Palladium-catalysed annulation reaction of allenyltins with β-iodo vinylic acids: selective synthesis of α-pyrones

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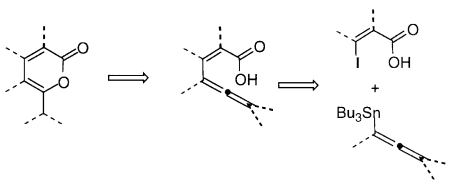
Palladium-catalysed regio- and stereoselective annulation of allenyl stannanes by β-iodo vinylic acids gives the corresponding α-pyrones in high yields. This annulation most probably proceeds through a Stille reaction/cyclisation sequence.

Five- and six-membered ring unsaturated lactones (butenolides or pyrones) constitute an important class of biologically active compounds and their synthesis has been the focus of considerable attention in synthetic organic chemistry[1] as well as in medicinal chemistry.[2] Numerous methods reported in the last decade for the synthesis of these structures involve transition metal (Ag, Hg, Rh, Pd) promoted intramolecular additions of carboxylic acids to alkynes.[3] In general, the lactonisation reaction of alk-4-ynoic acids proceeds through a stereoselective *trans* addition reaction *via* a *5-exo* process. In addition to the formation of γ-alkylidenebutenolides, in some cases six-membered lactones resulting from the *6-endo* mode have been obtained as minor products. This problem of regioselectivity was recently solved by Larock *et al.* who demonstrated that substituted isocoumarins or α-pyrones could be prepared by treating β-halogeno α,β-unsaturated esters with internal alkynes in the presence of a palladium catalyst.[4] Nevertheless, two α-pyrone regioisomers were obtained in the case of non-symmetric alkynes. On the other hand, we have previously described the synthesis of dienoic acids or enynes bearing a carboxylic acid function from β-iodovinylic acids and vinyltin or alkynylzinc reagents.[5] This methodology was then applied to the synthesis of γ-tributyltin methylidenebutenolides.[6] To broaden our synthesis strategy and to design a system suitable for *6-endo* lactonization, we planned the preparation of allenyl substituted alkenoic acids which we thought would exclusively undergo *6-endo* mode cyclisation mediated by a palladium complex (Scheme 1).[7]

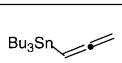
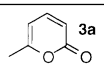
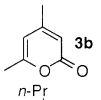
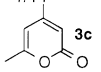
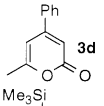
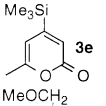
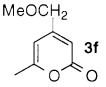
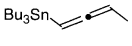
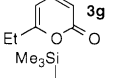
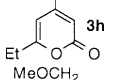
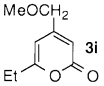
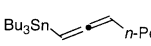
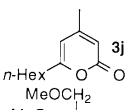
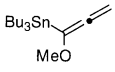
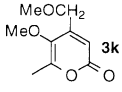
We report here the selective one pot synthesis of α-pyrones under palladium complex catalysis. Our investigation began with the coupling of tributylstannylallene[8] with (*Z*)-3-iodoprop-2-enoic acid[5] under conditions previously defined by our group.[6] Unfortunately, neither allenyl substituted propenoic acid nor cyclised products (5- or 6-membered ring lactones) were detected. Only a large amount of tin by-products were recovered, among them the tributylstannyl ester of the starting iodovinylic acid. In order to avoid the proteolysis of allenylstannane and to promote the cross coupling reaction, we examined the reaction under various conditions (solvent, catalyst, presence of additives,...). First the influence of the nature of the carboxylic acid derivative on conversion rates was examined. In DMF and in the presence of 1% of tetrakis(triphenylphosphine)palladium,† the ethyl ester of **1a** yielded exclusively ethyl hex-2-en-4-ynoate. The use of tributyltin carboxylate (Table 1 entry 4) under identical conditions to those used for the synthesis of tributyltin methylidenebutenolides, led to 52% yield of 6-methylpyran-2-one **3a**, without any trace of hexa-2,4,5-trienoic acid. Finally, we found that an 83% yield of **3a** could also be obtained from **1a** at rt in DMF using 5% palladium acetate, triphenylphosphine, sodium carbonate and tetrabutylammonium bromide.



Scheme 1

Next the nature of the solvent and of the palladium complexes were examined. THF was found to be ineffective whereas acetonitrile afforded a very poor yield (< 25%) of cyclised product. We also observed that phosphine-liganded palladium appeared to be more efficient than other palladium salts such as

Table 1 Synthesis of αpyrones

Entry	R (**1**)	Allenylstannane	α-Pyranone	Yield (%)
1	H (**1a**)		 **3a**	83
2	Me (**1b**)	"	 **3b**	85
3	*n*-Pr (**1c**)	"	 **3c**	81
4	Ph (**1d**)	"	 **3d**	87
5	Me_3Si (**1e**)	"	 **3e**	79
6	CH_2OMe (**1f**)	"	 **3f**	84
7	Me (**1b**)		 **3g**	85
8	Me_3Si (**1e**)	"	 **3h**	86
9	CH_2OMe (**1f**)	"	 **3i**	84
10	Me (**1b**)		 **3j**	84
11	CH_2OMe (**1f**)		 **3k**	82

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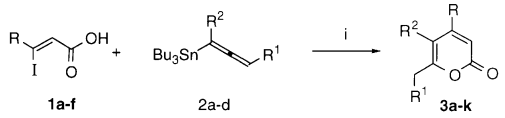
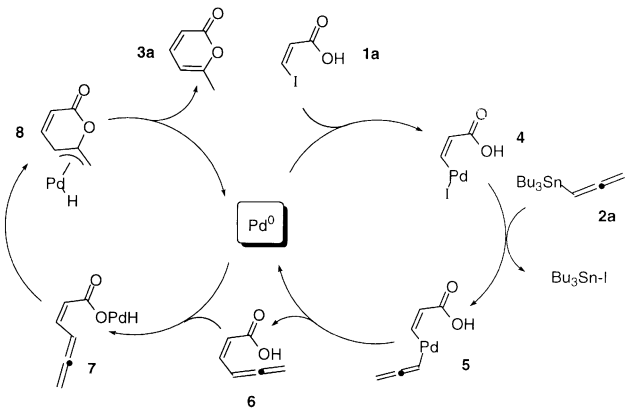


Scheme 2 $Pd(OAc)_2$ (5%), PPh_3 (10%), Na_2CO_3 (4 eq.), *n*-Bu_4NBr (1 eq.), DMF, rt.

palladium acetate (without additional triphenylphosphine) or bis(acetonitrile)palladium chloride. Tetrakis(triphenylphosphine)palladium gave approximately identical yields to the $Pd(OAc)_2/PPh_3$ couple.

The reaction of tributylstannylallene with a range of (*Z*)-3-substituted 3-iodoprop-2-enoic acids under regio- and stereocontrol gave good yields of 4-substituted-6-methylpyranones **3a**–**f** as the sole products (Table 1 entries 1–6) (Scheme 2). Other allenylstannanes were used under similar conditions in order to determine the scope of the reaction. High regioselectivity was observed in each case. The use of 3-alkylallenylstannanes (entries 7–10) showed that the regioselective heteroannulation reaction occurred only on carbons 1 and 2 of the allenyltin. On the other hand, γ-alkylidenepyranones previously obtained by Larock *et al*. from a reaction of allenes with (*Z*)-3-iodopropenoic acids were not observed. This almost certainly indicates a different mechanism to those proposed by Larock and Yamamoto respectively.[9,10]

A plausible mechanism for the heteroannulation reaction is shown in Scheme 3. First, a Stille mechanism[11] would yield 3-allenylpropenoic acid **6** by oxidative addition, transmetallation (formation of **5**) and reductive elimination. Cyclisation would then occur *via* an attack on the carboxylate function at the β-position of the allenyl moiety, which would give the π-allylpalladium intermediate. The latter would subsequently provide α-pyrone and regenerate the palladium(0) catalyst.[12]



Scheme 3 Postulated mechanism for heteroannulation.

An alternative pathway involving the attack of **4** on the central carbon atom of the stannylallene **2a** could be excluded on the basis of the experiments conducted with 1 or 3-substituted allenylstannanes since other regioisomers should have been obtained rather than **3h**–**g**‡.[9]

In conclusion, under palladium complex catalysis, β-iodovinylic α,β-unsaturated acids react with allenyl stannanes *via* heteroannulation selectively to provide diverse α-pyrones. Studies to extend this reaction to other γ-halogeno pronucleophiles are currently under way and will be reported in due course.

Notes and references

† General procedure for the heteroannulation summarised in Table 1: palladium acetate (112 mg, 0.5 mmol), triphenylphosphine (131 mg, 0.5 mmol), tetrabutylammonium bromide (3.2 g, 10 mmol) and sodium carbonate (5.3 g, 50 mmol) were progressively added to a degassed solution of 3-substituted-3-iodopropenoic acid **1** (10 mmol) in anhydrous DMF (40 mL). The mixture was stirred at rt for 10 min and allenylstannane **2** (10 mmol) was then added. The reaction mixture was stirred for 4 h. After conversion was complete (checked by TLC; reaction time < 10 h), the reaction was quenched with aqueous NH_4Cl solution. After ether extraction (3 × 20 mL) and usual treatments, the crude products were chromatographed on silica gel to obtain compounds **3a**–**k**. All new compounds were fully characterised spectroscopically.

‡ Selected data for **3k**: δ_H(200 MHz, $CDCl_3$) 2.18 (3H, s), 3.40 (3H, s), 3.59 (3H, s), 4.27 (2H, s), 6.15 (1H, s); δ_C(50.3 MHz, $CDCl_3$) 15.3, 59.7, 62.5, 68.9, 109.7, 138.5, 154.2, 154.6, 162.4. MS (70 ev): *m/z* = 184 (*M*, 23%), 169 (22), 141 (22), 45 (14), 43 (100), 39 (14).

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