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Synthesis of α-Pyrones via Palladium-Catalyzed Annulation of Internal Alkynes

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Abstract

A number of 3,5,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones have been prepared in good yields by the reaction of vinylic iodides, bromides or triflates bearing ester functionality with internal alkynes in the presence of a palladium catalyst. The methodology provides an especially simple, convenient, and regioselective route to α-pyrones containing aryl, silyl, *tert.*-alkyl and other hindered groups. The reaction is believed to proceed through a seven-membered palladacyclic salt in which the regiochemistry of the reaction is controlled by steric factors.

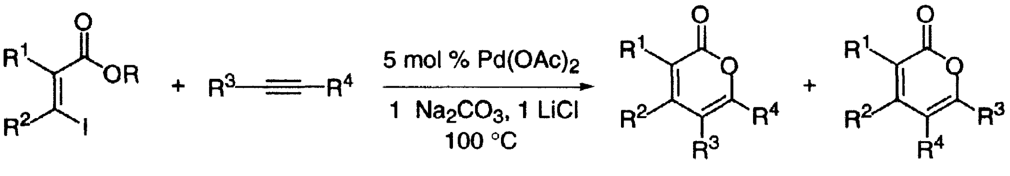
Keywords: *palladium and compounds; annulation; halo esters; pyrones.*

α-Pyrones are useful intermediates in the synthesis of a variety of important hetero- and carbocyclic molecules [1] and occur as structural subunits in numerous natural products that exhibit a wide range of biological activity [2]. Very recently, low molecular weight α-pyrones have been shown to be potent HIV-1 protease inhibitors [3].

We have previously reported that the reaction of methyl 2-iodobenzoate with internal alkynes affords isocoumarins in the presence of a palladium catalyst [4]. Due to the importance of α-pyrones, we were interested in extending this annulation methodology to their synthesis. Indeed, we have now found that the annulation of internal alkynes by cyclic and acyclic vinylic iodides, bromides and triflates provides a convenient, new synthesis of a variety of 3,5,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones.

The starting materials for our α-pyrone synthesis are readily prepared. β-Iodo substituted propenoates **1**, **4**, **8** and **11** (see Table 1) were synthesized by the MnO_2 oxidation [5] of (*Z*)-β-iodo-substituted 2-propenols, which were in turn synthesized by CuI-catalyzed Grignard addition to the appropriate propargylic alcohol and subsequent quenching by I_2 [6]. Bromides **13** and **15** and triflates **17** and **19** were synthesized according to standard literature procedures [7,8].

The palladium-catalyzed annulation of a variety of internal alkynes using these vinylic iodides, bromides and triflates has been carried out as shown in eq 1. The reaction conditions



(1)

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employed were those developed during earlier related work and have not been optimized for any specific example [4, 9]. The results are summarized in Table 1.

In general, this process affords good yields of highly substituted α-pyrones. Both acyclic and cyclic esters and a variety of internal alkynes have been successfully utilized. This process is generally regioselective, although mixtures of regioisomers have occasionally been observed. A substituent in the 3-position of the ester increases the regioselectivity of this annulation reaction. For example, the reaction of ester **1** with 4,4-dimethyl-2-pentyne afforded α-pyrones **2a** and **2b** in 54% yield as an inseparable 69:31 mixture. Similarly, α-pyrones **5a** and **5b** were obtained in 40% and 25% isolated yields respectively. However, the more substituted esters **8** and **13** reacted with the same alkyne to afford α-pyrones **9** (70% yield) and **14** (65% yield) as single regioisomers, respectively. This selectivity is no doubt due to increased steric hindrance during carbopalladation of the alkyne (see the later mechanistic discussion).

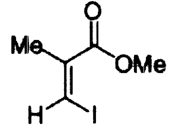
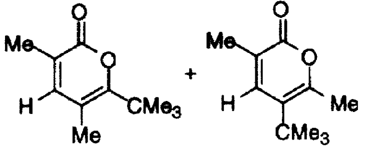
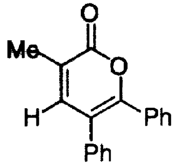
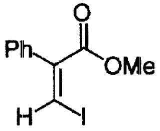
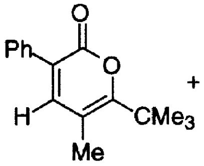
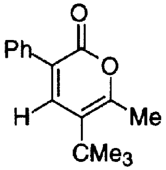
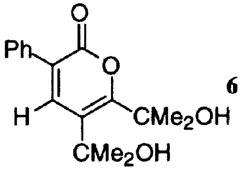
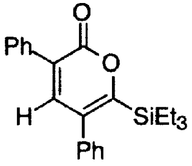
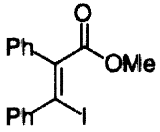
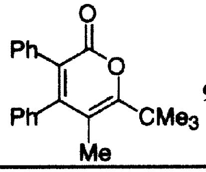
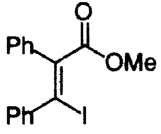
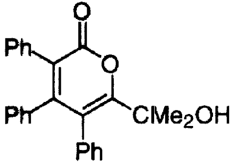
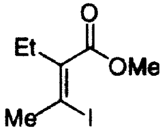
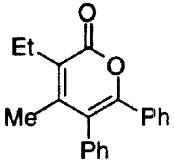
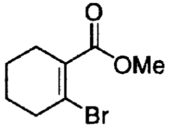
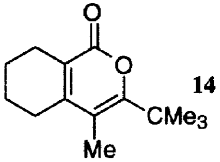
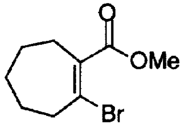
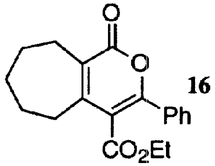
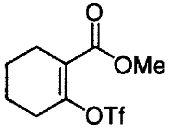
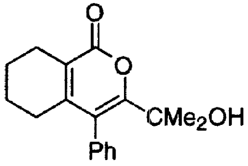
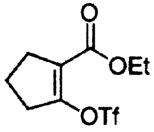
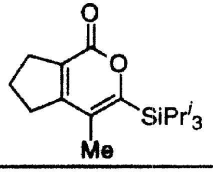
Other internal alkynes have also been successfully employed in this annulation process. Diphenylacetylene (entries 2 and 8), 2,5-dimethyl-3-hexyn-2,5-diol (entry 4), 2-methyl-4-phenyl-3-butyn-2-ol (entries 7 and 11) and ethyl 3-phenyl-2-propynoate (entry 10) have all afforded α-pyrones in good yields as single regioisomers. Trialkylsilyl-substituted α-pyrones in which C-Si bonds are available for further functionalization can also be obtained in modest to good yields (entries 5 and 12). The low yield of α-pyrone **7** is probably due to the desilylation of phenyl triethylsilyl acetylene during the reaction. It is worth mentioning that even cyclic vinylic bromides **13** and **15** have been successfully reacted with 4,4-dimethyl-2-pentyne and ethyl 3-phenyl-2-propynoate to afford α-pyrones **14** and **16** in 65% and 77% yields, respectively, as single regioisomers. Vinylic triflates can also be employed in this α-pyrone synthesis. In contrast to the acyclic triflate methyl 2,3-dimethyl-3-trifluoromethanesulfonyloxy-2-propenoate, which gave α-pyrones in only 10-20% yields, cyclic vinylic triflates **17** and **19** can be used to regioselectively annulate internal alkynes to afford bicyclic α-pyrones in good yields (entries 11 and 12).

This chemistry is not without its limits. During the course of this study, we have found that alkynes with propargylic hydrogens on the sterically more hindered end of the alkyne fail to afford any α-pyrone products using this annulation process. We have also found that the presence of a hydrogen next to the carbonyl in the starting ester lowers the yields of the palladium reactions, presumably due to β-hydrogen elimination in the vinylic palladium intermediate, although we have no solid evidence that this is the source of the problem. For example, ethyl (*Z*)-3-iodo-2-propenoate afforded only low yields (10-20%) of α-pyrones as a mixture of regioisomers if unsymmetrical internal alkynes are employed. Methyl (*Z*)-3-iodo-3-phenyl-2-propenoate failed to give any α-pyrones at all.

Consistent with our earlier work [4], these alkyne annulation reactions generally afford products in which the vinylic moiety of the starting ester adds to the less hindered end of the carbon-carbon triple bond. Only relatively unhindered vinylic substrates afford mixtures of regioisomers. The regiochemistry was established for the products of entry 3 of Table 1 by NOESY spectroscopy. For the minor product **5b** of entry 3, there was an NOE interaction between C^4-H and C^5-$C(CH_3)_3$ and no interaction between C^4-H and C^6-CH_3. This compound was therefore assigned the structure shown in Table 1. The rest of the products in Table 1 have been assigned by analogy with the above observations.

Based on the above results and our previous work [4], we believe that this annulation process proceeds as shown in Scheme 1 by a sequence involving (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst, (2) oxidative addition of the starting halide or triflate to Pd(0), (3) vinylpalladium coordination to the alkyne and subsequent insertion of the alkyne to form a new vinylpalladium intermediate, (4) attack of the carbonyl oxygen on the vinylpalladium intermediate to form a seven-membered palladacyclic salt, and (5) reductive elimination of an

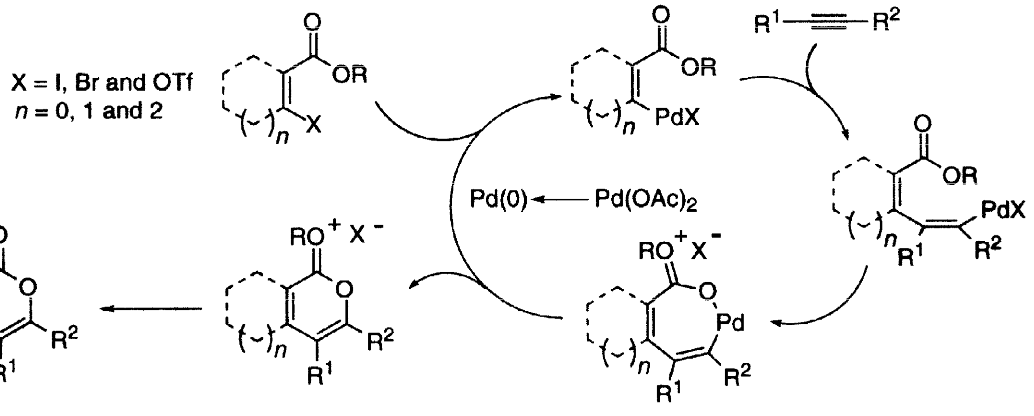
Table 1. Synthesis of α-Pyrones via Annulation of Internal Alkynes.[a]

Entry	Ester	Alkyne[b] time (h)	Product(s) % yield (isomer ratio)[c]
1	 **1**	$MeC{\equiv}CCMe_3$ 28	 54% (**2a** : **2b** = 69 : 31)
2		$PhC{\equiv}CPh$ 5	 **3** 40%
3	 **4**	$MeC{\equiv}CCMe_3$ 10	 **5a** 40% +  **5b** 25%
4		$RC{\equiv}CR$ $R = CMe_2OH$ 10	 **6** 70%
5		$PhC{\equiv}CSiEt_3$ 22	 **7** 30%
6	 **8**	$MeC{\equiv}CCMe_3$ 9	 **9** 70%
7	 **8**	$PhC{\equiv}CCMe_2OH$ 15	 **10** 59%
8	 **11**	$PhC{\equiv}CPh$ 12	 **12** 51%
9	 **13**	$MeC{\equiv}CCMe_3$ 48	 **14** 65%
10	 **15**	$PhC{\equiv}CCO_2Et$ 7	 **16** 77%
11	 **17**	$PhC{\equiv}CCMe_2OH$ 40	 **18** 79%
12	 **19**	$MeC{\equiv}CSiPr^i_3$ 21	 **20** 64%

[a] See reference 9 for the experimental procedure. [b] 2 Equivalents of alkyne were used, except 4,4-dimethyl-2-pentyne (5 equiv).
[c] Yields refer to isolated yields. All of the compounds gave satisfactory ^1H NMR, ^{13}C NMR, HRMS and IR spectra.

oxonium salt with simultaneous regeneration of the palladium(0) catalyst. Loss of the R group of the ester may occur either during the reaction itself by either an S_N1 or S_N2 process or during the aqueous workup.

Scheme 1



In conclusion, a variety of 3,5,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones have been prepared in modest to good yields by the reaction of acyclic and cyclic vinylic iodides, bromides and triflates bearing ester functionality with internal alkynes in the presence of a palladium catalyst.

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References

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[9] **General Procedure for the Synthesis of α-Pyrones.** $Pd(OAc)_2$ (3 mg, 0.013 mmol), Na_2CO_3 (26.5 mg, 0.25 mmol), DMF (5 ml), LiCl (10.6 mg, 0.25 mmol), the alkyne (0.5 mmol), and the ester (0.25 mmol) were placed in a 2 dram vial. The vial was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with satd NH_4Cl, dried over anhydrous Na_2SO_4, and decanted. The solvent was evaporated under reduced pressure and the product was isolated by chromatography (EtOAc/hexanes) on a silica gel column.