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Synthesis of Polysubstituted Benzoic Esters from 1,2-Dihydropyridines and Its Application to the Synthesis of Fluorenones

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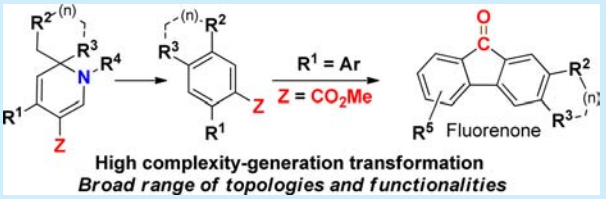
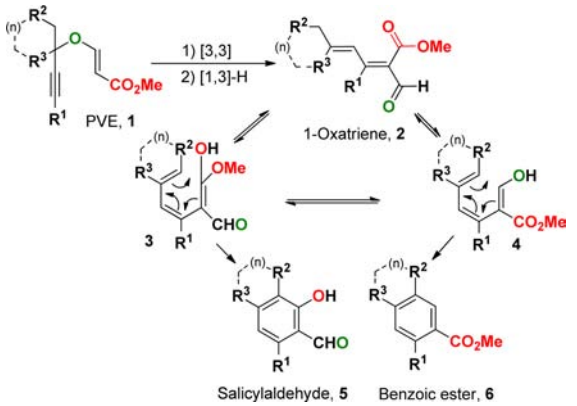
Supporting Information

ABSTRACT: A convenient, instrumentally simple, and efficient methodology to transform 1,2-dihydropyridines into benzoic esters is described. The generated multisubstituted benzoic esters feature different topologies spanning from simple aromatic rings to fused benzocycloalkane systems. As an extension of this methodology, these benzoic esters are efficiently transformed into an array of fluorenone frameworks featuring interesting and novel topological patterns.



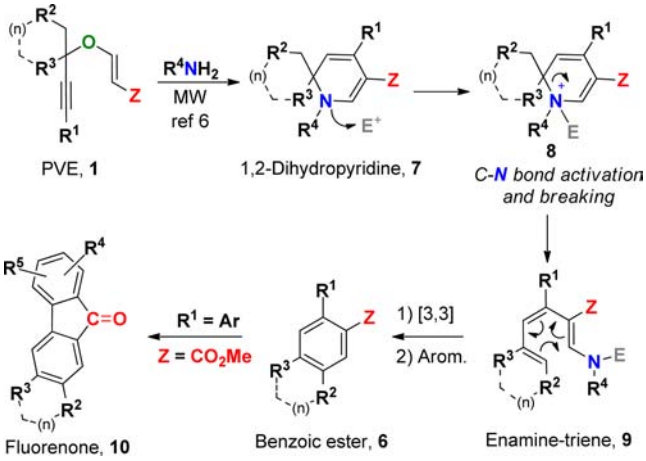
In recent years, we have been interested in the study of the propargyl Claisen rearrangement of propargyl vinyl ethers (PVEs, **1**) under different reaction conditions.[1] In the absence of additional reagents, these compounds rearrange to valuable polysubstituted salicylaldehyde derivatives **5** when they are submitted to microwave (MW) irradiation in the presence of catalytic amounts of imidazole.[2] During the course of this research, we have observed on certain occasions the presence of small amounts of the benzoic ester side product **6** (Scheme 1).

Scheme 1. PVEs Rearrange into Salicylaldehydes under Microwave Irradiation



Theoretical calculations on the proposed mechanism for the formation of the desired salicylaldehydes indeed revealed the possibility of obtaining benzoic esters by a slightly different and more energetic mechanistic pathway involving the intermediate enol ester **4** instead of the enol aldehyde **3**.[2] Because of the importance of benzoic esters as building blocks in the industrial production of fine chemicals, agrochemicals, pharmaceuticals, and materials,[3] we decided to undertake the study of this transformation. Although a number of benzannulation-based synthetic methodologies for accessing benzoic esters are known,[4] their direct assembly from propargyl vinyl ethers (1-oxatrienes) should constitute a novel synthetic avenue to highly substituted benzoic esters.[2] Since we anticipated that it would be difficult to reverse the energetic signature of the salicylaldehyde pathway to obtain benzoic esters **6** as the major products from the starting PVEs **1**, we envisioned an indirect synthetic strategy to obtain these compounds via the formation of the corresponding 1,2-dihydropyridines (1,2-DHPs, **7**)[5] (Scheme 2) and their subsequent rearrangement to benzoate derivatives **6**. The approach takes advantage of the

Scheme 2. Indirect Synthesis of Benzoic Esters 6 from PVEs 1 via the Formation of 1,2-dihydropyridines 7



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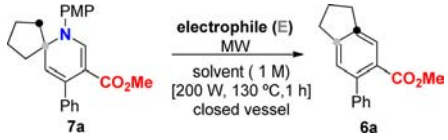
straightforward formation of 1,2-DHPs from the reaction of PVEs with primary amines at elevated temperatures[6] and the expected reactivity of the dihydropyridine ring toward electrophiles (Scheme 2). We envisioned that in the presence of a suitable electrophile, the C−N bond should be activated via the formation of the corresponding ammonium derivative **8**, which should collapse to the corresponding enamine−triene intermediate **9** by a controlled C−N bond-breaking process. This intermediate should be well-suited to host a tandem [3,3]-sigmatropic rearrangement/amine elimination to deliver the expected benzoate core. In this communication, we report our results on the development of this strategy as well as its application to the synthesis of novel substituted fluorenones **10**, an important structural motif present in some natural products and in a variety of molecules of biological (pharmaceutical) or physical (materials) relevance.[7]

We undertook this study by exploring the reaction of readily available 1,2-DHP **7a**[6a] with different electrophiles under different conditions (Table 1). Although *N*-iodosuccinimide

Table 1. Study of the Electrophile-Assisted Rearrangement of 1,2-DHP 7a into Benzoate 6a



			yield (%)	
entry	electrophile[a] (mol %)	solvent	**7a**	**6a**
1	–	DCE	90	3
2	I_2 (20)	DCE	0	62
3	I_2 (10)	DCE	6	55
4	NIS (50)	DCE	0	70
5	NBS (50)	DCE	18	40
6	NCS (50)	DCE	32	34
7	NIS (100)	DCE	0	48
8	NIS (20)	DCE	35	32
9[b]	NIS (20)	DCE	35	32
10	NIS (50)	DME	0	57
11	NIS (50)	MeCN	0	57
12	NaI (50)	DCE	100	0
13	CSA (100)	DCE	0	70
14[c]	CSA (100)	MeOH	0	95

[a]Abbreviations: DCE = 1,2-dichloroethane; DME = 1,2-dimethoxyethane; NIS = *N*-iodosuccinimide; NBS = *N*-bromosuccinimide; NCS = *N*-chlorosuccinimide; CSA = (±)-camphorsulfonic acid. [b]4 h. [c]1% yield of decarboxylated **6a**.

(NIS) proved to be a good substoichiomteric electrophile for this transformation (entry 4), the best results were achieved when camphorsulfonic acid was used in stoichiometric amounts with methanol as the solvent (entry 14). Under these conditions, the reaction delivered benzoate derivative **6a** nearly quantitatively (95% isolated yield). The rest of the starting material was transformed into the corresponding decarboxylated derivative (traces).

Once the best reaction conditions were found, we next studied the scope of the reaction (Figure 1). It was found that the reaction was general and highly efficient for 1,2-DHPs **7** bearing a medium-sized ring incorporated into their structures (R^2 and R^3 embedded into a five- to eight-membered ring) and an aromatic R^1 substituent (**6a**−**d**, **6f**−**h**). The electronic nature

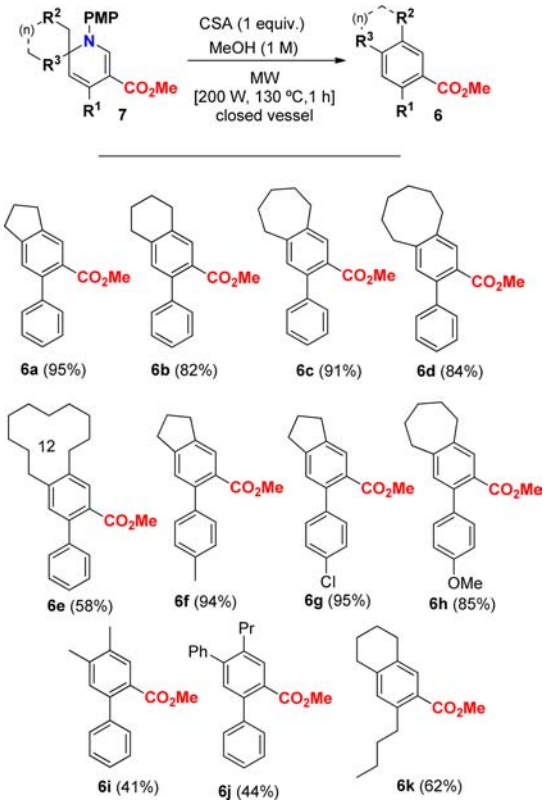


Figure 1. Scope of the electrophile-assisted rearrangement of 1,2-DHPs **7** into benzoates **6**.

of the aromatic R^1 substituent did not play an important role in the reaction outcome (compare the pairs **6a**/**6g**, **6a**/**6f**, and **6c**/**6h**). We were pleased to observe that the reaction was also tolerant of aliphatic substituents at R^1 position. This was the case for 1,2-DHP **7k** (R^1 = *n*-Bu), which delivered the corresponding benzoate derivative **6k** in 62% yield. This result highlights the importance of the extra stabilization of enamine−triene intermediate **9** (Scheme 2) by the aromatic substituent R^1 in the energetic pathway of the process and thus in the efficiency of the reaction. More intriguing was the influence of the substitution pattern at C2 of the starting 1,2-DHP **7**. The absence of a cycle or the presence of a large-sized one (12-membered ring) seemed to have a deleterious effect on the reaction (compare **6a**−**d** with **6e**, **6i**, and **6j**). In these cases, the formation of the desired products was accompanied by the formation of a significant amount of the aromatized but decarboxylated hydrocarbon (see the Supporting Information). At this time we do not have a clear explanation to account for the observed amplified decarboxylation of these substrates other than that acyclic substituents at R^2 and R^3 might enhance the flexibility of enamine−triene intermediate **9** and retard the electrocyclization leading to the desired product (Scheme 2). In terms of chemical diversity and complexity, the process was able to generate a wide array of polysubstituted benzoic esters **6** with topologies including bi- and terphenyls and more complex fused benzocycloalkane systems spanning from 2,3-dihydro-1*H*-indenes (**6a**-like) or 5,6,7,8-tetrahydronaphthalene (**6b**-like) to 5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulenes (**6e**-like). The access to these complex topologies from simple linear precursors (PVEs) highlights the complexity-generating power of this protocol and its practical utility for accessing relevant structural motifs incorporating benzene−cycloalkane

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annulated rings.[8] The sensibility of the PVEs to Brønsted acids (they are activated enol ethers) did not allow the development of a catalytic version of the reaction via in situ formation of the 1,2-DHP intermediates and their subsequent rearrangement.

With the standardized protocol in hand, we decided to transform these complex benzoic esters **6** bearing an ortho aryl substituent (R^1 = Ar) into the corresponding fluorenone derivatives **10** (Figure 2). Among the plethora of synthetic

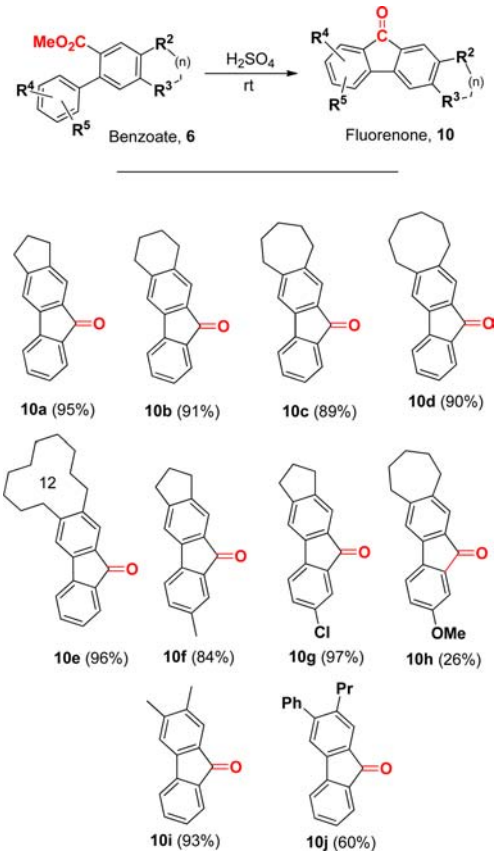

Figure 2. Acid-assisted formation of fluorenones **10** from benzoates **6**.

methods described for the synthesis of fluorenones,[9] the Friedel–Crafts-type acylation of biarylcarboxylic acids and derivatives constitutes one of the most used and practical ones.[10] We carried out these transformations using sulfuric acid as the activating agent and solvent (Figure 2). In general, these novel fluorenones were obtained in high yields (~90% average yield) independent of the cycloalkane ring size. As could be expected, the substitution on the aromatic ring brought important differences in the yield of the reaction, and the presence of a methoxy substituent at the 4′-position of 1,1′-biphenyl-2-carboxylate **6h** reduced the yield from 90% to 26% (compare **10d** and **10h**). Moreover, halogens or alkyl groups at this position were well-tolerated (e.g., **10f** and **10g**). It has been reported that the presence of acceptor–donor substituents on the aromatic ring has an influence on the electrooptical properties of fluorenes.[7d] From this perspective, this fluorenone synthesis constitutes a convenient and practical synthetic methodology to construct novel fluorene frameworks incorporating a varied and rich substitution pattern on the aromatic rings for use in materials science. On the other hand, the influence of the cycloalkane-fused motif on the properties of these fluorenone derivatives remains to be explored.

In summary, we have reported a convenient, instrumentally simple, and efficient methodology to transform propargyl vinyl ethers armed with two substituents at the propargylic position into polysubstituted benzoic esters featuring different topologies spanning from simple aromatic rings to fused benzocycloalkane systems. As an extension of this methodology, we have efficiently transformed the *o*-arylbenzoic esters into an array of fluorenone frameworks featuring interesting topological patterns. In this context, fluorenones **10b** and **10c** constitute the fluorene framework of a family of carbapenem antibacterial small molecules.[11] The study of the properties of these fluorenones is under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01260.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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