A Convenient Formal [4 + 2] Heterocyclization Route to Bis (triflyl)tetrahydroquinolines

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Abstract: We report the sustainable and efficient synthesis of a new type of quinoline derivatives bearing one or two SO$_2$CF$_3$ groups. The protocol is metal-, catalyst- and irradiation-free, involves the use of readily available and stable precursors, and avoids the formation of side products. Also, the mild conditions of the process allow the tolerance of a wide range of functional groups.

The tetrahydroquinoline (THQ) heterocyclic scaffolds is widely found in a large number of natural products, such as angustureine, benzastatin D, and pharmaceutically active drugs (Scheme 1, top). [1] As a result, the development of efficient synthetic strategies to this privileged nitrogen heterocycle has experienced notable interest. [1] Main synthetic approaches are Povarov reaction (Scheme 1a), partial reduction of quinolines (Scheme 1b), and transition-metal catalyzed cyclizations (Scheme 1c). Despite the power of the above methods, they normally use harsh reaction conditions, some of them utilize expensive transition metals, and cause environmental pollution. The widespread occurrence of sulfones in pharmaceuticals, agrochemicals, and advanced materials, coupled to its synthetic power makes the sulfone motif as a very attractive functional group. [2] Among sulfones, the SO$_2$CF$_3$ (Tf, triflyl) group is of particular attractiveness because its presence in an organic molecule improves the bioavailability. [3]

We describe herein a novel and sustainable approach towards a class of unprecedented THQs containing a Tf$_2$C unit, based on a formal [4 + 2] heterocyclization from 1-(2-aminophenyl)prop-2-en-1-ol precursors (Scheme 1d). Low energy consumption, the absence of any metal or catalyst, use of equimolar reactants, efficiency, simple work-up, and the use of a safe solvent are the main features of our synthetic protocol to meet some of the principles of green chemistry. [4]

Yanai has reported that betaine 1 having both a 2-fluoropyridinium cation as well as a stabilized carbanion moiety quickly equilibrated in acetonitrile to form mixtures of the betaine along with (CF$_3$SO$_2$)C=CH$_2$ and volatile 2-fluoropyridine, which permits it to be employed as shelf-stable, eco-

Scheme 1. Selected examples of natural products and drugs containing the THQ motif (top) and synthetic approaches (bottom).
friendly[5] and easy-to-handle source of \((\text{CF}_3\text{SO}_2)_2\text{C} = \text{CH}_2\).[6] We have recently taken advantage of this ability of 1, revealing the usefulness of 1-arylbuta-2,3-dien-1-ols as building blocks in the stereocontrolled preparation of bis(triflyl)ated \(\alpha,\beta\)-enones and indolines.[7] In continuation of this effort, when we used precursor 2a possessing a 1-(2-aminophenyl)-3-phenylprop-2-en-1-ol moiety, a new product, bis(triflyl)ated tetrahydroquinoline 3a was isolated (Scheme 2). Captivated by the unanticipated discovery, we aspired to comprehensively study this transformation. The effect of solvents (water, ethanol, acetone, ethyl acetate, acetonitrile, toluene, and DCE) was evaluated. The reaction gave rise to the desired product 3a in more of the tested solvents, but did not proceed in hot water and evolved poorly in ethanol (Scheme 2). Ethyl acetate was selected as the solvent of choice taking into account environmental, health and safety criteria.[8] We suspect that the assembly of \(\text{Tf}_2\text{C} = \text{CH}_2\) as 2-\(\pi\) partner could be realized through the union with and in situ generated aza-ortho-quinone methide[9] via a cascade reaction. Moreover, conducting the reaction in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) did not trim the yield, thus discarding the implication of radical intermediates.

With the optimized condition on hand, the scope for the THQ formation reaction was investigated. A good tolerance to the protective group at the anilide moiety was observed. For the 1-(2-aminophenyl)prop-2-en-1-ol precursor, the electronic properties of the anilide ring in 2a–q did not importantly influence the performance of the annulation sequence and good yields of bicycles 3a–q were achieved (Scheme 3). Interestingly, placement of either aliphatic or aromatic (both electron-rich and electron-poor) scaffolds in the starting prop-2-en-1-ol moiety was well tolerated, and the desired benzo-fused THQs 3 were obtained in good yields. Besides, the C-halogen functionality is compatible with this transformation, and may supply a reactive platform for further functionalization of the THQ core through cross-coupling protocols. Compounds 3 are potentially valuable as its scaffold incorporates a THQ core, a bis(triflyl) functionality and an alkene moiety. However, when the protocol was applied to 2,3-disubstituted alkenol 3p–Me, a complicated mixture was formed and the assembly of the desired azacycle could not be attained (Scheme 3).

Allylic alcohols 4a–c showed the same above reactivity when they were used instead of isomeric 2 as starting materials for the formation of THQs 3 (Scheme 4a). However, the use of tertiary allylic alcohol 5 resulted in a dramatic influence in the reactivity and bis(triflyl)ethylated DHQ 6 was formed as exclusive product (Scheme 4b).

The reaction between aminophenyl-tethered alkenol 2a and betaine 1 was investigated without isolation of bis(triflyl)ated tetrahydroquinoline 3a through the further addition of a base. Thus, bis(triflyl)ated adduct 3a suffered in situ a loss of TfH to provide 3-[(trifluoromethyl)sulfonyl]-1,2-dihydroquinoline 7a in a 91% overall yield. It should be noted that the hydrodetriflylation step proceeded with total selectivity giving rise exclusively to the 1,3-diene moiety. Several 1,2-dihydroquinoline-based triflones 7 were synthesized running the reaction in this manner. This one-pot protocol allowed us the preparation of 1,2-dihydroquinoline-based triflones 7a, h, j in excellent yields starting from alkenols 2 and betaine 1 (Scheme 5).

Next, we explore the substrate scope of the intermolecular annulation by the reaction of betaine 1 with (2-aminophenyl)
methanols in which the alkene has been replaced by hydrocarbons with different degree of unsaturation. Functionalized anilides with alkynol instead of alkenol substituents gave complex mixtures of products, likely due to off-target reactions between the alkyne and Tf₂C=CH₂.

Notably, as shown in Scheme 6, the reaction progressed in hot ethyl acetate with a variety of 1-(2-aminophenyl)buta-2,3-dien-1-ol precursors 8ₐ–j, bearing substituents of distinct electronic nature in different positions at the benzene ring, affording the required bis(triflyl)ated THQs 9ₐ–h in good yields. Besides, the reaction proceeded well when different amide-like functionalities were incorporated in the nitrogen atom. Considering the relevance of organic compounds bearing C=C bonds, the reaction between precursor 8ₐ and deuterated Yanai’s reagent [D₂]₁ was explored. Note-worthy, bis(triflyl)ated THQ [D₂]₉ₐ was smoothly obtained in 77% yield (Scheme 6). Due to the widespread use of allenes as versatile building blocks for the synthesis of functionalized organic compounds of chemical and pharmacological relevance, the presence of an allene moiety is relevant as it may enable further functionalization.

To demonstrate the synthetic utility of our protocol, follow-up transformations were performed. For instance, we easily transformed bis(triflyl)ated THQ 3₃c into (E)-4-styryl-3-(triflyl)quinoline 10c by sequential basic and acidic treatment (Scheme 7a, left). Besides, bis(triflyl)ated THQ 3₃f underwent Suzuki-Miyaura coupling in aqueous medium with concomitant TfH release to provide triflylated dihydroquinoline (DHQ) 7fa (Scheme 7a, right). Base-promoted loss of TfH in bis(triflyl)ated THQs 3₃c and 3₃h followed by hydrogenation yielded 4-phenethyl-3-(triflyl)quinoline 11h (Scheme 7b, left) and 4-phenethyl-3-(triflyl)-1,2-dihydroquinoline 12c (Scheme 7b, right), respectively. Furthermore, selective ring opening of bis(triflyl)ated THQ 3₃a to yield 13a occurred under reductive conditions (Scheme 7c, left), while formation of Tf-decorated enal 14a proceeded smoothly upon treatment of 3₃a with ozone (Scheme 7c, right). Detriflylation of allenyl-THQ 9b was achieved under basic conditions furnishing the stable trienyl DHQ 15b, which suffered further hydration under Au-catalysis giving rise to ketone 16b (Scheme 7d). Noteworthy, all the transformations depicted in Scheme 7 were performed in one-pot from the appropriate precursors 2 or 8 without isolation of bis(triflyl)ated THQs 3 or 9.

A possible pathway for the formation of bis(triflyl)ated tetrahydroquinolines 3 and 9 from (2-aminophenyl)-tethered allenols(allenols) 2 and 8 is depicted in Scheme 8. First, the azato-quinone methide INT-I should be generated from 2 and 8 through dehydration catalyzed by bis(trifluoromethyl)sulfonyl methane A, which may be formed in situ from betaine 1 in
presence of water.\textsuperscript{13}\textsuperscript{a} Afterward, the formation of a zwitterionic intermediate INT-II should take place through nucleophilic attack of the nitrogen atom of species INT-I onto the methylene carbon atom of in situ generated \textit{TF}$_2$C=\textit{CH}$_2$. Ring closure with concurrent formation of THQs 3 and 9 would finally occur by intramolecular attack of the bis(triflyl) carbamation towards the allyl carbocation.

To summarize, the easily prepared and bench stable 2-(2-fluoroprop-1-yloxy)quinoline 1 is competent for the user-friendly preparation of tetrahydroquinolines bearing one or two SO$_2$CF$_2$ groups. This sustainable approach is carried out in ethyl acetate under ambient conditions, does not require the use of metals, additives or irradiation, and is applicable to various types of unsaturated alcohols.

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Conflict of Interest

The authors declare no conflict of interest.

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The formation of intermediate aza-ortho-quinone methide INT-I from alkenols 2 and 8 may be catalyzed by bis((trifluoromethyl)sulfonyl)methane A, which arises from betaine 1 in presence of water, and should be ascribed to its acidic nature. For the use of Tf₂CH-based carbon acid 1 as acid catalysis in Mukaiyama aldol reaction by Yanai et al., see Ref. [6b].