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Formation of substituted *N*-oxide hydroxyquinolines from *o*-nitrophenyl Baylis–Hillman adduct: a new key intermediate intercepted by ESI-(+)-MS(/MS) monitoring

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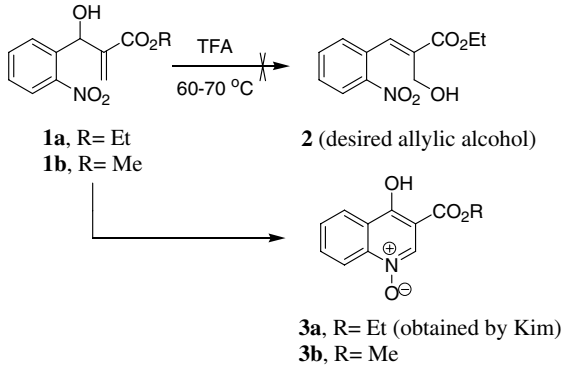
Abstract—A new mechanistic proposal on the formation of *N*-oxide hydroxyquinolines from BH adducts based on the interception by electrospray ionization mass spectrometry of a new key *o*-trifluoroacetylated intermediate.

Quinolines are outstanding among the heterocycles. This uniqueness arise mainly from their close association to biologically active compounds such as those with anti-malarials,[1] substances acting on the central nervous system[2] and anti-tumorals.[3] This prominent pharmacological importance has therefore motivated many efforts to find efficient methodologies for the preparation[4] of quinolines. *N*-oxide quinolines are also important in heterocyclic chemistry since they act as efficient intermediates when directing aromatic electrophilic substitutions.[5]

The Baylis–Hillman (BH) reaction is of major importance in organic synthesis[6] and has been increasingly used to form new C–C σ bond. This single-step versatile reaction yields highly functionalized molecules (α-methylene-β-hydroxy derivatives) which are conveniently manipulated as key synthons in various synthetic approaches.[6,7] BH adducts are therefore unique building blocks and have found important applications such as in the synthesis of bioactive heterocyclic compounds with potential pharmaceutical or commercial applications.[8,9]

Seeking to prepare some allylic derivatives, Kim et al.[10] treated with trifluoroacetic acid (TFA) some *o*-nitrophenyl BH adducts derived from *o*-nitrobenzaldehyde. Surprisingly, instead of the desired allylic rearrangement product **2** arising from allylic rearrangement, the *N*-oxide hydroxyquinolines **3a** were formed via intramolecular cyclization accompanied with the elimination of water (Scheme 1).

This simple approach constitutes now an elegant strategy to prepare highly substituted *N*-oxide hydroxyquinolines **3a** via BH adducts **1a**. Scheme 2 depicts the



Scheme 1. Unexpected formation of *N*-oxide hydroxyquinolines **3** from **1**.

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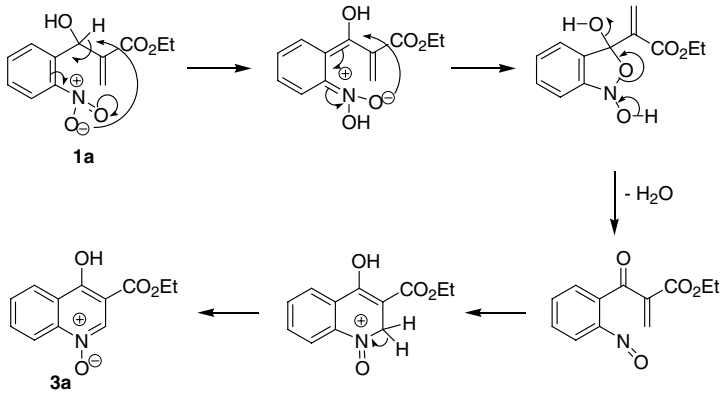

Scheme 2. Mechanism proposed by Kim et al. to rationalize formation of the *N*-oxide hydroxyquinolines **3** from the BH adduct **1**.

mechanism proposed by Kim et al.[10] to rationalize the unexpected formation of **3a**. The first step involves intramolecular proton transfer within **1a** with the abstraction of the benzylic hydrogen by the nitro group. Cyclization then occurs with the participation of the *o*-nitro group, which restores the aromaticity of the benzene ring. The N,O-acetal-type cyclic intermediate then undergoes C–O cleavage followed by elimination of water to form a nitroso α-methylene β-ketoester intermediate. Finally, as facilitated by protonation of the carbonylic oxygen, the *o*-nitroso group promotes re-cyclization via intramolecular Michael addition to afford **3a** (Scheme 2).

Curiously, this synthetically useful reaction was found to work only when TFA is employed, and attempts to use acetic or formic acids failed.[10] This unique reaction requirement of TFA catalysis intrigued us since apparently, judging from the proposed reaction mechanism (Scheme 2), TFA would work solely as a convenient source of protons.

Electrospray ionization mass spectrometry (ESI-(+)-MS) as well as its tandem version (ESI-MS/MS) are being increasingly used as a new tool to probe mechanisms of major organic reactions[11] such as the BH reaction[12] via the interception and characterization of their key intermediates. To elucidate therefore this key reaction requirement of TFA catalysis for the self-cyclization of **1a** to **3a**, we monitored this interesting reaction by ESI-(+)-MS(/MS) hoping to intercept and characterize key intermediates, and thus to have a more detailed view of its unique mechanism.[12]

We started our investigation preparing BH adduct **1b** (methyl ester instead of ethyl), which was accomplished in an almost quantitative yield in 8 h.[13] Then, based on the experimental conditions described by Kim et al.[10,14,15] we treated **1b** with TFA at 60–70 °C and monitored the reaction by ESI-(+)-MS[16] for 10 h in 1 h intervals. Aliquots of 10 μL of the reaction medium were taken and diluted with methanol, and directly infused to the ESI source of a tandem mass spectrometer. The mass spectrometer used was a Qtrap (Applied Biosystems, Concord, Ontario, Canada) with a QqQ (linear ion trap) configuration.

As the reaction starts, the major ions 'fished'[17] directly from the reaction solution to the gas phase by ESI(+) and subsequently detected by MS are those attributed to the reactant BH adduct, that is, $[\mathbf{1b}+H]^+$ of *m*/*z* 238, $[\mathbf{1b}+Na]^+$ of *m*/*z* 260 and $[(\mathbf{1b})_2+Na]^+$ of *m*/*z* 497 (Fig. 2a). However, after 150 min, (Fig. 2b) two new ions of *m*/*z* 334 and *m*/*z* 220 became the most abundant. We attributed the ion of *m*/*z* 334 to the interception, in its protonated form, of the O-trifluoroacetylated BH adduct **4** (Fig. 1). This structural assignment was corroborated by ESI-(+)-MS/MS, which shows that $[\mathbf{4}+H]^+$ dissociates mainly by the neutral loss of TFA (114 Da) to form the ion of *m*/*z* 220. Subsequently, this ion dissociates to the ion *m*/*z* 188 by methanol loss, which dissociates in turn to the ion of *m*/*z* 160 by loss of CO (Fig. 2d).

The ion of *m*/*z* 220 detected by ESI-(+)-MS (Fig. 2a) was trickier to assign. At first glance, it was attributed to a fragment of $[\mathbf{1b}+H]^+$ of *m*/*z* 238, since this ion was found by ESI-MS/MS to dissociate by the loss of water (spectrum not shown) to form the ion *m*/*z* 220.

Indeed at the beginning, most of the low abundance ions of *m*/*z* 220 are likely to arise from such a loss. However, as Figure 2c and most particularly Figure 3 show, the abundance of the ion of *m*/*z* 220 increases steadily as the reaction progresses, even after **1b** is totally consumed, as monitored by the abundance of $[\mathbf{1b}+H]^+$ of *m*/*z* 238 (Fig. 3). This steady increase indicates that, as the reaction progresses, most of the ions of *m*/*z* 220 correspond to detection of the final product **3b** in its protonated form $[\mathbf{3b}+H]^+$.

Note also that, as the abundance of $[\mathbf{1b}+H]^+$ of *m*/*z* 238 decreases, that of $[\mathbf{4}+H]^+$ of *m*/*z* 334 (Fig. 2c) initially raises and then after ca. 3 h falls down slowly.

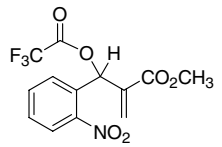

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Figure 1. The O-trifluoroacetylated BH adduct **4** intercepted and characterized by ESI-(+)-MS(/MS).

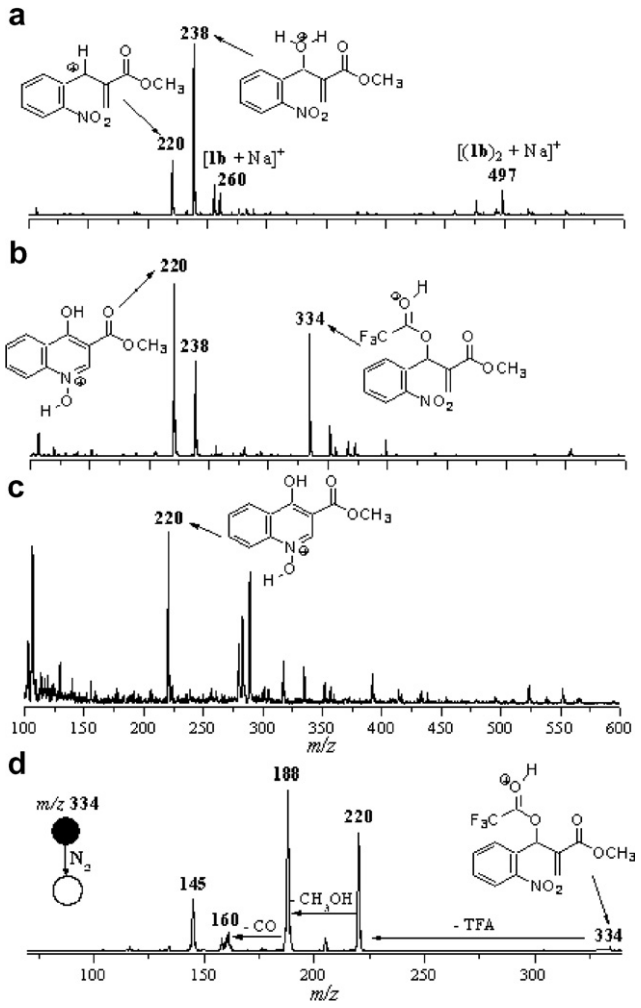


Figure 2. ESI(+) mass spectra in the positive ion mode for (a) solution reaction at the beginning; (b) after 150 min; (c) after 360 min; (d) ESI-(+)-MS/MS of the ion of *m*/*z* 334.

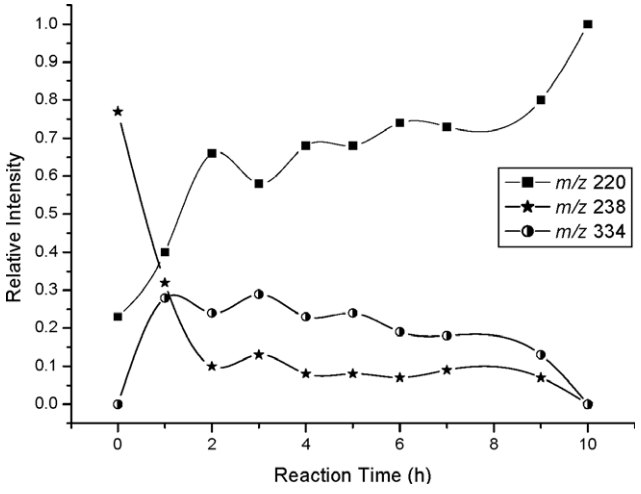


Figure 3. Relative abundance of the ions of *m*/*z* 220, 238 and 334 versus reaction time.

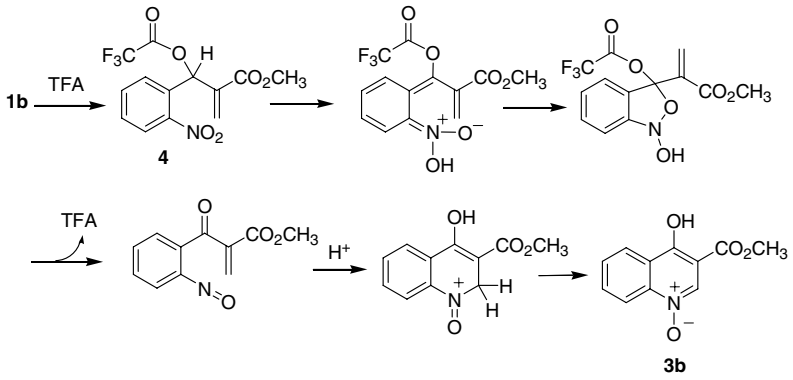
This pattern matches perfectly that expected if **4** is formed from **1b** and assigned as a new reaction intermediate leading to the final product, that is, **3b**. Based on these experimental observations, it seems that the *o*-trifluoroacetylated Baylis–Hillman adduct **4** is a key reaction intermediate, and that its formation is the main factor inducing the reaction deviation from **2** to form instead the *N*-oxide hydroxyquinolines **3b** (Scheme 1). We rationalize this role by assuming that, after TFA acetylation, the carbinolic hydrogen of **4** becomes much more acidic (lower pK_a). This enhanced acidity would facilitate therefore the crucial intramolecular proton transfer step that promotes the observed deviation and induces the first cyclization process leading to **3b** (Scheme 3).

The reaction was also performed and monitored by ESI-(+)-MS in the presence of acetic acid. The *o*-nitro Baylis–Hillman **1b** was dissolved in acetic acid and the reaction was heated at 60–70 °C for 6 h. Several ESI-(+)-MS obtained throughout 6 h (not shown) show no major change, displaying essentially the same major ions associated with **1b** as those seen in Figure 2a. No ions that could be attributed to the acetylated BH adduct were detected. Indeed, therefore, only TFA (used in excess) seems to be able to auto-catalyze acylation of the Baylis–Hillman adduct **1**. After TFA O-acylation, the acidity of the carbinolic proton of **1** is drastically enhanced favoring the self-cyclization reaction leading to **3b**. Since formic and acetic acids are not able to promote analogous acylation, they fail to provide **3b** and no detectable reaction occurs.

Theoretical calculations at B3LYP/6-31^{++}G** level on the gas phase dissociation ($HA \rightarrow H^+ + A^-$) as well as by simulating an equilibrium with water ($HA + H_2O \rightarrow H_3O^+ + A^-$) were also performed to investigate whether and by how much TFA O-acetylation increases the acidity of the α-hydrogen of **4** as compared with that of **1b**. The gas-phase results indicate that indeed **4** ($\Delta G^o = 336.7$ kcal/mol) shows a greater acidity than **1b** ($\Delta G^o = 361.5$ kcal/mol). This tendency is also observed with the equilibria with water. In this case, the carbinolic proton of **4** shows a greater acidity ($\Delta G = 179.1$ kcal/mol) than **1b** ($\Delta G = 184.7$ kcal/mol). All calculations refers to 298 K and 1 atm and were performed with the Gaussian 03 package.

Searching for experimental evidences to support the MS results observed, we prepared an authentic sample of trifluoroacetate **4** to investigate whether it could be directly converted into **3b**. The Baylis–Hillman adduct **1b** was treated, at 0 °C, with trifluoroacetic anhydride (1.5 equiv) and triethylamine (1.5 equiv) in anhydrous dichloromethane.[18] After 30 min, the solvent was evaporated and the residue was purified by silica gel column chromatography to afford the corresponding trifluoroacetate **4**, in an 80% yield.

Two different experimental conditions were tested: (i) **4** was simply dissolved in acetonitrile and the resulting solution was refluxed and (ii) a few drops of acetic acid was added to the acetonitrile solution of **4**, which was also refluxed. To our delight, after few hours we observed for the solution to which a catalytic amount of acetic acid was added that **4** was smoothly transformed into **3b**. The conversion was almost total and all the



Scheme 3. A new key intermediate **4** incorporated in the mechanism leading to **3** from BH adducts **1**.

spectral data were identical to **3b** produced from **1b** by TFA treatment. This experimental result constitutes therefore evidence of the key role played by the trifluoroacetate BH adduct **4** into the formation of **3b**, as revealed by the ESI/MS(/MS) experiments. It is also clear that the presence of an acid is crucial for cyclization of **4**.

Based therefore on data from the ESI-MS(/MS) monitoring, the solution experiments with HOAc (lack of) catalysis and experimental transformation of trifluoroacetate **4**, we propose an extended mechanism for the preparation of *N*-oxide hydroxyquinolines **3b** from *o*-nitrophenyl BH adducts **1b** (Scheme 3) with the participation of the new key intermediate **4** formed the TFA O-acylation of **1b**.

In summary, ESI-MS(/MS) monitoring has permitted us to intercept and characterize a new key reaction intermediate for the self-cyclization *o*-nitrophenyl Baylis–Hillman adducts to *N*-oxide hydroxy quinoline catalyzed by TFA. The interception of the TFA acylated BH adduct **4** shows that this reaction deviates from the expected route (that would otherwise from **2**) because the acidity of the benzylic proton of **4** is enhanced as compared to the starting BH adduct **1b**. This enhanced acidity favors intramolecular proton transfers that induces cyclization involving the *o*-nitro group. Finally, we experimentally demonstrated that **4** is, as expected from the extended mechanistic view, is easily transformed into **3b** under mild acidic conditions.

Additional NMR and EM data for the new compounds are available, as well as the theoretical parameters.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.037.

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