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Silver(I)-Catalyzed Addition of Zirconocenes to Epoxy Esters: A New Entry to 1,4-Dicarbonyl Compounds and Pyridazinones

Peter Wipf* and Joey-Lee Methot

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

pwipf+@pitt.edu

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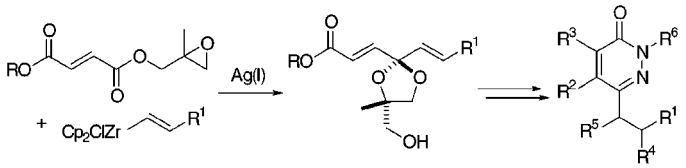
ABSTRACT



The Ag(I)-catalyzed tandem epoxy ester rearrangement–dioxycarbenium ion addition reaction with alkenyl zirconocenes provides 1,4-keto esters that can be further converted to substituted pyridazinones. The use of a fluorous tag in a cyclization-assisted cleavage strategy demonstrates the feasibility of extending this methodology to high-throughput organic synthesis.

Though not commonly found in nature, pyridazinones have been used as scaffolds in the pharmaceutical industry for a wide range of SAR studies.[1] For example, azelastine (**1**) is an antihistamine while zardaverine (**2**) exhibits PDE III and PDE IV inhibitory activity (Figure 1). SR-46559 (**3**) is a selective muscarinic M1 receptor agonist of potential use in treating Alzheimer's disease. The significant commercial interest in the pharmaceutical uses of pyridazinones is further illustrated by the large number of patents filed in this area that cover positive inotropic agents for the treatment of congestive heart failure, antidepressants, α1/α2 antagonists, potassium channel activators, antiasthmatics, and others.[1,2]

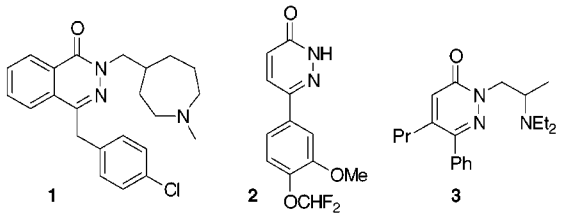


Figure 1. Therapeutically relevant pyridazinones.

As part of our program in organozirconocene chemistry,[3] we now report a versatile new protocol for the synthesis of 1,4-dicarbonyl compounds and highly substituted pyridazinones from fumarate-derived epoxy esters.

Our general approach is outlined in Scheme 1. Epoxy ester **4** is readily available from monoethyl fumarate by DCC coupling to β-methallyl alcohol followed by *m*-CPBA oxidation (90% overall yield). The epoxide is converted in a single step to divinyl acetal **5** via a cationic alkenyl

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(2) See, for example: (a) Tisler, M.; Stanovnik, B. *Adv. Heterocycl. Chem.* **1990**, *49*, 385. (b) Kuroda, S.; Akahane, A.; Itani, H.; Nishimura, S.; Durkin, K.; Kinoshita, T.; Tenda, Y.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1979.

(3) (a) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639. (b) Wipf, P.; Takahashi, H.; Zhuang, N. *Pure Appl. Chem.* **1998**, *70*, 1077. (c) Wipf, P.; Tsuchimoto, T.; Takahashi, H. *Pure Appl. Chem.* **1999**, *71*, 415.

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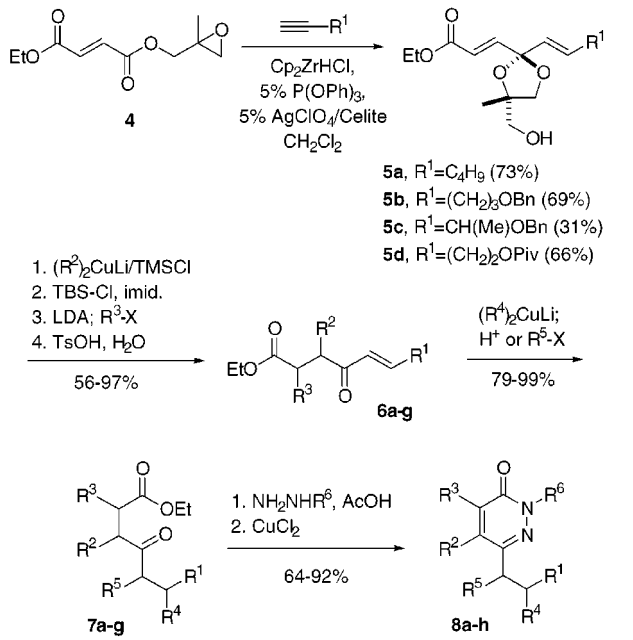
Scheme 1



zirconocene mediated epoxide rearrangement−addition reaction.[4] This mild room-temperature tandem process is quite functional group compatible and provides acetals with high diastereocontrol. Upon acidic hydrolysis, this reaction provides a direct route to α,β-unsaturated ketones from the corresponding alkyne and epoxy ester.

Divinyl acetals **5** were further elaborated to enones **6a**−**g** by a sequence of conjugate addition, enolate alkylation, and hydrolysis steps. A second cuprate addition provided δ-keto esters **7a**−**g**. Cyclization with hydrazines and oxidation completed the pyridazinone synthesis (Table 1).[5]

Our original cationic zirconocene protocol[4a−c] was modified to include 5 mol % of triphenyl phosphite as an additive as well as adsorption of $AgClO_4$ onto Celite to ensure a high level of reproducibility in the epoxy ester addition step. Typically, a solution of the alkyne in CH_2Cl_2 (0.3 M) was treated with a slight excess of zirconocene hydrochloride[6] and stirred for 20 min. At 0 °C, 5 mol % of $P(OPh)_3$, the epoxy ester **4**, and 5 mol % of $AgClO_4$/Celite[7] were added sequentially and the mixture was stirred at room temperature overnight. Under these conditions, divinyl acetal **5a** was obtained in 73% yield from 1-hexyne. Benzyl ether- and pivaloate ester-functionalized alkynes gave **5b** and **5d** in 69% and 66% yields, respectively. Benzyl ether-protected 2-methyl-3-butyn-1-ol gave the desired acetal **5c** in 31% yield with 42% of recovered starting material.

The mechanism of the key zirconocene reaction is likely to involve coordination of the cationic species to epoxy ester **II**, and by anchimeric assistance, the epoxide opens to give intermediate **III** (Figure 2).[4a] The observed generally >95%

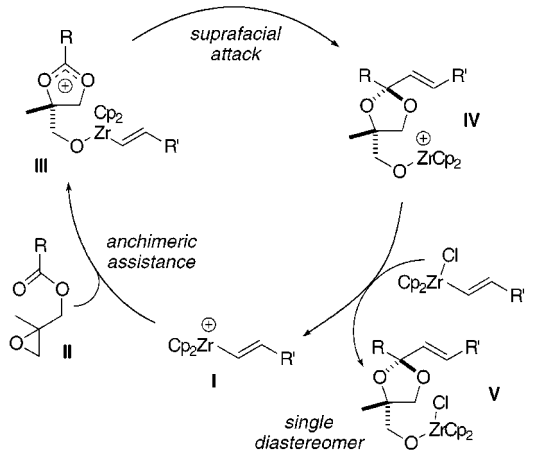


Figure 2. Proposed mechanism of tandem epoxide opening−rearrangement−addition reaction with cationic zirconocenes.

diastereoselectivity of acetal formation suggests an intramolecular alkoxide-directed mode of attack onto the cyclic dioxycarbenium ion. The chain reaction continues with chloride ion abstraction, thus providing new cationic zirconocene **I** and releasing acetal **V**. The triphenyl phosphite likely serves to stabilize the cationic metal species, allowing for longer reaction times and greater catalytic turnover. Preadsorption of $AgClO_4$ onto Celite provides a uniform, easy to handle source of Ag(I).

Conjugate addition to divinyl acetals **5** proceeded smoothly with lower-order cuprates (5 equiv) in the presence of TMSCl[8] in THF upon warming from −78 to −30 °C. Little diastereoselectivity was observed in this step. TsOH-mediated hydrolysis of the acetal in refluxing acetone/water led to enones **6a**−**c**,**e**,**f**. The two-step yields ranged from 82 to

Table 1. Conversion of Acetals **5a**−**d** to Pyridazinones **8a**−**h** (Overall Yields)

entry	acetal	R^1	R^2	R^3	R^4	R^5	R^6	yield, %	pyridazinone
1	**5a**	C_4H_9	Me	H	Me	H	H	86	**8a**
2	**5a**	C_4H_9	C_4H_9	H	C_4H_9	Me	Me	53	**8b**
3	**5a**	C_4H_9	CH_2CH_2Ph	H	CH_2CH_2Ph	H	H	68	**8c**
4	**5a**	C_4H_9	Me	CH_2OBn	C_4H_9	H	H	44	**8d**
5	**5b**	$(CH_2)_3OBn$	Me	H	Ph	H	Bn	56	**8e**
6	**5b**	$(CH_2)_3OBn$	Me	H	Ph	H	Ph	64	**8f**
7	**5c**	CH(Me)OBn	C_4H_9	H	C_4H_9	H	H	60	**8g**
8	**5d**	$(CH_2)_2OPiv$	C_6H_{13}	Me	Me	H	Me	41	**8h**

97%. Diphenethyl cuprate was prepared from excess phenethyl iodide and *tert*-butyllithium,[9] followed by cannulation at −78 °C to $CuBr·SMe_2$.

For the introduction of an R^3 substituent after the first cuprate addition, the primary alcohol was protected as a TBS ether. Ester deprotonation (LDA) and alkylation (R^3-X) at −78 °C followed by acidic hydrolysis gave enones **6d** (R^3 = CH_2OBn) and **6g** (R^3 = Me) in 68% and 56% overall yields, respectively.

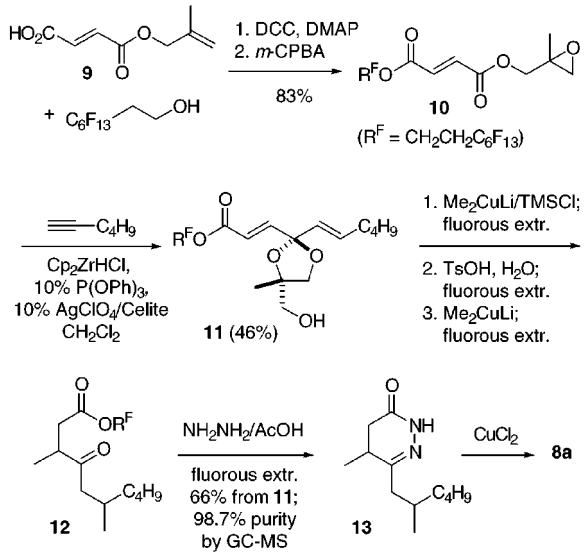
The lower-order cuprate addition to enones **6a**−**g** proceeded uneventfully at −78 °C to provide 1,4-dicarbonyl compounds **7a** and **7c**−**g** in yields ranging from 90% to 99%. Trapping of the intermediate enolate with excess MeI gave **7b** in 79% yield upon warming to room temperature. Diphenyl cuprate addition was assisted with TMS-Cl, and the resulting silyl enol ether was cleaved with TBAF/H_2O to give **7e**.

Cyclocondensation of keto esters **7** with hydrazines and acetic acid (20 equiv of each) in EtOH was complete after stirring overnight or heating at reflux for several hours. Sterically hindered ketones (**7b**) required 2 d at reflux. The use of substituted hydrazines did not significantly retard the rate of cyclization. Oxidation of the dihydropyridazinones to **8a**−**h** was best achieved with 2.0 equiv of $CuCl_2$[10] in refluxing MeCN for 30−90 min. Yields for the two-step process ranged from 64 to 92%.

Recent interest in the rapid synthesis of heterocyclic scaffolds has led to an explosive development in solid-phase techniques that facilitate purification.[11] The use of fluorous tags and liquid/liquid extraction schemes is an attractive solution phase alternative to SPOS.[12] This technique takes advantage of the affinity of partially fluorinated compounds toward highly fluorinated solvents during liquid−liquid extractions, while nonfluorinated reagents and byproducts remain in the organic phase. Advantages of fluorous tags include minimal reoptimization requirements, reaction monitoring by TLC, and intermediate characterization by standard methods.

Our new route to pyridazinones was highly suitable for the first demonstration of a fluorous version of cyclization-assisted ester cleavage.[13] Fumarate **10** was readily obtained in 83% yield by DCC coupling of acid **9**[14] with 1*H*,1*H*,2*H*,2*H*-perfluorooctanol and epoxidation with *m*-CPBA (Scheme 2).

Scheme 2



Diester **10** is soluble in most common organic solvents, yet extracts into excess FC-72[15] from MeOH/H_2O (2:1). The cationic zirconocene reaction with 1-hexyne provided **11** in 46% yield. At this stage, unreacted epoxide was removed chromatographically.

Conjugate addition with Me_2CuLi and acid hydrolysis proceeded well on substrate **11**. At each step the product was extracted into FC-72 from MeOH/H_2O. The crude keto ester **12** was cyclized with NH_2NH_2/AcOH, and the fluorous alcohol tag was removed by an FC-72/MeCN extraction providing dihydropyridazinone **13** in 66% yield from **11**. GC-MS analysis indicated >98% purity. Oxidation of this material provided pyridazinone **8a**.

In conclusion, the Ag(I)-catalyzed cascade reaction of alkenyl zirconocenes with epoxy esters was extended toward an efficient synthesis of highly branched 1,4-dicarbonyl compounds **7** and pyridazinones **8**. Introduction of a chemically inert fluorous tag facilitates purification of intermediates and illustrates the first application of a fluorous cyclization-assisted cleavage strategy.

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Supporting Information Available: Full experimental procedures as well as ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) All new compounds were fully characterized by 300 or 500 MHz ^1H NMR, 75 or 125 MHz ^{13}C NMR, IR, MS, and HR-MS. Copies of NMR spectra are included in the Supporting Information.

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(7) A total of 20 wt % of $AgClO_4$ adsorbed onto Celite from an aqueous solution and dried in vacuo.

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(13) For a pioneering solid support version of this strategy, see: Camps, F.; Cartells, J.; Pi, J. *An. Quim.* **1974**, *70*, 848. Review: Obrecht, D.; Villalgordo, J. M. *Solid-supported combinatorial and parallel synthesis of small-molecular weight compound libraries*; Pergamon: Oxford, 1998.

(14) Prepared in 56% yield by slow addition of NEt_3 to a cold (−75 °C) solution of fumaryl chloride and β-methallyl alcohol, followed by hydrolysis.

(15) FC-72 is a commercially available (3M; $389/gallon) fluorocarbon solvent consisting of C_6F_{14} isomers (bp 56 °C). It is immiscible with most common organic solvents.