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Synthesis of Functionalized 4-Methylenetetrahydropyrans by Oxidative Activation of Cinnamyl or Benzyl Ethers

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Abstract

Oxidative activation of benzyl or cinnamyl ether bearing allylsilane derivatives using a catalytic amount of DDQ and 2 equivalents of CAN in the presence of PPTS provided functionalized 4-methylenetetrahydropyrans in good yields and excellent diastereoselectivity. The reaction could be applied to the synthesis of a variety of substituted tetrahydropyran derivatives.

Keywords

Methylenetetrahydropyrans; Sakurai reaction; Cyclization; Stereoselective; Allylsilane

Functionalized 4-methylenetetrahydropyrans are embedded in many biologically important natural products including anticancer agents such as zampanolide, enigmazole A, and phorboxazole.^{1–3} Previous construction of such substituted tetrahydropyran derivatives involved the synthesis of 4-oxotetrahydropyran followed by olefination of the ketone.^{4–7} A number of asymmetric methodologies have been developed over the years that incorporated the *exo*-olefin directly. These include, a Mukaiyama Aldol-Prins cascade reaction developed by Rychnovsky and co-workers,⁸ and intramolecular Sakurai cyclizations by Marko and co-workers,⁹ Keck and co-workers,¹⁰ and Floreancig and co-workers.¹¹ Recently, in the context of our synthesis of (–)-zampanolide, we have developed a related intramolecular oxidative cyclization protocol using DDQ and a Brønsted acid to construct the substituted 4-methylenetetrahydropyran subunit.¹² As shown in Scheme 1, β-cinnamyloxyester **1** was efficiently converted to allylsilane **2**. Treatment of **2** with DDQ and PPTS at –38 °C in acetonitrile for 3 h afforded **3** in 81% yield as a single diastereomer. Encouraged by the observed high diastereoselectivity of the oxidative Sakurai-type cyclization process, we have now investigated the scope of this reaction with a variety of different substrates. Furthermore, we examined this reaction at a lower temperature as well as using a catalytic amount of DDQ along with other stoichiometric oxidants. Herein, we report the results of our studies in which a range of functionalized 4-methylenetetrahydropyrans were

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Supplementary Data

Supplementary data (Experimental procedures and ¹H NMR spectra for all new compounds.) associated with this article can be found in the online version.

synthesized diastereoselectively using a catalytic amount of DDQ and 2 equivalents of ceric ammonium nitrate (CAN).

A number of related oxidative protocols have been reported in the literature. Floreancig and co-workers reported a C-H activation protocol for the synthesis of a 4-oxo-tetrahydropyran with an alkenyl acetate as the intramolecular nucleophilic cyclization group.¹³ She and co-workers recently reported a Prins type methodology and introduced bromine into the pyran ring.¹⁴ For our studies, a model substrate **4a** with allylsilane and cinnamyl ether functionalities was prepared in gram quantities. Our choice of this model was based upon the fact that a cinnamyl ether functionality can be installed readily as described previously.¹²

The etherification substrate, the β -hydroxyester can be conveniently prepared in optically active form utilizing Noyori hydrogenation with very high enantioselectivity.¹⁵ Also, the styrenyl side chain can be selectively differentiated from other olefins for further synthetic manipulation.¹⁶ Allylsilane **4a** was prepared by an aldol reaction of isovaleraldehyde and ethyl acetate followed by etherification and subsequent conversion to the silane derivative as described previously for compound **2**.¹²

As shown in Table 1, we investigated a variety of oxidative C-H activation conditions for an effective Sakurai-type cyclization reaction. We attempted cyclization of **4a** with 1.5 equivalent of DDQ and 1.5 equivalent of InCl_3 in CH_2Cl_2 at -78°C . These conditions, within a 3 h period resulted in 4-methylenetetrahydropyran **5a** in 40% yield (Table 1). Encouraged by this result, we then examined conditions using a catalytic amount of DDQ (20 mol %) and a stoichiometric amount of various oxidants to decrease the amount of organochloride byproducts.¹⁷ We were also interested in using inexpensive and other readily available oxidants. In order to improve oxidant solubility, acetonitrile was used instead of CH_2Cl_2 and the reaction temperature was optimized to -38°C . As can be seen, under these reaction conditions, oxidants KMnO_4 , MnO_2 , and $\text{PhI}(\text{OAc})_2$ were ineffective (entries 2–4). However, the use of a catalytic amount (20 mol %) of DDQ and 2 equivalents of ceric ammonium nitrate (CAN) in the presence of PPTS (2 equiv.) for 16 h provided tetrahydropyran **5a** exclusively in 70% yield after chromatography (entry 5). The presence of PPTS was essential with DDQ/CAN combinations as the corresponding reaction in the absence of PPTS resulted in the decomposition of the starting material (entry 7). Our attempted optimization with pyridine however, resulted in a significantly slower reaction. Thus, PPTS is necessary for this oxidative cyclization, however, the exact role of PPTS is unclear. The assignment of *cis*-stereochemistry was established based upon extensive ^1H -NMR NOESY experiments of **5a**. The stereochemical outcome of this oxidative cyclization can be rationalized based upon the Zimmermann-Traxler¹⁸ transition state **6** shown in Scheme 2. As shown, the C2 cinnamyl substituent in the incipient tetrahydropyran ring assumes an equatorial position which explains the stereochemistry of the newly created asymmetric center in product **5a**.

After optimization of the reaction conditions, we examined the scope of this catalytic process with a variety of allylsilane/benzyl/cinnamyl ether substrates. The results are shown in Table 2. As can be seen, electron rich 4-methoxy cinnamyl substrate provided **5b** in very good yield (entry 1). A furyl allyl substrate under the above catalytic conditions provided significant decomposition of product **5c**. Therefore, this cyclization was carried out using 1.5 equivalents of DDQ to provide **5c** within 30 min in 61% isolated yield. We have also examined a 4-methoxy benzyl derivative which provided **5d** in 81% yield (entry 3). The scope of the reaction was investigated with a benzyl ether side chain and an alcohol side chain. As shown, the sidechain benzyl ether was stable during the cyclization reaction and product **5e** was obtained in 79% yield (entry 4). Also, the cyclization proceeded smoothly in the presence of a primary alcohol (entry 5). Substrates **4g** and **4h** containing vinyl and

chlorine substituents provided very clean cyclization products **5g** and **5h**, respectively (entries 6 and 7). The presence of a bulky *t*-butyl sidechain did not diminish the reactivity and the resulting tetrahydropyran derivative **5i** was obtained in very good yield (entry 8). A PMB type substrate **4j** also gave rise to the cyclized product **5j** in good yield and selectivity (entry 9). The oxidative cyclization also proceeded in a manner of annulation to provide the bicyclic derivative **5k** (entry 10). The reaction with an (*E*)-(3-alkoxybut-1-enyl)benzene substrate afforded tetrahydropyran **5l** with a quarternary center in 63% yield as a mixture (*dr* = 4.7:1) of diastereomers. The mixture was separated by silica gel chromatography and **5l** with *i*-Bu and Me groups being *trans* to each other was the major isomer. After the exploration of cyclization substrate scope, we carried out the cyclization reaction in gram scale using optically active material. Substrate **2** (Scheme 1) was prepared in 97% *ee* as described previously.¹² Subsequent oxidative cyclization was carried out in 1.8 g scale by treatment of **2** with DDQ/CAN/PPTS in acetonitrile at –38 °C to yield the 4-methylenetetrahydropyran derivative **3** in 71% yield and 97% *ee*.

This tetrahydropyran derivative was previously converted to (–)-zampanolide.¹²

In summary, we have developed a useful oxidative protocol for a Sakurai-type cyclization using a catalytic amount of DDQ and 2 equivalents of CAN and PPTS as a promoter. The protocol provides access to a variety of functionalized 4-methylenetetrahydropyrans in very good yield and excellent diastereoselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

1. (a) Tanaka J, Higa T. *Tetrahedron Lett.* 1996; 37:5535–5538. (b) Field JJ, Singh AJ, Kanakkanthara A, Halphi T, Northcote PT, Miller JH. *J. Med. Chem.* 2009; 52:7328–7332. [PubMed: 19877653]
2. Oku N, Takada K, Fuller RW, Wilson JA, Peach ML, Pannell LK, McMahon JB, Gustafson KR. *J. Am. Chem. Soc.* 2010; 132:10278–10285. [PubMed: 20590096]
3. (a) Searle PA, Molinski TF. *J. Am. Chem. Soc.* 1995; 117:8126–8131. (b) Molinski TF. *Tetrahedron Lett.* 1996; 37:7879–7880.
4. (a) Smith AB III, Verhoest PR, Minibiole KP, Lim J. *J. Org. Lett.* 1999; 1:909–912. (b) Smith AB III, Safonov IG, Corbett RM. *J. Am. Chem. Soc.* 2001; 123:12426–12427. [PubMed: 11734051]
5. Louis I, Hungerford NL, Humphries EJ, McLeod MD. *Org. Lett.* 2006; 8:1117–1120. [PubMed: 16524282]
6. Ding F, Jennings MP. *Org. Lett.* 2005; 7:2321–2324. [PubMed: 15932188]
7. Zurwerra D, Gertsch J, Altmann KH. *Org. Lett.* 2010; 12:2302–2305. [PubMed: 20415434]
8. Kopecky DJ, Rychnovsky SD. *J. Am. Chem. Soc.* 2001; 123:8420–8421. [PubMed: 11516301]
9. (a) Marko IE, Bayston DJ. *Tetrahedron Lett.* 1993; 34:6595–6598. (b) Marko IE, Plancher J-M. *Tetrahedron Lett.* 1999; 40:5259–5262. (c) Leroy B, Marko IE. *Tetrahedron Lett.* 2001; 42:8685–8688.
10. Keck GE, Covell JA, Schiff T, Yu T. *Org. Lett.* 2002; 4:1189–1192. [PubMed: 11922815]
11. Aubele DL, Wan S, Floreancig PE. *Angew. Chem.* 2005; 117:3551–3554. *Angew. Chem. Int. Ed.* 2005; 44:3485–3488.
12. Ghosh AK, Cheng X. *Org. Lett.* 2011; 13:4108–4111. [PubMed: 21749032]

13. (a) Tu W, Liu L, Floreancig PE. *Angew. Chem. Int. Ed.* 2008; 47:4184–4187. (b) Tu W, Floreancig PE. *Angew. Chem. Int. Ed.* 2009; 48:4567–4571. (c) Liu L, Floreancig PE. *Org. Lett.* 2010; 12:4686–4689. [PubMed: 20863093]
14. Yu B, Jiang T, Li J, Su Y, Pan X, She X. *Org. Lett.* 2009; 11:3442–3445. [PubMed: 19603799]
15. (a) Noyori R, Ikeda T, Ohkuma T, Widhalm M, Kitamura M, Takaya H, Akutagawa S, Sayo N, Saito T, Taketomi T, Kumobayashi H. *J. Am. Chem. Soc.* 1989; 111:9134–9135. (b) Claffey MM, Hayes CJ, Heathcock CH. *J. Org. Chem.* 1999; 64:8267–8274. [PubMed: 11674747]
16. Zhang W, Carter RG. *Org. Lett.* 2005; 7:4209–4212. [PubMed: 16146389]
17. Cosner CC, Cabrera PJ, Byrd KM, Thomas AM, Helquist P. *Org. Lett.* 2011; 13:2071–2073. [PubMed: 21395252]
18. Zimmerman HE, Traxler MD. *J. Am. Chem. Soc.* 1957; 79:1920–1923.
19. All new compounds gave satisfactory spectroscopic and analytical results (for more details, please see supplementary data). Representative example: **4-Methylenetetrahydropyran 3**: To a suspension of DDQ (147 mg, 20 mol%), PPTS (1.63 g, 6.48 mmol), CAN (3.51 g, 6.48 mmol), and 4 Å MS (3.6 g) in MeCN (120 mL) was added a solution of **2** (1.8 g, 3.24 mmol). The suspension was stirred at –38 °C for 16 hours and quenched with Et₃N (1 mL). The mixture was filtered through a silica gel column with hexanes/ethyl acetate (v/v = 95:5) as the eluent. The concentrated product was purified by silica gel chromatography with hexanes/ethyl acetate (v/v = 95:5) as eluent to give 4-methylenetetrahydropyran **3** as an oil (1.17 g, 71%). The analysis data comply with the reported value.¹² **4-Methylenetetrahydropyran 5a**: To a suspension of **4a** (33 mg, 0.1 mmol) and 4 Å MS (100 mg) in MeCN (4 mL) was added DDQ (4.5 mg, 20 mol%), PPTS (50.4 mg, 0.2 mmol) and CAN (110 mg, 0.2 mmol) at –38 °C. Then the mixture was stirred at –38 °C until TLC showed full conversion. Et₃N (0.2 mL) was added. The mixture was filtered through a short silica gel pad with hexanes/ethyl acetate (v/v = 97:3) as eluent to give crude product that was purified by silica gel chromatography with hexanes/ethyl ether = 97:3 as eluent to give **5a** as colorless oil (17.9 mg, 70%). ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.21 (m, 5H), 6.62 (d, *J* = 16 Hz, 1H), 6.26 (dd, *J* = 5.9, 16.0 Hz, 1H), 4.77 (s, 2H), 3.97–3.93 (m, 1H), 3.46–3.40 (m, 1H), 2.35 (d, *J* = 13.2 Hz, 1H), 2.23 (d, *J* = 13.2 Hz, 1H), 2.15 (t, *J* = 13.2 Hz, 1H), 1.97 (t, *J* = 12.7 Hz, 1H), 1.91–1.83 (m, 1H), 1.64–1.57 (m, 1H), 1.33–1.26 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 144.5, 136.8, 130.1, 128.4, 127.4, 126.4, 108.6, 78.6, 45.3, 41.0, 40.9, 24.3, 23.0, 22.5. IR (thin film, cm^{–1}) 2954, 1732, 1652, 1500, 1315, 1133, 1079, 965, 890, 745, 692. R_f = 0.35, hexanes/ethyl ether = 98:2 UV. MS (EI) *m/z* 256 (M⁺).

Scheme 1. Oxidative cyclization leading to substituted-4-methylenetetrahydro-2H-pyran **3**

Scheme 2.
Possible reaction pathway with a catalytic amount of DDQ.

Table 1

The screening of cyclization conditions.^a

Entry	Condition	Time (h)	Yield (%)
1	DDQ (1.5 equiv), InCl ₃ (1.5 equiv), CH ₂ Cl ₂ , -78 °C	3	40 ^b
2	DDQ (20 mol%), KMnO ₄ (1.5 equiv), PPTS (1.5 equiv) in MeCN, -38 °C	24	<10 ^c
3	DDQ (20 mol%), MnO ₂ (1.5 equiv), PPTS (1.5 equiv) in MeCN, -38 °C	24	< 10 ^c
4	DDQ (20 mol%), PhI(OAc) ₂ (1.5 equiv), PPTS (1.5 equiv) in MeCN, -38 °C	24	< 10 ^c
5	DDQ (20 mol%), CAN (2 equiv), PPTS (2 equiv) in MeCN, -38 °C	16	70 ^b
6	CAN (2 equiv), PPTS (2 equiv) in MeCN, -38 °C	24	NR ^d
7	DDQ (20 mol%), CAN (2 equiv) in MeCN, -38 °C	0.5	decomp

^a All the reactions were carried out in the presence of 4 Å MS.^b Yield after chromatography.^c Conversion yield by ¹H NMR.^d NR, no reaction.

Table 2

Substrate scope of oxidative cyclization.^a

Entry	Product	Time (h)	Yield (%)
1.	5b	16	75
2.	5c	0.5	61 ^b
3.	5d	14	81
4.	5e	16	79
5.	5f	20	73
6.	5g	12	79
7.	5h	16	82
8.	5i	20	79
9.	5j	16	73
10.	5k	10	79

Entry	Product	Time (h)	Yield (%)
11.	 (<i>dr</i> = 4.7:1) 5l	3	63 ^b

^a DDQ (20 mol%), CAN (2 equiv), PPTS (2 equiv), 4Å MS, MeCN, −38 °C.

^b DDQ (1.5 equiv), PPTS (1.5 equiv), 4Å MS, MeCN, −38 °C.