Terceiro Simpósio Iberoamericano de Química Orgânica (SIBEAQO-III)

Book of Abstracts

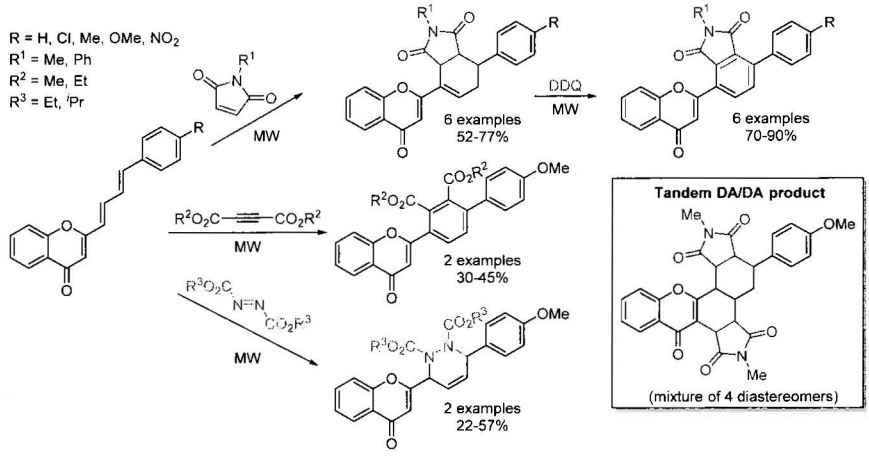
September 23-26, 2016
Porto, PORTUGAL

2-[(1*E*,3*E*)-4-ARYLBUTA-1,3-DIEN-1-YL]-4*H*-CHROMEN-4-ONES AS DIENES IN DIELS–ALDER REACTIONS: EXPERIMENTAL AND COMPUTATIONAL STUDIES

Albuquerque HMT,[a] Santos CMM,[a,b] Lima CFRAC,[c] Santos LMNBF,[c] Cavaleiro JAS,[a] Silva AMS.[a]

[a]*Department of Chemistry & QOPNA, University of Aveiro, Campus de Santiago, 3810-193 Aveiro, Portugal.* [b]*School of Agriculture, Polytechnic Institute of Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal.* [c]*CIQ-UP, Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade do Porto, Portugal.*
E-Mail: helio.alburquerque@hotmail.com

The synthesis and reactivity of 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones[1] as dienes in Diels–Alder (DA) reactions towards several electron-poor and electron-rich dienophiles under microwave irradiation was studied. The optimized reaction conditions were achieved by using *N*-methylmaleimide[2] as dienophile and $Sc(OTf)_3$ as Lewis acid under microwave-assisted and solvent-free conditions. The Lewis acid improved the reaction yields since it prevented the adducts obtained to undergo a second DA reaction, thus avoiding formation of a bisadduct. The α,β:γ,δ-diene of the starting chromones showed to be the most reactive and the computational results confirmed the experimental findings. Theoretical calculations also allowed explaining some unexpected lack of reactivity by some dienophiles. The adducts prepared were dehydrogenated by using DDQ, however, the aza-adducts showed to be sensitive to the high energetic reaction conditions necessary to perform the aromatization.



Ackowledgements
Thanks are due to University of Aveiro and FCT/MEC for the financial support of the QOPNA research unit (FCT UID/QUI/00062/2013) and CIQ-UP (Pest-C/QUI/UI0081/2013) through national founds 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. HMTA and CFRACL. are grateful to FCT for their PhD (SFRH/BD/86277/2012) and Post-doc (SFRH/BPD/77972/2011) grants, respectively.

References

(1) Esteves CIC, Santos CMM, Brito CM, Silva AMS, Cavaleiro JAS. *Synlett* **2011**, *2011*, 1403.
(2) Albuquerque HMT, Santos CMM, Cavaleiro JAS, Silva AMS. *Eur. J. Org. Chem.* **2015**, 4732.

2-[(1*E*,3*E*)-4-ARYLBUTA-1,3-DIEN-1-YL]-4*H*-CHROMEN-4-ONES AS DIENES IN DIELS–ALDER REACTIONS: EXPERIMENTAL AND COMPUTATIONAL STUDIES

Hélio M. T. Albuquerque,[a]* Clementina M. M. Santos,[a,b] Carlos F. R. A. C. Lima,[a,c] Luís M. N. B. F. Santos,[c] José A. S. Cavaleiro[a] and Artur M. S. Silva[a]

[a] Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal, helio.albuquerque@ua.pt

[b] Scholl of Agriculture, Polytechnic Institute of Bragança, 5300-253 Bragança, Portugal

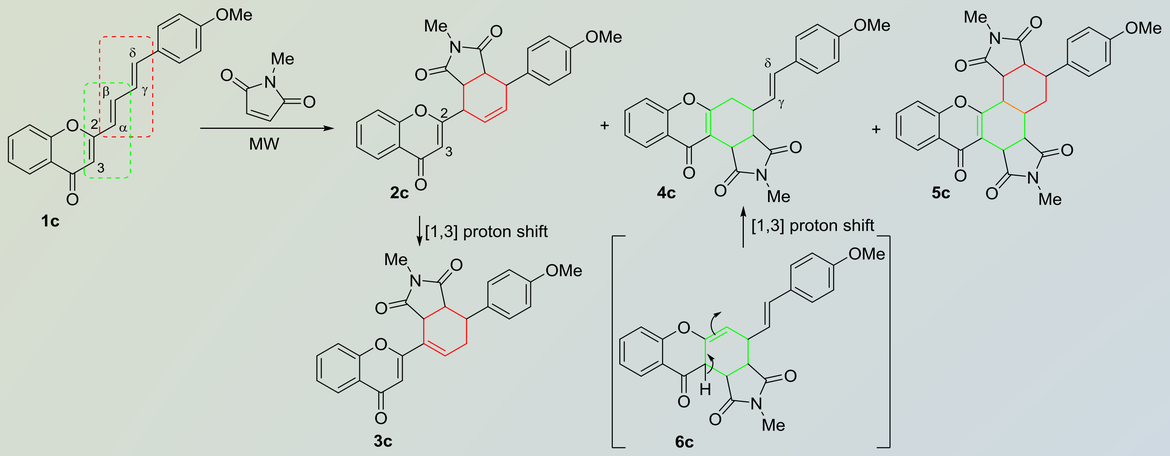
[c] CIQ-UP, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Portugal

Introduction

Chromones are a well-known class of heterocyclic compounds, which exhibit diverse biological properties.[1] These oxygen-containing heterocycles are also known for their ability to undergo several chemical transformations, such as condensation, oxidation, dimerization and Diels-Alder (DA) reactions, among many others.[2] Our research group reported some studies involving chromone derivatives in DA reactions, particularly under microwave (MW) irradiation. Following our previous studies in this field,[3] herein the experimental and computational studies on MW-assisted DA reaction of 2-[(1*E*,3*E*)-4-(4-methoxyphenyl)buta-1,3-dien-1-yl]-4*H*-chromen-4-ones[4] with the electron-poor dienophile *N*-methylmaleimide (NMM) are presented and discussed.

Experimental Studies

Table 1: DA reaction of chromone **1c** with *N*-methylmaleimide under MW irradiation.



Entry	NMM (equiv)	Solvent	T (°C)	Time (min)	Lewis acid	**3c** Yield (%)[a]	**5c** Yield (%)[a]	Recovered **1c** (%)[a]
1	1	DMF	160	40	---	31	---	10
2	3	DMF	160	40	---	30	---	---
3	5	DMF	160	20	---	35	25	---
4[b]	5	DMF	160	10	---	22	Traces	Traces
5	10	DMF	160	10	---	48	28	---
6	15	DMF	160	20	---	21	31	---
7[c]	10	DMF	130	10	---	30	Traces	Traces
8	2	---	165	15	$AlCl_3$	27	---	57
9	2	---	165	10	$Sc(OTf)_3$	62	---	21
10	3	---	165	10	$Sc(OTf)_3$	67	---	5
11	4	---	165	10	$Sc(OTf)_3$	67	---	8

[a] Isolated yields. [b] Adduct **4c** was isolated in 6% yield. [c] Adduct **2c** was isolated in 8% yield.

- The α,β:γ,δ-diene system of chromone **1c** showed to be the more reactive one, however, adduct **3c** was isolated in only 21-48% yield (Table 1, entries 1-7).

- Adduct **3c** results from a spontaneous [1,3] proton shift of cycloadduct **2c**. The low yields can be explained on the basis of a second DA reaction on adduct **3c**, which affords bisadduct **5c** (Table 1, entries 3, 5 and 6) in a tandem process.

- Adduct **4c** was obtained in only 6% yield suggesting that 3,2:α,β-diene also undergo DA reaction in less extension than α,β:γ,δ-diene (Table 1, entry 4).

- The addition of $Sc(OTf)_3$ in solvent-free conditions increased adduct **3c** yield by avoiding the formation of bisadduct **5c** (Table 1, entries 10 and 11). The Lewis acid chelation with carbonyl group of chromone **1c** makes 3,2:α,β-diene more electron-poor, unfavoring the DA reaction at this site (Figure 1).

- The optimized reaction conditions for chromone **1c** (Table 1, entry 10) were applied to chromone derivatives **1a,b,d,e** (Table 2).

Acknowledgements: Thanks are due to University of Aveiro and FCT/MEC for the financial support of the QOPNA research unit (FCT UID/QUI/00062/2013) and CIQ-UP (Pest-C/QUI/UI0081/2013) through national founds 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. and C.F.R.A.C.L. are grateful to FCT for their PhD (SFRH/BD/86277/2012) and Post-doc (SFRH/BPD/77972/2011) grants, respectively.

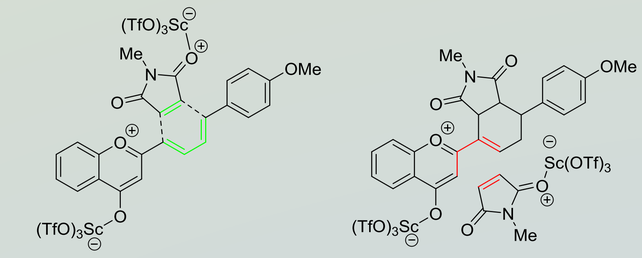
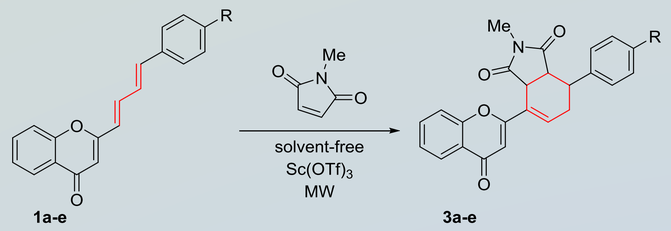


Figure 1: Lewis acid effect on DA reaction. **A)** $Sc(OTf)_3$ chelation with chromone **1c** and *N*-methylmaleimide. **B)** $Sc(OTf)_3$ chelation with adduct **3c** and *N*-methylmaleimide.

Table 2: DA reaction of chromones **1a-e** with *N*-methylmaleimide under MW irradiation.[a]



a) R = H, **b)** R = Cl, **c)** R = OMe, **d)** R = Me, **e)** R = NO_2

Entry	Derivative	**3** Yield (%)[b]	Recovered **1** (%)[b]
1	**1a**	77	---
2	**1b**	55	14
3	**1c**	67	5
4	**1d**	71	---
5	**1e**	52	25

[a] Reactions were carried out using 3 equiv of *N*-methylmaleimide, 1 equiv of $Sc(OTf)_3$ at 165 °C for 10 minutes under MW irradiation. [b] Isolated yields.

Computational Studies

- Computational results were obtained by M06-2X/6-31+G(d,p) level of theory.

- The s-*trans* conformation of chromones **1** is the major species at 160 ºC (0.89 molar fraction), however, since conversion between s-*trans* and s-*cis* (0.01 molar fraction) is rather fast at high temperatures, small quantities should suffice to DA reactions to proceed smoothly.

- Obtained products:
  - ✓ compound **4** should be a minor product of the DA reaction;
  - ✓ the preferred pathway for bisadduct **5** shall be a second DA reaction on adduct **3**;
  - ✓ the [1,3] proton shift of the DA adducts should be thermodynamically spontaneous.

- The Lewis acid:
  - ✓ shall bind preferentially to the C=O group of the chromone ring and chelation with other groups/atoms of the diene and of the dienophile is of minor importance;
  - ✓ increases the HOMO/LUMO gap between diene and dienophile (by decreasing the HOMO energy of the diene);
  - ✓ decreases the double bond character of the reactive chromone double bond, thus decreasing the reactivity of the 3,2:α,β-diene.

Conclusions

The α,β:γ,δ-diunsaturated system of chromone **1** was the most reactive diene in DA reaction, affording adduct **3**, which results from a DA reaction followed by a [1,3] proton shift. Experimental evidence was confirmed by computational studies, which indicated that derivative **4** should be a minor product of DA reaction, being the adduct **3** thermodynamically more stable. The addition of $Sc(OTf)_3$ increased significantly adducts **3** yields by chelation with carbonyl group of chromones **1**, avoiding the formation of bisadduct **5**.

Studies with other dienophiles were also performed and in some cases the corresponding adducts obtained in good yields.

References:

[1] A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte, F. Borges, *Chem. Rev.* **2014**, *114*, 4960-4992.
[2] M. A. Ibrahim, T. E. Ali, Y. A. Alnamer, Y. A. Gabr, *Arkivoc* **2010**, 98-135.
[3] H. M. T. Albuquerque, C. M. M. Santos, J. A. S. Cavaleiro, A. M. S. Silva, *Eur. J. Org. Chem.* **2015**, 4732-4743.
[4] C. I. C. Esteves, C. M. M. Santos, C. M. Brito, A. M. S. Silva, J. A. S. Cavaleiro, *Synlett* **2011**, 1403-1406.