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Phosphine-Catalyzed Synthesis of Highly Functionalized Coumarins

Christopher E. Henry and Ohyun Kwon*

Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, California 90095-1569

ohyun@chem.ucla.edu

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ABSTRACT

2-Styrenyl allenoates are converted into cyclopentene-fused dihydrocoumarins through phosphine-catalyzed regio- and diastereoselective [3 + 2] cycloadditions. Remarkably, changing the solvent from THF to benzene promotes the conversion of the 2-(2-nitrostyrenyl) allenoate into a tricyclic nitronate through a previously undocumented mode of phosphine catalysis. This nitronate was subjected to efficient face-, regio-, and exo-selective 1,3-dipolar cycloadditions to provide tetracyclic coumarin derivatives.

Coumarins are heterocycles that are frequently encountered in natural products[1] and used widely in medicinal compounds (e.g., warfarin).[2] Functionalized coumarins also find applications in perfumary,[3] as fluorescent materials,[4] and as dyes in laser technology.[5] Not surprisingly, considerable effort has been exerted toward the synthesis of coumarins through the use of Perkin, Pechmann, Wittig, Reformatsky, Claisen, and Knoevenagel reactions.[6] These traditional methods, however, generally require harsh reaction conditions, often resulting in low product yields. More recently, transition-metal-catalyzed reactions have been reported for the synthesis of coumarins,[7] but these examples have been limited to products possessing simple substituents. As part of a program geared toward the design and development of nucleophilic phosphine catalysis for the synthesis of a diverse array of small organic molecules, here we report the expeditious intramolecular phosphine-catalyzed transformation of 2-styrenyl allenoates into highly functionalized coumarins.[8]

Phosphine-catalyzed annulation of activated alkenes and alkynes is a highly attractive synthetic method for preparing a variety of carbocycles and heterocycles from readily available starting materials.[9,10] In particular, much effort has been devoted to the [3 + 2] cycloaddition of allenoates with

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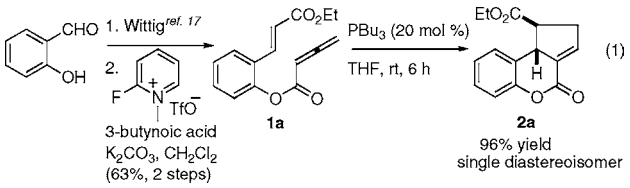
α,β-unsaturated carbonyl compounds to form cyclopentenes,[11] e.g., this process has been applied to natural product synthesis[12] and an enantioselective variant of the reaction has been developed;[13] in addition, thorough mechanistic studies have been reported by Yu and co-workers and by us.[14] Unfortunately, unlike the [3 + 2] cycloadditions of allenoates with imines to form dihydropyrroles,[15] intermolecular annulations between allenoates and alkenes generally suffer from the formation of a mixture of regioisomeric cyclopentenes. For example, Lu's original report indicated that the [3 + 2] annulation between ethyl allenoate and methyl acrylate furnished a 4:1 mixture of regioisomeric cyclopentenes, favoring α-addition of the phosphonium dienolate intermediate to the acrylate in a Michael-type manner.[11a] In contrast, in Fu's asymmetric phosphine catalysis of allenes with β-substituted enones to form cyclopentenes, the preference for α-addition of the allenoates to activated (non-β-substituted) alkenes was reversed to γ-addition.[13c]

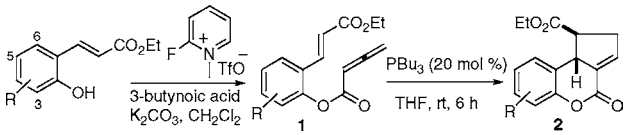
For many C−C bond-forming processes, exclusive regioselectivity is achieved when the reactions are performed intramolecularly.[16] We sought to apply this principle to an intramolecular variant of the allene/alkene [3 + 2] cycloaddition of substrate **1a** (eq 1). Compound **1a** was synthesized from salicylaldehyde through a Wittig reaction[17] followed by coupling with 3-butynoic acid under the influence of Mukaiyama's reagent;[18,19] presumably, the initial 3-butynoate product isomerized to the allenoate under the coupling



reaction conditions.[20] Treatment of **1a** with 20 mol % of tributylphosphine in THF at room temperature for 6 h produced **2a** in 96% isolated yield as a single diastereoisomer.[21] Thus, this catalytic reaction provided a tricyclic dihydrocoumarin structure directly from a cinnamyl allenoate through a regioselective annulation process.

This reaction proved to be effective for transforming various other commercially available salicylaldehyde derivatives into cyclopentene-fused dihydrocoumarins (Table 1).

Table 1. Syntheses of Cyclopentene-Fused Dihydrocoumarins **2**[a]



entry	R (**1**)	yield (%)[b]	product (**2**)	yield[c] (%)
1	H (**1a**)	72	**2a**	96
2	3-methyl (**1b**)	64	**2b**	98
3	3-methoxy (**1c**)	77	**2c**	74
4	4-methoxy (**1d**)	71	**2d**	94
5	5-methoxy (**1e**)	73	**2e**	70
6	5-fluoro (**1f**)	45	**2f**	91
7	5-bromo (**1g**)	38	**2g**	93
8	5-nitro (**1h**)	45	**2h**	9[d]

[a] See the Supporting Information for details. [b] Isolated yield for the formation of **1**. [c] Isolated yield for the formation of **2**. [d] The allenoate hydrolyzed to form the 2-hydroxycinnamate; the resulting phenol was added to the starting cinnamyl allenoate at the β-carbon atom in 81% yield.

Both electron-withdrawing and -donating substituents on the benzene ring were compatible with the reaction conditions (entries 1−7). A substrate containing a nitro substituent provided the lowest product yield (entry 8); this result is consistent with our previous findings for [4 + 2] allenoate/arylimine annulations.[8a]

Next, we turned our attention to establishing the role played by the activating substituent on the alkene moiety. Although 2-(2-phenylsulfonyl)styrenyl allenoate **1i** readily

(10) For recent examples, see: (a) Kumar, K.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 787. (b) Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023. (c) Ung, A. T.; Schafer, K.; Lindsay, K. B.; Pyne, S. T.; Amornraksa, K.; Wouters, R.; Van der Linden, I.; Biesmans, I.; Lesage, A. S. J.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2002**, *67*, 227. (d) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595. (e) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677. (f) Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129. (g) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118. (h) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (i) Zhao, G.-L.; Min, S. *Org. Biomol. Chem.* **2005**, *3*, 3686. (j) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (k) Nair, V.; Biju, A. T.; Mohanan, K.; Suresh, E. *Org. Lett.* **2006**, *8*, 2213.

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(16) For an example of γ-selective intramolecular alkyne/alkene [3 + 2] cycloaddition, see: Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682.

(17) Bunce, R. A.; Schilling, C. L. *Tetrahedron* **1997**, *53*, 9477.

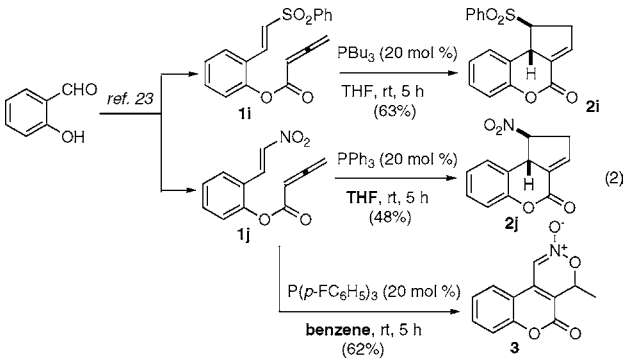
(18) Mukaiyama, T.; Usui, M.; Shimada, E. *Chem. Lett.* **1975**, 1045.

(19) Use of the common (peptide) coupling reagents [DCC, TCT, Hf-(IV) salts, HBTU, HATU, and PyBroP] failed to provide the allenoate product. Presumably, the product allenoate is susceptible to nucleophilic attack by either a base present in the reaction medium or the byproducts derived from the coupling reagents. See the Supporting Information for details regarding the isolation and characterization of the product of *N*-hydroxybenzotriazole addition to the allenoate when using HBTU.

(20) Eglinton, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3197.

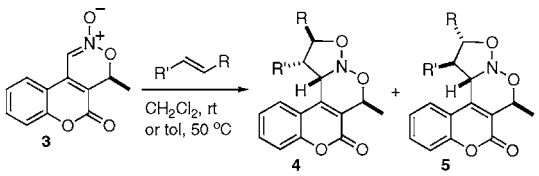
(21) The connectivity and relative stereochemistry of this compound were assigned through NMR spectroscopic analyses. See the Supporting Information for details.

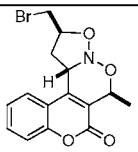
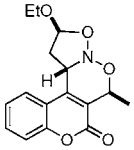
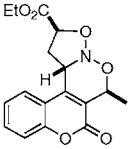
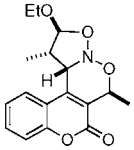
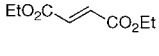
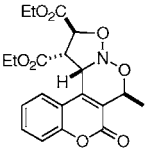
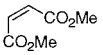
underwent the annulation reaction to produce the tricyclic coumarin derivative **2i** in 63% yield (eq 2),[22] the nitrostyrenyl derivative **1j** did not provide the desired annulation product when subjected to the optimized reaction conditions (20 mol % PBu_3, THF, rt). Catalysis using the less-nucleophilic PPh_3 produced the desired annulation product in moderate yield (48%), accompanied by a minor product **3** (12%). In an attempt to further improve the yield of the [3 + 2] annulation product, we examined the use of some other common organic solvents. Surprisingly, the reaction of the nitrostyrenyl derivative **1j** with PPh_3 in benzene provided the nitronate **3** as the major product in 58% yield, in addition to a 14% yield of the cyclopentene adduct **2j**.[23] The corresponding reaction catalyzed by the even-less-nucleophilic tris(*p*-fluorophenyl)-phosphine furnished **3** in a slightly improved yield (62%; 19% **2j**).



Having synthesized this nitronate, we tested its synthetic utility in 1,3-dipolar cycloadditions to form highly functionalized coumarin derivatives (Table 2). Nitronates are versatile 1,3-dipoles that undergo reactions with neutral, electron-rich, and electron-poor dipolarophiles.[24] Indeed, when we treated nitronate **3** with allyl bromide, we obtained the tetracyclic coumarin derivatives **4a** and **5a** in 97% isolated yield as a 7:1 mixture of exo and endo products (entry 1). The connectivity and relative stereochemistry of the nitroso acetals **4a** and **5a**, as well as **4d**, were confirmed through X-ray crystallographic analysis.[25] This reaction exhibited exclusive facial and regioselectivity as well as good exo selectivity. Both electron-rich and -poor alkenes underwent [3 + 2] cycloadditions with **3** in excellent yields (93−94%)

Table 2. 1,3-Dipolar Cycloadditions of Nitronate **3**[a]



entry	dipolarophile	major product	yield (%)[b]	4/5
1		 **4a**	97	7:1
2		 **4b**	93	9:1
3		 **4c**	94	11:1
4		 **4d**	95	9:1
5		 **4e**	83	10:1
6		N/A	0[c]	N/A
7		N/A	NR[d]	N/A

[a] See the Supporting Information for details. [b] Isolated yield. [c] Complex mixture of products. [d] Mostly recovered starting material.

with high exo selectivity (*exo*/*endo* = 9−11:1; entries 2 and 3). Trans-disubstituted alkenes were viable substrates (entries 4 and 5), but cis-disubstituted alkenes were recalcitrant to the reaction (entries 6 and 7). In all the examples, the carbon atom bearing the activating substituent formed a bond to the oxygen atom of the nitronate 1,3-dipole. The product nitroso acetals possess up to four stereogenic centers and are replete with functional groups. Their Raney nickel-catalyzed N−O bond cleavages producing corresponding amino alcohols and their application to the syntheses of alkaloid natural products are well documented.[26]

Scheme 1 provides two possible mechanisms that account for the formation of nitronate **3**. We excluded the possibility

(22) NOE analyses confirmed the trans stereochemistry of the [3 + 2] annulation product. See the Supporting Information for details.

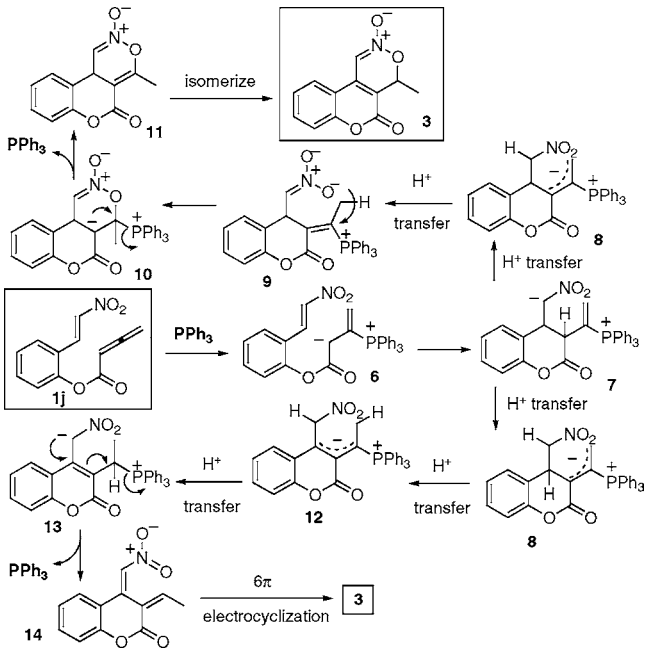
(23) See the Supporting Information for the syntheses of **1i** and **1j**.

(24) For reviews on the preparation and use of nitronates, see: (a) Takaeuchi, Y.; Furusaki, F. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1977; Vol. 21, p 207. (b) Shipchandler, M. T. *Synthesis* **1979**, 666. (c) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. (d) Breuer, E.; Aurich, H. G.; Nielsen, A. *Nitrones, Nitronates, and Nitroxides*; Wiley: New York, 1990; p 105. (e) Döpp, H.; Döpp, D. In *Modern der Organischen Chemie (Houben-Weyl)*, 4th ed.; Klamann, D., Hagemann, H., Eds.; Georg Thieme: Stuttgart, 1990; Vol. E14b/1, p 880.

(25) Crystallographic data for **4a**, **5a**, and **4d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 602367−602369. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

(26) Denmark, S. E.; Cottell, J. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley-Interscience: New York, 2002; pp 83−167.

Scheme 1. Proposed Mechanisms for the Formation of Nitronate **3**



of a Diels−Alder reaction occurring between the nitroalkene and the allene based on our observation that the reaction did not proceed in the absence of a phosphine.[27] Attempts to facilitate the Diels−Alder reaction under thermal or Lewis acid catalysis conditions resulted only in recovery of the starting material. Accordingly, we propose mechanisms involving phosphine as a catalyst. Nucleophilic addition of triphenylphosphine to allenoate **1j** produces the zwitterionic intermediate **6**. Intramolecular Michael addition of the allylic anion to the nitroalkene in **6** leads to the cyclized intermediate **7**. Proton transfer of the most acidic proton, i.e., the one positioned α to the carbonyl group, yields the allylic anion **8**. 1,5-Proton transfer in **8** furnishes **9**, which undergoes 6-endo cyclization to form **10**. Expulsion of the phosphine from **10** produces the nitronate **11**, which can isomerize to the nitronate **3**. In the other scenario, 1,4-proton transfer in **8** yields **12**. A subsequent 1,4-proton transfer in **12** provides **13**, which generates the nitrodiene **14** upon expulsion of triphenylphosphine. Finally, 6π electrocyclic ring closure of nitrodiene **14** provides the nitronate **3**. To the best of our knowledge, the literature lacks examples of the proposed 6π electrocyclization. The closest precedent is a 6-π-electron 5-atom electrocyclization of nitrosostyrenes to benzonitronates found in an indole synthesis from nitrobenzenes via reductive cyclization.[28]

In summary, we have discovered two diverting reaction modalities for the nucleophilic phosphine-mediated reactions of 2-styrenyl allenoates. Tertiary phosphines in THF facilitated intramolecular [3 + 2] annulation to provide cyclopentene-fused dihydrocoumarins in excellent to good yields with exclusive diastereoselectivity. The reaction of 2-(2-nitrostrenyl)allenoate **1j** with triphenylphosphine in benzene, on the other hand, led to the formation of the tricyclic nitronate **3** through an unprecedented mode of catalysis. We have demonstrated the synthetic potential of this nitronate through its 1,3-dipolar cycloadditions with a number of dipolarophiles. The reactions described herein are simple and efficient approaches toward the syntheses of structurally complex coumarins and add to the number of recently discovered phosphine-catalyzed annulation reactions of allenoate precursors. Our future efforts will focus on intramolecular phosphine catalysis of other allenoates derived from salicylaldehydes and their application to the synthesis of coumarin-containing natural products.

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Supporting Information Available: Representative experimental procedures and spectral data for all new compounds. Crystallographic data for compounds **4a**, **4d**, and **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) For reviews on hetero-Diels−Alder reaction of nitroalkenes, see: (a) Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes: Conjugated Nitro Compounds*; Wiley: New York, 1994; p 131. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(28) Davis, I. W.; Guner, V. A.; Houk, K. N. *Org. Lett.* **2004**, *6*, 743.