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Microwave-Assisted Domino Access to C_2-Chain Functionalized Furans from Tertiary Propargyl Vinyl Ethers

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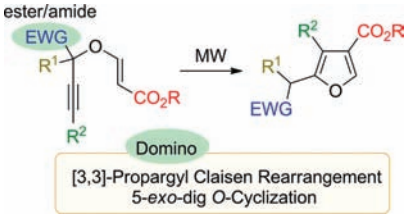
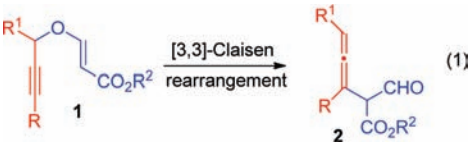
ABSTRACT



Tertiary propargyl vinyl ethers armed with an electron-withdrawing group (amide or ester) at the tertiary propargylic position have been efficiently transformed into trisubstituted C_2-chain functionalized furans. The metal-free domino transformation involves a microwave-assisted tandem [3,3]-propargyl Claisen rearrangement/5-*exo*-dig O-cyclization reaction. The manifold can be performed in a one-pot fashion from the primary components (1,2-ketoester/1,2-ketoamide or tertiary propargyl alcohols).

The [3,3]-Claisen rearrangement of propargyl vinyl ethers **1** (PVEs) constitutes a synthetically convenient route to substituted β-allenals **2** (eq 1),[1] which have proven to be suitable reactive units for the synthesis of important heterocycle cores.[2,3] In the presence of metallic catalysts, these intermediates have been selectively transformed into furans,[2a−e] pyrroles,[2f] 2*H*-pyrans,[2g] dihydropyrans,[2h] or 1,2-dihydropyridines.[2i,j] Recently, we have shown how the microwave irradiation of PVEs constitutes an alternative manner to obtain these reactive intermediates in the absence of metals and how these intermediates can be efficiently transformed into substituted salicylaldehyde derivatives,[3a] 1,2-dihydropyridines,[3b] or pyridines[3c] via selective microwave-assisted (MWA) domino chemistry.



Tertiary PVEs **3** (Scheme 1), armed with an electron-withdrawing group (EWG) (amide or ester) at the tertiary propargylic position, constitute interesting building blocks with an unexplored synthetic potential. These units can be conveniently prepared by the triethylamine-catalyzed

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(4) ABB′ 3CRs refers to a three-component reaction that utilizes two different components (A and B) to give a product which incorporates into its structure one unit of component A and two chemo-differentiated units of component B (B and B′). For full details and more examples of this type of multicomponent reactions, see: Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484.

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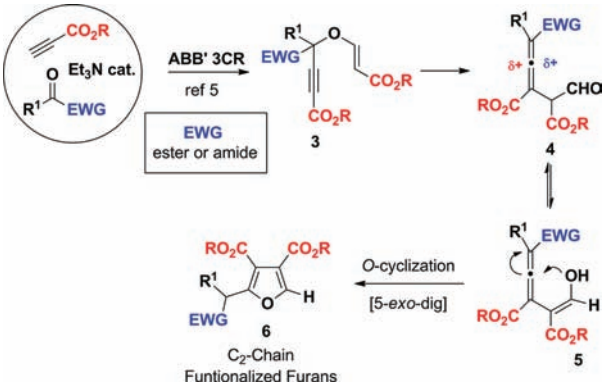
ABB′ three-component reaction (ABB′ 3CR)[4] of alkyl propiolates and 1,2-ketoesters or 1,2-ketoamides[5] or by treatment of the corresponding tertiary propargyl alcohol with alkyl propiolate in the presence of triethylamine.[6] We envisioned that the [3,3]-propargyl Claisen rearrangement of these platforms should afford the mixture of the corresponding β-allenals **4** and their enolic tautomers **5**, which possess a highly electrophilic central allenic carbon and a reactive hydroxyl enol functionality conveniently placed to perform a 5-*exo*-dig O-cyclization reaction (Scheme 1). The O-cyclization of **5** should afford trisubstituted furans **6** bearing a functionalized C_2-chain linked to the heterocyclic ring. The synergistic activation of the central allene position by the two EWG groups should allow for the accomplishment of this transformation in the absence of activating metals.[7]

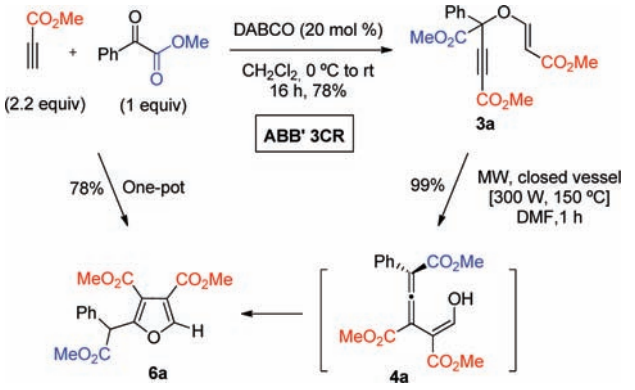
Scheme 1. Synthesis of C_2-Chain Functionalized Furans **6**



These trisubstituted furans **6** would represent, to the best of our knowledge, unprecedented hybrid structures of 3, 4-disubstituted furans and C_2-substituted acetic esters (or amides),[8] which cannot be easily obtained by direct cyclization of simple acyclic precursors.[9] Because of the importance of substituted furans in organic,[10] pharmaceutical,[11] and material chemistry,[12] we decided to carry out the experimental study of this unprecedented domino transformation. We report herein the results of these studies.

We undertook this work studying the MWA rearrangement of the PVE **3a**, which was synthesized in 78% yield following our previously reported ABB′ 3CR protocol[5] (Scheme 2). After exploring different sets of experimental conditions, we found that the MW irradiation of a solution of **3a** in DMF (closed vessel, 300 W, 150 °C, 1 h) cleanly afforded the furan derivative **6a** in 99% yield. In a previous report,[13] we had shown how the coupling of two domino processes in just one-pot reaction offered important advantages in terms of operational simplicity, efficiency, and work economy. Thus, we assayed conditions to perform the entire process in a one-pot fashion. After several experimental trials, we found that furan **6a** could be obtained in 78% yield (Scheme 2) directly from methyl 2-oxo-2-phenylacetate and methyl propiolate, without isolation of the PVE intermediate **3a**.[14]

Scheme 2. Synthesis and MWA Rearrangement of PVE **3a** into Furan **6a**



Once the experimental feasibility of our initial hypothesis was established, we explored the influence of the electron-withdrawing group allocated at the tertiary propargylic position by replacing the ester group with an

(5) Tejedor, D.; Santos-Expósito, A.; García-Tellado, F. *Chem.—Eur. J.* **2007**, *13*, 1201.

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(7) Furan syntheses based on propargyl−allenyl interconversion and subsequent O-cyclization normally requieres metal activation. See ref 2 for selected examples. For selected reviews, see: (a) Kirsch, S. F. *Synthesis* **2008**, 3183. (b) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (c) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076. (d) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850.

(8) We have not found precedents for these hybrid structures, featuring this substitution pattern, in our structure-driven search in SciFinder database.

(9) For selected examples of metal-catalyzed methodologies for the synthesis of substituted furans bearing a functionalized chain, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536 and references cited therein. (b) Albrecht, L.; Ransborg, L. K.; Gschwend, B.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 17886. (c) Hashmi, A. S. K.; Lothar Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. For recent reviews of general synthetic methodologies to substituted furans, see: (d) Hou, X. L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Oxford, 2008; Vol. 19, p 176. (e) Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles* **2007**, *73*, 87.

(10) For selected reviews, see: (a) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 2003; Vol. 15. (b) Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1997; Vol. 2. (c) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4.

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(12) Zhang, L. Z.; Chen, C. W.; Lee, C. F.; Wu, C. C.; Luh, T. Y. *Chem.Commun.* **2002**, 2336.

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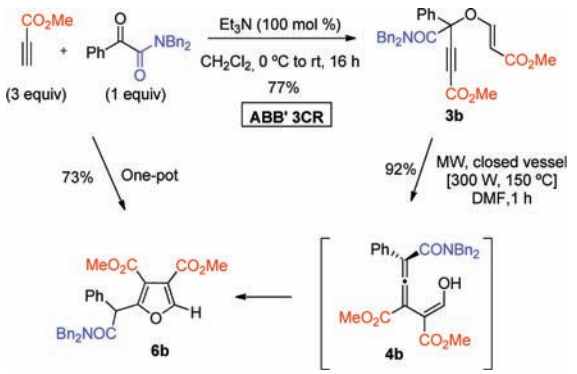
(14) It has to be noted that although these two-step sequential processes are defined as one-pot, they require a change of reaction vessel (from a round-bottom flask to a MW special closed vessel) because the CEM MW oven requires pressure-resistant special glass flasks.

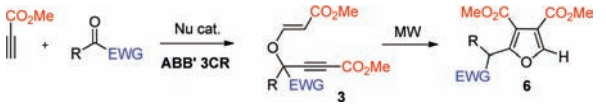
amide group (Scheme 3). Thus, we prepared the amide-containing PVE derivative homologous **3b**. This was synthesized directly from *N*,*N*-dibenzyl-2-oxo-2-phenylacetamide and methyl propiolate following a modified version of our previously reported triethylamine-catalyzed ABB′ 3CR protocol.[5] In this case, we used an excess of methyl propiolate (3 equiv) and a stoichiometric amount of triethylamine as the nucleophile activator to ensure a convenient yield of **3b** (77%). MW irradiation of a solution of this PVE in DMF (closed vessel, 300 W, 150 °C, 1 h) delivered the furan derivative **6b** in 92% yield. This result highlights that this domino rearrangement/cyclization reaction is not particularly sensible to the nature of the EWG allocated on the propargylic position, supporting either amides or esters as activators. Again, the process could be performed in a one-pot format, delivering furan **6b** in 73% yield.

Scheme 3. Synthesis and MWA Rearrangement of PVE **3b**



We next studied the scope of this reaction with regard to the nature of the tertiary PVE. Accordingly, we prepared the set of PVEs **3a**–**e** spanning aromatic and aliphatic substitution at the propargylic position (Table 1). These PVEs were prepared by the corresponding ABB′ 3CR of methyl propiolate and the corresponding 1,2-ketoester or 1,2-ketoamide. PVE **3d**, armed with an ester function and an unbranched aliphatic chain at the propargylic position, could not be prepared by this protocol.[15] Instead, it had to be prepared by a two-step process, entailing the alkynylation[16] of methyl 2-oxo-4-phenylbutanoate and the subsequent amine-catalyzed reaction of the corresponding tertiary propargylic alcohol with methyl propiolate.[6] In general, furans **6a**–**e** were obtained in excellent yields regardless whether an amide or an ester were used as the second activators of the central allenic position. Remarkably, PVEs **3c**–**e** afforded the corresponding furans **6c**–**e** in very good yields, in spite of the tendency of the nonbranched aliphatic substituents at the propargylic position to drive the domino process toward the formation of substituted salicylaldehyde derivatives (see below).[3a] With regard to the reaction processing, the two domino reactions could be coupled in a one-pot process with good overall yields (50–78%).

Table 1. One-Pot Synthesis of Trisubstituted Furans **6** from Methyl Propiolate and 1,2-Ketoesters (or 1,2-Ketoamides)[a]



entry	EWG	R		3 (yield %)[b]	6 (yield %)[b]	one-pot
1	CO_2Me	Ph	**a**	79	99	78[c]
2	$CONBn_2$	Ph	**b**	77	92	73[c]
3	$CONBn_2$	Et	**c**	60	85	50
4	CO_2Et	$Ph(CH_2)_2$	**d**	69[d]	93	64[e]
5	$CONBn_2$	$Ph(CH_2)_2$	**e**	61	80	51

[a] See Supporting Information for experimental details. [b] Isolated yields. [c] MW was performed in xylene. [d] PVE was formed in two steps from methyl propiolate and methyl 2-oxo-4-phenylbutanoate. [e] From the corresponding tertiary propargylic alcohol.

The scope of the reaction was further studied using tertiary PVEs **8** armed with an aliphatic or aromatic substituent at the sp-terminal alkyne position (Scheme 4, Table 2). These platforms were assembled by the two-step process aforementioned. In general, the triethylamine-catalyzed reaction of the corresponding tertiary propargyl alcohols **7** with an excess of methyl propiolate afforded tertiary PVEs **8** with modest to good yields (see Supporting Information for details). After some experimental work, we could establish an experimental protocol for the efficient transformation of PVE **8a** into the furan derivative **9a**. During this experimental work, we observed that the formation of PVE **8a** was always accompanied by a small amount of furan **9a** (~10%), which resulted in an added difficulty in the isolation and characterization of this PVE intermediate. For this reason, we decided to perform the process without the isolation of the intermediate PVE **8a**. Thus, when the crude product of the reaction of formation of **8a** was directly submitted to MW irradiation, furan **9a** was generated in good yield (70%) (Table 2 entry 1). The reaction was extended to the tertiary alcohols **7b**–**f**, featuring different combinations of aromatic/aliphatic substituents (Table 2). In general, the overall yields of these one-pot processes ranged from moderate to good, with the overall chemical efficiency compromised by the formation of the tertiary PVE intermediates. That was significant in the case of alcohol **7e**, which delivered the corresponding furan **9a** in 50% overall yield (entry 5). When this process was performed in a stepwise manner, the PVE **8e** (57%) was transformed into furan **9e** in 95% yield (data not shown). A remarkable property of these PVEs is their biased reactivity toward the 5-*exo*-dig O-cyclization

(15) The triethylamine-catalyzed reaction of methyl propiolate and unbranched aliphatic 1,2-ketoesters affords the corresponding isotetronic acid derivatives via an enolate-driven domino ABB′ 3CR. For more details, see: Tejedor, D.; Santos-Expósito, A.; García-Tellado, F. *Chem. Commun.* **2006**, 2667.

(16) Lithium acetylides were prepared according the standard procedure. See: Nielsen, T. E.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 6366.

reaction even in the absence of activating substituent at the internal position of the allene (R^1). Ester **8c** and amide **8d** constitute excellent examples of this reactivity control because they feature an aliphatic chain at the propargylic position, which could steer the reaction outcome toward the formation of the salicylaldehyde derivative[3a] (*e.g.*, **10**, Scheme 4). Interestingly, this competing reactivity profile was only observed in the case of the amide alcohol **7d**, which delivered the mixture of furan **9d** (58%) and salicylaldehyde **10** (18%) (entry 4). Its homologous ester alcohol **7c** afforded the furan **9c** as a sole compound and in excellent yield (85%, entry 3). These results show that the 5-*exo*-dig cyclization pathway requires strong activation of the intermediate allenal **I** when a hydrogen atom is available at the homopropargylic position of the PVE. Otherwise, the formation of dienal **II** becomes competitive. Interestingly, when the reaction of the amide alcohol **7d** was performed in the presence of aniline[2f] (1.2 equiv), the imine derivative **11** was obtained in 48% yield together with **9d** (38%). It is remarkable that the presence of aniline increases the formation of the salicylaldehyde derivative (from 18 to 48%) but does not afford the corresponding *N*-phenylpyrroles[2f] or *N*-phenyl-1,2-dihydropyridines.[3b] These facts seem to point out that the aniline role in this reaction is to serve as a Lewis base catalyst for the dienal **II** and enol **III** formation.

In summary, we have shown how tertiary PVEs armed with an electron-withdrawing group (amide or ester) at the tertiary propargylic position can be efficiently transformed into trisubstituted C_2-chain functionalized furans in the absence of metals. This unprecedented domino transformation involves a microwave-assisted tandem [3,3]-propargyl Claisen rearrangement/5-*exo*-dig O-cyclization reaction. The manifold is robust, and it tolerates diverse patterns of substitution decorating the PVE platform. In addition, the manifold can be performed in a one-pot fashion from the primary components (1,2-ketoesters/1,2-ketoamide or tertiary propargyl alcohols) using a simple and bench-friendly experimental protocol.

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Scheme 4. Synthesis of Furans **9** and Salicylaldehyde **10** from Alcohols **7**

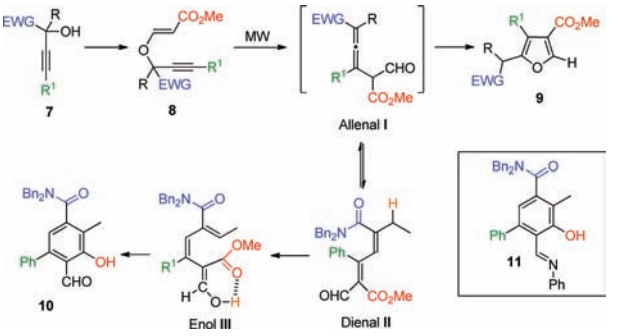

Table 2. One-Pot Synthesis of Furans **9** from Alcohols **7**.[a]

entry	EWG	R	R^1		**9** (yield %)[b]
1	CO_2Me	Ph	Ph	**a**	70
2	$CONBn_2$	Ph	Ph	**b**	74
3	CO_2Me	Et	Ph	**c**	85
4	$CONBn_2$	Et	Ph	**d**	58[c,d]
5	CO_2Me	Ph	Bu	**e**	50
6	CO_2Me	Et	Bu	**f**	76[e]

[a] See Supporting Information for experimental details. [b] Isolated yields. [c] From **8d**. [d] **10** was also obtained in 18% yield. [e] From **8f**.

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.