CHEMISTRY
A EUROPEAN JOURNAL

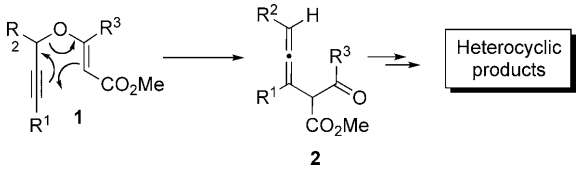
DOI: 10.1002/chem.201003532

A Microwave-Assisted Domino Rearrangement of Propargyl Vinyl Ethers to Multifunctionalized Aromatic Platforms

David Tejedor,*[a, b] Gabriela Méndez-Abt,[a, b] Leandro Cotos,[a, b] Miguel A. Ramirez,[c] and Fernando García-Tellado*[a, b]

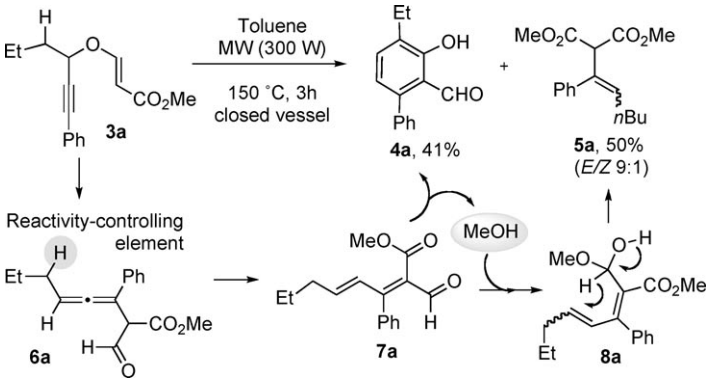
In memory of Professor Rafael Suau

Propargyl vinyl ethers (PVEs) **1** constitute a privileged group of small size, structurally simple, readily available, and densely functionalized scaffolds.[1–4] Efforts from our group,[2] and others,[3] have revealed the synthetic potential of these platforms in accessing important heterocyclic cores. The key to the chemical reactivity encoded in these structures is the [3,3] propargylic sigmatropic rearrangement[5] shown in Scheme 1. The allenyl compounds **2**, thus obtained,



Scheme 1. [3,3] Propargylic sigmatropic rearrangement of PVEs.

are reactive units and well suited to participate in a wide array of chemical transformations. Thus, in the presence of metallic catalysts, they have been selectively transformed into furans,[3a–d] 2*H*-pyrans,[3e] dihydropyrans,[3f] 1,2-dihydropyridines,[3g] or pyrroles.[3h] Recently, we have described a metal-free, microwave-assisted domino synthesis of substituted 1,2-dihydropyridines[2c] and pyridines,[2d] from PVEs **1** and primary amines, via the thermally-assisted formation of a homoallenyl ester intermediate **2**. During the course of these studies, we discovered a new chemical reactivity of these platforms when a solution of PVE **3a** in toluene was submitted to microwave (MW) irradiation in a sealed vial (Scheme 2). The reaction cleanly afforded the unexpected



Scheme 2. Unexpected new chemical reactivity of **3a**, after microwave (MW) irradiation.

mixture of compounds **4a** and **5a** in 91% overall yield. These structures featured an unprecedented chemical outcome for this domino process, which is enabled by the presence of a hydrogen atom at the homopropargylic position. Fascinated by these unexpected results, we undertook the study and scope of this novel domino reaction. Overall, this reaction should provide an expedient route to useful multifunctionalized phenolic platforms,[6] such as **4**, which constitute key structural motifs for the preparation of numerous pharmacologically important natural products (e.g., coumarins,[7a] flavones,[7b] and several mycotoxins[7c]) and catalysts.[8] In addition, PVEs **3** are easily accessible starting materials, spanning a wide substitution pattern. They are conveniently assembled from commercial sources (aldehydes, alkynes, and alkyl propiolates) in one or two straightforward synthetic steps.[2]

We hypothesized that the formation of products **4a** and **5a** should result from a domino process triggered by the expected microwave-assisted rearrangement of PVE **3a** to the corresponding dienic ester **7a**, via the formation of a transi-

[a] Dr. D. Tejedor, G. Méndez-Abt, L. Cotos, Dr. F. García-Tellado
Química Biológica y Biotecnología
Instituto de Productos Naturales y Agrobiología
Consejo Superior de Investigaciones Científicas
Avda. Astrofísico Francisco Sánchez 3
38206 La Laguna, Tenerife (Spain)
Fax: (+34) 922-2260135
E-mail: fgarcia@ipna.csic.es
dtejedor@ipna.csic.es

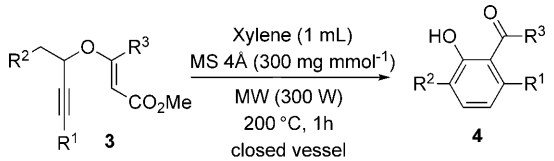
[b] Dr. D. Tejedor, G. Méndez-Abt, L. Cotos, Dr. F. García-Tellado
Instituto Canario de Investigación del Cáncer (Spain)

[c] Dr. M. A. Ramirez
Instituto Universitario de Bioorgánica Antonio González
Universidad de La Laguna
Avda. Astrofísico Francisco Sánchez 2
38206 La Laguna, Tenerife (Spain)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003532.

ent homoallenyl ester **6a**.[9] A subsequent tandem cyclization–aromatization reaction should afford the corresponding phenolic derivatives **4a** with the concomitant elimination of one equivalent of methanol. Addition of this liberated methanol to the intermediate **7a** should trigger a second reaction path affording the product **5a** via the formation of hemiacetal **8a**. In this scenario, it was expected that the removal of the generated methanol should funnel the whole transformation towards the exclusive formation of **4a**. With this idea, we designed an experimental protocol that included molecular sieves (4 Å) in the reaction mixture, to act as a methanol scavenger. Under these new conditions, the formation of the malonate derivative **5a** was totally suppressed. After several experiments, the reaction was standardized, and scaffold **3a** was conveniently converted into the salicylaldehyde **4a** in 76% yield (Table 1, entry 1). Salicyladehyde

Table 1. Substitution of R groups on **3** to test the scope of the domino reaction.



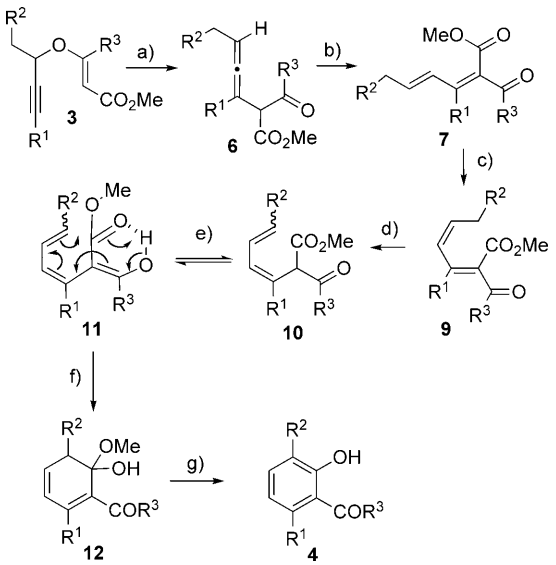
Entry	R^1	R^2	R^3	4	Yield [%][a]
1	Ph	Et	H	**4a**	76
2	Ph	*i*Pr	H	**4b**	72
3	Ph	*t*Bu	H	**4c**	67
4	Ph	H	H	**4d**	27
5	Ph	Ph	H	**4e**	89
6	Ph	$PhCH_2$	H	**4f**	61
7	Ph	F	H	**4g**	63
8	*p*-$MeOC_6H_4$	Et	H	**4h**	72
9	3,4-$Cl_2C_6H_3$	Et	H	**4i**	77
10	*p*-MeC_6H_4	Et	H	**4j**	81
11	Ph	Et	Me	**4k**	65[b]
12	Ph	Et	*n*Pen	**4l**	72[b]
13	Ph	Et	Ph	**4m**	75[b]
14	*n*Bu	Et	H	**4n**	43[c]
15	CO_2Me	*n*Pr	H	**4o**	70
16	CO_2Me	Ph	H	**4p**	56
17	CO_2Me	H	H	**4q**	29
18	Me_3Si	Et	H	**4r**	30

[a] Yield of isolated product. [b] Generally, the reaction gave the same yields in the absence of molecular sieves 4 Å. [c] Diester **5n** was also obtained (see the Supporting Information for details).

4a, incorporating a phenyl substituent at the C6 position of the ring, can be regarded as a functionalized biphenyl derivative, and therefore, a pharmacologically privileged structural motif.[10] The common synthetic approach to salicylaldehydes relies mainly on the direct electrophilic substitution of a suitable phenol derivative. From a preparative point of view, this transformation suffers from regioselective drawbacks when the positions *ortho* and *para* with respect to the hydroxyl functionality are not conveniently blocked.[11] From this perspective, the direct generation of a 3,6-disubstituted salicylaldehyde derivative is notable.

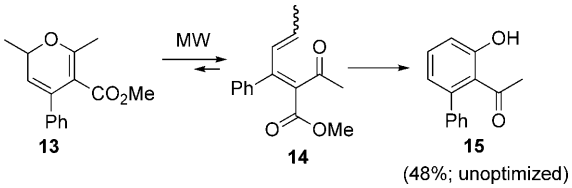
With the standardized protocol in place, we next studied the scope of this domino reaction (Table 1). In general, the reaction was tolerant to substitution of the starting PVE; the reaction accommodated different aromatic substituents at the terminal position of the alkyne, regardless of their electronic nature (Table 1, entries 1–10). However, substitution of the aromatic substituent with an aliphatic substituent at this position, resulted in a lower yield of the corresponding salicylaldehyde derivative (Table 1, entry 14). Derivative **3e**, with a benzyl substituent at the propargylic position and a phenyl group at the terminal alkyne position, generated the *p*-terphenyl derivative **4e** in an excellent yield of 89% (Table 1, entry 5). Fully substituted propargylic platforms **3k–3m** afforded the corresponding phenolic ketones **4k–4m** in good yields (Table 1, entries 11–13). In these cases, the use of a methanol scavenger is unnecessary because the corresponding intermediate ketals **8k–8m** (Scheme 2) cannot rearrange and they remain in equilibrium with their dienic precursors **7k–7m**. Conjugated alkynes **3o–3q** were also convenient substrates for this reaction, affording the corresponding methyl 2-formyl-3-hydroxybenzoate derivatives **4o–4q** (Table 1, entries 15–17). Interestingly, the substitution at the homopropargylic position increased the chemical efficiency of the reaction from 29% (**4q**) to 70% (**4o**) and 56% (**4p**). A silicon substituent at the alkyne position was also tolerated (Table 1, entry 18), although with diminished efficiency (30%). Finally, the reaction delivered valuable *o*-fluorophenol derivatives in an easy and efficient manner (Table 1, entry 7).

With regard to the mechanism of this domino reaction, a working proposal is outlined in Scheme 3. The reaction manifold is launched by the microwave-assisted propargyl Claisen rearrangement of the starting PVE **3** to generate the



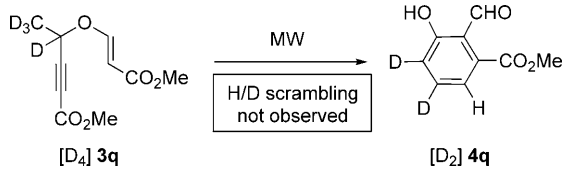
Scheme 3. A mechanistic proposal for the domino process. Microwave-assisted reactions: a) propargyl Claisen rearrangement; b) pseudo-pericyclic [1,3] hydride shift; c) 4*E*–4*Z* isomerization; d) [1,5] hydride shift; e) enolization; f) electrocyclization; g) aromatization.

allenic intermediate **6**, which rearranges to the corresponding dienyl intermediate **7** by a thermally allowed pseudopericyclic [1,3] hydride shift.[12] A tandem 4*E*/4*Z* isomerization–[1,5] hydride shift–enolization reaction affords the key dienyl enol intermediate **11**. Finally, electrocyclization and aromatization deliver the phenolic derivative **4**. Three experimental observations reinforced this mechanistic picture (see the Supporting Information for further details): 1) MW irradiation of the 2*H*-pyran derivative **13**[3b] afforded phenol **15** by the well-established reversible electrocyclic ring opening to 1-oxatriene derivative **14** (Scheme 4)[13]; 2) MW irradiation of tetradeuterated PVE derivative **3q** delivered exclusively dideuterated salicylate **4q** (Scheme 5), excluding any hydrogen/deuterium (H/D) scrambling during the process; 3) (*E*)-dimethyl 2-(pent-2-en-1-ylidene)malonate did not react under the standardized conditions.[14] This finding highlights the importance of the acyl group, which modulates the acidity of the allylic hydrogen involved in the double-bond isomerization, to provide the required enol **11**. Preliminary calculations support this mechanistic picture (see the Supporting Information for details).

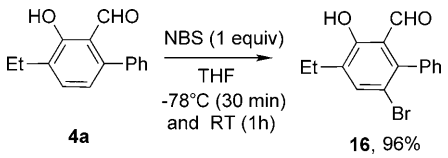


Scheme 4. Reversible electrocyclic ring opening of 2*H*-pyran derivative **13** to 1-oxatriene derivative **14**, to give phenol **15**.

Finally, functionalization of the phenolic products can be easily carried out as exemplified by bromination of **4a** by treatment with *N*-bromosuccinimide (Scheme 6).



Scheme 5. MW irradiation of tetradeuterated PVE derivative **3q** to give exclusive formation of dideuterated salicylate **4q**.



Scheme 6. Bromination of salicylaldehyde derivative **4a** with *N*-bromosuccinimide.

In summary, we have shown how readily available PVEs **3**, can be efficiently converted into convenient multifunctionalized aromatic products by using a microwave-assisted, novel domino process involving a key electrocyclization reaction. Efforts directed towards the application of this methodology in natural product synthesis are ongoing in our laboratory and will be reported in due course.

Experimental Section

Representative procedure: Propargyl vinyl ether **3a** (0.700 mmol), activated molecular sieves 4 Å (250 mg) and dry xylene (1 mL) were placed in a sealed microwave vial and the mixture was irradiated for 1 h in a single-mode microwave oven (300 W, 200 °C). The reaction mixture was filtered through a pad of celite using dichloromethane as a solvent. After removing the solvent at reduced pressure, the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 95:5) to yield **4a** (76 %). M.p. 38.8–39.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 1.28$ (t, $^3J(H,H) = 7.2$ Hz, 3H), 2.74 (q, $^3J(H,H) = 7.2$ Hz, 2H), 6.83 (d, $^3J(H,H) = 7.6$ Hz, 1H), 7.34–7.36 (m, 2H), 7.43–7.46 (m, 4H), 9.84 (s, 1H), 12.22 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 13.6$, 22.3, 117.4, 121.0, 128.0, 128.3, 130.1, 132.0, 135.7, 137.7, 145.0, 160.8, 197.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3021.7$, 2974.3, 2933.3, 2880.2, 1641.7, 1426.1, 1316.5, 1222.2 cm^{-1}; MS (70 eV): *m*/*z* (%): 226 (100) $[M+H]^+$, 225 (27), 211 (62), 208 (22), 197 (20), 165 (14), 152 (14).; elemental analysis calcd (%) for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found: C 79.68, H 6.22.

Acknowledgements

This research was supported by the Spanish MICINN and the European RDF (CTQ2008-06806-C02-01 and CTQ2008-06806-C02-02), the Spanish MSC ISCIII (RETICS RD06/0020/1046), FUNCIS (REDESFAC PI01/06). G.M.A. and L.C. thank the Spanish MEC for FPU and FPI grants, respectively. The authors thank Dr. T. Martín and Professor V. S. Martín for insightful discussions, Professor F. Cossío for mechanistic advice, and Anna Jurado for technical assistance.

Keywords: allenes · domino reactions · electrocyclic reactions · heterocycles · propargyl vinyl ethers

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Received: December 7, 2010
Published online: February 15, 2011

