Facile Oxidative Rearrangements Using Hypervalent Iodine Reagents

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Aromatic substituents migrate in a novel oxidative cyclization mediated by iodine(III) reagents. 4-Arylbut-3-enoic acids are cyclized and rearranged to 4-arylfuran-2(5H)-ones by hypervalent iodine compounds in good to excellent yields under mild reaction conditions. Other ring sizes are also accessible. The mechanism of the reaction is described in detail, and calculations highlight the cationic nature of the intermediates in the rearrangement. The fast access to heavily substituted furanones is used for the synthesis of biologically active derivatives.

Introduction

Hypervalent iodine reagents have received particular attention in the area of synthetic chemistry and have found wide applications in synthesis due to their environmentally friendly nature, low toxicity and easy accessibility.[1] Because of their high electrophilic nature, hypervalent iodine(III) compounds have been frequently used to activate carbon–carbon double bonds. The facile formation of cationic intermediates has been used in different rearrangements for the synthesis of functionalized molecules,[2] including oxidative ring expansions[3] and iodine(III)-mediated ring contractions.[4] We have developed oxidative cyclizations[5] including the cyclization of unsaturated acids with a 1,2-migration of aryl groups.[6]

Results and Discussion

Herein, we report a novel oxidative rearrangement of 4-arylbuto-3-enic acids to 4-arylfuran-2(5H)-ones mediated by hypervalent iodine compounds in high yields under mild reaction conditions. Optimal reagents reaction conditions were established using 4,4-diphenylbut-3-enoic acid (1a) as model substrate.[7] The rearrangement of 1a to 4,5-diphenylfuran-2(5H)-one (2a) was carried out in acetonitrile using a hypervalent iodine reagent with two equivalents of trimethylsilyl triflate (TMSOTf; see Scheme 1). We have recently used this reagent combination for the generation of the highly reactive [bis(trifluoroacetoxy)iodo]benzene,[8] which is very reactive but also leads to side-product formation with 2a formed in 84% yield.

The rearranged product 2a was obtained in very good yields with different iodine(III) reagents in combination with TMSOTf (see Supporting Information, Table S1). The combination of TMSOTf and iodine(III) reagents of type PhI(R)=I(OTf)2 (R = R' = OCOCF3; R = R' = OAc; R = OH, R' = OTs) leads to the in situ formation of PhI(OTf)2 resulting in yields between 85% and 93%, whereas iodosylbenzene (PhIO) or the cyclic hypervalent iodine(V) reagent 2-iodoxybenzoic acid (IBX) with TMSOTf led to product 2a in only 32% and 21% yield, respectively. A bridged reagent with two iodine(III) moieties ([μ-oxbis(trifluoroacetoxy)iodo]benzene)[9] is very reactive but also leads to side-product formation with 2a formed in 84% yield.

The substituents R and R' in trivalent iodine compounds PhI(R)=I can be exchanged easily, their nature has a strong influence on the reactivity. We investigated different Lewis acids to activate [bis(trifluoroacetoxy)iodo]benzene as shown in Table 1, as there is no reaction without activating the hypervalent iodine reagent (Table 1, Entry 1). Initially, TMSOTf and tert-butyl(dimethyl)silyl triflate (TBDMSOTf) were used and 2a was isolated in similar yields (93% and 88%, respectively; Table 1, Entries 2 and 3). The combination of hypervalent iodine reagents and boron trifluoride diethyl etherate, BF3·Et2O, has already been studied,[10] and, here, a weak activation was observed, and rearranged product 2a was isolated in only 18% yield together with a different rearranged product 3a, which was obtained in 67% yield (Table 1, Entry 3). Rearrangement products such as 3a have already been reported using hypervalent iodine

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reagents. Rearranged cyclic product 2a was not observed by using a Brønsted acid such as camphorsulfonic acid and only product 3a was formed (Table 1, Entry 5). Koser’s reagent, PhI(OH)OTs, also led mainly to compound 3a (Table 1, Entry 6).

With these optimized reaction conditions, a series of 4-arylbut-3-enoic acids 1 were rearranged to yield 4-arylfuranones 2 in 78–95% yield. The oxidative rearrangement proceeds smoothly with substrates 1 having both mono- and disubstitution at position C-4, as shown in Table 2. The rearranged products 2 were obtained in good yields with substrates 1 bearing two aryl substituents (Table 2, Entries 1–3). Substrate 1c containing a 1:1 mixture of E and Z isomers leads to a mixture of two rearranged products 2c in a 1:1 ratio in overall 88% yield (Table 2, Entry 3). The α-methylated substrates 1d and 1g reacted similarly well as the unsubstituted substrates to product 2d and 2g in 81% and 87% yield, respectively (Table 2, Entries 4 and 8).

Table 1. Different activators in the rearrangement of 1a.[a]

| Entry | Activator | 2a Yield [%] | 3a Yield [%] |
|-------|-----------|--------------|--------------|
| 1     | –         | 0            | 0            |
| 2     | TMSOTf    | 93           | 0            |
| 3     | TBDMSOTf  | 88           | 0            |
| 4     | BF3·OE2   | 18           | 67           |
| 5[a]  | camphorsulfonic acid | 0 | 92 |
| 6[a]  | PhI(OH)OTs | 5 h | 20 |

[a] Reagents and conditions: a) PhI(OCCF3)2 (1 equiv), activator (2 equiv), MeCN, RT, 30 min; b) When the reaction was performed by using substrate (E)-1f, rearranged product 3f was obtained in 89% yield. c) Koser’s reagent PhI(OH)OTs was used for this reaction. In addition to 2a and 3a, compound 4a was observed in 8% yield.

Finally, (E)-pent-3-enoic acid 1h with an aliphatic substituent R1 was employed as starting material, and product 4h was isolated exclusively (Table 2, Entry 9). This result clearly indicates that the presence of an aryl functionality at the C-4 position in substrates 1 is essential to perform these rearrangements.

Scheme 2. Schematic representation of the dissociative mechanism for the elimination in the formation of 4f.

Table 2. Oxidative rearrangements of compounds 1a–h.[a]

| Entry | Substrate 1 | Yield of 2 [%] | Yield of 4 [%] |
|-------|-------------|----------------|----------------|
| 1     | 1a: R1 = R2 = Ph, R3 = H | 93 | – |
| 2     | 1b: R1 = R2 = 4-ClC6H4, R3 = H | 95 | – |
| 3     | 1c: R1 = Ph, R2 = 4-BrC6H4, R3 = H | 88 | – |
| 4[a]  | 1d: R1 = R2 = Ph, R3 = Me | 81 | – |
| 5     | 1e: R1 = Ph, R2 = R3 = H | 78 | – |
| 6     | (E)-1f: R1 = Ph, R2 = R3 = Me | 89 | – |
| 7     | (Z)-1f: R1 = Me, R2 = Ph, R3 = H | trace | 81 |
| 8     | 1g: R1 = Ph, R2 = R3 = Me | 87 | – |
| 9[a]  | 1h: R1 = Me, R2 = R3 = H | 73 | – |

[a] Reagents and conditions: a) PhI(OCCF3)2 (1 equiv), TMSOTf (2 equiv), MeCN, RT, 30 min; b) The use of PhI(OH)OTs instead of PhI(OCCF3)2 yielded 2d in 76% yield together with 4d in 16% yield. c) Reaction time was 5 h.

Even other ring sizes are accessible using substrate 5a, which is prepared through a Wittig reaction. Rearranged product 6a was isolated in 76% yield. (E)-5-Phenylhex-4-enoic acid 5b was synthesized from cyclopropyl methyl ketone (see Supporting Information). Surprisingly, only the acyclic rearranged product 7b was isolated in 79% yield and no cyclization occurred (Scheme 3). The hexenoic acid 8a also cyclized, and compound 9a was confirmed by X-ray analysis to be the cyclization product. The same product 9 is also obtained in a slower reaction by treatment of 8 with triflic acid only, probably through activation of the carboxylic acid and cyclization following by elimination.

Asymmetric oxidative rearrangements of 4-arlybutenoic acids 1 could probably be achieved by using chiral hypervalent iodine reagents. Lactate-based chiral hypervalent iodine reagents have been synthesized by Fujita et al. and employed as chiral reagent in highly enantioselective spirolactoniza-
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When using 1a or (E)-1f in such transformations, the products 2a and 2f were obtained only as racemates in 28% and 73% yield, respectively (see Supporting Information).

Calculations

The exclusive formation of product 2f when substrate (E)-1f is reacted with hypervalent iodine reagents in contrast to the formation of 4f upon treating (E)-1f with a combination of (SePh)2 and PhI(OCOCF3)2 can be explained by either a dissociative stepwise mechanism or by a concerted one-step mechanism (Scheme 4). In case of a dissociation of the complex anti-I-10, the relative stability of the ions 15 and 12 might govern the observed product distribution. In a different scenario, the relative stability of the precursor anti-I-10 towards the dissociation or, in other words, the relative barriers of dissociation versus elimination could be an explanation. Calculations were conducted to analyze the first case scenario of the dissociation model and the possible one-step mechanism in more detail.

The dissociation of either I-10 or the corresponding reaction products with a selenium electrophile, Se-10 (Figure 1), should in principle result in the formation of the secondary carbenium ion 15. However, the nature of 15 is fleeting: It is neither a ground state nor a transition state (TS). Instead, optimizations started off from 15, a classical carbenium ion, or from 20, a nonclassical carbenium-ion structure, and led either to the resonance-stabilized cation 17 or to the rearranged cation 12, as shown in Figure 2. The latter is a precursor to the elimination product 2f that is observed as the main product of the reaction (E)-1f with hypervalent iodine reagents. The transition state 18 that connects 17 and 12 shows interesting features. The reorganization of the bonds would enable the formation of 14 and 15, the very definition of a “merged transition state”. This bonding characteristic of the TS is thought to be indicative for bifurcating potential energy surface (PES). The intrinsic reaction coordinate (IRC) was calculated starting from 19 to map out the minimum energy pathway (MEP). The MEP occurs through a shallow plateau that corresponds to the nonclassical carbenium ion 20 and then proceeds to the rearranged ion 12. Further studies including molecular dynamic simulations are currently conducted to investigate the driving force for the formation of 14 over 15 and to clarify if the potential bifurcation exists. IRC calculations confirm that struc...
ture 15 is neither a saddle point of first order (transition state) nor a ground state. A possible reaction path “downhill” from intermediate 17 occurs through a merged transition state 19 that incorporates features necessary for the bond reorganization for 14 and 15. The hydride shift proposed in the transformation from 12 to 14 was confirmed by the synthesis and reaction of the deuterated compound 1i to the cyclized derivative 2i, as shown in Scheme 5.

Alternatively, the dissociation of adducts 1-10 or Se-10 could occur concertedly with the rearrangement of the phenyl group (one-step mechanism). In this case, rearrangement is only expected to occur in case the migrating phenyl group is orientated anti to the leaving group (Scheme 4). The steric impact of a syn configuration should prevent a migration of the phenyl group (Figure 1). Control experiments employing (Z)-1f instead of (E)-1f using hypervalent iodine compounds indeed resulted in the exclusive formation of 4f, hence no rearrangement occurred.

The different chemoselectivities of PhI(OCOCF₃)₂ compared with the combination of (SePh)₂/PhI(OCOCF₃)₂ and the dependence of product formation on the double bond configuration of starting material 1f strongly indicate a concerted mechanism of elimination/rearrangement in case of 1-10. The complete absence of rearrangement in case of the selenium compounds suggests that the barrier for dissociation is higher compared with the barrier for the elimination of the β-proton. This effect can be rationalized by the different bond strengths: Carbon–selenium bonds are shorter than carbon–iodine bonds, and equally the bond-dissociation energy (BDE) for C–Se is higher than the BDE for C–I.

The first reaction steps of PhI(OTf)₂ with unsaturated acid (E)-1f are all exothermic (Figure 3). The formation of iodonium ion (E)-I-21 is favored by 16 kcal mol⁻¹ and the subsequent cyclization by 86 kcal mol⁻¹. Comparable results are obtained with the double bond isomer (Z)-1f (see Supporting Information).

Interestingly, the labile ligands of the iodine compound play a crucial role for its reactivity. The experimental observation that PhI(OCOCF₃)₂ alone is not reactive in this reaction is possibly explained by the predicted strongly endothermic first step of the electrophilic addition of the iodine moiety to the double bond.

In a further attempt, the reaction was performed in two steps. Acid (E)-1f was cyclized with iodine monochloride to give the iodolactone 22 in 78% yield. Unsuccessful reagents to oxidize the iodine atom in 22 include peracetic acid, sodium perborate and PhI(OCOCF₃)₂. Oxidation with oxone led to compound 3f in 86% yield (Scheme 6), whereas treatment with PhI(OTf)₂ resulted in the formation of 23 probably via similar intermediates as described above. Compound 2f was, however, not detected. No further information on the reaction mechanism could be obtained by these experiments.

Furanone scaffolds are basic structural motifs found in various naturally occurring biologically active compounds.
synthetic furanones with interesting pharmacological and pharmacokinetic properties have been reported. For example, furanone derivative 25b is known as a selective cyclooxygenase-2 (COX-2) inhibitor. Rofecoxib (25b) was synthesized in a straightforward manner from acid 24b in 83% yield, and unsubstituted acid 24a led to the cyclized and rearranged product 25a, also a bioactive compound, in 87% yield (Scheme 7). Conclusion

In conclusion, we have developed an efficient novel oxidative rearrangement mediated by hypervalent iodine reagents of 4-arylbut-3-enoic acids leading to highly substituted furanone derivatives in good to excellent yields under mild reaction conditions. We have studied mechanistic details for these transformations by calculations, and a deuterium-labelled compound was also synthesized to provide further insight. Our approach to prepare functionalized furanone architectures is very simple, economical and does not require any specialized reagents or catalysts. We have used this methodology for a successful synthesis of the cyclooxygenase-2 (COX-2) inhibitor, Rofecoxib. Further investigations of this approach to the synthesis of furanones are currently in progress.

**Experimental Section**

**General procedure for cyclizations:** A solution of the γ,δ-unsaturated acid 1 (0.2 mmol) in acetonitrile (2 mL) was added to a solution of [bis(trifluoroacetoxy)iodo]benzene (86 mg, 0.2 mmol) and TMSOTf (0.072 mL, 0.4 mmol) in acetonitrile (2 mL) at RT. The reaction was monitored by TLC and is usually complete within 30 min. Acetonitrile was removed in vacuo, water (5 mL) was added, and the mixture extracted with CH2Cl2 (3 × 5 mL). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The product mixture was purified by flash chromatography using CH2Cl2 as eluent.

**Calculations:** DFT calculations were performed using the Gaussian03 suite of programs. Reactants, transition states (TSs), intermediates, and products were fully optimized with the hybrid density functional B3LYP(22) using the Pople-type 6-31+G(d,p) basis set(23) for all compounds without iodine and a composite basis set consisting of 6-31+G(d,p) for C, H, Se, O, F and LANL2DZ for I incorporating a relativistic pseudopotential (effective core potential, ECP) that largely accounts for scalar relativistic effects in iodine. Solvent effects of acetonitrile were approximated using the SCRF approach employing PCM as implemented in Gaussian03(21). Energies in solution were obtained as single point calculations on gas-phase geometries (SCRF = PCM/B3LYP/6-31+G**). All TSs have been characterized by one imaginary frequency (first-order saddle points) on the potential energy surface (PES). To determine minimum energy pathways (MEPs), intrinsic reaction coordinate (IRC) analyses were performed, in order to confirm that a specific TS connects the different local minima. In addition, the imaginary frequencies were visually analyzed and proven to be the correct eigen vibration by animating it in Gabedit. Vibrational frequencies and zero-point vibrational energies (ZPE) were determined within the harmonic oscillator approximation, at the same level of theory as that for geometries. All energies reported in this paper are free energies or enthalpies in kcal mol⁻¹ at 298 K and 1 atm if not stated otherwise. Frequencies remained unscaled.

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