Rearrangement of 3-(4,5-dimethoxy-2-vinylphenyl)-2-methyl-5-nitroisoquinolin-1(2H)-one to 2-(6,7-dimethoxy-1-oxoisoquinolin-2(1H)-yl)-N-methylbenzamide: A Mechanistic Proposal †

Mónica Treus 1, Cristian O. Salas 2, Juan C. Estévez 1, Ricardo A. Tapia 2 and Ramón J. Estévez 1,*

1 Centro Singular de Investigación en Química Biológica e Materiales Moleculares and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; monicatreus@hotmail.co.uk (M.T.); juancarlos.estevez@usc.es (J.C.E.)
2 Departamento de Química Orgánica, Facultad de Química, Pontificia Universidad Católica de Chile, 702843 Santiago de Chile, Chile; cosalas@uc.cl (C.O.S.); rtapia@uc.cl (R.A.T.)
* Correspondence: ramon.estevez@usc.es; Tel.: +34-881-815-731

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1-Benzylisoquinolines are biogenetic precursors of a wide range of natural products of pharmacological interest, including benzo[c]phenanthridines, which exhibit antineoplastic activity. This pharmacological property has been related to the presence of a 2-phenylheteronaphthalene subunit embedded in its structural framework.

As a part of our past work on isoquinolines, we reported in 2010 novel access to 2-phenylnaphthalenes 4 from 1-benzylideneisoquinolines 1 via the novel (Z)-alkyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates 2 and 2-phenyl-naphthalenes 3, and their transformation into benzo[c]phenanthrin-1-ones 5 (Scheme 1) [1].


Treatment of the known 1-benzylideneisoquinoline 1a with LDA at 0 °C provided the styrlyurethane 2a resulting from a Hoffman-like elimination resulting with the cleavage of its C3-N bond. Ulterior reflux of a solution of compound 2a in o-xylene containing 10% Pd/C provided phenylnaphthalene derivative 3a as a result of a thermically induced electrocyclic cyclization. After,
compound 3a was easily converted into its N-methyl derivative 4a by treatment with MeI in a basic medium. Finally, benzo[c]phenanthride 5a was easily obtained by a Bischler–Napieralski cyclization carried out by refluxing a solution 4a and P2O5 in POCl3. This strategy for the synthesis of benzo[c]phenanthridin-1-ones 5a was also applied to the preparation of benzo[c]phenanthride 5b, via compounds 2b, 3b and 4b.


Proceeding as for 1a and 1b, the reaction of compound 1c with LDA in THF at 0 °C for 1.5 h gave a complex reaction mixture (Scheme 2). However, when a solution of compound 1c and NaH in DMF was heated at 130 °C for 3 h, the isoquinoline 8a resulted, probably by means of a nitro-facilitated thermal electrocyclic cyclization of 1a involving its N-ethoxycarbonyl substituent. This resulted in the formation of protoberberine derivative 6, which could spontaneously be converted into compound 8a by a Hofmann-like elimination by the action of hydride.

Methylation of 8a provided 8b, which when subjected to the conditions of the transformation of 2a into 3a did not gave the expected benzophenanthride 5c. Alternatively, 8b was subjected to a known protocol for the transformation of 3-(2-vinylphenyl)-isoquinolin-1(2H)-ones (8) benzo[c]phenanthridin-1-ones (5). The treatment of 8b with thallium trinitrate allowed us to obtain the acetal derivative 9, which was directly solved in a MeOH/H2O mixture and heated at 70 ºC for two days, after adding p-toluensulfonic acid [2,3]. Surprisingly, the resulting compound was the isoquinolin-1-one 10.

Scheme 3. Rearrangement of 3-(2-(2,2-dimethoxyethyl)-4,5-dimethoxyphenyl)-2-methyl-5-nitroisooquinolin-1(2H)-one (9) to 2-(6,7-dimethoxy-1-oxoisooquinolin-2(1H)-yl)-N-methylbenzamide (10): alternative mechanistic pathways.

Compound 10 could result from the expected 5c, via an unknown rearrangement. However, although this possibility was not discarded, we assumed that the nitro group prevented the cyclization required for the transformation of compound 9 into benzo[c]phenanthride 5c in favor
of a novel, complex rearrangement involving the transformation of 9 into the benzazepindione 11 (Scheme 3). A benzylic acid rearrangement could explain the transformation of compound 11 into compound 12, which could undertake a decarboxylative oxidation leading the isoquinoline 10.

Transformation of nitroisoquinoline 9 into benzazepindione 11 could occur via the mechanism depicted in Scheme 4.

Scheme 4. Rearrangement of -(2-(2,2-dimethoxyethyl)-4,5-dimethoxyphenyl)-2-methyl-5-nitroisoquinolin-1(2H)-one (9) to 2-(7,8-dimethoxy-1,2-dioxo-1,2-dihydro-3H-benzo[d]azepin-3-yl)-N-methylbenzamide (11).

Hydrolysis of ketal 9 provided nitroisoquinoline 13. Protonation of this compound resulted in the formation of its conjugated acid 14, which spontaneously opened to the corresponding δ-ketoacid amide 15. Isomerization of this compound to compound 16 was followed by an intramolecular Michael-like reaction leading to the complex oxazole 17. The opening of the oxazole ring of this compound gave the nitroso δ-ketoacid amide 18, which undertook a cyclization, via its enol 19, that provided the complex benzazetidine 20. Protonation of this compound, followed by the opening of the azetidine ring of the resulting conjugate acid 21 could explain the formation of the key nitrene 22, that should rearrange to the α-ketophenylacetic acid amide 23, precursor of the benzazepindione 11.

This mechanistic proposal for the striking transformation of isoquinoline 9 into isoquinoline 10 is open to discussion. Any comment or alternative mechanism will be welcomed.
References

