Cycloaromatization

Brønsted Acid-Mediated Cycloaromatization of 1H-Indol-2-yl Propargyl Benzoates to 7H-Benzo[c]carbazoles

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Abstract: A synthetic method for the efficient assembly of benzo[c]carbazole derivatives that relies on silica gel-activated benzoic acid-mediated cycloaromatization of 1H-indol-2-yl propargyl benzoates under atmospheric conditions is described. Robust with a variety of substitution patterns tolerated, the reaction provides a one-step strategy to construct a member of the N-heterocycles family in good to excellent yields. A tentative mechanism is proposed in which the cycloaromatization process is thought to involve a Brønsted acid-mediated formal 1,3-acyloxy migration/6π-electrocyclization pathway.

The benzo[c]carbazole motif is a prominent structural feature that is found in a variety of pharmaceutical compounds of current interest.[1] The highly conjugated nitrogen-containing heterocycle also serves as a pivotal building block in materials science due to its charge-transporting properties.[2] For this reason, the development of efficient synthetic methods to prepare benzo[c]carbazoles containing a variety of substitution patterns from readily accessible starting materials continues to be an active pursuit in organic chemistry.[3, 4]

The rearrangement of propargyl esters triggered by an initial Lewis acid-catalyzed 1,2- or 1,3-acyloxy migration step is among one of the most powerful and efficient strategies to rapidly increase molecular complexity.[5–7] For example, we recently disclosed one such synthetic method to construct tricyclic bridged cyclohexenone and -heptenone derivatives that relied on gold(I)-mediated double cycloisomerization of 1,11-dien-3,9-dyne benzoates.[8, 9] Inspired by these works, we queried whether 1H-indol-2-yl propargyl benzoates might undergo a gold(I)-catalyzed tandem [3,3]sigmatropic rearrangement/6π-electrocyclization to afford the benzo[c]carbazole ring system (Scheme 1, path a). In doing so, we serendipitously found in the course of this study that the posited cycloisomerization of the substrate could be realized when subjected to silica gel-activated benzoic acid (Scheme 1, path b).[8, 9] To our knowledge, this type of reactivity involving a Brønsted acid-mediated formal 1,3-acyloxy migration has not been previously explored. A reason presumably for this could be due to the substrate class preferably undergoing a Meyer–Schuster rearrangement to give the α,β-unsaturated carbonyl compound under Brønsted acidic conditions.[10, 11] Herein, we disclose the details of this chemistry that provides an expedient synthetic route to a member of the carbazole compound family in good to excellent yields and regioselectivity. Added to this, the reaction features operational simplicity under conditions that do not require the exclusion of air or moisture.

The initial focus of the present study was to realize the optimum reaction conditions for the gold(I)-catalyzed rearrangement of 1H-indol-2-yl propargyl benzoate 1a to the corresponding benzo[c]carbazol-5-yl benzoate (Scheme 2a). This consequently led us to find that this could be achieved in the presence of 5 mol% of [IPrAu(PhCN)NTf₂] (IPr = 1,3-bis(2,6-dimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene) and 4 Å molecular sieves (MS) in toluene at room temperature for 36 h. Under these reaction conditions, both the benzo[c]carbazol-5-yl benzoate 2a and ketone 3a were obtained in respective yields of 71 and 12%. The structure of the latter N-heterocyclic adduct was ascertained by NMR spectroscopic analysis and by X-ray crystallography.[12] The discovery of the silica gel-activated, benzoic acid-mediated variant of this transformation was observed by chance during a subsequent preparation of the starting benzoate from its alcohol precursor 1a (Scheme 2b).
In our hands, an attempt to purify the crude mixture furnished from the reaction of the propargyl alcohol with benzoyl chloride by flash column chromatography for a third time was found to unexpectedly give 3a in 73% yield.

The formation of the benzo[c]carbazol-5-yl ketone adduct via a mechanistically intriguing Brønsted acid-mediated cycloaromatization process led us to further examine and gain a better understanding of the rearrangement (Table 1). This initially revealed subjecting 1a in 9:1 n-hexane/ETOAc to benzoic acid (1 equiv) and unactivated silica gel at room temperature or its absence at reflux temperature for 24 h led to no reaction being detected by TLC analysis and $^1$H NMR measurements (entries 1 and 2). On the other hand, repeating the former reaction conditions at reflux temperature gave 2a and 3a in respective yields of 14 and 20% (entry 3). An increase in the yield of the carboxylic ester product to 59 and 73% yield along with the ketone derivative in 8 and 11% yield was achieved on changing the solvent from n-hexane/ETOAc to non-distilled toluene with unactivated or activated silica gel (entries 4 and 5). In contrast, the analogous transformations in non-distilled dichloromethane or 1,2-dichloroethane with unactivated silica gel were found to give 3a in 40 and 63% yield along with 2a in 10 and 14% yield (entries 6 and 7). Our investigations subsequently found the analogous reaction mediated by 2 equivalents of benzoic acid and activated silica gel in non-distilled toluene at reflux temperature for 10 h furnished 2a and 3a in 91 and 5% yield, respectively (entry 8). However, control experiments at Brønsted acid loadings of 10 or 50 mol% for 24 h were observed to give the two N-heterocyclic adducts in lower yields of 43 and 6%, and 31 and 13% (entries 9 and 10). Likewise, a control reaction under these latter conditions but mediated by 1.1 equivalent of p-TsOH.H$_2$O instead of benzoic acid for 30 min and in the absence of silica gel was found to give 3a in 80% yield (entry 11). A final set of two control experiments in the absence of either the Brønsted acid or silica gel for 10 h afforded both the benzoate and ketone adducts in yields of 41 and 5% or 2a in 3% yield (entries 12 and 13). On the basis of the above results, the procedure described in entry 8 was deemed to provide the optimum reaction conditions to selectively access 2a.

To define the generality of the benzoic acid-mediated procedure in the presence of activated silica gel in non-distilled toluene, the reactions of a series of 1H-indol-2-yl propargyl benzoates was examined (Table 2). Overall, the experimental conditions were observed to be broad, with starting benzoates 1b–t containing a variety of substitution patterns giving the corresponding benzo[c]carbazol-5-yl benzoates 2b–t in 36–95% yield. Reactions of starting materials in which the acetylene phenyl moiety contained an electron-withdrawing carboxyl group in place of the phenyl motif at the C3 position of the indolyl structure also gave the corresponding benzo[c]carbazol-5-yl benzoates 2b–t in 57–94% yield. In these transformations, the corresponding benzoates was examined (Table 2). Overall, the experimental conditions were observed to be broad, with starting benzoates 1b–t containing a variety of substitution patterns giving the corresponding benzo[c]carbazol-5-yl benzoates 2b–t in 36–95% yield. Reactions of starting materials in which the acetylene phenyl moiety contained an electron-withdrawing carboxyl group in place of the phenyl motif at the C3 position of the indolyl structure also gave the corresponding benzo[c]carbazol-5-yl benzoates 2b–t in 57–94% yield. In these transformations, the corresponding benzoates was examined (Table 2). Overall, the experimental conditions were observed to be broad, with starting benzoates 1b–t containing a variety of substitution patterns giving the corresponding benzo[c]carbazol-5-yl benzoates 2b–t in 36–95% yield. Reactions of starting materials in which the acetylene phenyl moiety contained an electron-withdrawing carboxyl group in place of the phenyl motif at the C3 position of the indolyl structure also gave the corresponding benzo[c]carbazol-5-yl benzoates 2b–t in 57–94% yield.
Using 1g, 1i and 1r as representative examples, we next examined the scope of this new methodology for the synthesis of benzo[\(c\)]carbazol-5-yl ketones (Table 3). By applying the \(\text{p-TsOH}\cdot\text{H}_2\text{O}\)-mediated protocol described in Table 1, entry 11, the reaction of 1g gave 3g in 38% yield. Under similar conditions, the analogous experiments with 1i and 1r afforded the corresponding nitrogen-containing heterocycles 3i and 3r in yields of 76 and 32% yield.

With the above results implying a Brønsted acid-mediated tandem formal [3,3]-sigmatropic rearrangement/6π-electrocyclization pathway, attention was turned to demonstrate if this is the case by performing a series of control experiments. To determine if the 1,3-acyloxy shift occurred in an intra- or intermolecular manner, we first examined the reaction of propargyl acetate 1u (Scheme 3a). Under the benzoic acid-mediated standard conditions, this test gave 2a and 3a along with benzo[\(c\)]carbazol-5-yl acetate 2u in respective yields of 47, 6 and 24%, which implied the likelihood that the migration step proceeded via an intermolecular pathway. This was further supported by a second experiment showing both 2a and 2v were obtained as a 1:3:4 mixture of inseparable products in 22% yield on treating 1a to the standard conditions mediated by \(\text{p-Chlorobenzoic acid}\) in place of benzoic acid (Scheme 3b). The benzoic acid-mediated reaction of 1w was also examined in an attempt to support the formation of the ensuing allenic ester due to the posited 1,3-acyloxy shift and its possible involvement in the 6π-electrocyclization step to give the product (Scheme 3c). However, this proved unsuccessful as subjecting the substrate to the standard conditions was found to result in only a mixture of decomposition products being observed by TLC analysis and \(^1\)H NMR measurements.

In a second set of control experiments, the origin of the ketone adduct 3 obtained in the course of the study was next...
investigated. With this in mind, we examined the reaction of \(2a\) in the presence of 1 equiv of p-TsOH·H₂O in toluene at reflux for 10 h (Scheme 4a). This experiment gave a mixture of decomposition products and led us to conclude that the formation of the carbonyl compound from the benzoate product undergoing a Bronsted acid-mediated tandem hydrolysis/aerial oxidation pathway was unlikely. This was further supported by our findings showing \(2a\) and \(3a\) being obtained in yields of 69 and 6% on repeating the reaction of \(1a\) under the conditions described in Table 1, entry 8, for 24 h (Scheme 4b). The possibility of a Meyer–Schuster rearrangement pathway being operative was subsequently considered but ruled out based on the outcome of control reactions illustrated in Scheme 4c and 4d. The benzoic acid-mediated reaction of \(S1a\) under the unactivated silica gel conditions shown in Scheme 4c, which may be envisaged to be formed from the hydrolysis of \(1a\) in the course of the transformation, gave \(2a\) and \(3a\) in 5 and 14% yield along with the recovery of the substrate in 50% yield. Moreover, subjecting the \(\alpha,\beta\)-unsaturated carbonyl compound \(5r\), which would be the product of a Meyer–Schuster rearrangement, to the benzoic acid-mediated standard reaction conditions was found to result in the recovery of the substrate in near quantitative yield (Scheme 4d).

On the basis of the above findings, a speculative mechanism for the present benzoic acid-promoted reaction to form benzo[\(c\)]carbazol-5-yl benzoates and ketones is put forward in Scheme 5. Using the reaction of \(1a\) as a representative example, this could involve the protonation of the substrate by the silica gel-activated Bronsted acid. This results in debenzylation of the ensuing protonated adduct \(Ila\) to give the allenic cation species \(IIa\), which is subsequently susceptible to nucleophilic attack by a molecule of benzoic acid or water. In the case of nucleophilic attack by a molecule of benzoic acid, this would furnish the putative allenic benzoate \(Ia\), the active species that is thought to undergo 6,7-electrocyclization. Tautomerization of the tetracyclic intermediate \(IVA\) furnished from this step is then reasoned to deliver the product \(2a\). On the other hand, nucleophilic attack of \(Ia\) by a molecule of water might give the protonated allenic alcohol \(Va\) that participates in the pericyclic reaction step. Tautomerization followed by aerial oxidation of the resulting enol species \(Vla\) would provide the benzo[\(c\)]carbazol-5-yl ketone \(3a\).

In summary, we have serendipitously elucidated an efficient silica gel-activated Bronsted acid-mediated cycloaromatization process for the construction of benzo[\(c\)]carbazole derivatives from 1H-indol-2-yl propargyl benzoates. While the mechanism of the reaction remains a subject of debate, our findings suggest a pathway involving an initial formal 1,3-acyloxy shift that triggers product formation via a 6,7-electrocyclization process. This is intriguing such as a Bronsted acid-mediated formal [3,3]-sigmatropic rearrangement would represent the first example of this mode of reactivity. Efforts to explore the detailed mechanistic aspects of this reaction and its potential scope and synthetic applications are in progress and will be reported in due course.

**Experimental Section**

**Procedure for the synthesis of benzo[\(c\)]carbazol-5-yl benzoates**

2: A mixture of activated silica gel (0.25 g, heated at 120 °C for 2 days at atmospheric pressure prior to use) and benzoic acid (0.0244 g, 0.2 mmol) was stirred in non-distilled toluene (4.0 mL) for 5 min. To the stirring mixture, (N-tosyl-1H-indol-2-yl)propargyl ester 1 (0.1 mmol) was added and the resulting mixture was refluxed for 10 h. Upon completion, the reaction mixture was filtered through a short pad of Celite and washed with dichloromethane,
and the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (n-hexane/toluene = 2:3) gave the major product 2.

Procedure for the synthesis of benzof[cd]carbazol-5-y1 ketones 3: To a stirring solution of p-TsOH·H2O (0.0209 or 0.0314 g, 0.11 or 0.17 mmol) in non-distilled toluene (4.0 mL) was added (N-tosyl-1H-indol-2-yl)propargyl ester 1 (0.10 or 0.15 mmol) and the resulting mixture was refluxed for 10 h. Upon completion, the reaction mixture was filtered through a short pad of Celite and washed with dichloromethane, and the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (n-hexane/toluene = 1:1) as eluent gave product 3.

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