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Application of a catalyst-free Domino Mannich/Friedel-Crafts alkylation reaction for the synthesis of novel tetrahydroquinolines of potential antitumor activity

Juan-Carlos Castillo [a, b, **], Elizabeth Jiménez [c], Jaime Portilla [d], Braulio Insuasty [a], Jairo Quiroga [a], Rodolfo Moreno-Fuquen [e], Alan R. Kennedy [f], Rodrigo Abonia [a, *]

[a] Research Group of Heterocyclic Compounds, Department of Chemistry, Universidad del Valle, A. A. 25360, Cali, Colombia
[b] Grupo de Investigación Núcleo, Departamento de Química y Bioquímica, Universidad de Boyacá, Carrera 2a Este No. 64-169, Tunja, Colombia
[c] Grupo de Investigación en Bioquímica Aplicada, Department of Chemistry, Universidad de los Andes, Carrera 1 No. 18A-10, Bogotá, Colombia
[d] Bioorganic Compounds Research Group, Department of Chemistry, Universidad de los Andes, Carrera 1 No. 18A-10, Bogotá, Colombia
[e] Department of Chemistry, Universidad del Valle, A. A. 25360, Cali, Colombia
[f] WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, Scotland, UK

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ABSTRACT

A useful and efficient method to construct diversely substituted 1,2,3,4-tetrahydroquinolines in good to excellent yields has been developed through a catalyst-free Domino Mannich and intramolecular Friedel-Crafts alkylation reactions of *N*-arylamines with paraformaldehyde and electron-rich olefins *via* the formation of *N*-aryl-*N*-alkylmethyleneiminium ions as the key intermediates to afford the target products. Nine of the new compounds were evaluated in the US National Cancer Institute (NCI), where compound 5f (R1 = 6-MeO, R2 = *p*-ClC6H4 and X = pyrrolidin-2-onyl) presented a remarkable activity against 57 cancer cell lines, with the most important GI50 values ranging from 1.46 to 8.28 μM from *in vitro* assays. Further studies performed over the active compound 5f on HCT116 colon cancer cells indicated that its effect on cell death is exerted through a cell cycle arrest (S phase) in a dose dependent manner, as well as suppression on the cell proliferation process.

1. Introduction

Tetrahydroquinolines are important "privileged scaffolds" due to their presence in natural occurring products and their wide range of applications as drugs,[1a-c] pharmaceuticals,[1d] agrochemicals,[1e] dye-sensitized solar cells (DSSC),[1f-h] and chiral ligands in asymmetric synthesis.[1i-j] Particularly, the 1,2,3,4-tetrahydroquinoline is an important moiety which is found in numerous biologically active natural products, as well as synthetic pharmacologically relevant agents with interesting antiviral,[2a] antibacterial,[2b] antifungal,[2c] antimalarial,[2d] antitrypanosomal,[2e] antidepressant,[2f] and vasodilator activities.[2g] Regarding the cancer chemotherapy, the 1-aroyl-1,2,3,4-tetrahydroquinoline 1 had antiproliferative activity correlated with the inhibition of tubulin polymerization,[3a] whereas the torcetrapib 2,[3b] was developed to treat hypercholesterolemia and prevent cardiovascular disease (Fig. 1). The tetrahydroquinoline derivatives 3,[3c] were found to have moderate to high modulating activity in multidrug resistance (MDR), which is one of the obstacles in the chemotherapy of cancer.

Previously, we reviewed the most common synthetic routes to construct the 1,2,3,4-tetrahydroquinoline framework 5. The first one and more common route involves an intramolecular formation of the new C_4—C_{4a} bond starting with materials containing a benzene ring 4 (Entry 1, Scheme 1). Thus, numerous synthetic strategies with this requirement have been reported, involving Lewis and Brønsted acid-catalyzed intramolecular Friedel-Crafts reactions,[4a-c] Pd-catalyzed intramolecular Heck cyclizations of 2-iodo-*N*-arylamine containing allyl moieties,[4d-e] and intramolecular radical cyclizations of *N*-allyl-*N*-*o*-iodoacrylamides with Bu_3SnH/Et_3B,[4f] or secondary amides containing a xanthate moiety with lauroyl

* Corresponding author. Research Group of Heterocyclic Compounds, Department of Chemistry, Universidad del Valle, A. A. 25360, Cali, Colombia.
** Corresponding author. Grupo de Investigación Núcleo, Departamento de Química y Bioquímica, Universidad de Boyacá, Carrera 2a Este No. 64-169, Tunja, Colombia..
E-mail addresses: juacastillo@uniboyaca.edu.co (J.-C. Castillo), rodrigo.abonia@correounivalle.edu.co (R. Abonia).

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peroxide.[4g] Other less frequent synthetic approaches involved an intramolecular iodo-arylation of *N*-protected-*N*-allylaniline derivatives with iodonium ion (IPy_2BF_4),[4h] an organocatalytic asymmetric intramolecular hydroarylation of aniline derivatives bearing an α,β-unsaturated aldehyde moiety,[4i] an intramolecular epoxide ring-opening of diphenylamine,[4j] and *N*,*N*′-di(2-naphthyl)-1,4-diaminobenzene containing 2,3-epoxypropyl as N-substituent.[4k]

Alternatively, Katritzky et al. showed that *N*-aryl-1*H*-benzotriazole-1-methanamines 6 react with electron-rich alkenes under acid catalysis to led tetrahydroquinolines 5 *via* the *in situ* formation of *N*-arylmethyleneiminium ions 7 as the key intermediates (Entry 2, Scheme 1).[5a-d] Other reagents have also been used in the generation of the key methyleneiminium ions 7 for the synthesis of tetrahydroquinolines.[5e] Although the above methods undoubtedly provide access to a wide variety of structurally diverse tetrahydroquinolines, they had the disadvantages of requiring high reaction temperatures, undesired side reactions, metal-based or Lewis/Brønsted acid catalyzed reaction conditions. Nowadays, the development of alternative routes to construct substituted tetrahydroquinolines continue to be an important goal in contemporary organic synthesis, where the sequential creation of two or more C–C bonds in a single chemical operation is significantly valuable. Thus, in a continuation of our earlier studies on multiple bond-forming transformations (MBFTs) involving benzylamine derivatives as starting materials,[6a-e] we are reporting here an efficient metal- and catalyst-free approach to construct novel and diversely substituted 1,2,3,4-tetrahydroquinolines of biological interest from *N*-aryl-*N*-benzylamines as precursors under mild reaction conditions.

2. Results and discussion

This idea was based on the mechanistic hypothesis that a catalyst-free domino Mannich/intramolecular Friedel-Crafts alkylation sequence would be possible through the formation of an *N*-aryl-*N*-alkylmethyleneiminium ion type 10 as the key intermediate (Scheme 2). The present study was initiated with the stirring of a mixture of *N*-benzylaniline 8a (1.0 equiv.), polyformaldehyde (1.5 equiv.) and *N*-vinyl-2-pyrrolidone 9a (1.1 equiv.) in methanol at room temperature for 24 h. The reaction was complete after this time but a mixture of products was obtained. After performing a careful column chromatography, it was possible to isolate the tetrahydroquinoline 5a in only 16% yield.[6b] Encouraged by this result, a solvent screening revealed that solvents significantly influence the reaction yields because of the relative insolubility of the polyformaldehyde. Low yields were observed when solvents such as MeOH, AcOEt, THF or DMF were used. However, CH_3CN showed the best result, affording the desired compound 5a in 90% yield as unique product (Scheme 2). The overall eco-compatibility of the process is highlighted.

The main spectroscopic features of the structure of compound 5a corresponded to the presence of C=O absorption band at 1682 cm^{-1} in the IR spectrum. Six signals corresponding to methylenic protons between 1.92 and 4.50 ppm and a doublet of

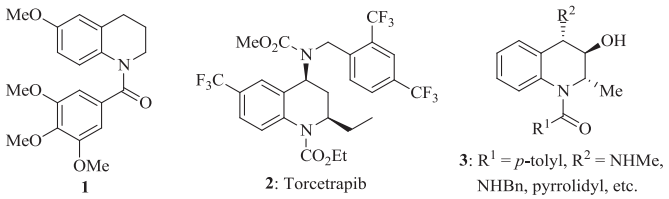
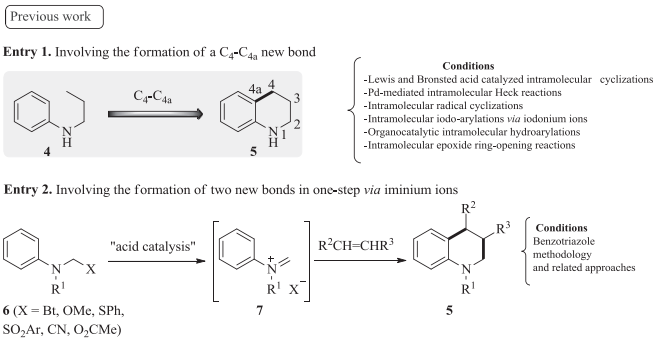


Fig. 1. Some tetrahydroquinoline derivatives with remarkable biological activity.

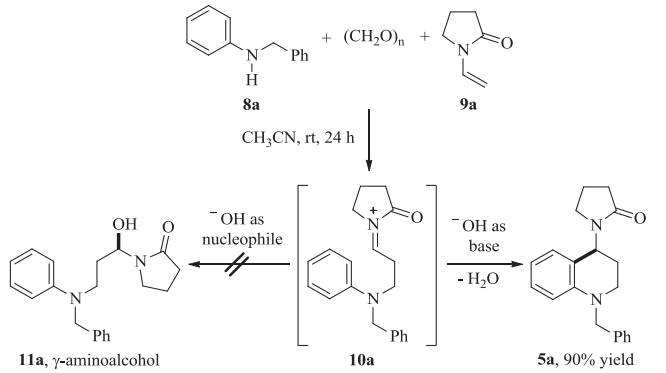


Scheme 1. More common synthetic approaches to construct the 1,2,3,4-tetrahydroquinoline framework **5**.

doublets integrating for 1H at 5.43 ppm (dd, $J = 5.5$, 9.0 Hz) assigned to the new aza–methynic (N–CH) proton, along with nine aromatic protons are the most relevant signals in the ^1H NMR spectrum. The presence of six methylene carbon atoms between 18.4 and 55.3 ppm, a signal of the aza–methynic carbon atom (N–CH) at 48.2 ppm, seven aromatic CH, three quaternary Cq carbon atoms and the (C=O) at 175.5 ppm in the ^{13}C NMR spectrum, are in agreement with the proposed structure for compound 5a. Finally, a molecular ion with *m/z* 306 and a base peak with *m/z* 83, also confirmed its structure.

With the optimal reaction conditions in hand, we turned our attention to obtain various *N*-arylimines from solvent-free reactions between equimolar amounts of several anilines and diverse aromatic aldehydes. Subsequently, the reduction of the imines by treatment with $NaBH_4$ in methanol at room temperature afforded the corresponding *N*-aryl-*N*-benzylamines **8b–l** in quantitative yields. The appearance in each case of an IR absorption band attributable to the N–H functionality in the 3373–3442 cm^{-1} range confirmed the reduction of their corresponding *N*-arylimines. The fully characterization of compounds **8b–l** is reported in the Experimental Section.

In order to explore the scope and limits of this Domino Mannich/Friedel-Crafts alkylation type reaction, some electron-rich alkenes **9a–c** and polyformaldehyde were subjected to reaction with the previously synthesized amines **8** along with the commercially available heterocyclic amines **8p–q** and primary amine **16** under the established procedure. The results are listed in Table 1. The reaction was found to be general, and diversely substituted tetrahydroquinolines **5a–p** were synthesized. It was found that both electron-donating and electron-withdrawing substituents on the benzene ring of **8** were suitable for this



Scheme 2. Selective synthesis of the tetrahydroquinoline **5a** from the *N*-benzylaniline **8a** in CH_3CN at room temperature.