An Efficient Synthesis of 2,6-Disubstituted 2,3-Dihydro-4*H*-pyran-4-ones via Sonogashira Coupling of *p*-Toluenethiol Esters

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Received 15 February 2010

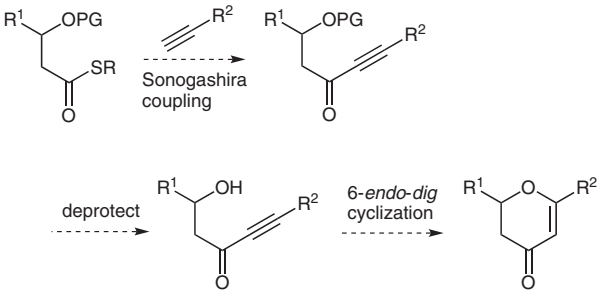
Abstract: An efficient strategy for the synthesis of 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-ones has been developed, which relied on Sonogashira coupling of alkynes and *p*-toluenethiol esters and AgOTf-promoted 6-*endo-dig* cyclization of the derived β-hydroxy ynones.

Key words: palladium, cross-coupling, cyclization, heterocycles, dihydropyrans

Thiol esters serve as a stable and easy-to-handle surrogate for acid chlorides in palladium-catalyzed reactions.[1] Fukuyama and co-workers reported a mild and efficient reduction of ethanethiol esters with triethylsilane in the presence of Pd/C, which constitutes the prototype of palladium-catalyzed reactions of thiol esters.[2] Subsequently, they also reported that coupling of ethanethiol esters with organozinc reagents[3] or terminal alkynes[4] under palladium catalysis is also feasible, which allows for efficient synthesis of unsymmetrical ketones. Meanwhile, Liebeskind et al. have described palladium-catalyzed coupling of *p*-toluenethiol esters with organotin[5] or organoboron reagents,[6] which also provides access to unsymmetrical ketones.

It is well known that 2,3-dihydro-4*H*-pyran-4-one derivatives are the versatile intermediates for the synthesis of functionalized tetrahydropyrans and spiroacetals. Several methods, such as hetero-Diels–Alder reaction,[7] palladium-catalyzed oxidative cyclization of β-hydroxy enones,[8] and intramolecular oxa-conjugate cyclization of β-hydroxy ynones,[9] have been reported for the synthesis of 2,3-dihydro-4*H*-pyran-4-one derivatives, although preparation of suitable precursors for these reactions is difficult in some cases.[8b] Herein, we report a new strategy for the synthesis of 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-ones, which relied on Sonogashira coupling of readily accessible terminal alkynes and *p*-toluenethiol esters and 6-*endo-dig* cyclization of the derived β-hydroxy ynones, as summarized in Scheme 1.

We initially examined palladium-catalyzed coupling of thiol esters **1a–d** and alkyne **2** as a model case (Table 1). Coupling of ethanethiol ester **1a** and **2** (2 equiv) under the conditions reported by Fukuyama et al.[4] [$PdCl_2$(dppf), (2-furyl)$_3$P, CuI] in DMF–Et_3N (5:1) at 50 °C for 22 hours gave ynone **3** in 39% yield (entry 1). Prolonged reaction time was necessary for consumption of **1a**, during which time 1,4-addition of ethanethiol to the product ynone **3** was observed as a side reaction. To improve the product yield, we screened a variety of reaction conditions. We found that *p*-toluenethiol ester **1b** displays better reactivity than **1a**; reaction of **1b** and **2** under the same conditions for 4 hours gave **3** in an improved 73% yield (entry 2). Benzenethiol ester **1c** and *p*-nitrobenzenethiol ester **1d** proved to be less efficient than **1b** (entries 3 and 4). We preferred to use *p*-toluenethiol esters in the following experiments not only because of their good reactivity profile but also because of easy handling of crystalline *p*-toluenethiol. We found $Pd_2(dba)_3{\cdot}CHCl_3$ to be the optimal source of palladium for the present reaction (entries 5 and 6). When a mixture of **1b** and **2** was reacted in the presence of a $Pd_2(dba)_3{\cdot}CHCl_3$/(2-furyl)$_3$P catalyst system and CuI in DMF–Et_3N (5:1) at 50 °C for 4.5 hours, the desired ynone **3** was isolated in 77% yield (entry 5). Although longer reaction time (22 h) was necessary, the reaction proceeded even at room temperature to give **3** in a comparable yield of 80% (entry 6).



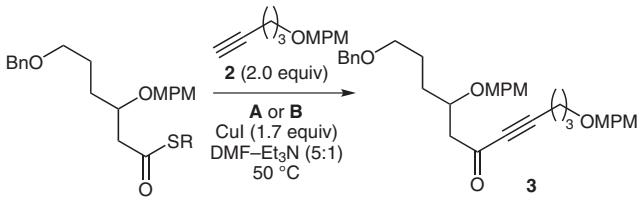
Scheme 1 Our strategy for the synthesis of 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-ones

Various combinations of terminal alkynes and *p*-toluenethiol esters were tolerated under the optimized conditions to deliver the corresponding ynone in 73–82% yield (Table 2).[10]

For each ynone, the MPM group was removed by treatment with DDQ to give the respective β-hydroxy ynone in 85–100% yield (Table 3). We found that β-hydroxy ynones thus obtained underwent smooth 6-*endo-dig* cyclization upon exposure to AgOTf[9a,b] in CH_2Cl_2 at room temperature, leading to 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-one derivatives in excellent yields (94–100%).[11] This 6-*endo-dig* cyclization could be performed either under catalytic or stoichiometric conditions without affect-

SYNLETT 2010, No. 8, pp 1239–1242
Advanced online publication: 23.03.2010
DOI: 10.1055/s-0029-1219794; Art ID: U01010ST

Table 1 Optimization of Reaction Conditions



1a R = Et
1b R = 4-MeC_6H_4
1c R = Ph
1d R = 4-$O_2NC_6H_4$

A $PdCl_2(dppf)$ (0.1 equiv), $(2\text{-furyl})_3P$ (0.25 equiv)
B $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv), $(2\text{-furyl})_3P$ (0.4 equiv)

Entry	Thiol ester **1**	Catalyst system	Yield (%)
1	**1a**	A	39
2	**1b**	A	73
3	**1c**	A	70
4	**1d**	A	65
5	**1b**	B	77
6[a]	**1b**	B	80

[a] The reaction was performed at r.t.

ing the product yield (entry 2), but the reaction proceeded faster under the latter conditions; the reaction completed within 3.4 hours under the stoichiometric conditions, while it took 9.5 hours to complete under the catalytic conditions.

In conclusion, we have developed an efficient method for the synthesis of 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-one derivatives. We have found that efficiency of Sonogashira coupling of terminal alkynes and thiol esters could be significantly enhanced by the use of *p*-toluenethiol esters as an electrophilic component, affording the corresponding β-alkoxy ynones in good yields. AgOTf-promoted cyclization of the derived β-hydroxy ynones furnished 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-ones in excellent yields. Application of the present method to the synthesis of natural products is currently under investigation.

Acknowledgment

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References and Notes

(1) For reviews, see: (a) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87. (b) Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2009**, *48*, 2276.
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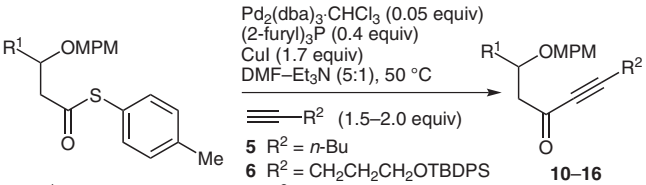
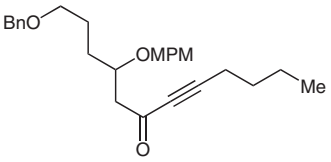
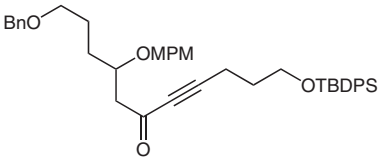
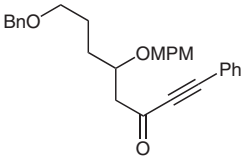
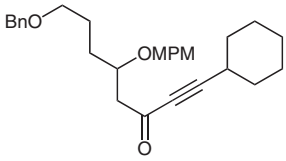
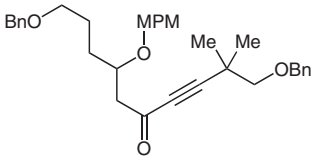
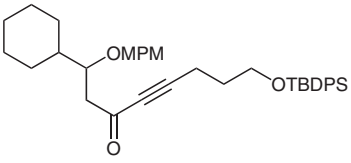
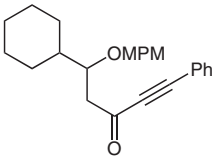
Table 2 Synthesis of Various Ynones



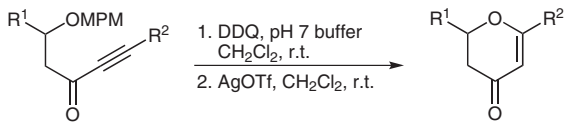
1b $R^1 = CH_2CH_2CH_2OBn$
4 R^1 = cyclohexyl

5 R^2 = *n*-Bu
6 $R^2 = CH_2CH_2CH_2OTBDPS$
7 R^2 = Ph
8 R^2 = cyclohexyl
9 $R^2 = CMe_2CH_2OBn$

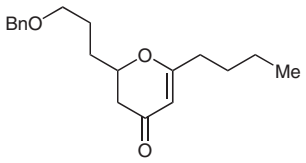
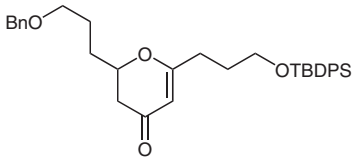
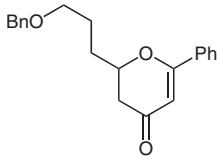
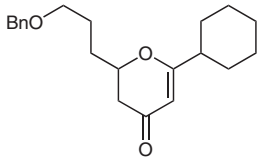
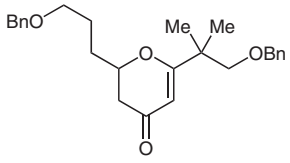
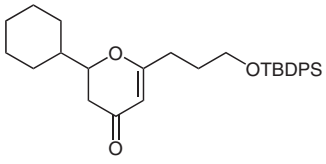
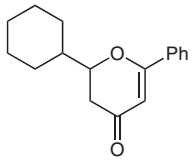
Entry	Thiol ester	Alkyne	Product (yield, %)
1[a]	**1b**	**5**	 **10** 80%
2[b]	**1b**	**6**	 **11** 80%
3[a]	**1b**	**7**	 **12** 82%
4[a]	**1b**	**8**	 **13** 75%
5[b]	**1b**	**9**	 **14** 82%
6[b]	**4**	**6**	 **15** 80%
7[a]	**4**	**7**	 **16** 73%

[a] Conditions: 2.0 equiv of alkyne were used.
[b] Conditions: 1.5 equiv of alkyne were used.

Table 3 Synthesis of Various 2,6-Disubstituted 2,3-Dihydro-4*H*-pyran-4-ones



10–16 **17–23**

Entry	Ynone	Product	Yield step 1 (%)	Yield step 2 (%)
1	**10**	 **17**	85	96[a]
2	**11**	 **18**	92	98[a] 98[b]
3	**12**	 **19**	90	97[a]
4	**13**	 **20**	100	100[a]
5	**14**	 **21**	96	98[a]
6	**15**	 **22**	88	98[b]
7	**16**	 **23**	88	94[a]

[a] Cyclization was performed using AgOTf (1.1 equiv) in CH_2Cl_2 at r.t.
[b] Cyclization was performed using AgOTf (0.1 equiv) in CH_2Cl_2 at r.t.

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(9) For example, see: (a) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997. (b) Nicolaou, K. C.; Frederick, M. O.; Burtoloso, A. C. B.; Denton, R. M.; Rivas, F.; Cole, K. P.; Aversa, R. J.; Gibe, R.; Umezawa, T.; Suzuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 7466. (c) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2008**, *47*, 7927.
(10) **Typical Procedure for Sonogashira Coupling of *p*-Toluenethiol Esters and Terminal Alkynes (Table 2, Entry 1)**
To a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (13.2 mg, 0.0128 mmol), CuI (82.7 mg, 0.434 mmol), and $(2\text{-furyl})_3P$ (23.7 mg, 0.102 mmol) in degassed DMF (1.1 mL) was added a solution of **1b** (118.7 mg, 0.2555 mmol) in degassed DMF (1.1 mL), 1-hexyne (0.059 mL, 0.51 mmol), and Et_3N (0.430 mL). The resultant mixture was stirred at 50 °C for 4.4 h. After being cooled to r.t., the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–10% EtOAc–hexanes) gave ynone **10** (86.7 mg, 80%) as a yellow oil.
Spectroscopic Data for Ynone 10
IR (film): 2930, 2210, 1670, 1513, 1455, 1247, 1095, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 –7.26 (m, 5 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 4.47–4.37 (m, 4 H), 4.00 (m, 1 H), 3.77 (s, 3 H), 3.44 (t, *J* = 5.0 Hz, 2 H), 2.86 (dd, *J* = 7.5, 7.0 Hz, 1 H), 2.63 (dd, *J* = 5.0, 4.5 Hz, 1 H), 2.36–2.29 (m, 2 H), 1.74–1.60 (m, 4 H), 1.58–1.50 (m, 2 H), 1.49–1.36 (m, 2 H), 0.89 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.1, 159.1, 138.4, 130.4, 129.3 (2 C), 128.3 (2 C), 127.5 (2 C), 127.4, 113.6 (2 C), 94.9, 81.2, 74.7, 72.8, 71.1, 70.1, 55.2, 50.6, 31.0, 29.6, 25.4, 21.9, 18.6, 13.4. ESI-HRMS: *m/z* calcd for $C_{27}H_{34}NaO_4$ $[M + Na]^+$: 445.2349; found: 445.2365.
(11) **Typical Procedure for Deprotection and AgOTf-Promoted 6-*endo-dig* Cyclization of β-Alkoxy Ynone (Table 3, Entry 1)**
To a solution of ynone **10** (79.4 mg, 0.188 mmol) in CH_2Cl_2–pH 7 buffer (10:1, v/v, 1.9 mL) cooled to 0 °C was added DDQ (48.4 mg, 0.207 mmol), and the resultant mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. aq $NaHCO_3$ solution. The whole mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–30% EtOAc–hexanes) gave a β-hydroxy ynone (48.5 mg, 85%) as a yellow oil.
Spectroscopic Data for β-Hydroxy Ynone
IR (film): 3427, 2930, 2862, 2210, 1669, 1455, 1362, 1160, 1097 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.25 (m,

5 H), 4.49 (s, 2 H), 4.12 (m, 1 H), 3.49 (t, *J* = 6.5 Hz, 2 H), 3.06 (br, 1 H), 2.69 (d, *J* = 6.0 Hz, 2 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 1.79–1.67 (m, 2 H), 1.63–1.49 (m, 4 H), 1.45–1.37 (m, 2 H), 0.90 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.5, 138.2, 128.4 (2 C), 127.6 (2 C), 127.5, 95.5, 81.0, 72.9, 70.1, 67.3, 52.3, 33.5, 29.6, 25.9, 21.9, 18.6, 13.4. ESI-HRMS: *m/z* calcd for $C_{19}H_{26}NaO_3$ $[M + Na]^+$: 325.1774; found: 325.1770.

To a solution of the above β-hydroxy ynone (38.0 mg, 0.126 mmol) in CH_2Cl_2 (12.6 mL) was added AgOTf (35.5 mg, 0.138 mmol), and the resultant mixture was stirred at r.t. for 3.2 h under exclusion of light. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (30% EtOAc–hexanes) gave 2,3-dihydro-4*H*-pyran-4-one **17** (36.5 mg, 96%) as a yellow oil.

Spectroscopic Data for 2,3-Dihydro-4*H*-pyran-4-one 17

IR (film): 2955, 1666, 1604, 1398, 1099, 737 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 5.29 (s, 1 H), 4.49 (s, 2 H), 4.31 (m, 1 H), 3.50 (t, *J* = 5.0 Hz, 2 H), 2.43–2.30 (m, 2 H), 2.25–2.15 (m, 2 H), 1.89–1.68 (m, 4 H), 1.53–1.46 (m, 2 H), 1.35–1.28 (m, 2 H), 0.89 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.4, 177.9, 138.33, 128.4 (2 C), 127.6 (2 C), 104.1, 104.0, 78.9, 73.0, 69.6, 41.0, 34.5, 31.3, 28.4, 25.3, 22.1, 13.7. ESI-HRMS: *m/z* calcd for $C_{19}H_{27}O_3$ $[M + H]^+$: 303.1955; found: 303.1965.