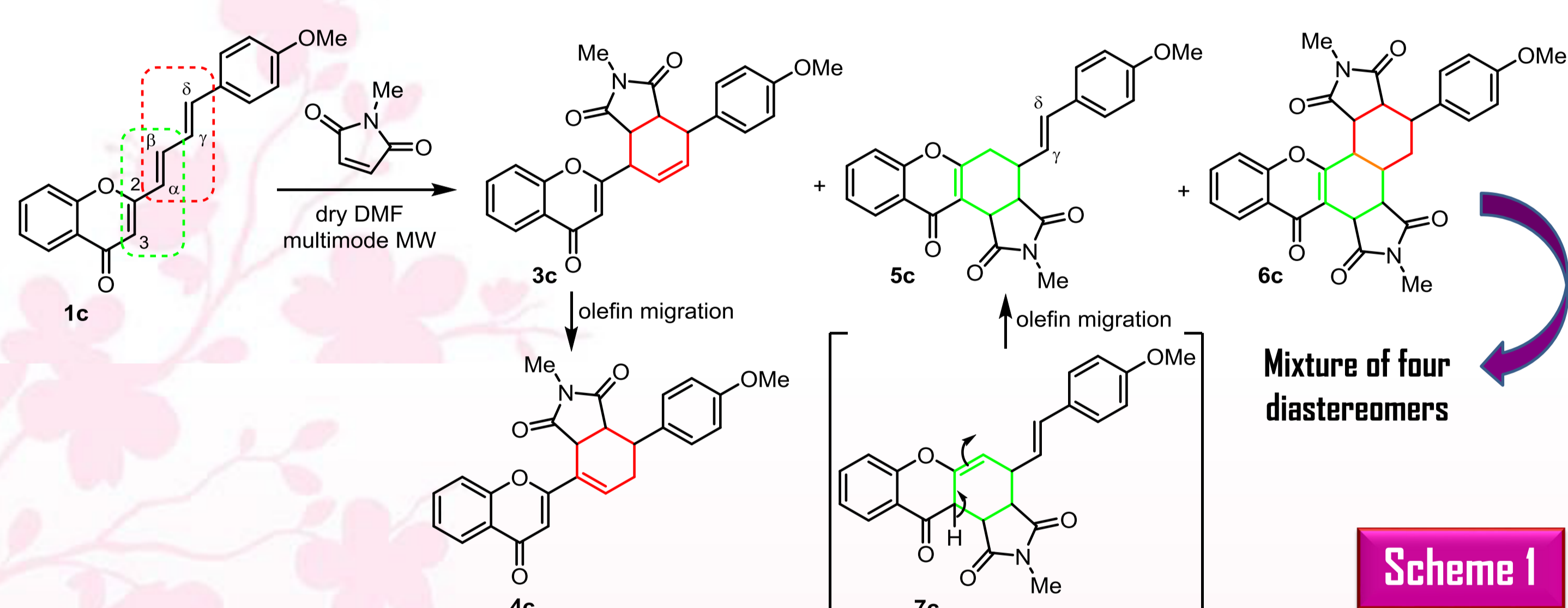
4*H*-chromen-4-ones commonly referred as chromones are a class of naturally occurring heterocyclic compounds implicated in a series of biological and pharmacological properties [1]. It is also an interesting scaffold involved in a range of chemical transformations for the preparation of novel and more complex oxygen- and nitrogen-containing heterocyclic derivatives [2].

Following our interest in the chemistry of chromones, we design two different building blocks, 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **1** and (*E*)-2-(4-arylbut-1-en-3-yn-1-yl)-4*H*-chromen-4-ones **2**, and explore the reactivity of their unsaturated systems in cycloaddition reactions.

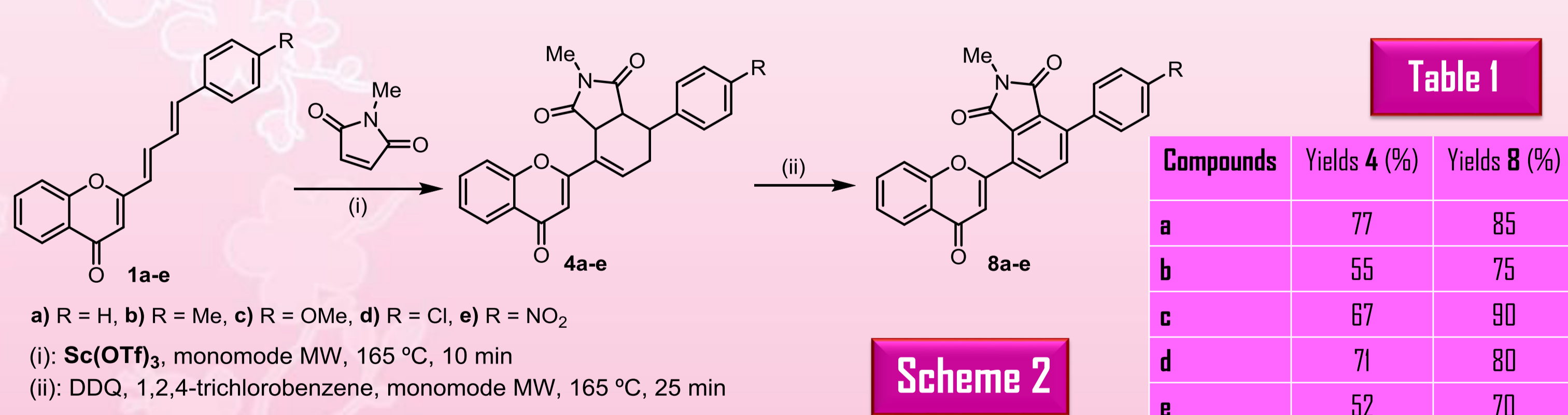
CHROMONES 1 AS DIENES IN DIELS-ALDER REACTIONS

Attempts for the reaction of chromone **1c** with *N*-methylmaleimide (NMM) under multimode MW irradiation (Scheme 1) led to the isolation of three main products **4c**, **5c** and **6c** [3]:

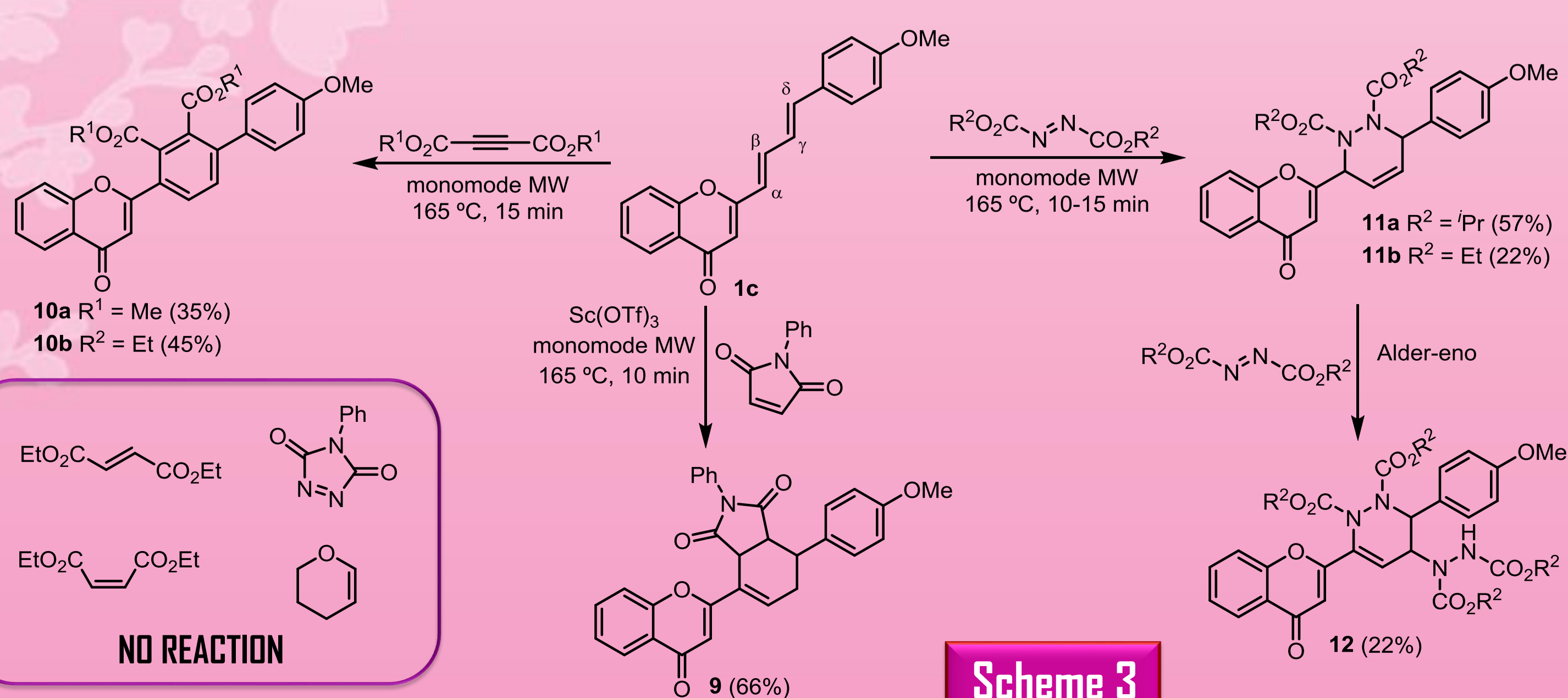
- ❖ Adduct **4c** in 21-48% yield, showing that $\alpha,\beta,\gamma,\delta$ -diene system of chromone **1c** was the more reactive one, and results from a spontaneous olefin migration of cycloadduct **3c**.
- ❖ Adduct **5c** in 6% yield, suggesting that 3,2: α,β -diene also undergo Diels-Alder (DA) reaction in less extension than $\alpha,\beta,\gamma,\delta$ -diene system.
- ❖ Bisadduct **6c** were isolated as a mixture of four diastereomers (two major and traces of the other two diastereomers) when a large excess of *N*-methylmaleimide is employed. Their formation involves a cascade of four reactions: DA to give intermediate **3c** and subsequent olefin migration to afford cycloadduct **4c**. The new diene on adduct **4c** easily undergoes a novel DA reaction to afford a new intermediate that provides bisadduct **6c** after another olefin migration.



- ❖ To improve the yields of adduct **4c**, several attempts were performed by reacting chromone **1c** with NMM in solvent-free conditions, under monomode MW irradiation. The best reaction conditions were achieved with 3 equiv of NMM in the presence of 1 equiv of Sc(OTf)₃ for 10 min at 165 °C (Scheme 2). The Lewis acid chelation with carbonyl group of chromone **1c** makes the 3,2: α,β -diene more electron-poor, unfavoring the DA reaction at this site.
- ❖ The optimized reaction conditions for chromone **1c** were applied to other chromone derivatives **1a,b,d,e** (Table 1).
- ❖ Adducts **4a-e** were oxidized to the flavone derivatives **8a-e** in high yields with DDQ under monomode MW irradiation (Table 1) [3].



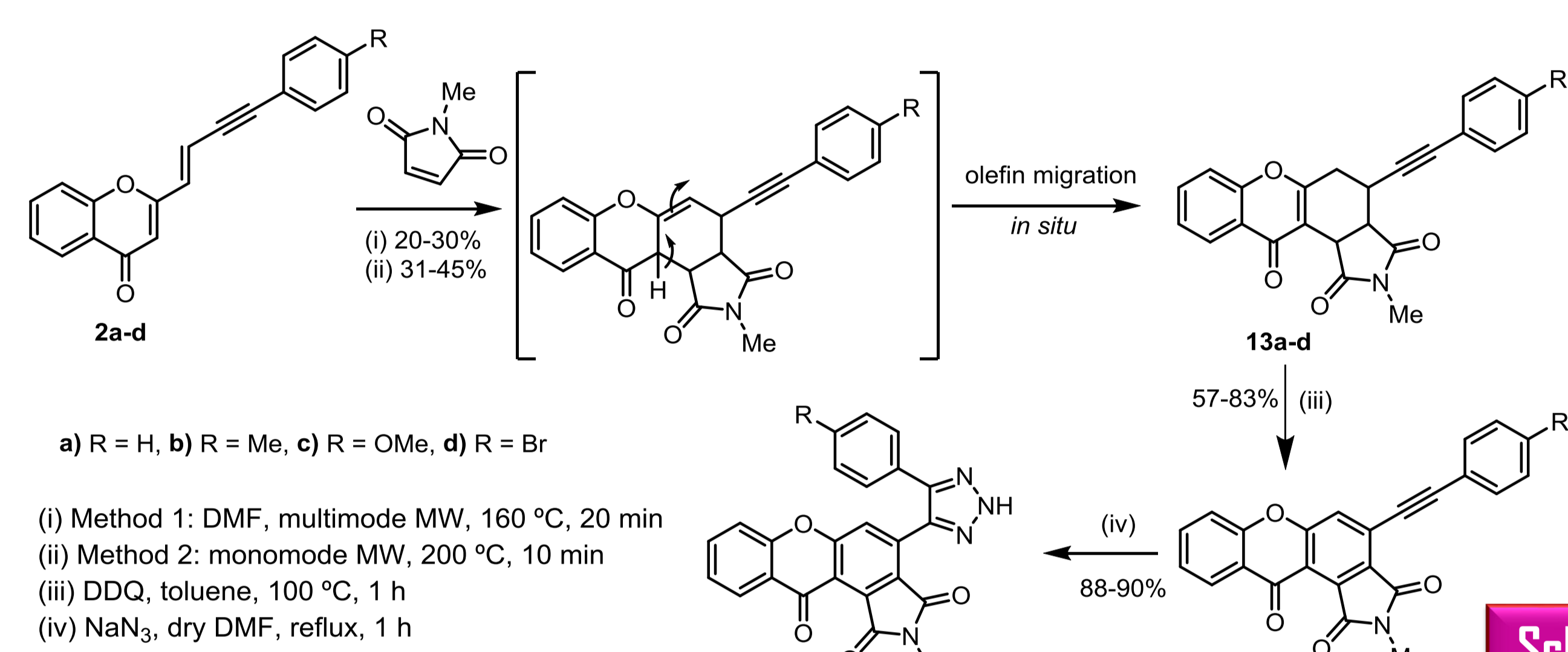
- ❖ DA reaction of chromone **1c** was extended to other dienophiles such as *N*-phenylmaleimide, dimethyl and diethyl acetylenedicarboxylate, diethyl and di-isopropyl azodicarboxylate, with success. No reaction occurs using diethyl fumarate and maleate, 4-phenyl-1,2,4-triazoline-3,5-dione and 3,4-dihydro-2*H*-pyran as dienophiles (Scheme 3) [3].



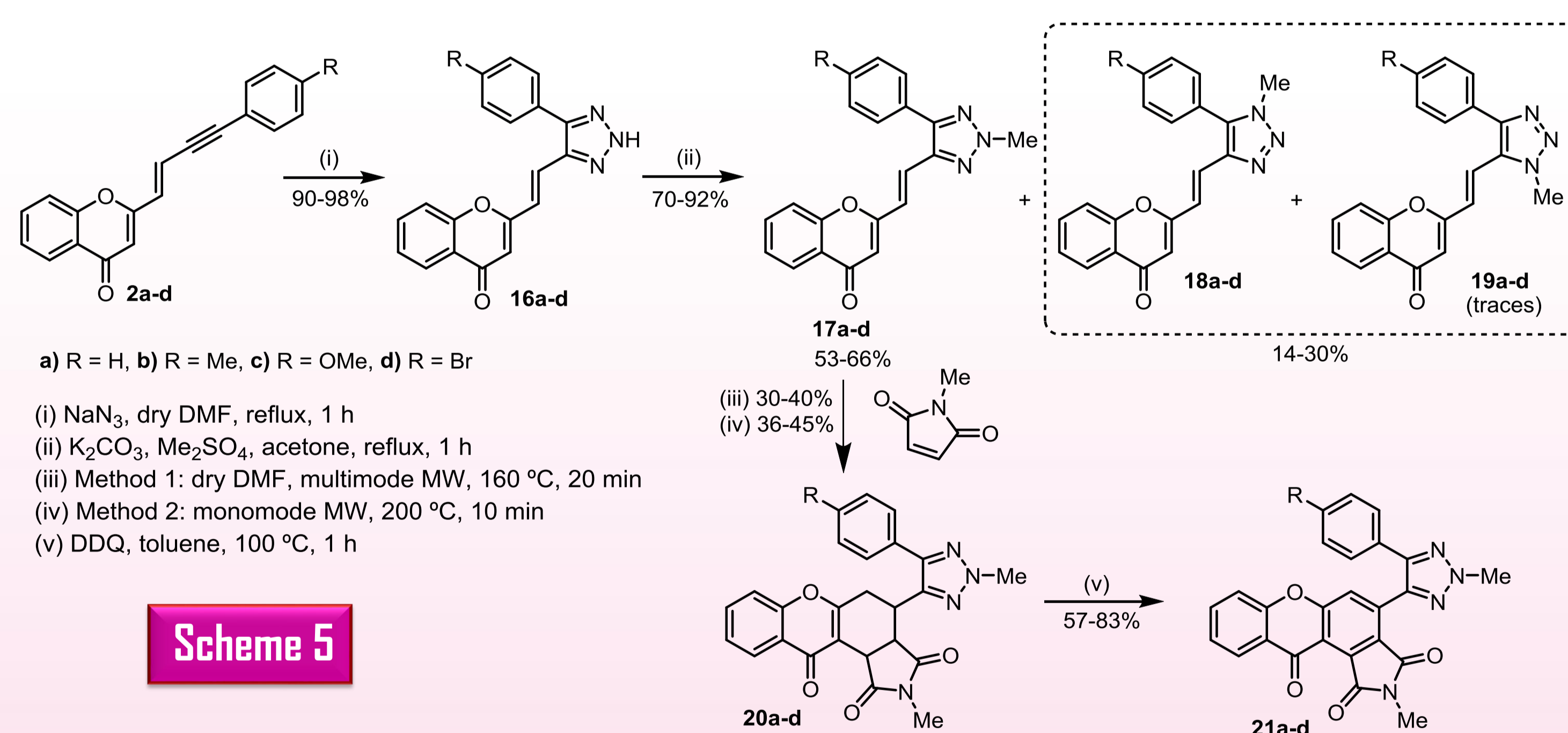
CHROMONES 2 IN CYCLOADDITION REACTIONS

- ❖ The reactivity of both unsaturated systems of chromones **2** was explored by two different strategies (Strategy A and Strategy B).

- ❖ **Strategy A:** (i and ii) DA reaction of chromones **2a-d** with NMM (using multimode and monomode MW irradiation) to afford adducts **13a-d**, (iii) oxidation with DDQ to provide the aromatized compounds **14a-d**, (iv) 1,3-dipolar cycloaddition reaction of the acetylene moiety with sodium azide to afford xanthone-1,2,3-triazole dyads **15a-d** (Scheme 4) [4].



- ❖ **Strategy B:** (i) 1,3-dipolar cycloaddition reaction of chromones **2a-d** with sodium azide to afford adducts **16a-d**; (ii) methylation of the NH group to avoid secondary reactions led to the formation of three isomers: **17a-d** as major isomers and an inseparable mixture of isomers **18a-d** and **19a-d**, in low yields; (iii and iv) DA reaction of **17a-d** with NMM using multimode and monomode MW irradiation to provide adducts **20a-d**; (v) oxidation with DDQ to provide the xanthone-1,2,3-triazole dyads **21a-d** (Scheme 5) [4].



CONCLUSIONS

- ❖ The $\alpha,\beta,\gamma,\delta$ diene system of chromones **1** were more reactive than 3,2: α,β -diene system, in DA reactions with electron-poor dienophiles.
- ❖ DA reaction of chromones **1** with NMM was more selective when performed in the presence of Sc(OTf)₃.
- ❖ Two different strategies were applied to the synthesis of xanthone-1,2,3-triazole dyads **15a-d** and **21a-d** starting from chromones **2**. Strategy A involved three steps (providing dyads **15a-d**) while one additional step for the protection of the triazol NH group was necessary in strategy B (providing dyads **21a-d**).
- ❖ All DA reactions were performed using multimode and monomode MW irradiation, in the late procedure reactions were performed in solvent-free conditions with small reaction times and higher yields were obtained.

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