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Preparation and decarboxylative rearrangement of (*Z*)-enyne esters

Jacqueline C. S. Woo, Shawn D. Walker* and Margaret M. Faul

Chemical Process Research and Development, Amgen Inc., One Amgen Center Dr., Thousand Oaks, CA 91320, USA

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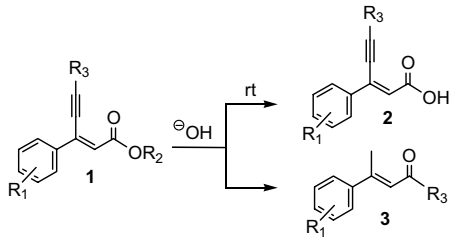
Abstract—A method to assemble (*Z*)-enyne esters via palladium-catalyzed cross coupling reactions of enol tosylates is reported. A base-mediated one-pot decarboxylative rearrangement of the enynes to enones is described. The scope of this process is examined.

Metal-catalyzed alkynylation reactions have emerged as powerful tools for the preparation of substituted alkynes. Of these, the Pd/Cu-catalyzed Sonogashira coupling and Pd-catalyzed Negishi coupling reactions are among the most important methods for stereoselective synthesis of enynes.[1] Due to the widespread occurrence of enynes and richness of functionality available for further elaboration, improved methods to assemble and exploit these compounds are desirable. In particular, 1,3-enyne esters and acids are valuable synthetic scaffolds, serving as precursors to heterocycles,[2] polysubstituted aromatics[3] and dienes.[4]

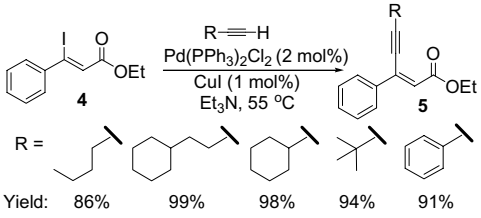
We report herein an interesting dichotomy observed during the alkaline hydrolyses of (*Z*)-enyne esters of general structure **1**. At room temperature, hydrolyses proceed as expected to afford enyne acids **2**. However, when the reactions are carried out at elevated temperatures, the major products obtained are enones **3**, the overall result of decarboxylative rearrangement (Scheme 1). We report herein the scope and mechanistic details of this enyne rearrangement sequence. In addition, during the course of these studies a new, practical palladium-catalyzed synthesis of enynes from enol tosylates has been developed.

To investigate the scope of the one-pot rearrangement process, two series of enyne esters were prepared. In one series, enynes possessing different alkyne groups were examined, and in the second series different aromatic (and an aliphatic) substituents on the alkene were studied. Sonogashira cross coupling reactions[5] of alkynes with iodide **4**[6] provided the first series of enynes **5** (Scheme 2).



Scheme 1.

To prepare the series of substrates with varying aromatic substitution, an expedient method was desired. Cross coupling partners like vinyl iodide **4** are often derived from acetylenic esters that may require one or more synthetic steps to prepare. In addition, these iodides are frequently oils which necessitate tedious chromatographic purification to remove minor geometric isomers and impurities. As a convenient alternative, we considered the use of crystalline enol tosylates as cross coupling partners.[7] The tosylates were prepared from commercially available β-ketoesters as a mixture of geo-



Scheme 2.

* Corresponding author. Tel.: +1 805 313 5152; fax: +1 805 375 4531; e-mail: walkers@amgen.com

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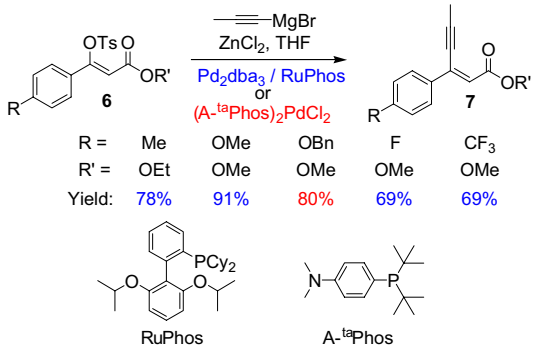
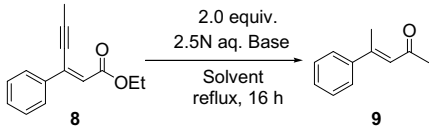
metric isomers favoring the (*Z*)-stereoisomer (*Z*/*E* = 4–99:1).[8] The desired (*Z*)-isomers were obtained in high geometric purity (>99%) by recrystallization from isopropanol. Our preliminary attempts at Pd-catalyzed alkynylation of tosylates with alkynylzinc halides met with limited success using PPh_3 as supporting ligand (<10% conversion). On the other hand, application of a highly active Pd/RuPhos[9] catalyst system permitted efficient cross coupling of a propynylzinc reagent (1.5 equiv) with a variety of enol tosylates **6** (Scheme 3, R = Me, OMe, F, CF_3; R′ = OEt, OMe).[10] Interestingly, the one-component catalyst[11] (A-^{ta}Phos)$_2$PdCl$_2$ was also an effective promoter for the alkynylation reaction, providing the (*Z*)-enyne in good yield (Scheme 3, R = OBn, R′ = OMe). Although the coupling reactions were typically conducted at 40 °C overnight, the reaction times could be reduced to 2–6 h by increasing the temperature to 70 °C.[12]

With a number of enyne esters in hand, we turned our attention to evaluating their performance in the rearrangement process. A model enyne **8** was selected and reaction conditions were examined to optimize the yield of the rearranged product **9** (Table 1).[13] Since conversion to **9** was slow at room temperature, reaction mixtures were heated at reflux in the indicated solvents. For alkaline hydrolyses, a marked counterion effect was observed (Table 1, entries 1–3) and the best conditions employed 2 equiv of aqueous KOH in refluxing THF/MeOH (entry 3). Under these reaction conditions, the starting ester **8** was rapidly hydrolyzed to the corresponding acid, but overnight heating was required to complete the transformation to **9**.[14] The process to the enone was somewhat less efficient with only 1 equiv of KOH (entry 4) or when the reaction was conducted in the absence of THF cosolvent (entries 5 and 6).[15]



Scheme 3.

Table 1. Optimization of the rearrangement reaction

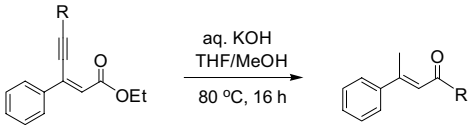


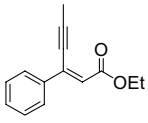
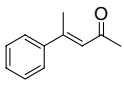
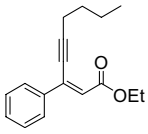
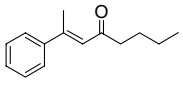
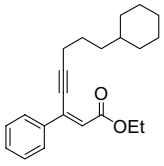
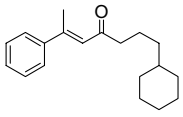
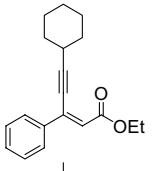
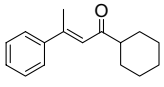
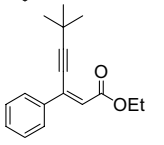
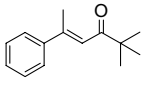
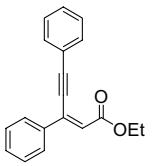
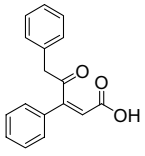
Entry	Base	Solvent[a]	Yield[b]
1	LiOH	THF/MeOH (1.5:1)	10
2	NaOH	THF/MeOH (1.5:1)	28
3	KOH	THF/MeOH (1.5:1)	64
4	KOH	THF/MeOH (1.5:1)	51[c]
5	KOH	MeOH	32
6	KOH	EtOH	56

[a] Reactions were performed 0.5 M[8] at 80 °C.
[b] Assay yields from quantitative HPLC analysis against a purified standard.
[c] Used 1.0 equiv KOH.

The remaining enyne esters were then subjected to the optimized rearrangement conditions.[16] As shown in Table 2, enones were isolated in moderate to good yields from substrates possessing aliphatic substituents on the alkyne (entries 1–5). In entries 4 and 5, the rearrangement was presumably slowed by the presence of branching cyclohexyl and *tert*-butyl groups, respectively, and the reaction times were increased to 48 h. In entry 6, where R = phenyl, a ketoacid was isolated.

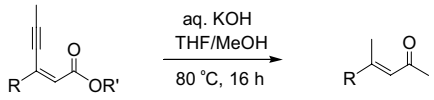
Table 2. Effect of alkyne variation on enyne rearrangement

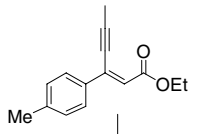
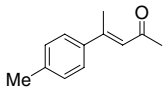
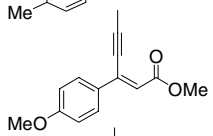
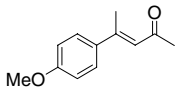
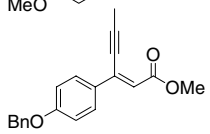
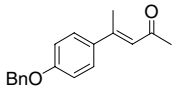
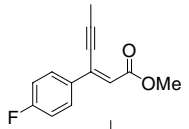
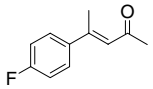
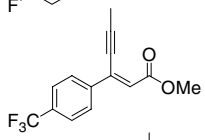
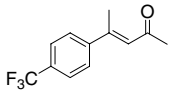
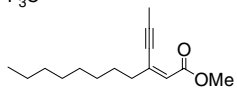
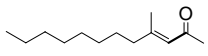


Entry	Enyne ester	Rearrangement product	Yield[a] (%)
1			72
2			41
3			46
4			56[b]
5			46[b]
6			15[c]

[a] Yield of isolated product (average of two runs). All products exhibit satisfactory spectroscopic and physical properties.
[b] Heated at 80 °C for 48 h.
[c] ^{1}H NMR analysis of the crude reaction mixture revealed (unidentified) decomposition products.

Table 3. Effect of alkene variation on enyne rearrangement



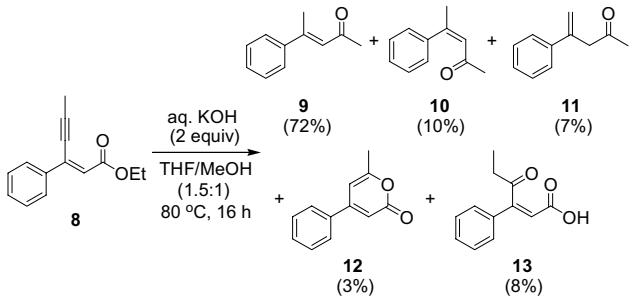
Entry	Enyne ester	Rearrangement product	Yield[a] (%)
1			59
2			69
3			74
4			68
5			48
6[b]			<10[c]

[a] Yield of isolated product (average of two runs). All products exhibit satisfactory spectroscopic and physical properties.
[b] Prepared over two steps from methyl-2-undecynoate, see Refs. 6 and 12.
[c] Complex mixture.

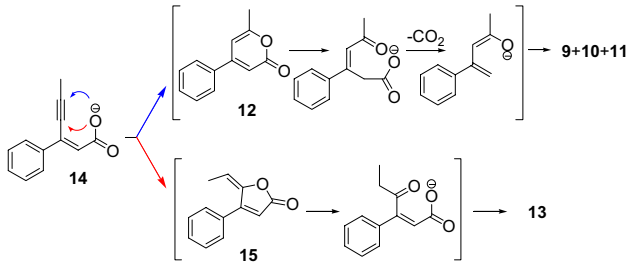
As summarized in Table 3, electron-neutral (entry 1), electron-rich (entries 2 and 3) and electron-deficient (entries 4 and 5) aromatic enynes all provided good yields of enone products. However, a complex mixture was observed when rearrangement of an alkyl substituted enyne was attempted (entry 6).

To further evaluate the process, the rearrangement procedure was performed on gram scale with substrate **8**. Along with target enone **9**, most of the minor byproducts observed by HPLC analysis of the crude reaction mixture were isolated and characterized by ^{1}H NMR, ^{13}C NMR and LCMS (Scheme 4). The final reaction mixture consisted of the isomeric enones **9**, **10** and **11**, pyranone **12**, and ketoacid **13** in the ratios indicated.

The isolation of pyranone **12** suggested that formation of enone **9** may occur via base-induced cyclization of **8** followed by a decarboxylation–alkene isomerization sequence. Thus, under the reaction conditions, enyne ester **8** is initially hydrolyzed and the resulting carboxylate **14** cyclizes onto the triple bond (Scheme 5). Examples of cyclizations of carboxylic acids onto carbon–carbon triple bonds promoted by transition metal catalysts,[17] Lewis acids,[18] and Bronsted acid/base catalysts[19]



Scheme 4.

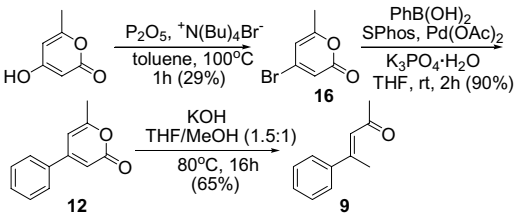


Scheme 5.

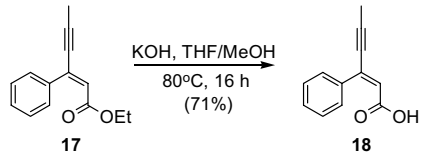
have been reported. The intramolecular cyclization can afford both pyranone **12** and furanone **15**, as Baldwin's rule predicts that both 5-*exo*-dig and 6-*endo*-dig cyclization modes are favorable.[20] Pyranone **12** undergoes further ring-opening hydrolysis under these conditions and the resulting δ-ketoacid decarboxylates during heating.[21] Protonation and alkene isomerization account for the isolated enones **9**, **10**, and **11** with the thermodynamically most stable product predominating. Furanone **15** would also ring open under the basic reaction conditions, and upon protonation affords ketoacid **13**. Taken as a whole, these results indicate that the 6-*endo* cyclization is favored over 5-*exo* by a factor of ~10:1 in this case. Similarly, for the examples shown in Tables 2 and 3, decarboxylative rearrangement via the 6-*endo*-dig cyclization mode generally accounts for the major products in both series. The only exception is entry 6 in Table 2 where the alkyne possesses a phenyl substituent and the ketoacid resulting from sequential 5-*exo*-dig cyclization and furanone hydrolysis was isolated.

To confirm that pyranone **12** would ring open and decarboxylate to provide enone **9** under our reaction conditions, an authentic sample was prepared (Scheme 6). Bromide **16**, prepared by bromination of 4-hydroxy-6-methyl-2*H*-pyran-2-one,[22] was then converted to **12** via mild Pd/SPhos-catalyzed[23] Suzuki–Miyaura coupling with phenylboronic acid. In agreement with our proposal, subjection of pyranone **12** to the optimized reaction conditions afforded enone **9** in 65% yield.

In addition, no rearrangement/decarboxylation products were observed for a starting material lacking the geometric requirements for intramolecular cyclization; (*E*)-enyne ester **17** provided acid **18** as the exclusive product (Scheme 7).



Scheme 6.



Scheme 7.

In conclusion, we have developed a practical method to assemble (*Z*)-enyne esters via Pd-catalyzed cross coupling reactions of enol tosylates with alkynyl zinc reagents. We have demonstrated that rearrangement of these enyne esters occurs through the action of base to provide enones. Finally, we presented evidence that this rearrangement occurs through a sequence of reactions including (i) ester hydrolysis, (ii) 6-*endo*-dig cyclization, (iii) pyranone hydrolysis, and (iv) decarboxylation accompanied by alkene isomerization.

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12. *General procedure for tosylate cross-coupling*: To a cold (−45 °C) stirred mixture of propynylmagnesium bromide in THF (3.4 mL, 0.50 M, 1.7 mmol) was added a solution of $ZnCl_2$ in THF (3.9 mL, 0.50 M, 1.95 mmol). The reaction mixture was allowed to warm to rt and then stirred for an additional 30 min. A mixture of tosylate (1.14 mmol) and Pd catalyst [0.023 mmol $Pd_2(dba)_3$/0.091 mmol RuPhos or 0.057 mmol (A-^{ta}Phos)$_2$PdCl$_2$] in THF (2 mL) was added and the addition flask rinsed with THF (1 mL). The resulting mixture was heated at 40 °C for 24 h, cooled, filtered and concentrated. The residue obtained was purified by flash chromatography on silica gel (ethyl acetate–hexanes) to afford the (*Z*)-enyne ester.
13. Enyne **8** was prepared in 70% yield via Negishi coupling [$Pd(PPh_3)_4$, THF, rt, 16 h] of propynylzinc bromide with iodide **4**.
14. Additional base charges or extended heating times resulted in competitive retro-aldol reaction of the enone products.
15. At higher temperatures (e.g., ethylene glycol, 200 °C) acetophenone was obtained as the major product, presumably due to retro-aldol reaction of the initially formed enone **3**. Product **3** was not observed under neutral (LiCl, DMSO) or acidic (TsOH, PhMe or HCl/H_2O) conditions were examined.
16. *General procedure for decarboxylative rearrangement*: To a stirred solution of (*Z*)-enyne ester (1.31 mmol) in THF (1.5 mL) and MeOH (1 mL) was added aqueous KOH (1.05 mL, 2.5 N, 2.62 mmol) and the resulting mixture was heated at 80 °C for 16 h. The reaction mixture was cooled to rt, diethyl ether (20 mL), aqueous HCl (5.0 mL, 1.0 N) and water (10 mL) were added and the layers were separated. The aqueous phase was extracted with ether (20 mL) and the combined organic layers were concentrated. The residue obtained was purified by flash chromatography on silica gel (ethyl acetate–hexanes) to afford the desired enone.
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