Synthesis of New Curcuminoid Derivatives with Potential Antioxidant and Hypoglycemic Properties

Catarina A. A. Henriques,[a,b] Ana P. Lopes,[a,b] M. Fátima M.M. Piedade,[b,c] M. Paula Robalo,[a,b]

a) Área Departamental de Engenharia Química, ISEL, Instituto Politécnico de Lisboa, R. Conselheiro Emídio Navarro, 1959-007 Lisboa, Portugal; b) CQE, Complexo I, Instituto Superior Técnico da Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal; c) Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

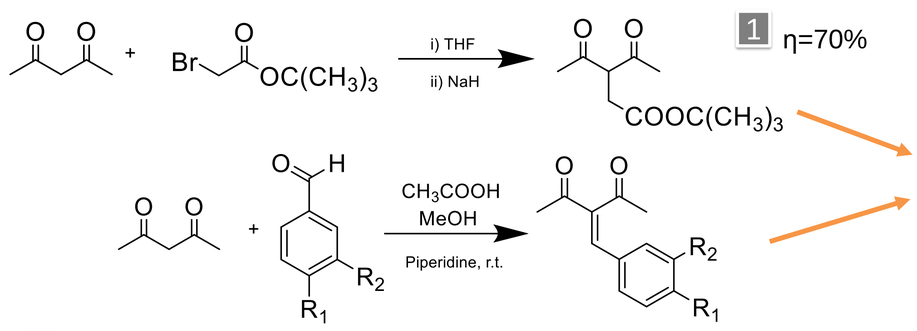
E-mail: mprobalo@deq.isel.ipl.pt

Introduction

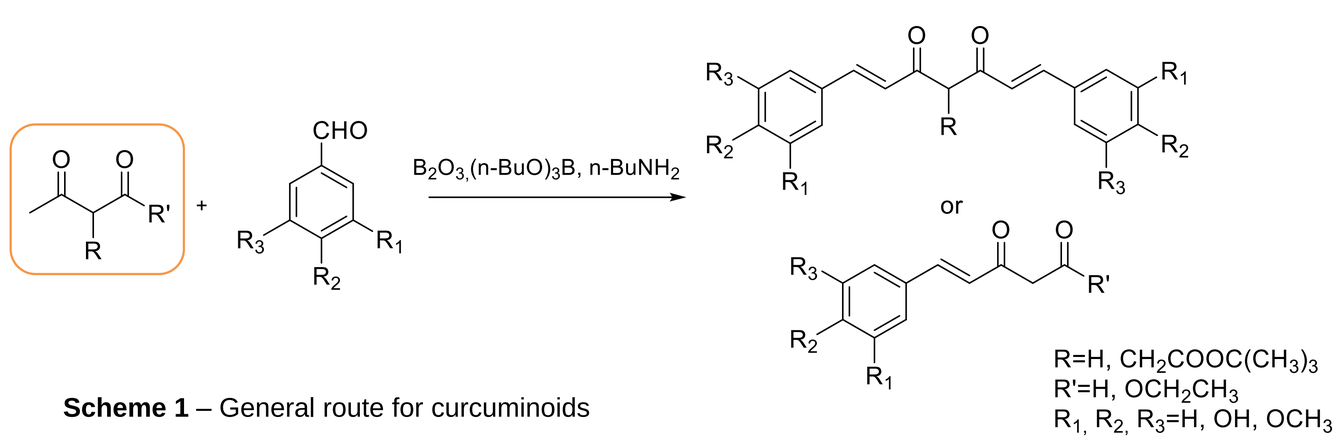
Curcumin is the principal constituent of turmeric i.e., the ground rhizomes of *Curcuma longa*. This compound has been used to therapeutic or protective effects against a variety of diseases such as cancer, lung, neurological, liver, metabolic, autoimmune, cardiovascular and numerous other chronic diseases. For this reason, curcumin is considered a nutraceutical that present some disadvantages such as its insolubility and stability in water.[1] Recent studies with diabetic rats suggest that substitution of the central position on the β-diketone chain leads to curcuminoid derivatives that potentiate the effects of curcumin, improving the fasting glucose and the endothelial function on type 2 diabetes.[2] Therefore, this work presents the synthesis of curcuminoid derivatives (scheme 1) [3,4] where several modifications have been introduced to the curcumin structure, such as the introduction of different groups in the β-diketone chain, the exchange of substituting groups in the aromatic rings or the formation of monocurcuminoids.

Synthesis

Functionalization of α-position



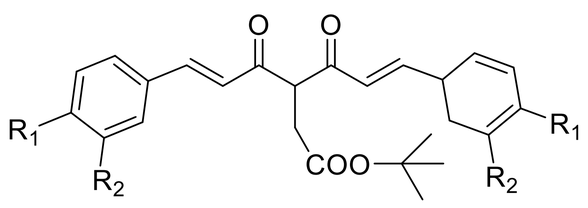
Curcuminoids Synthesis



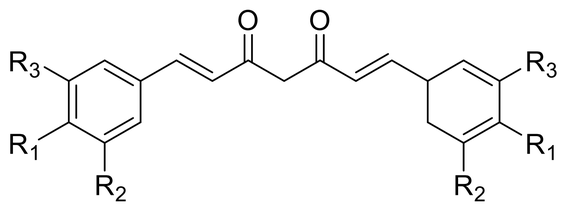
Scheme 1 – General route for curcuminoids

Results

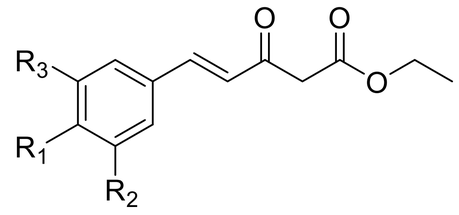
Compounds



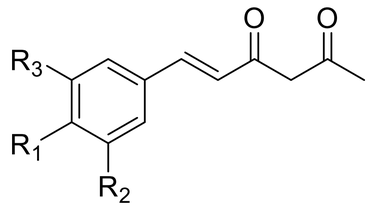
6 R1=OH; R2=OCH3; η=58%
7 R1=OCH3; R2=OH; η=75%



8 R1=OH; R2=OCH3;R3=H; η=72%
9 R1=OH; R2, R3=H; η=81%
10 R1=OH; R2, R3=OCH3; η=80%



11 R1= OCH3; R2=OH; R3=H η=84%
12 R1=OH; R2=OCH3; R3=OCH3



13 R1=OCH3; R2=OH; R3=H η=64%
14 R1=OH; R2=H; R3=H η=78%
15 R1=OH; R2=OCH3; R3=OCH3 η=52%

Keto-enol tautomerism

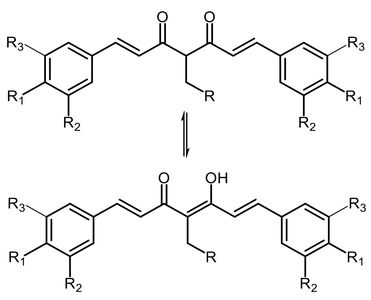


Table 1 – Tautomers distribution determined by NMR

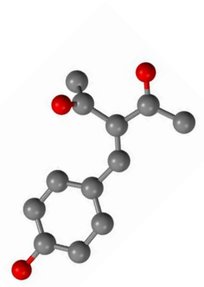
Compound	DK form (%)	KE form (%)
(6)	34	66
(7)	27	83
(8-10)	0	100
(11)	0	100
(13)	0	100

X-Ray Diffraction

6

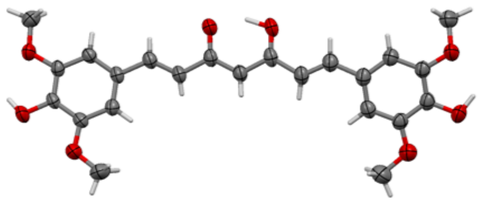
Space group: Monoclinic, P21/n

13



Space group: Monoclinic, P121/c1

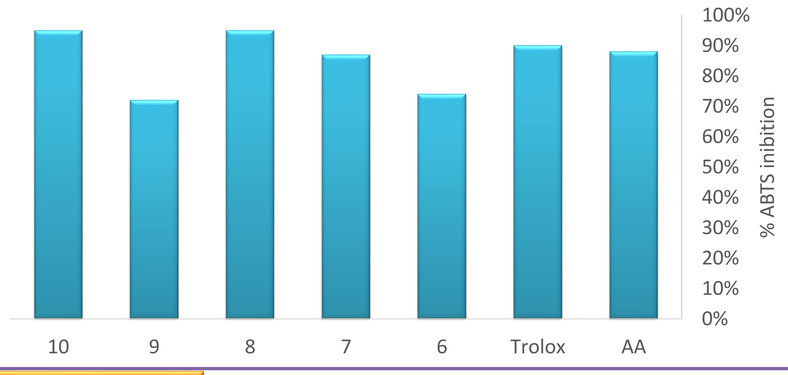
10



Space group: Monoclinic, P21/n

Antioxidant Capacity

ABTS Test (at 734nm)



Solubility Tests

Solubility in water: 2.5 x10^{-5} to 1.0 x 10^{-4} M

Conclusions

- The general synthetic routes proposed seemed to be convenient for the formation of the curcumin analogous with high purity and good to excellent yields.
- The α-substituent plays a crucial role in establishing the keto-enol tautomerism characteristic of these β-diketones. NMR analysis allowed the evaluation of keto-enolic tautomerism in solution for these compounds: except for compounds 6 and 7, which have both forms, all other compounds are in the enolic form; the X-ray structures of compounds 6 and 10 show the two different forms in the solid state.
- Curcumin showed higher antioxidant capacity than ascorbic acid (AA) and trolox; the presence of methoxy groups adjacent to the OH group seems to be important for the antioxidant capacity (compound 10). However, the exchange of positions of this group with OH (compounds 6 and 7) lowers the antioxidant capacity.

References

1. Gupta SC, Patchva S, Koh W, et al. Discovery of Curcumin, a Component of the Golden Spice, and Its Miraculous Biological Activities. *Clin Exp Pharmacol Physiol*. 2012;39(3):283–299.
2. Oliveira S, Monteiro T, Henriques L, et al. Development of a curcumin derivative with hypoglycemic properties: Impact on oxidative stress and endothelial function in type 2 diabetes. *Eur J Clin Invest*. 2019;49:125.
3. Martichonok V V, Chiang PK, Dornbush PJ, et al. On Regioselectivity of Aldol Condensation of Aromatic Aldehydes with Borate Complex of Acetylacetone. *Synth Commun*. 2014;44(9):1245–1250. doi:10.1080/00397911.2013.850094
4. Stanchev S, Jensen F, Manolov I. Synthesis and DFT Study of the Sprectral Behavior of New 4-Hydroxycoumarins. *Int J Quantum Chem*. 2008;108(8):1340–1351.

6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020

sponsored: MDPI *pharmaceuticals*