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Catalytic and selective conversion of (*Z*)-2-en-4-ynoic acids to either 2*H*-pyran-2-ones in the presence of $ZnBr_2$ or (*Z*)-5-alkylidenefuran-2(5*H*)-ones in the presence of Ag_2CO_3

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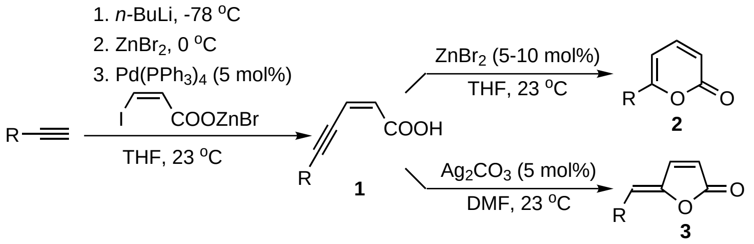
Abstract—Treatment of (*Z*)-5-alkyl-2-en-4-ynoic acids (**1**), prepared by the Pd-catalyzed alkynylzinc–β-haloacrylic acid coupling, with 5–10 mol% of $ZnBr_2$ can produce 6-alkyl-2*H*-pyran-2-ones (**2**) along with minor amounts of (*Z*)-5-alkylidenefuran-2(5*H*)-ones (**3**) in >90% combined yields, with often very high (≈95/5) pyranone/furanone ratios. On the other hand, lactonization of **1** catalyzed by Ag_2CO_3 provides a selective synthesis of (*Z*)-5-alkylidenefuran-2(5*H*)-ones (**3**) in >90% yields along with minor amounts (≤5%) of **2**. © 2002 Published by Elsevier Science Ltd.

We report herein that treatment of 5-alkyl-2-en-4-ynoic acids (**1**) with 5–10 mol% of $ZnBr_2$ in THF can produce 6-alkyl-2*H*-pyran-2-ones (**2**) in high yields (Scheme 1). The pyranone/furanone ratio of approximately 95/5 have been observed with **1** containing *n*-hexyl, isobutyl, and cyclohexyl groups bonded to the C5 atom (entries 1–3 in Table 1). The use of DMF in place of THF in entry 3 lowered the **2**/**3** ratio to 67/33, although the combined yield was 91%. Cyclization of **1** to produce **2** in low yields (≤21%) along with the formation of (*Z*)-5-alkylidene-furan-2(5*H*)-ones (**3**) in 18–62% yields in the presence of a catalytic amount of AgI or Ag or 1 equiv. of HgO is known.[1] In the same publication, *o*-1-pentynylbenzoic acid was preferentially converted to 3-propylisocoumarin in good yields in the presence of catalytic amounts of $AgClO_4$, $AgNO_3$, AgOTf, or Ag_2CO_3. *However, (Z)-2-en-4-ynoic acids (1) have not previously been catalytically converted to 2 in high yields as the major products.* During our study reported herein, conversion of **1** to **2** in low selectivity (**2**/**3** <4) by iodolactonization with 3 equiv. each of I_2 and $NaHCO_3$[2a] followed by consecutive treatment with Zn and HCl was reported.[2b] As the results shown in Scheme 2 indicate, the current procedure is superior to that reported previously in that it is a $ZnBr_2$-catalyzed one-step reaction of higher product yields and higher selectivity.

We further report that the preparation of (*Z*)-5-organyl-2-en-4-ynoic acids by the Pd-catalyzed alkynylzinc–β-haloacrylic acid coupling[3–5] followed by lactonization catalyzed by Ag_2CO_3 provides a superior, albeit two-step, alternative to the recently developed one-pot alkyne-alkene coupling–lactonization tandem process[6–8] run under Sonogashira coupling conditions[9] for selective synthesis of (*Z*)-5-alkylidenefuran-2(5*H*)-ones (**3**) (Table 2).[10]



Scheme 1.

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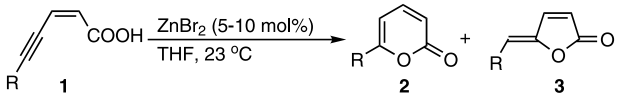
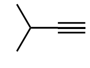
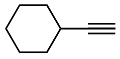
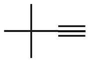
Table 1. Selective conversion of (*Z*)-2-en-4-ynoic acids to 2*H*-pyran-2-ones catalyzed by $ZnBr_2$ in THF



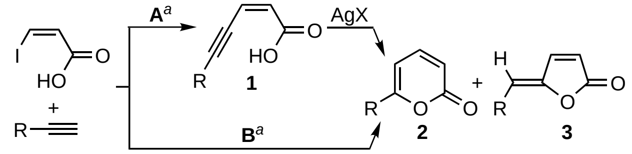
entry	alkyne	yield of **1**	time (h)	**2** : **3**	combined yield (%) based on **1**	based on alkyne
1	*n*-Hex—≡	95	24	94 : 6	95	90
2		94	24	96 : 4	98	92
3		93	48	96 : 4	92	86
4		92	72	66 : 34	93	86
5	Ph—≡	94	72	50 : 50	94	88

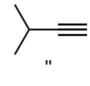
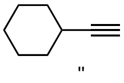
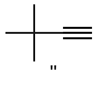
Thus, in those cases where the R groups of the starting alkynes are *n*-Hex, *i*-Pr, cyclohexyl, *t*-Bu, and Ph, the overall yield of **3** are 82–88% over the two steps. These results favorably compare with the yield range of 46–74% for **3** observed in the one-pot tandem process. Furthermore, whereas the **3**/**2** ratio observed in the one-pot tandem process for those cases where the R groups are *n*-Hex, *i*-Pr, and cyclohexyl are only 2–4, those observed in the Ag-catalyzed lactonization are 19–22. These comparative results are summarized in Table 2. Some of the reported difficulties associated with the one-pot Pd-catalyzed cross-coupling-lactonization tandem process,[6,7] such as alkyne dimerization and Michael-type addition reactions have not been observed in the two-step process.

Although *o*-alkynylbenzoic acids have been converted to dihydrobenzofuranone derivatives in high yields in the presence of Ag_2CO_3, AgI, or Ag,[1] AgI-catalyzed conversion of 5-phenyl-2-penten-4-ynoic acid into the corresponding **3**[1] and $AgNO_3$-catalyzed synthesis of TBS-protected lissoclinolide[10] are the only previously reported examples of the Ag-catalyzed high-yield conversion of **1** into **3**. In cases where R is alkyl, however, we find that $AgNO_3$ and a few of other Ag salts, such as AgOTf and $AgBF_4$, are unsatisfactory for selectively converting **1** into **3**. On the other hand, the use of Ag_2CO_3 or AgOAc, namely carbonate or carboxylate salts of Ag, leads to selective synthesis of **3** (Table 3).

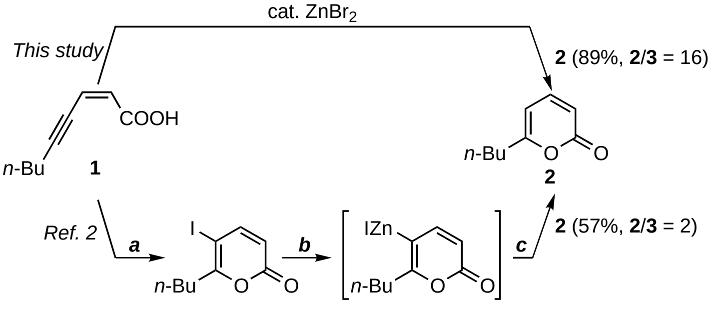
On the basis of all of the findings presented above, it now appears reasonable to state that (i) the preparation of (*Z*)-2-en-4-ynoic acids (**1**) by the Pd-catalyzed cou-

Table 2. Comparison of Ag-catalyzed lactonization of (*Z*)-2-en-4-ynoic acids with Pd-catalyzed alkyne–alkene cross-coupling–lactonization tandem process



entry	alkyne	procedure[a]	**2** : **3**	yield of **2** + **3** (%) based on **1**	based on alkyne
1A	*n*-Hex—≡	**A**	4 : 96	96	90
1B	"	**B**	34 : 66	[b]	77
2A		**A**	5 : 95	99	93
2B	"	**B**	20 : 80	[b]	75
3A		**A**	3 : 97	95	88
3B	"	**B**	20 : 80	[b]	65
4A		**A**	2 : 98	95	86
4B	"	**B**	3 : 97	[b]	76
5A	Ph—≡	**A**	2 : 98	94	88
5B	"	**B**	[c]	[b]	46 [d]

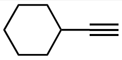
[a] Procedure **A**: (1) Compound **1** was prepared under the cross-coupling conditions described in Ref. 11; (2) Ag_2CO_3 (5–10 mol%), DMF, 23°C, 1 h; Procedure **B**: CuI (5–10 mol%), Et_3N (4 equiv.), $Pd(PPh_3)_4$ (5 mol%), MeCN, 23°C, 12 h. [b] The formation of compound **1** was never observed under conditions **B**. [c] Ratio not determined. [d] Ref. 6.



a: I_2 (3 eq), $NaHCO_3$ (3 eq), 65%; ***b***: Zn; ***c***: HCl, 88%.

Scheme 2.

Table 3. The effects of Ag catalysts and solvents in the Ag-catalyzed lactonization of (*Z*)-2-en-4-ynoic acids

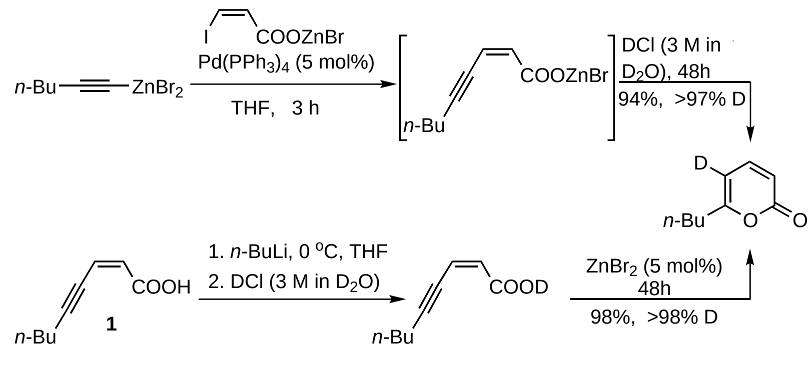
entry	alkyne	catalyst	solvent	**2**: **3**	combined yield (%)[a]
1	*n*-Hex—≡	Ag_2CO_3	DMF	4 : 96	96
2	"	AgOAc	DMF	9 : 91	97
3	"	$AgNO_3$	DMF	64 : 36	95
4	"	$AgNO_3$	MeOH	89 : 11	96
5	"	AgOTf	DMF	80 : 20	93
6	"	$AgBF_4$	DMF	88 : 12	93
7		Ag_2CO_3	DMF	3 : 97	95
8	"	AgOAc	MeCN	4 : 96	95
9	"	AgOAc	DMF	8 : 92	97
10	"	AgOAc	MeOH	9 : 91	92
11	"	$AgNO_3$	MeOH	57 : 43	93
12	"	AgOTf	DMF	88 : 48	93

[a] Combined yield of **2** and **3** based on **1**.

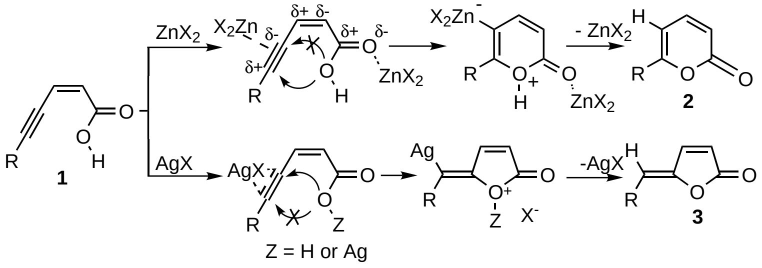
pling of alkynylzincs with (*Z*)-β-haloacrylic acids, (ii) the $ZnBr_2$-catalyzed cyclization of **1** to produce 2*H*-pyran-2-ones (**2**),[11] and (iii) the Ag_2CO_3-catalyzed cyclization of **1** to give (*Z*)-5-alkylidenefuran-2(5*H*)-ones (**3**),[12] all combine to provide an unprecedentedly general and selective protocol for the synthesis of **2** and **3** from terminal alkynes and (*Z*)-β-haloacrylic acids (Scheme 1).[13,14]

In our hands, Pd catalysts, such as $Pd(PPh_3)_4$, have not been effective in converting preformed and purified (*Z*)-2-en-4-ynoic acids into **2** and/or **3**. Only a very slow cyclization to give **2** and **3**, which can take place at comparable rates even in the absence of a Pd complex, has been observed. This point, however, is under further investigation. Interestingly, the zinc salts of (*Z*)-2-en-4-ynoic acids cannot be lactonized under the influence of $ZnBr_2$ either. However, addition of 3 M DCl in D_2O (1 mol equiv.) to the zinc salt of (*Z*)-2-nonen-4-ynoic acid induced a slow but smooth and quantitative lactonization with incorporation of D at the C4 position to the extent of >98%, indicating the intermediacy of the corresponding zinco derivative of 2*H*-pyran-2-one (Scheme 3).

At this point, factors affecting the pyranone/furanone ratio are not yet very clear. It is nevertheless tempting to speculate that polarization of the unsaturated bonds in (*Z*)-2-en-4-ynoic acids would favor the formation of 2*H*-pyran-2-ones via a Lewis acid-catalyzed polar process, whereas transition metal-catalyzed processes, in which bond polarization is less important, may stereoelectronically favor a 5-*exo*-mode cyclization (Scheme 4). Irrespective of the precise mechanisms of these cyclization reactions, however, the selective conversion of **1** into **2** and **3** catalyzed by $ZnBr_2$ and Ag_2CO_3, respectively, significantly complement a few related lactonization protocols developed over the past decade.



Scheme 3.



Scheme 4.

Acknowledgements

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11. A representative procedure for the synthesis of **1** from the corresponding terminal alkyne is as follows: A solution of EtMgBr (1 M solution in THF, 2.1 mL) in 5 mL of THF was successively treated with ZnBr$_2$ (1 M solution in THF, 2.1 mL, freshly prepared from flame-dried ZnBr$_2$) and (*Z*)-3-iodo-2-propenoic acid (3.96 g, 2 mmol) in 2 mL of THF at 0°C under an Ar atmosphere. In a second flask a solution of a terminal alkyne (2 mmol) in 5 mL of THF was treated with *n*-BuLi (2.5 M solution in hexanes, 2.2 mL) at −78°C under an Ar atmosphere. After 10 min, the reaction mixture was treated with ZnBr$_2$ (1 M solution in THF, 2.2 mL), warmed to 0°C, transferred by cannula into the first flask, treated with Pd(PPh$_3$)$_4$ (115 mg, 0.1 mmol), and then warmed to 23°C. After 2–5 h the reaction mixture was diluted with Et$_2$O, washed with aqueous NH$_4$Cl and then with aqueous NaHCO$_3$, and treated with 1N NaOH. The aqueous layer was washed with hexanes, acidified with 1N HCl, extracted with Et$_2$O and dried over MgSO$_4$ to give the desired (*Z*)-2-en-4-ynoic acid (**1**). No further purification was necessary.
12. A representative procedure for the metal-catalyzed lactonization of **1** to give **2** or **3** is as follows: To a solution of **1** (0.25 mmol) in 2–5 mL of solvent indicated in Tables 1–3 was added an appropriate metal salt (5–10 mol%) at 23°C. After the completion of the reaction indicated by TLC analysis, the reaction mixture was then filtered through a short path silica gel column and concentrated at reduced pressure. The products ratios and yields were determined by ^{1}H NMR spectroscopy and GC analyses using mesitylene as an internal standard. Chromatography on silica gel (95/5 hexane/EtOAc, v/v) allowed the separation of **2** and **3** and their isolation as pure substrates.
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14. For the synthesis of 2*H*-pyran-2-ones by the Pd-catalyzed reaction of allenylstannanes with (*Z*)-β-iodoacrylic acids, see: Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchene, A.; Parrain, J. L. *Chem. Commun*. **2000**, 1987.