o-Propargylphenols: A Gateway to Divergent Synthesis of 2-Substituted Benzofurans and Chromenes

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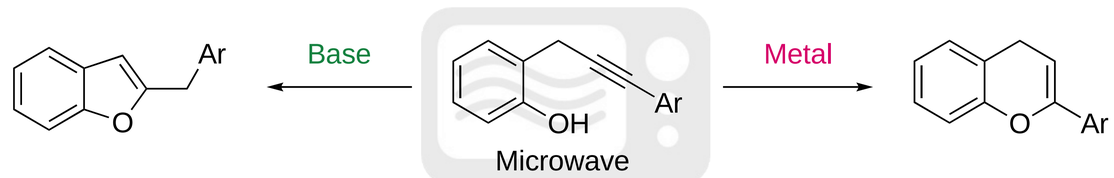
Introduction

Oxygen-containing heterocycles represent an important class of molecules, due to their physicochemical properties. In particular, two of the most studied scaffolds are benzofurans and chromenes, widely present as main skeletons in natural compounds and synthetic drugs.[1]

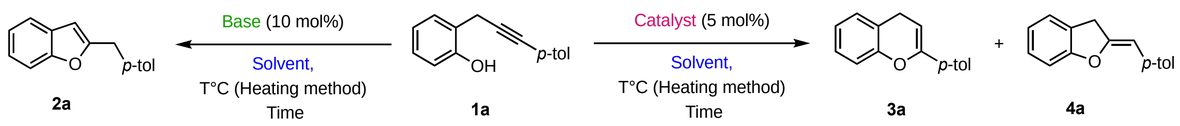
Due to their importance, chromene and benzofuran nuclei have gained enormous attention in the development of different synthetic strategies, involving a plethora of methods and type of reactions.[2] In this context, Divergent Synthethic Strategy emerges as a promising tool, in order to obtain a variety of products under different reaction conditions, starting from the same simple and affordable substrates.

Objective

On the bases of these premises, and in connection with the research interests of our group in diversity-oriented synthesis and discovery of novel strategies for the preparation of oxygen-containing heterocycles starting from arylalkynes bearing a proximate nucleophilic group,[3] the objective of this project is the development of a divergent approach for the regioselective synthesis of benzofuran and 4H-chromene nuclei starting from substituted *o*-propargylphenols.

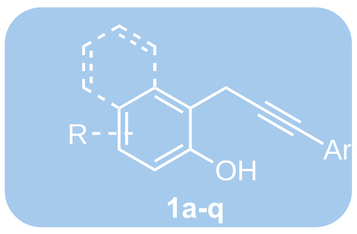


Screening of reaction conditions



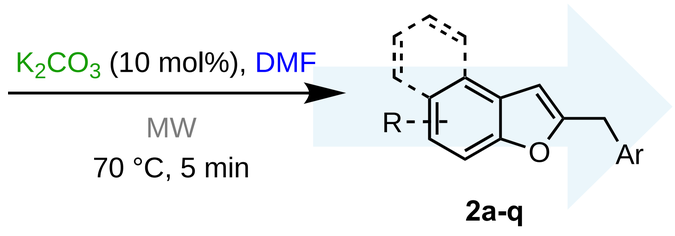
Entry	Solvent	Base	T (°C)	Time	2a yield (%) [a]	1a rec. (%)
1	DMF	$CsCO_3$	RT (o.b.)	16 h	-	Quant.
2	CH_3CN	$CsCO_3$	70 (o.b.)	16 h	46	-
3	CH_3CN	K_2CO_3	70 (o.b.)	16 h	75	-
4	CH_3CN	KOH	70 (o.b.)	16 h	35	-
5	CH_3CN	TEA	70 (o.b.)	16 h	-	Quant.
6	DCE	K_2CO_3	70 (o.b.)	16 h	-	Quant.
7	THF	K_2CO_3	70 (o.b.)	20 h	-	Quant.
8	MeOH	K_2CO_3	70 (o.b.)	24 h	12	76
9	DMSO	K_2CO_3	70 (o.b.)	2 h	79	-
10	DMF	K_2CO_3	70 (o.b.)	4.5 h	82	-
11	DMF	K_2CO_3	90 (o.b.)	1 h	93	-
12	DMF	K_2CO_3	90 (MW)	30 min	64	-
13	DMF	K_2CO_3	90 (MW)	10 min	83	-
14	DMF	K_2CO_3	90 (MW)	5 min	83	-
15	**DMF**	**K_2CO_3**	**70 (MW)**	**5 min**	**89**	**-**

Entry	Solvent	Catalyst	T (°C)	Time	3a Yield (%)	4a yield (%)
1	DCE	JohnPhosAuNTf$_2$	RT (o.b.)	24 h	21	-
2	DCE	JohnPhosAuNTf$_2$	70 (o.b.)	2 h	75	5
3	DCE	$AgSbF_6$	70 (o.b.)	24 h	NR	-
4	DCE	CuBr	70 (o.b.)	24 h	NR	-
5	DCE	$Fe(OTf)_3$	70 (o.b.)	24 h	NR	-
6	DCE	$NaAuCl_4$	70 (o.b.)	24 h	NR[c]	-
7	DCE	$Ph_3PAuNTf_2$	70 (o.b.)	24 h	26	-
8	DCE	IPrAuNTf$_2$	70 (o.b.)	3 h	31	-
9	DCE	$P(OAr)_3AuNTf_2$	70 (o.b.)	2 h	47	7
10	Toulene	JohnPhosAuNTf$_2$	70 (o.b.)	2 h	68	-
11	THF	JohnPhosAuNTf$_2$	70 (o.b.)	2 h	60	27
12	DMF	JohnPhosAuNTf$_2$	70 (o.b.)	1 h	52	-
13	DCE	JohnPhosAuNTf$_2$	70 (MW)	30 min	61	6
14	DCE	JohnPhosAuNTf$_2$	85 (MW)	15 min	68	5
15	**DCE**	**JohnPhosAuNTf$_2$**	**100 (MW)**	**15 min**	**79**	**9**

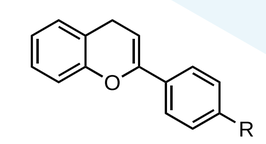


$AuPPh_3NTf_2$ (5 mol%), DCE

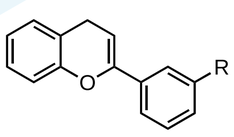
MW
100 °C, 15 min
4 Å mol sieves



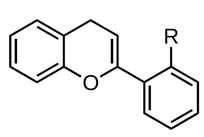
2-Propargylphenols have been selected as strategic starting material for the following reasons: (1) their chemistry is almost unexplored,[4] (2) their structure displays great potential as precursors for different cyclization paths, (3) the nucleophilic attitude of phenol oxygen is modulable by changing the reaction conditions, (4) cyclization products are relevant nuclei in the field of biologically active compounds.



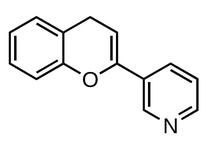
R= Me**, 3a**, 77% (+ **4a** 9%)
H, **3b**, 44% (+ **4b** 16%)
F, **3b**, 44% (+ **4b** 16%)
OMe**, 3d**, 69% (+ **4d** 0%)



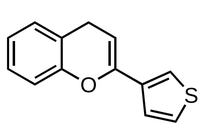
R= Me**, 3e**, 82% (+ **4e** 10%)
F, **3f**, 39% (+ **4f** 35%)
OMe, **3g**, 46%[a] (+ **4g** 13%)



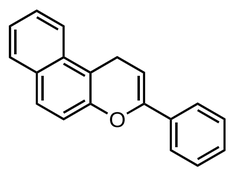
R= Me**, 3h**, 77% (+ **4h** 0%)
F, **3i**, 53% (+ **4i** 0%)[b]
OMe, **3j**, 85% (+ **4j** 15%)



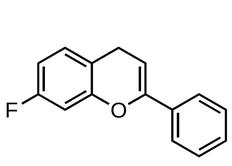
3k, 0% (+ **4k** 0%)



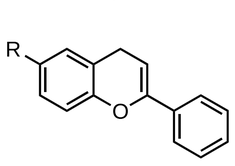
3l, 46% (+ **4l** 33%)



3m, 68% (+ **4m** 28%)

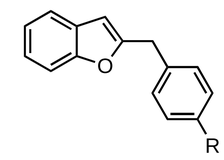


3n, 70% (+ **4n** 30%)

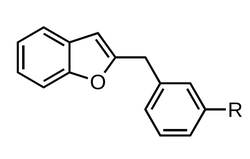


R= F, **3o**, 67% (+ **4o** 11%)
NO_2, **3p**, 46% (+ **4p** 53%)
NH_2, **3q**, 25% (+ **4q** 0%)[c]

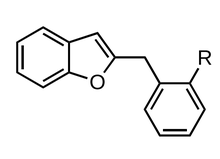
[a] highly instable;
*[b] 20% of benzofuran **2i**;*
*[c] 6% of benzofuran **2q**.*



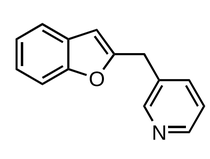
R= Me**, 2a**, 89%
H, **2b**, 87%
F, **2c**, 86%
OMe, **2d**, 79% (90°C)



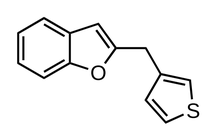
R= Me, **2e**, 72%
F, **2f**, 82%
OMe, **2g**, 98%



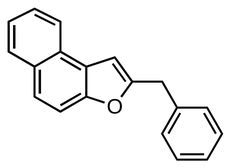
R= Me, **2h**, 91% (90°C)
F, **2i**, 80% (90°C)
OMe, **2j**, 93% (90°C)



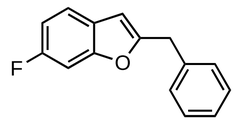
2k, 87%



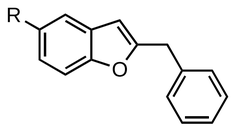
2l, 80%



2m, 58%

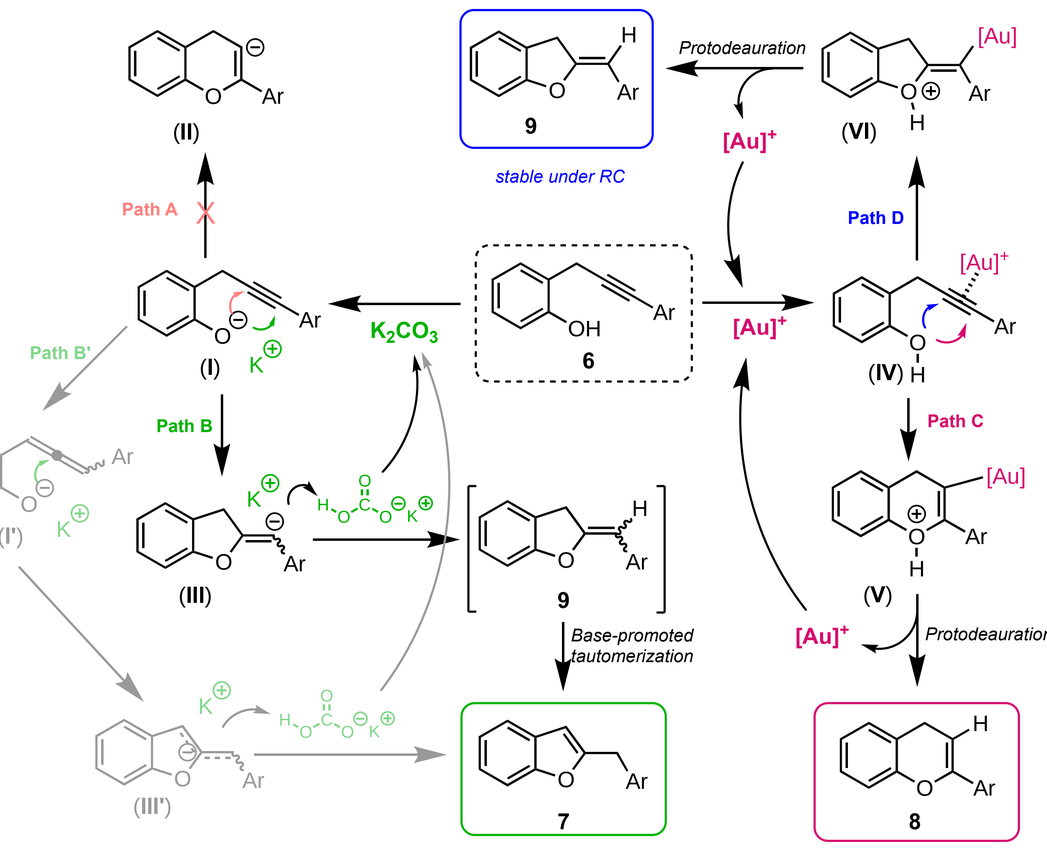


2n, 100% (110°C)



R= F, **2o**, 80%
NO_2, **2p**, 71%
NH_2, **2q**, 78%

Proposed mechanism



Conclusions

- A robust protocol for synthesizing o-propargylphenols (17 examples) was developed
- o-Propargylphenols showed to be versatile starting materials for simple and complex heterocyclic scaffolds, in particular for 17 benzofurans and 16 chromenes
- Benzofurans synthesized under base conditions presented regioselectivity, with yields ranging from 43 to 98%, while chromenes synthesized under cationic gold catalysis showed variable yields, 22–93%, with slightly lower regioselectivity
- We demonstrated the potential of diversity-oriented synthesis for molecular complexity exploration
- Future investigations will explore further potential of o-propargylphenols in the lab

References

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2. a) *Molecules,* **2020**, 25, 2327; b) *Adv. Synth. Catal.*, **2023**, 365, 1290.
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4. *Tetrahedron,* **2006**, 62, 6121-6131.

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