Recent Advances in the Synthesis of 2H-Pyrans

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Abstract: In this review, we discuss the nature of the different physicochemical factors affecting the valence isomerism between 2H-pyrans (2HPs) and 1-oxatrienes, and we describe the most versatile synthetic methods reported in recent literature to access to 2HPs, with the only exception of 2HPs fused to aromatic rings (i.e., 2H-chromenes), which are not included in this review.

Keywords: 2H-pyran; heterocycles; synthesis; valence isomerism; 1-oxa-triene; dienone; oxa-electrocyclization; Knoevenagel; propargyl Claisen; cycloisomerization

1. Introduction

The 2H-pyran (2HP) ring constitutes a structural motif present in many natural products (Figure 1) [1] and is a strategic key intermediate in the construction of many of these structures [2,3]. In spite of their importance, the literature of 2HPs is relatively scarce [4–9], mainly due to the instability associated with the heterocyclic ring, which makes these heterocycles establish an equilibrium with their opened isomeric forms (Scheme 1). Fusion of a 2HP to an aromatic ring confers stability to these heterocycles. Thus, while simple 2HPs are difficult to synthesize as pure and isolated compounds, many of their benzo derivatives (i.e., 2H-chromenes) constitute stable molecules, with a broad spectrum of biological activities and a widespread representation in the higher plants (Figure 1). Because the chemistry and reactivity of 2H-chromenes have been already previously revised [1,10–15], they will not be included in this review. Instead, we will focus on the recent advances on accessing 2HPs, either as simple and stable monocyclic structures or as part of fused polycyclic structures, excluding the 2H-chromene system.

Scheme 1. Valence tautomerism of 2H-pyrans (2HPs).
2. Dienone/2HP Equilibrium

2HPs are prone to undergo spontaneous valence isomerization [16] to the corresponding 1-oxatrienes through a reversible pericyclic oxa-6π-electrocyclization process (Scheme 1) [17]. This valence tautomerism determines the chemistry of these heterocycles, which commonly exist as a conjugation of the tetrasubstituted dienones [18]. Authors found that the irradiation afforded a mixture of cis-β-ionone (2) and 2HP 3, with a value for the equilibrium constant $K = 4.61$ at 327 °K ($K = 1.52$ at 386 °K), and values for $k_1 = 1.4 \times 10^3$ s$^{-1}$ and $k_1 = 1.3 \times 10^4$ s$^{-1}$. In addition, measurements at different temperatures gave activation energies ($E_a$) of 20 Kcal/mol for the cis-dienone to 2HP reaction, and 27 Kcal/mol for the reverse process [19].

Further studies on the conformation of conjugated dienones allowed the establishment of some general patterns for these dienone/2HP equilibria (Scheme 3) [20]. It was observed that steric destabilization of the dienones shifted the equilibria toward the 2HPs. This was the case for tetrasubstituted dienones 4 and 5, which fully isomerized to the corresponding 2HPs. On the other hand, simpler dienones 8–12, which could adopt a stable planar conformation, existed in the opened form. Likewise, trisubstituted dienones 6–7, which are representative examples of dienones featuring non-stable planar conformations, preferred their closed forms. Along with these results, the authors also observed that the substitution of a δ-alkyl substituent (R$^5$ or R$^6$) by a substituent able to extend the conjugation of the π-system (e.g., vinyl group) favored the dienone form (Scheme 3). A main conclusion from these and other studies [20,21] is that the existence of the 2HP form depends primarily on the...
steric destabilization of the dienone rather than on its specific substitution pattern. Thus, the design of stable 2HPs must include, among other structural/electronic criteria, enough steric destabilization on the dienone to penalize the valence isomerization.

\[ \text{(E)-dienone} \quad \rightarrow \quad 2\text{HP} \]

\[ \text{Increasing preference for dienone} \]

**Scheme 3. Implications of the cis-dienone conformation on the valence isomerism.**

More recently, Krasnaya et al. carried out a systematic investigation on the influence of substituents and solvents on the valence isomerization of trisubstituted α-acyl-dienones 13 (Scheme 4). In this study, the authors quantified the equilibrium compositions of 26 differently substituted α-acyl-dienones 13 (Table 1), and determined the thermodynamic and activation parameters for some of these equilibria (Scheme 5) [22].

\[ \text{(E)-13} \quad \rightarrow \quad 14 \quad \text{5-acyl-2HP} \quad \rightarrow \quad (Z)-13 \]

\[ \text{Typical spectroscopic data for characterization} \]

| Substituent | dienone | 2HP |
|-------------|---------|-----|
| 4           | R^1 = R^2 = R^3 = Me | -   |
| 5           | R^1 = R^2 = R^3 = Me | -   |
| 6           | R^1 = R^2 = R^3 = Me | -   |
| 7           | R^1 = Me, R^2 = R^3 = 'Bu | -   |
| 8           | R^2 = R^3 = Me | +   |
| 9           | R^1 = R^2 = R^3 = Me | +   |
| 10          | R^1 = R^2 = R^3 = Me | +   |
| 11          | R^1 = R^2 = R^3 = -(CH₂)ₓ | +   |
| 12          | R^1 = Bu, R^2 = Me | +   |

**Scheme 5. Thermodynamic data for 13a–c/14a–c valence isomerization.**
Table 1 summarizes the earlier observed importance of structural effects on the valence equilibrium, and it confirms some general patterns:

1. The successive substitution at position C₂ in the ring (C₅ on dienone) leads to an increase in the content of 2HP (steric strain on the dienone) (compare entries 1–3 and 7–8).
2. The elongation of the conjugated system results in an increase in the content of dienone (resonance delocalization) (compare entries 15, 25 and 17, 26).
3. Substitution at the C₂-position of the ring (C₅ on dienone) with two methyl groups strongly shifts the equilibrium toward the 2HP (entries 17, 19). In this case, it is possible to observe only the 2HP (compare entries 7, 17 with 11, 19).
4. Aprotic polar solvent shifts the equilibrium toward the formation of the dienone.
5. Although the electronic effect of the acyl group at the C₅-position of the ring (Cα in the dienone) is masked in Table 1, other studies have shown that the presence of an electron-withdrawing substituent(s) at the ring, preferentially at this C₅-position, favors the 2HP [23–25]. Table 1 shows that although this effect could be operative in α-acyl-dienones 13, it can be completely surpassed by other structural/electronic effects (Table 1, entries 11–14).

Table 1. α-Acyl-dienones 13 and their equilibrium isomeric compositions.

| Entry | R     | R¹ | R⁴ | R⁵ | R⁶ | (E)-13 | 2HP¹ 14 | (Z)-13 |
|-------|-------|----|----|----|----|--------|--------|--------|
| 1     | EtO   | Me | H  | H  | Me | 30     | 30     | 40     |
| 2     | EtO   | Me | H  | H  | H  | 45     | 30     | 25     |
| 3     | EtO   | Me | H  | Me | Me | 17     | 68     | 15     |
| 4     | MeO   | Me | H  | H  | H  | 43     | 37     | 30     |
| 5     | MeO   | Me | H  | Me | Me | 40     | 40     | 20     |
| 6     | MeO   | Me | H  | Me | Me | 26     | 62     | 12     |
| 7     | Me    | Me | H  | Me | Me | 72     | 28     | -      |
| 8     | Me    | Me | H  | Me | Me | 64     | 36     | -      |
| 9     | t-BuO | Me | H  | Me | Me | 18     | 17     | 65     |
| 10    | EtO   | Arb | H  | Me | Me | 84     | 9      | 7      |
| 11    | EtO   | Ph | H  | H  | Me | 67     | -      | 33     |
| 12    | EtO   | Ph | H  | Me | Me | 86     | -      | 14     |
| 13    | EtO   | Me | H  | H  | Ph | 60     | -      | 40     |
| 14    | Me    | Me | H  | H  | Ph | 100    | -      | -      |
| 15    | MeO   | Me | Me | Me | Me | -      | 83     | 17     |
| 16    | MeO   | Me | Me | H  | Ph | -      | 100    | -      |
| 17    | Me    | Me | Me | Me | Me | -      | 100    | -      |
| 18    | Me    | Me | Me | H  | Ph | -      | 100    | -      |
| 19    | EtO   | Ph | Me | Me | Me | -      | 100    | -      |
| 20    | MeO   | Me | H  | H  | -(CH₂)₅- | 30  | 23      | 47     |
| 21    | MeO   | Me | Me | H  | c-C₅H₁₁ | -      | -      | 100    |
| 22    | MeO   | Me | H  | -(CH₂)₅- | 16  | 67      | 17     |
| 23    | MeO   | Me | Me | -(CH₂)₅- | -    | 100    | -      |
| 24    | MeO   | Me | H  | -(C₅H₁₁) | 47  | 31      | 22     |
| 25    | MeO   | Me | Me | Me | H  | HC=CMₑ₂ | 75    | -      | 25     |
| 26    | Me    | Me | Me | Me | H  | HC=CMₑ₂ | 100   | -      | -      |

a The composition was determined by ¹H-NMR in CDCl₃ at 30 °C. b Ar = p-nitrophenyl. c The E and Z are topomers.

With regard to thermodynamic parameters of some of these equilibria (Scheme 5), Krasnaya et al. found that, in all cases, the enthalpies of the α-acyl-dienones 13 were appreciably higher than those of 5-acyl-2HPs 14, which is in full agreement with the observed increase in the dienone content with the increase in temperature. As should be expected, the entropy contents were also higher for the closed structures. In all the investigated cases, ΔG° values were on the order of 21.88 Kcal/mol to 22.86 Kcal/mol.
Finally, other structural factors, such as annulation, also favor the 2HP form. It has been well established that annulation favors the closed form by restricting conformational freedom (entropic trap), and it has been used as a design element in the synthesis of stable 2HPs [26,27]. Scheme 6 graphically summarizes the main conclusions of these studies. Structures 3, 15, 16 represent prototypical examples of room temperature stable 2HPs.

3. Synthesis of the 2HP Core

The most common route for synthesizing these heterocycles relies on the oxa-6π-electrocyclization of dienones, the so-called 1-oxatriene pathway [28]. As already discussed in the previous section, this methodology requires endowing the 1-oxatriene unit with structural or electronic information, or both, to shift the valence equilibrium toward the 2HP form (Scheme 7). Thus, different synthetic pathways to the 1-oxatriene core have been successfully explored, involving, among others, the classic Knoevenagel condensation between active methylene compounds and α,β-unsaturated aldehydes (enals), Claisen rearrangements of propargyl vinyl ethers, Stille coupling of vinyl stannanes and vinyl iodides, and cycloisomerization of dienols (Scheme 7).

Scheme 6. (a) Summary of parameters affecting the valence isomerization. (b) Prototypical examples of stable 2HPs.

3.1. The Knoevenagel/Electrocyclization Protocol

The Knoevenagel condensation constitutes the most common access to 1-oxatrienes, and most generally involves the reaction of an enal with a 1,3-dicarbonyl compound [29]. The sequential performance of the Knoevenagel condensation and the electrocyclization reaction generates 2HPs.
(Scheme 8). From a synthetic point of view, the whole tandem process can be considered a formal \([3 + 3]\) cycloaddition \([2,28]\). There is a plethora of examples of this strategy in the literature, mainly in the field of total synthesis of natural products. In this review, we will pay attention exclusively to established synthetic methods that allow or have allowed general access to these heterocycles. Specific cases utilized to access a particular structure or a specific natural product will not be covered. We refer the reader to the excellent published reviews covering this issue \([2,3]\).

\[\text{enal} + \text{3-dicarbonyl} \rightarrow \text{1-oxatriene} \rightarrow \text{2HP} \]

Scheme 8. Knoevenagel/electrocyclization strategy.

Fusion to a ring favors the electrocyclization of the 1-oxatriene intermediate, and it has been used as a steering element to synthesize stable 2HPs. As an earlier example, the pyridine-mediated condensation of different cyclic 1,3-dicarbonyl compounds 17 and functionalized enals 18 generated the stable bicyclic 2HPs 19 in good yields (Scheme 9a) \([30]\). Therefore, the double substitution at the terminal position of the enal also contributed to the global stability of 2HPs 19. Using this methodology, the same authors synthesized the alkaloid flindersine (21) in 86% yield and in just one synthetic step (Scheme 9b).

\[\text{enal} + \text{3-dicarbonyl} \rightarrow \text{1-oxatriene} \rightarrow \text{2HP} \]

Scheme 9. Knoevenagel/electrocyclization: (a) synthesis of annellated 2HPs 19 and (b) synthesis of flindersine (21).
The iminium-mediated Knoevenagel condensation (IMKC) [31,32] has been currently used to condense 1,3-dicarbonyl (active methylene) compounds with 2-alkenyliminiums (activated enals), and it constitutes a very versatile route to 1-oxatrienes [2,33]. The chemical outcome of the reaction is that of a formal [3 + 3] cycloaddition between enols and enals (see Scheme 8). The reaction is productive when functionalized cyclohexane-1,3-diones (e.g., 21) (Scheme 10) or 4-hydroxypyrones 25 (Scheme 11) are used as the active methylene compounds in the process. In this manner, 2HPs 23a–g were synthesized from the functionalized cyclohexa-1,3-dione 21 and different functionalized enals 22 (Scheme 10) [34]. These 2HPs were used as key intermediates in the total synthesis of (−)-daurichromenic acid and analogues. The use of Lewis [35] or Brønsted [36] acids, In^3+ [37], or iodine [38] as catalysts resulted complementary to the iminium formation and afforded similar reaction outcomes.

Scheme 10. Synthesis of 2HPs 23 by iminium-mediated Knoevenagel condensation (IMKC) of cyclohexa-1,3-dione 21 and enals 22.

This methodology is well suited for use in diversity oriented synthesis programs [39], as long as the structural control elements are incorporated into the library design. Thus, a small and structurally varied library of 2HPs 26 was constructed using the β-alanine-mediated IMKC between 4-hydroxypyranone 25 and different enals 24 (Scheme 11) [40]. In vitro studies of antiproliferative/cytotoxic activity with human SH-SY5Y neuroblastoma cells showed IC_{50} values ranging from 6.7 to >200 μM. 2HP 26a exhibited the highest cytotoxicity to the neuroblastome cells and necrotic effects on the human IPC melanoma cells.

Although the use of cyclic 1,3-dienones has been beneficial for the synthesis and stability of the resulting 2HPs, it is not a mandatory requirement, and acyclic active methylene compounds, such as methyl acetoacetate 27, have been successfully condensed with 2-alkyl-2-enals 28 to deliver the corresponding stable 2,3,6-trisubstituted 2HPs 29 (Scheme 12) [41].
Scheme 11. Construction of a small library of annulated 2HPs 26 by the IMKC of 4-hydroxypyranone 25 and functionalized enals 24. A selection of library members is shown.

Scheme 12. Synthesis of 2,3,6-trisubstituted 2HPs 29 by IMKC of methyl acetoacetate 27 and enals 28.

Pyrano[3,2-c]quinolone is a core structural motif in alkaloids and is endowed with important pharmacological and therapeutic activities. As part of a research program aimed at developing efficient synthesis of natural product-like small molecules, a small 23-membered library focused on carbohydrate fused pyrano[3,2-c]quinolone structures 32 was synthesized and subjected to antiproliferative activity studies (Scheme 13) [42]. The library was synthesized using the microwave assisted pyrrolidine-AcOH catalyzed IMKC of formyl galactal (30-Gal) and formyl glucal (30-Glu) with 4-hydroxyquinolones 31, and although the electron donating or electron withdrawing character of groups R1, R2, R3, and R4 of 4-hydroxyquinolones significantly affected neither the yield nor the reaction completion time, the best yields were obtained when unsubstituted 31 was used (70% with 30-Gal and 71% with 30-Glu). The other combinations gave yields ranging from 62 to 69%.
The Knoevenagel/electrocyclization strategy is suitable to be performed in water (Scheme 14) [43]. This methodology was applied to the synthesis of biologically interesting 2HPs of general structure 39, comprising pyranocoumarin, pyranoquinolinone, and pyranonaphthoquinone derivatives along with selected natural and non-natural products (X = CH₂, O, NH). The reactions were performed by mixing the 1,3-dicarbonyl compound 33–37 with enal 38 in water at 80 °C for 4–6 h. Although authors did not specify the physical conditions of these reactions, the high hydrophobicity of the reactants suggested that these reactions were carried out as aqueous suspensions (the so-called “on water” conditions [44], rather than as homogeneous solutions. Solvent-free protocols have been also described for the IMKC reaction [45,46].

3.2. From Other Heterocycles

The condensation of methyl coumalate (40) with a wide range of active methylene compounds 41 has been implemented to access an extensive series of 2,3,5,6-tetrasubstituted 2HPs 42 (Scheme 15) [47]. The reaction involved a domino 1,6-Michael/6π-electrocyclic ring opening/[1,5]-H transfer/(decarboxylation)/6π-electrocyclization reaction. The methyl substituent allocated at C₂ position of the 2HP ring corresponds to the α-methylene group alpha to the lactone in the coumalate ring (highlighted as CH in Scheme 15).
The protocol used secondary propargyl vinyl ethers (they bear only one substituent at the propargylic position; \( R \)). The scope of the reaction was wide, tolerating a good variety of the substituents. The presence of the substituent \( R \) was fundamental for the stability of the 2HP ring and corresponds to the \( \alpha \)-methine group alpha to the lactone in the coumalate and 1,3-dicarbonyl compounds.

A one pot synthesis of 2,2,4,6-tetrasubstituted 2HPs has been developed using Bayliss–Hillman carbonates \( 43 \) and \( \beta,\gamma \)-unsaturated \( \alpha \)-oxo-esters \( 44 \) (Scheme 16) [48]. The one-pot reaction involved a phosphine-catalyzed condensation of \( 43 \) and \( 44 \) to give intermediate 4,5-dihydrofuran \( 45 \), which, in the presence of pyrrolidine and heat, rearranged to the 2HP \( 46 \). Authors gave a tentative mechanism for this pyrrolidine-catalyzed rearrangement. All the examples incorporated an aromatic (heterocyclic) substituent at \( R_1 \), but the authors do not explain if this was a mandatory property of this substituent.

Stable 2,4,5,6-tetrasubstituted 2HPs \( 49 \) have been synthesized by the phosphine-catalyzed [3 + 3] annulation of ethyl 5-acetoxypenta-2,3-dienoate \( 47 \) and 1,3-dicarbonyl compounds \( 48 \) (Scheme 17) [49]. The scope of the reaction was wide, tolerating a good variety of the substituents. The presence of the ester group at the \( C_5 \) position of the ring was fundamental for the stability of the 2HPs.

Propargyl vinyl ethers \( 50 \) have been successfully rearranged into stable 2,4,5,6-tetrasubstituted 2HPs \( 51 \) through a one pot procedure involving a Ag(I)-catalyzed propargyl Claisen rearrangement followed by a tandem DBU-catalyzed isomerization/6π-oxa-electrocyclization reaction (Scheme 18) [50]. The protocol used secondary propargyl vinyl ethers (they bear only one substituent at the propargylic position; \( R_3 \)), and it required the installation of an ester group at the \( C_5 \) position of the ring and substitution at the \( C_6 \) position to give stability to the monocyclic 2HP.
Propargyl vinyl ethers 50 have been successfully rearranged into stable 2,4,5,6-tetrasubstituted 2HPs through a one pot procedure involving a Ag(I)-catalyzed propargyl Claisen rearrangement/6π-electrocyclization/MeOH elimination set of reactions [54]. Again, the presence of an ester functionality at the position C5 of the ring was mandatory to stabilize the final 2HP 53. The double substitution at C2 favored the 2HP formation (steric information) and offered a wide range of optional substitution patterns at the ring (Alk/Alk, Ar/Alk, Ar/Ar). The protocol delivered 2HP structures in moderate to good yields. In all the conditions explored in [51–53]. Authors found that the structure of the diyne and aldehydes has been successfully rearranged into stable 2,4,5,6-tetrasubstituted 2HPs from propargyl vinyl esters 52 (Scheme 19) [51–53]. The strategy made use of an imidazole-catalyzed all-pericyclic domino manifold entailing a sequential propargyl Claisen rearrangement/[1,7]-H shift/oxa-6π-electrocyclization set of reactions. Again, the presence of an ester functionality at the position C2 of the ring was mandatory to stabilize the final 2HP 53. The double substitution at C2 favored the 2HP formation (steric information) and offered a wide range of optional substitution patterns at the ring (Alk/Alk, Ar/Alk, Ar/Ar). The protocol delivered 2HP structures endowed with different topologies, including monocycles (53-mc), 2,2-spiro-bicycles (53-sbc), and 2,2-spiro-macrohreibicycles (53-smbc). The main limitation arose from the presence of a tBu substituent at the alkyne position (R1): In this case, the reaction followed a different pathway through a sequential [1,7]-H shift/6π-electrocyclization/MeOH elimination set of reactions [54].

Scheme 18. One pot synthesis of 2,3,4,6-tetrasubstituted 2HPs 51 from propargyl vinyl ethers 50.

Scheme 19. All pericyclic domino synthesis of 2,2,4,5-tetrasubstituted 2HPs 53 from propargyl vinyl ethers 52.
An alternative protocol using propargyl alcohols 54 and alkyl ethylenedicarboxylates 55 has been developed (Scheme 20) [24,55]. The protocol generated 2,3,4,5,6-pentasubstituted 2HPs 56, incorporating two identical ester functionalities at C5 and C6, and a halogen atom at C3. The protocol used DABCO as the catalyst and N-iodosuccinimide (NIS) or N-bromosuccinimide (NBS) as the halogenation agent to generate 2HPs 56 in moderate to good yields. In all the conditions explored in Scheme 20, the substituents at the propargyl alcohol were aromatics (R1/R2 = Ar). The authors did not specify if this was a limitation to the procedure, or was just an inconvenient choice of starting materials.

![Scheme 20](image)

**Scheme 20.** Synthesis of 2,3,4,5,6-pentasubstituted 2HP 56 from propargyl alcohols 54 and dialkyl acetelynedicarboxylates 55.

3.4.2. From Diynes

The Ni(0)-catalyzed cycloaddition of diynes 57 and aldehydes 58 has been explored in the construction of bicyclic 2HPs 59 (Scheme 21) [26,56]. Authors found that the structure of the diyne 57, mainly the substitution at the terminal positions (R1 ≠ H), and the length of the chain connecting the alkyne units, exerted a great influence on the bicyclic 2HP formation reaction. The worst yield was observed when acetaldehyde was used as the aldehyde (28%), whereas the best was observed with n-butanal (90%).

![Scheme 21](image)

**Scheme 21.** Ni(0)-catalyzed synthesis of bicyclic 2HP 59 from diynes 57 and aldehydes 58.

A transition metal-free, cycloisomerization of diynols 60 to generate bicyclic 2HPs 61 has been reported (Scheme 22) [26]. The reaction was catalyzed by a cooperative catalytic system entailing Ca2+/H+-catalyst (5 mol%) and camphorsulphonic acid (10 mol%), in the presence of benzaldehyde as a mild Lewis basic electron donor. The reaction was carried out without exclusion of air and moisture, and it tolerated a wide range of functionalities on the electron rich 2HP ring. The main limitations arose from substituents R2/R1 at the propargylic terminal position, which only allowed the alkyl/alkyl combination, and from R1, which had to be aromatic. The only limitation for the aromatic substituent at R1 was the presence of a free hydroxyl group at the ortho position of the ring. As long these restrictions were kept, excellent yields of 2HPs were obtained. The mechanistic proposal involved the formation of a propargylic tertiary cation 61, which afforded the cyclic 1-oxa-2,4,5-triene intermediate 62, which isomerized to 63 and rearranged into 2HP 64.
was convergent, highly diastereoselective, and required mild reaction conditions with low catalyst loadings (5 mol%). In the pattern of construction depicted in Scheme 23, the main restriction came from the nature of the vinyl iodide R1, which had to be aromatic. The only limitation for the aromatic substituent at R1 was the presence of a free hydroxyl group at the ortho position (R/R' ≠ H) to stabilize the 2HP ring form by steric destabilization of the 1-oxatriene form.

Scheme 22. Ca$^{2+}$/H$^+$-catalyzed synthesis of bicyclic 2HP 64 from diynols 60.

3.4.3. From Alkenes: Tandem Stille-Oxa-Electrocyclization Reaction

Highly substituted bicyclic 2HPs 67 have been synthesized by a palladium-catalyzed tandem Stille-oxa-electrocyclization reaction between vinyl stannanes 65 and vinyl iodides 66 (Scheme 23) [57,58]. The strategy was a convergent alternative to the known methods for constructing similar bicyclic 2HPs, and it has been used in the total synthesis of natural products [59–61]. Although it required the prior stereoselective construction of both vinyl derivatives, the strategy had several advantages: It was convergent, highly diastereoselective, and required mild reaction conditions with low catalyst loadings (5 mol%). In the pattern of construction depicted in Scheme 23, the main restriction came from the nature of the vinyl iodide 66, which had to have substituents at the vinyl (R$^3$ ≠ H) and allylic positions (R/R’ ≠ H) to stabilize the 2HP ring form by steric destabilization of the 1-oxatriene form.

Scheme 23. Stille-oxa-electrocyclization strategy to access bicyclic 2HP 67.

4. Summary and Conclusions

We have discussed the structural and electronic factors controlling the valence isomerism of 2HPs and how they can be harnessed to design effective synthesis of 2HPs. The most common routes to access these heterocycles relies on the 6π-electrocyclization of the corresponding 1-oxatriene isomers; thus, the synthetic challenge translates into the synthesis of the 1-oxatriene precursor. We have gathered the most transited routes to these species, including the proper Knoevenagel reaction, the tandem propargyl Claisen rearrangement/[1,3]-H shift reactions hosted by propargyl vinyl ethers, the cycloisomerization of diynes, and the Stille coupling of vinyl iodides and vinyl stannanes. From the large number of methods reported in the literature to access these heterocycles, we have selected only those able to generate stable rings with a convenient amount of structural/functional diversity. We...
hope that this review has filled the existing gap in literature regarding the reactivity and synthesis of these heterocycles, and that it finds use in future applications of these heterocycles.

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