The Microwave-assisted Organocatalyzed Rearrangement of Propargyl Vinyl Ethers to Salicylaldehyde Derivatives: A Combined Experimental and Theoretical Study.

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Abstract: Herein we describe the microwave-assisted imidazole-catalyzed transformation of propargyl vinyl ethers (PVEs) into multisubstituted salicylaldehyde motives. The reaction is instrumentally simple, scalable and tolerates a diverse grade of substitution at the propargylic position of the starting PVE. The generated salicylaldehyde motives incorporate a broad range of topologies, spanning from simple aromatic monocycles to complex fused polycyclic systems. The reaction is highly regioselective and operates under symmetry-breaking conditions. The preparative power of this reaction has been demonstrated in the first total synthesis of morintrifolin B (19), a benzophenone metabolite isolated from the small tree *Morinda citrifolia* L. A computational DFT study of the reaction has been accomplished, with full agreement between calculated values and observed experimental results. The theoretically calculated values support a domino mechanism comprising a propargyl Claisen rearrangement, a [1,3]-H shift, a [1,7]-H shift (enolization), a 6π -electrocyclization and an aromatization reaction.

Introduction

Propargyl vinyl ethers **1** (PVEs) constitute a privileged group of small size, densely functionalized and readily accessible linear scaffolds. The main key to the chemical reactivity encoded in these structures is the [3,3]-sigmatropic rearrangement (propargyl Claisen rearrangement) shown in Scheme 1A,^[1] which takes place irreversibly and under thermodynamic control to generate the allene **2**.^[2] Since the first seminal thermally-driven rearrangement achieved by Black and Landor in 1965,^[3] which served to determine that propargylic systems could be accommodated into the Claisen rearrangement, a vast number of propargyl Claisen rearrangements have been successfully performed.^[1] The main drawback of these rearrangements relied

on the high temperatures required to proceed which forced the use of high boiling solvents and harsh conditions. These experimental difficulties had prevented their use in preparative organic synthesis, in sharp contrast to its counterpart involving allyl vinyl ethers.^[4] However, this scenario dramatically changed in the last decade with the emergence of milder metal-catalyzed protocols^[5] and the replacement of conventional heating with laboratory microwave equipment.^[1] Under microwave heating, allenes **2** rearrange to the more stable diene derivatives **3** through a pseudo pericyclic [1,3]-H shift (Scheme 1A). Overall, this tandem rearrangement transforms a C_3 -O- C_2 linear structure, easily assembled through C-O bond forming chemistry, into an all- sp^2 -linear C_5 carbogenic block^[6] armed with a reactive carbonyl group (aldehyde or ketone), an ester group, and a doubly conjugated diene. An exception to this outcome is featured by the activated allenes **5** (EWG = ester or secondary amide),^[7] which directly rearrange to the furan derivatives **6** through a tandem enolization /O-cyclization/H-transfer process (Scheme 1B).^[8]

1A) General tandem propargyl Claisen rearrangement/[1,3]-H-shift

1B) Activated allenes: 5-exo dig. cyclization affords furanes

1C) Divergent tandem rearrangement: salicylaldehydes and trisubstituted olefins

Scheme 1. The μ w-assisted propargyl Claisen rearrangement of propargyl vinyl ethers **1**.

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A particularly striking reactivity profile arises from monosubstituted PVEs **7** ($R^3 = H$; hereinafter referred to as secondary PVEs) bearing a linear chain at the propargylic position (Scheme 1C). In these cases, the rearrangement affords a roughly equimolar mixture of salicylaldehyde **9** and the trisubstituted olefin **10**.^[9] The formation of salicylaldehyde **9** can be formally rationalized through a tandem enolization / 6- π -electrocyclization / aromatization process with the net generation of a methanol molecule per molecule of salicylaldehyde. On the other hand, the stereoselective formation of the trisubstituted olefin **10** should be mediated by the formation of the hemiacetal **13** to launch an internal redox process involving a [1,5]-H shift. Overall, the manifold constitutes a divergent chemical process able to produce two well differentiated products from the same reactive intermediate and through two interconnected pathways (the product of one pathway launches the other). Remarkably, the manifold could be selectively funneled toward each one of these two products with a careful design of the experimental conditions. Thus, salicylaldehydes **9** could be cleanly obtained in 60-80% yield by microwave irradiation of a xylene solution of PVEs **7** in the presence of molecular sieves (MS) 4 Å (300 mg/mol substrate).^[9] Although initially we used MS 4 Å as additive, we later discovered that pyridine (200 mol-%) could replace the MS rendering the process homogenous and easier to perform.^[10] It was assumed that the beneficial action of the two additives was related to a reduction of the activation barrier for the enolization process, otherwise the limiting step of the process. Although this is an uncommon reactivity for molecular sieves, there are some precedents for its use in enolization processes.^[11] On the other hand, the microwave irradiation of a methanolic solution of PVEs **7** exclusively afforded the olefin derivatives **10** in good-to-excellent yields (75-95%) and complete stereoselectivity (the two alkyl chains are placed in trans-position).^[12]

The salicylaldehyde motif constitutes an important building block for the preparation of numerous pharmacologically relevant coumarins,^[13a] flavonoids,^[13b] chromenes,^[13c,d] catechols,^[13e] and several mycotoxins,^[13f] as well as chiral catalysts based on Schiff base transition metal complexes (salen-catalysts).^[14] Salicylaldehydes are commonly prepared by direct formylation of the corresponding phenol derivatives^[15] using the classic Reimer-Tiemann conditions ($CHCl_3$ -KOH)^[15a] or the Duff procedure (hexamethylenetriamine-acetic-sulfuric acid).^[15b,c] Interestingly, the 3,6-disubstitution pattern present in the salicylaldehydes **9** cannot be easily accessed using these standard protocols. Among other drawbacks, these reactions present regioselectivity problems when the ortho and para positions to the hydroxyl functionality are not conveniently blocked.^[16]

The efficiency and instrumental simplicity of this reaction together with the importance of the salicylaldehyde motive prompted us to undertake a systematic study of this reaction aimed to transform it into a general, robust, and preparative protocol for accessing salicylaldehyde-based structural motives. The transformation of this reaction into a standard synthetic protocol with preparative value (academic and industrial) required the implementation of a catalytic version incorporating

the following reaction values: 1) the use of a cheap and easy handled catalyst (additive); 2) high tolerance to broad and diverse substitution patterns on the PVE; and 3) bench-friendly reaction processing. We report herein how these conditions could be met using imidazole (10 mol-%) as a basic catalyst and how this catalytic manifold could be used for the construction of salicylaldehyde motives supported on a broad range of topologies, which spanned from simple aromatic monocycles to complex fused polycyclic systems. We have also performed a theoretical study of this reaction which is in full agreement with the observed experimental results. Finally, the preparative power of this reaction has been demonstrated in the first total synthesis of morinifolin B (**19**),^[17] a benzophenone metabolite isolated from the small tree *Morinda citrifolia* L.

Results and Discussion

The catalytic synthesis of 3,6-disubstituted salicylaldehydes from secondary propargylic vinyl ethers. Although pyridine had proved to be a convenient additive for this transformation,^[10] the large excess required (200 mol-%) precluded its use in large scale preparative reactions. Guided by the current principles of sustainable chemistry,^[18] we searched for new additives to be used as true catalysts. For this study, we chose the transformation of the PVE **7a** into salicylaldehyde **9a** (Table 1). We had observed in earlier studies^{[9],[10]} that the substitution pattern adorning this PVE was one of the worst tolerated by this reaction either using MS 4 Å (43%)^[9] or pyridine (53%).^[10] Because the use of pyridine improved the efficiency of the reaction in a net 10%, we envisioned that this reaction could be a convenient benchmark for the assay of other basic additives better suited than pyridine to catalyze the required enolization of dienal **8** to the intermediate **11** (Scheme 1C). With this idea in mind, we assayed the bases shown in Table 1 (entries 1-15). Additionally, we assayed a set of common acids of moderate strength to see if they could also be suitable additives for this reaction (entries 16-18). The reactions were performed using our previously established conditions [xylene (1 mL), μ w (300 watt, 200 °C, and closed vessel), 1h] and using a catalytic amount (10 mol-%) of additive. Imidazole and 4-(*N,N*-dimethylamino)pyridine proved to be the best additives (entries 5 and 7), with the highest yields (84% and 78 % combined yield), respectively, and **9a/10a** ratios of 1.7 and 2.1, respectively. The yields and ratios were in both cases similar to those obtained using excess of pyridine (entry 4) and substantially better than those obtained with MS 4 Å (90% combined yield, 1:1 ratio, entry 19). Practical reasons (price and availability) made imidazole the preferred catalyst for this reaction. The use of acid additives had the reverse effect, generating the olefin **10a** as the main product although with moderate efficiency (entries 16-18).

The scope and efficiency of the catalytic manifold was first studied with the transformation of the secondary PVEs **7a-g** into the corresponding salicylaldehydes **9a-g** (Table 2).^[19] In general, the reaction delivered the corresponding salicylaldehydes **9a-f** in moderate-to-good yields (54-72%) depending on the substitution pattern of the PVE. Esters, isolated double bonds, and protected

Table 1. Optimization of the additive for the micro-wave-assisted synthesis of salicylaldehyde **9a**.

Reaction scheme: **7a** (with nPr and nBu substituents) reacts with Xylene (1ml), additive (10 mol-%), μw (300 watt), 200 °C, 1h, closed vessel to yield **9a** (with Et and nBu substituents) and **10a** (with MeO_2C and CO_2Me substituents).

entry	Additive	pK _a ^[a]	9a+10a (%)	ratio 9a/10a ^[b]
1	DABCO	2.97	64	1.5
2	Aniline	4.63	35	0.17
3	DMBA	4.68	36	0.16
4	Pyridine ^[c]	5.2	87	1.6
5	Imidazole	6.9	84	1.7
6	Collidine	7.4	68	1.4
7	DMAP	9.2	78	2.1
8	DIPEA	10.8	64	1.4
9	Quinuclidine	11	44	0.8
10	DBU	12	62	1.5
11	tBuOK	17	37	0.3
12	Indole	21 ^[d]	34	0.1
13	Pyrrole	23 ^[d]	34	0.1
14	Urea	26.9 ^[d]	42	0.7
15	TMP	37 ^d	74	1.8
16	C ₆ H ₅ CO ₂ H	4.2	58	0.8
17	C ₅ H ₁₀ NH ₂ ⁺ AcO ⁻	8.7	56	0.6
18	Phenol	9.95	55	0.1
19	MS 4A ^[e]		90	1

[a] In H₂O. [b] Determined by NMR. [c] 200 mol-%. [d] In DMSO. [e] 300 mg/mmol. Abbreviations: DMBA: 1,3-Dimethyl barbituric acid; DMPA: 4-dimethylaminopyridine; DIPEA: N,N-diisopropyl-ethylamine; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; TMP: 2,2,6,6-tetramethylpiperidine.

Table 2. Imidazole-catalyzed synthesis of salicylaldehydes **9** from secondary propargyl vinyl ethers **7**.

hydroxyl groups were well tolerated. Interestingly, the PVE **7g** bearing an electron-rich alkyne in its structure could be also transformed into the corresponding hydroxylated salicylaldehyde **9g** (38%). In spite of this moderate-low yield, the importance of hydroxylated aromatic platforms^[20] and the potential use of hydroxylated salicylaldehydes as convenient building blocks for accessing biological relevant molecules^{[13],[21],[22]} ensures a preparative value to this transformation. In addition, the ease and direct access to secondary PVEs containing the ethoxyacetylene motive (ethoxyacetylene is commercial available) allows for the fast access to a broad number of 3-substituted 6-ethoxy-salicylaldehyde platforms.

The catalytic synthesis of 3,4,6-trisubstituted salicylaldehydes from tertiary propargylic vinyl ethers. Once the catalytic version of the reaction could be standardized, we next studied its extension to PVEs **1** bearing two substituents at the propargylic position (R^2 and $R^3 \neq H$; hereinafter referred to as tertiary PVEs). The main advantages associated with the incorporation of tertiary PVEs to the reaction manifold are related to: 1) *skeletal complexity*: the use of cyclic ketones (mono or polycycles, simple or fused) should increase the power of the manifold to generate structural complexity and topological diversity; 2) *reactivity*: the presence of two substituents on the propargylic position of the tertiary PVE should favor both the propargyl Claisen rearrangement¹ and the enolization process (see Figure 1C), what should translate in a net increase in the reaction efficiency. With these ideas in mind, we prepared an extensive set of tertiary PVEs **1**^[23] incorporating a wide array of substituents and molecular topologies (Table 3). These PVEs were conveniently prepared from the corresponding tertiary propargyl alcohols and methyl propiolate according to our recently reported protocol.^[24]

In general, tertiary PVEs proved to be excellent substrates for this catalytic reaction affording the corresponding aromatic derivatives in good average yield. The PVEs **1a-d**^[23] derived from acyclic ketones, delivered the corresponding aromatic derivatives **14a-d** in good average yield and incorporating a varied substitution pattern at the aromatic ring, including alky, aryl or oxygen-containing functionalities. Remarkably, the latter functionalities are introduced with high efficiency (**14a**, 73%) and in a chemo-differentiated manner (one as a free OH, the another as a protected OH). This property enables the orthogonal manipulation of each hydroxyl group at the aromatic ring without taking special precautions or using special reagents. A very interesting aspect of this reaction is the breakage of the symmetry observed when symmetrical disubstituted PVEs (ketones) are used ($CH_2-R^2 = R^3$). In these cases, the reaction places the R^3 substituent at the C₅-position of the ring, delivering the R^2 substituent (the sec-alkyl chain) at the corresponding C₆-position. This is a very important property and it allows the final differentiation of the otherwise identical PVE's propargylic substituents, increasing the diversity generation power of the reaction manifold. The derivative **14d** is a nice example of this symmetry-breaking chemical differentiation ($R^3 = Et$; $R^2 = Me$).

The tertiary PVEs **1e-u**^[23] derived from symmetric monocyclic ketones, were also convenient substrates for the

Table 3. Imidazole-catalyzed synthesis of salicylaldehydes **14** from tertiary propargyl vinyl ethers **1**.

[a] The reaction was performed at gram-scale (1.1 g, 4.4 mmol). [b] The corresponding PVEs were not isolated. Yields refer to the 2-step process: formation of the PVE from the corresponding propargyl alcohol and microwave-assisted rearrangement. See experimental section and SI for details. [c] The yield was assigned by quantitative NMR integration of the crude reaction residue.

reaction, providing a wide set of fused bicyclic salicylaldehyde derivatives featuring varied aromatic functionalization. Thus, the PVEs **1e-o**, armed with a cyclohexane motive, delivered the corresponding 1-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carbaldehydes **14e-o** adorned with a wide array of substituents at the C_3 -position. The substituents ranged from simple hydrogen, the worst case (**14k**, 17%) to heteroatoms including silicon (**14j**, 85%), bromine (**14l**, 47%), oxygen (**14m**, 77%) or nitrogen (**14o**, 93%). The low yield of derived **14k** is in accordance with our previous results using MS $4\text{\AA}^{[9]}$ or pyridine^[10] and confirms that the substitution at the terminal alkyne position ($R^1 \neq \text{H}$) is necessary to favour the formation of the enol intermediate **11** (see Scheme 1C). In this line of thinking, it is remarkable the high efficiency of this reaction when a bulky *tert*-butyl group is allocated at the terminal position of the triple bond in the parent PVE (**14h**, quantitative). The

substitution of this group by less steric-demanding groups (*n*butyl or methyl) lowered the yield (54% and 55%, respectively). On the other hand, the generation of the salicylaldehyde **14p** (31%) incorporating a fused cyclobutene ring is outstanding and reflects the potential of this catalytic reaction to generate molecular topologies not easily accessible by other methods.^[25]

Other topologies based on the bicyclo[*n*.4.0] motive ($n = 3, 5$, and 10) were explored. The reaction proved to be general with regard to the size of the non-aromatic ring size (**14p-s**). An interesting case was offered by the derivative **14s**, incorporating a C_{12} -membered ring in its structure. These topologies incorporating sp^3 -rich macrocycles are highly appreciated and under exploited structural motifs for drug discovery.^[26] The reaction also allowed the efficient access to C_6 -substituted 8-hydroxy-1,2,3,4-tetrahydroisoquinoline-7-carbaldehydes (**14t**, 78%) and to 1-hydroxy-5,6,7,8-tetrahydronaphthalene-2-

carbaldehydes bearing a protected ketone at C₇ as a convenient handle for further ring functionalization (**14u**, 86%). Both structures constitute interesting scaffolds for medicinal chemistry.^[27] Salicylaldehydes **14v–z** represent examples of fused tricyclic structures with natural-product like topologies.^[28] Interestingly, in these cases, the formation of salicylaldehydes **14** is accompanied by the formation of the corresponding benzoate derivatives **15**, which could stem from the 6 π -electrocyclization/aromatization processes of another diene **2** conformation arising from the ketone-ester groups interchange (vide infra). The subtle influence of the ketone skeleton on the selectivity of the reaction was apparent from the somehow surprising formation of the benzoate derivative **15n**, the only benzoate detected in the mono- and bicyclic series. An also subtle electronic effect was observed in the reactions involving fused bicyclic ketones. Whereas the formation of the 9H-fluorene derivatives **14x–z** showed a clear deterioration of the reaction efficiency with the electronic richness of the aromatic ring (compare **14x** with **14y** and **14z**), the presence of an oxygen atom at the 9-position of the 9,10-dihydrophenanthrene core was irrelevant in terms of efficiency, but not in terms of selectivity (compare **14v/15v** and **14w/15w**).

The reaction proved to be highly regioselective when asymmetrically substituted tertiary PVEs (ketones) were used (Scheme 2). Thus, PVE **1aa** bearing two different alkyl substituents at the propargylic position ($R^2 = \text{Et}$, $R^3 = \text{Me}$) delivered the salicylaldehyde **14aa** in 63% yield (19:1 isomeric ratio). The reaction manifold selectively incorporated the more substituted homopropargylic carbon atom into the final aromatic ring. Exquisite regioselectivity was also observed in the synthesis of the derivative **14ab** (86%, 50:1 isomeric ratio), showing a clear preference for the benzylic position over the alternative one. The observed regioselectivity could be explained by the relative stabilities of the isomeric trienol

Scheme 2. Regioselectivity in the imidazole-catalyzed reaction.

intermediates (vide infra) (Scheme 2, inset figure), which in turns relies on the relative stability of the terminal double bonds.

Application toward the first total synthesis of morintrifolin B.

The easy access to these multisubstituted salicylaldehydes scaffolds brought us the opportunity to use them as convenient starting materials for the synthesis of more complex structures embodying the parent aromatic ring. Among all of the possible structures, we choose benzophenones because their chemical and biological relevance.^[29] Natural benzophenones constitute a more than 300-members family of compounds, which span great structural diversity and bioactive properties including antifungal, anti-HIV, antimicrobial, antioxidant, and antiviral activity.^[30] Morintrifolin B (**19**)^[17] is a naturally occurring benzophenone isolated from the small tree *Morinda citrifolia* L. (Rubiaceae), commonly known as “noni” and widely distributed in southern Asia and the Pacific islands. The plant has found popular medicinal use for the treatment of asthma, bone fractures, cancer, cholecystitis, dysentery, lumbago, menstrual cramps, urinary difficulties, and many other ailments.^[31] In spite of the pharmacological potential offered by the constituents of the plant, there are no reports to date about the synthetic or biological study for morintrifolin B. Because our interest in this kind of compounds, we undertook a short synthesis of this benzophenone metabolite from the salicylic acid derivative **9c** by simple phenol protection (BrBn, K₂CO₃, acetone, 93%) and aldehyde oxidation (NaClO₂, sulphamic acid, THF-H₂O, 87%). The trifluoroacetic anhydride-mediated reductive coupling with the 2-methoxy-resorcinol derivative **17** assembled the benzophenone core of **19**, which was suddenly submitted to selective deprotection (H₂, Pd/C) to give the intermediate **18** (49% for two steps) featuring the same hydroxylated pattern than the target natural product. Finally, the acid controlled transesterification of this intermediate with ethylene glycol afforded the morintrifolin B (**19**) in 80% yield. The five-step synthesis delivered morintrifolin B in an overall 32% yield from the corresponding propargyl vinyl ether **7c**. The synthetic extension to other structurally related benzophenones and the studies of their biological activity are in progress in our lab and

Scheme 3. Short synthesis of morintrifolin B.

will be reported in due course.

Computational studies on the reaction mechanism. In order to provide new insight into the reaction mechanism for the rearrangement of the propargyl vinyl ethers, we have performed a computational DFT study using a simplified model denoted as **R** in Scheme 4, where $R^1 = R^2 = R^4 = H$ and $R^3 = CH_3$. It is worth noting that some hydrogen transfer processes (enolization and [1,3]-H shifts) show unrealistically^[32] high free energy barriers (ca. 55 kcal/mol). In these cases one imidazole molecule can act as a catalyst taking advantage of its amphoteric character. The names of these stationary points end with “-Imz” to indicate the use of a molecule of imidazole as a suitable additive. All stationary points on the potential surface have been fully optimized with the hybrid density functional B3LYP method,^[33] employing the 6-311+G(d,p) basis set.^[34] Harmonic analyses were calculated at this level of theory to verify the nature of the corresponding stationary points (minima or transition states), as well as to provide the zero-point vibrational energy (ZPE) and the thermodynamic contributions to the enthalpy and free energy for $T=298$ K. Moreover, intrinsic reaction coordinate^[35] calculations were performed to ensure that the transition states connect the reactants and products belonging to the reaction coordinate under study. The final energies were obtained by performing single-point M06-2X^[36] calculations using also the 6-311+G(d,p) basis set at the optimized B3LYP geometries. The average difference between the B3LYP and M06-2X increments of energy is 3.1 kcal/mol. The raw data obtained with the B3LYP and M06-2X results are reported in the Supporting Information (SI), (see Tables S1-S5) along with the Cartesian coordinates of each stationary point (see Table S6). The values discussed in the text and the values reported in the Schemes are relative free energies evaluated at the M06-2X/6-311+G(d,p)//B3LYP/6-311+G(d,p) level. All quantum chemistry calculations in this work have been carried out with the Gaussian 09 program package.^[37] The complete list of energy results is reported in the Tables S1-S5 of the SI. In addition, exhaustive potential energy surface scans with all the reaction mechanisms studied and selected geometrical parameters are displayed in the Figures S1-S15 of the SI. The transition states and intermediates of the studied domino rearrangement present several conformers with very similar energetic values (e.g. rotation about sp^3 carbon atoms and isomerization process of double bonds).

The domino reaction starts with a thermally allowed [3,3]sigmatropic process of **R** to yield **Int1** (Scheme 4). This propargyl Claisen rearrangement shows an activation free energy barrier (**TS1**) of 32.9 kcal/mol, which is the highest activation energy along the alternative reaction paths (vide infra). As expected, **TS1** involves the cleavage and formation of a C-O and a C-C bond, respectively, as well as the conversion of a propargyl and an enol group into an allene and a carbonyl group, respectively (Figures 1 and S1). Allenyl intermediate **Int1** lies ca. 14 kcal/mol below **R**. Several conformations of **Int1** can be considered and in this work we have calculated six of them (**Int1a** - **Int1f**) with very similar relative energies (differences smaller than 2 kcal/mol, see the SI).

The next step of the domino process consists of conversion of allene **Int1** into unsaturated ester **Int3** (Scheme 4). This process formally corresponds to a thermal antarafacial [1,3] sigmatropic shift involving hydrogen atom **H**¹ and allyl scaffold C₁-C₃. The direct process is not geometrically favoured since the activation energy for this direct process is of ca. 63 kcal/mol (see the SI). However, our calculations indicate that this 1,3-prototropy is feasible under imidazole assistance. Thus, imidazole can remove **H**¹ proton from **Int1** via **TS2-Imz** and transfer it to C₃ through **TS3-Imz** (see Figure 1 and the SI for additional details) with overall activation energy of ca. 20 kcal/mol, since the intermediate ionic pair is almost isoenergetic with respect to **TS3-Imz**. An alternative route involving the corresponding enol-allenes intermediates **Int2** via tautomeric equilibria involving one molecule of imidazole can be also considered (see **TS4**, **TS5**, and **TS4-Imz** in Figures S3 and S6 in SI).

Scheme 4. . Reaction pathway for the domino process leading to the formation of salicylaldehyde derivative **P1**. Transition state descriptors noted by TS-Imz refer to saddle points assisted with a molecule of imidazole (see text). Relative free energies are given in kcal/mol.

Oxatriene **Int3** can be transformed into triene **Int4** via a thermally allowed antarafacial [1,7] sigmatropic shift. It is noteworthy that the geometry of saddle point **TS6** associated with this latter process permits to discard an alternative pseudopericyclic process^[38] involving one of the lone pairs of the sp^2 -hybridized oxygen atom of **Int3** (Figure 2). The activation energy of this sigmatropic shift is lower than the activation energy associated with the first suprafacial [3,3] pericyclic reaction via **TS1** (vide supra).

From **Int4** the reaction proceeds through a thermal disrotatory electrocyclization to yield 1,3-cyclohexadiene intermediate **Int5** (Scheme 4). The features of saddle point **TS7** associated with this pericyclic step are those expected for a $[\pi6_s]$ process, in which the hydroxy group OH^2 formed in the previous step is necessarily inward (pseudoaxial) with respect to the C-C bond being formed (Figure 2). It results in destabilizing four-electron torquoelectronic interactions and steric congestion for this transition structure.^[39] As a consequence, this step shows a

Figure 1. Fully optimized structures of saddle points **TS1** associated with [3,3]Propargylic Claisen rearrangement, **TS2-Imz** and **TS3-Imz** corresponding to [1,3]hydrogen shift, and **TS8-Imz** associated with aromatization process (see Scheme 4). Bond distances are given in Å.

Figure 2. Fully optimized structures of saddle points **TS6,12**, associated with [1,7] sigmatropic shifts, and **TS7,13**, corresponding to $[\pi6_s]$ electrocyclizations (see Schemes 4 and 5). Bond distances are given in Å. Blue asterisks indicate the position of R^2 groups in more substituted transition structures (see Scheme 2).

relatively high activation energy, the second highest found in our calculations along the whole reaction coordinate. It is likely that this step and the first one associated with the [3,3] sigmatropic shift via **TS1** (vide supra) are responsible for the necessity of dielectric heating to complete these reactions. However, the effect of R^2 substituents in more complex substrates (see Scheme 2) is not critical, since these groups will always occupy the outward position in the corresponding $[\pi6_s]$ transition structures (see the blue asterisks in Figure 2).^[40]

Finally, **Int5** can be subjected to an aromatization process to produce salicylaldehyde, **P1**, and the concomitant release of a methanol molecule (see Scheme 4 and Figures 1, S4, and S7 of the SI). In this reaction mechanism step, the assistance of one molecule of imidazole is required to achieve a feasible activation energy ($\Delta G^\ddagger=24.1$ kcal/mol, **TS8-Imz**). This final step is strongly exergonic and irreversible, as it would be expected from the large resonance energy of the phenyl group generated in the course of the elimination-aromatization reaction.

An intriguing aspect of these reactions is the formation of methyl benzoates **15** in several polycyclic systems (vide supra, Table 3). Our computational model indicates that methyl benzoate (**P2** in Scheme 5) can be formed via oxatriene **Int7**, whose difference with respect to **Int3** is the (*E*)-configuration of the $\text{C}_1=\text{C}_2$ double bond. Despite this difference, **Int7** is almost isoenergetic with respect to **Int3**, but its imidazole-assisted formation via **TS9-Imz** or (*Z*)-**Int6** (which in turn involves saddle points **TS10-Imz** and **TS11**, see Figures S9 and S12) is less favoured than in the previous case, which is in line with the minor formation of benzoates **15** in most cases (Table 3). Beyond **Int7**, the previously described antarafacial [1,7] sigmatropic shift leads to triene **Int8**, whose disrotatory electrocyclization leads in turn to cyclohexadienyl alcohol **Int9**. The relatively high energy of this latter pericyclic reaction is that expected for a transition structure involving an inward OH^2 group (see the optimized structure of **TS13** in Figure 2). However, once again, R^2 groups in more substituted systems should occupy outward positions, which in general should not jeopardize this reaction path. Finally, the imidazole-assisted elimination-aromatization step from **Int9** leads to methyl

Scheme 5. Reaction mechanism for the domino process leading to the formation of methyl benzoate **P2**. Transition states including **Imz** descriptor refer to saddle points assisted with a molecule of imidazole (see text). Relative free energies are given in kcal/mol.

benzoate **P2** with an energy barrier significantly higher than those found for **P1** (see Schemes 4 and 5). This result is in nice agreement with the experimentally found formation of benzoates **15** as minor products, especially in polycyclic systems.

Conclusions

We have achieved the catalytic version of the microwave-assisted formation of poly-substituted salicylaldehydes from propargyl vinyl ethers. The reaction manifold uses imidazole as the catalyst (10 mol-%) to deliver an array of topologically diverse salicylaldehyde scaffolds spanning from simple aromatic monocycles to complex fused polycyclic systems. The reaction is scalable and instrumentally simple to perform, highly regioselective and symmetry-disrupting: symmetrically substituted PVEs afforded asymmetrically (non-redundant) substituted salicylaldehydes. The preparative value of this transformation has been demonstrated in the five-step synthesis of the natural benzophenone-derived morintrifolin B. A computational DFT study using a simplified model has been performed. Calculations underpin a domino mechanism comprising a [3,3]Propargylic Claisen rearrangement/[1,3]hydrogen shift/[1,7]hydrogen shift/ 6π - electrocyclization / aromatization process. The use of imidazole lowers the energy of the two more difficult steps, i.e., the 1,3-prototropic rearrangement and the final aromatization step, otherwise energetically very disfavoured.

Experimental Section

General remarks. ^1H NMR and ^{13}C NMR spectra of CDCl_3 solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz (Bruker Ac 200 and AMX2-500), respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor. FT-IR spectra were measured in chloroform solutions using a Perkin Elmer FT-IR Spectrum BX spectrophotometer. Mass spectra (low resolution) (EI/CI) were obtained with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer. High-resolution mass spectra were recorded with a Micromass Autospec mass spectrometer. Microanalyses were performed with a Fisons Instruments EA 1108 carbon, hydrogen, and nitrogen analyzer. Analytical thin-layer chromatography plates used were E. Merck Brinkman UV-active silica gel (Kieselgel 60 F254) on aluminum. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes, or ethyl acetate and dichloromethane as eluents. All reactions were performed in oven-dried glassware. All starting materials were obtained from commercial suppliers and used as received. PVEs **1v**, **1w**, **1x**, **1y**, and **1z** partially rearranged during the isolation and characterization process, so an telescoped alternative procedure was used to prepare **14v**, **14w**, **14x**, **14y**, and **14z** (see below).

Representative procedure for the microwave-assisted synthesis of salicylaldehydes from the corresponding propargyl vinyl ethers. Synthesis of 1-Hydroxy-3-phenyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde (14e). Propargyl vinyl ether **1e** (1.0 mmol) and imidazole (0.10 mmol) in dry xylene (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode

microwave oven (300 Watt, 190 °C). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 95/5) to yield **14e** (229.6 mg; 91%). Amorphous solid. ^1H NMR (400 MHz, CDCl_3 , 25°C): δ 1.71-1.75 (m, 4H), 2.62-2.65 (m, 2H), 2.68-2.71 (m, 2H), 6.52 (s, 1H), 7.24-7.26 (m, 2H), 7.30-7.35 (m, 3H), 9.67 (s, 1H), 12.27 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ 22.13, 22.25, 22.39, 30.5, 115.3, 122.1, 125.3, 127.9, 128.2 (2C), 130.0 (2C), 137.8, 143.6, 147.3, 161.2, 196.6 ppm; IR (CHCl_3): ν = 2939.6, 1635.7, 1617.2, 1559.6, 1405.3, 1366.7, 1299.4 cm^{-1} ; LRMS (70 eV) m/z (%): 252 (100) [M^+], 251 (42), 234 (30), 233 (18), 223 (12), 165 (17). HRMS (EI-TOF) m/z : [M^+] Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2$ 252.1150; Found 252.1144.

Representative telescoped procedure for the synthesis of salicylaldehydes 14v, 14w, 14x, 14y, and 14z from the corresponding tertiary propargylic alcohols. Synthesis of 1-Hydroxy-3-phenyl-9,10-dihydrophenanthrene-2-carbaldehyde (14v). The corresponding propargyl alcohol (1.0 mmol) and DABCO (0.10 mmol) were dissolved in hexane (1 mL) (a small amount of CH_2Cl_2 was used when the alcohol did not dissolved well in hexane). Methyl propiolate was slowly added dropwise (1.5 mmol) and the reaction was stirred for 5 minutes. The reaction mixture was filtered through a short column filled with silica gel using *n*-hexane/EtOAc (60/40). The solvent was evaporated off and the mixture was dissolved in xylenes (1 mL) and transferred into a microwave-special closed vial. Imidazole (0.10 mmol) was added and the reaction mixture was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 190 °C). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 95/5). **1-Hydroxy-3-phenyl-9,10-dihydrophenanthrene-2-carbaldehyde (14v)** (153.2 mg; 51%). Amorphous solid. ^1H NMR (400 MHz, CDCl_3 , 25°C): δ 2.89-2.93 (m, 2H), 2.97-3.01 (m, 2H), 7.28-7.34 (m, 4H), 7.42-7.51 (m, 5H), 7.76-7.79 (m, 1H), 9.83 (s, 1H), 12.36 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ 19.8, 28.1, 116.7, 117.0, 124.4, 124.9, 127.0, 128.1, 128.39 (2C), 128.41, 129.2, 130.1 (2C), 133.1, 138.0, 138.6, 142.1, 145.4, 160.1, 196.6 ppm; IR (CHCl_3): ν = 2945.1, 2896.7, 2844.7, 1633.7, 1617.8, 1545.8, 1479.8, 1400.2, 1363.5, 1331.6, 1307.2, 1288.7, 1239.0 cm^{-1} ; LRMS (70 eV) m/z (%): 300 (100) [M^+], 299 (41), 282 (27), 281 (32), 253 (16), 252 (21), 239 (12), 165 (15). HRMS (EI-TOF) m/z : [M^+] Calcd for $\text{C}_{21}\text{H}_{16}\text{O}_2$ 300.1150; Found 300.1142. Further elution delivered pure **methyl 3-phenyl-9,10-dihydrophenanthrene-2-carboxylate (15v)**: Amorphous solid (31.4 mg; 10%). ^1H NMR (400 MHz, CDCl_3 , 25°C): δ 2.93 (bs, 4H), 3.64 (s, 3H), 7.24-7.32 (m, 3H), 7.35-7.44 (m, 5H), 7.33 (d, $^3J(\text{H,H}) = 7.1$ Hz, 2H), 7.77 (t, $^3J(\text{H,H}) = 7.1$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , 25°C): δ 28.5, 28.8, 51.8, 124.2, 126.1, 127.10, 127.12, 127.8 (2C), 128.3, 128.41 (3C), 129.1, 129.7, 133.4, 136.2, 137.4, 137.9, 141.6, 141.7, 168.8 ppm; IR (CHCl_3): ν = 3028.8, 2951.1, 2841.6, 1716.4, 1603.0, 1436.2, 1305.8, 1252.4 cm^{-1} ; LRMS (70 eV) m/z (%): 314 (57) [M^+], 283 (24), 252 (10), 239 (10), 170 (13), 169 (100), 141 (16), 115 (17), 91 (20). HRMS (EI-TOF) m/z : [M^+] Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2$ 314.1307; Found 314.1305.

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FULL PAPER

David Tejedor,* Leandro Cotos, Daniel Márquez-Arce, Mikel Odriozola-Gimeno, Miquel Torrent-Sucarrat, Fernando P. Cossío and Fernando García-Tellado*[a]
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The Microwave-assisted Organocatalyzed Rearrangement of Propargyl Vinyl Ethers to Salicylaldehyde Derivatives: A Combined Experimental and Theoretical Study

Complex and diverse: The microwave-assisted rearrangement of propargyl vinyl ethers in the presence of a catalytic amount of imidazole generates topologically complex salicylaldehyde derivatives adorned with a diverse and varied substitution pattern.