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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5367–5370

Sequential cross-metathesis/phosphorus-based olefination: stereoselective synthesis of 2,4-dienoates

Tapas Paul and Rodrigo B. Andrade*

Temple University, Department of Chemistry, Philadelphia, PA 19122, United States

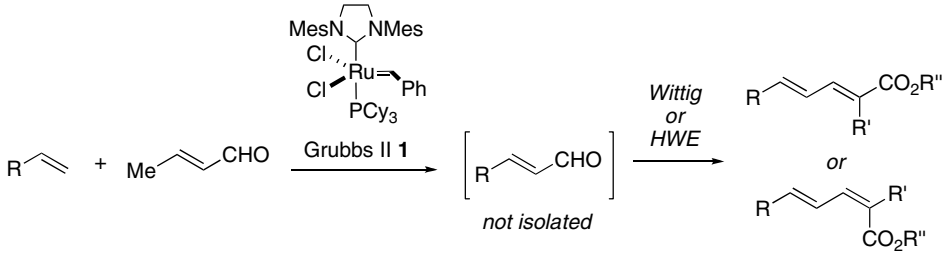
Received 12 April 2007; revised 5 June 2007; accepted 6 June 2007
Available online 9 June 2007

Abstract—A variety of stereodefined 2,4-dienoates have been prepared in a stereoselective manner by sequencing olefin cross-metathesis (CM) with phosphorus-based olefination reactions (Wittig and Horner–Wadsworth–Emmons) in good yield using commercially available reagents.

1. Introduction

The development of both one-pot and tandem reaction sequences is driven by the need to streamline linear synthetic processes.[1] This often translates into an increase in overall product yield resulting from the elimination of intermediary purification steps, which are both time consuming and expensive, particularly when chromatography is required. In order to maximize chemical yield, all reactions in the tandem sequence should ideally be clean and efficient with an emphasis on the first. The identification of reactions that meet these criteria is the first step towards realizing this goal. Olefin cross metathesis[2] has emerged as a powerful method for the stereoselective preparation of carbon–carbon double bonds in high yield, particularly when coupling terminal and electron-deficient olefins.[3] In the presence of commercially available Grubbs Second-generation catalyst[4] **1**, terminal and electron-deficient olefins (e.g., crotonaldehyde) can be coupled in high yield and with high *E*:*Z* selectivity (>20:1). The reaction is typically clean and high-yielding, producing an (*E*)-2-enal, which can be subsequently treated with an appropriate phosphorus-based olefinating reagent (e.g., stabilized phosphorane or phosphonate) in a tandem or one-pot fashion to yield a stereodefined 2,4-dienoate, depending on the conditions employed. The reaction sequence is summarized in Scheme 1.

Traditional syntheses of 2,4-dienoates generally involve the iterative olefination of aldehydes using stabilized Wittig[5] or Horner–Wadsworth–Emmons (HWE)[6] reactions, which often require reduction–oxidation sequences to access key enal intermediates between couplings. The



Scheme 1. Generalized cross-metathesis/phosphorus-based olefination sequence.

Keywords: One-pot; Tandem; Cross-metathesis; Olefination; 2,4-Dienoates.
* Corresponding author. Tel.: +1 215 204 7155; fax: +1 215 204 9851; e-mail: randrade@temple.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.031

use of vinylogous phosphonates certainly is a more efficient alternative.[7] Finally, the chemoselective CM reaction between terminal olefins and 2,4-dienoates[8] has recently been disclosed and applied towards synthesis.[9] While good chemoselectivity is achieved with the (2*Z*,4*E*)-dienoate system, which must also be prepared prior to coupling, (2*E*,4*E*)-dienoates display modest chemoselectivity. Recently, employing 2,4-dienamides obtained from commercially available sorbic acid has ameliorated this problem.[10] Herein we offer a convenient, efficient alternative to the aforementioned methods, which utilizes only commercially available reagents for the rapid assembly of either (2*E*,4*E*)- or (2*Z*,4*E*)-dienoates by modifying the second olefination step.[11]

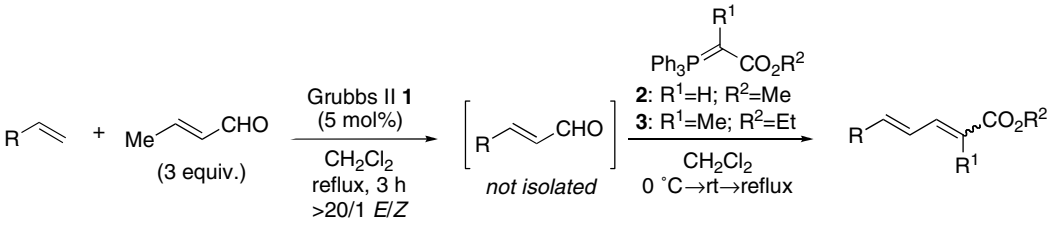
2. Results

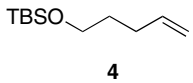
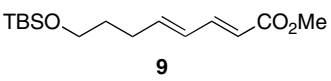
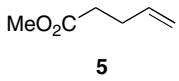
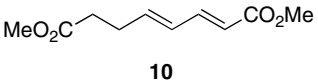
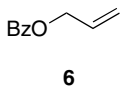
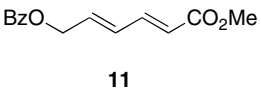
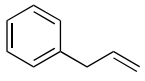
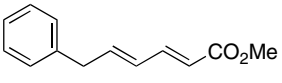
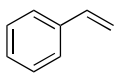
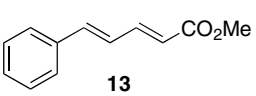
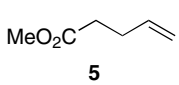
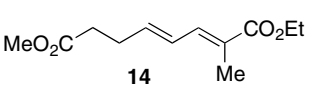
The one-pot CM/Wittig olefination sequence is summarized in Table 1.[12] A variety of terminal olefins were prepared and subjected to 5 mol % **1** and crotonaldehyde in refluxing dichloromethane to effect the first cross-metathesis step. It was determined that refluxing the olefin with an excess (3.0 equiv) of crotonaldehyde for 3 h was the optimal protocol.

The reaction mixture was then cooled to 0 °C, treated with a slight excess of phosphorane **2** and subsequently warmed to rt. While screening conditions for the second step, we discovered that equimolar phosphorane (3.0 equiv) did not result in higher product yields and that 1.2 equiv of either **2** or **3** would suffice. Our hypothesis that excess crotonaldehyde had decomposed over the course of the reaction was supported by the fact that very little methyl sorbate (the byproduct of the Wittig reaction and crotonaldehyde) was isolated from the reaction mixture when 3 equiv of **2** were employed. Yields as high as 77% (see entry 1) were realized with this procedure, corresponding to an average of 88% per step. Upon adding phosphorane **2**, the solution was warmed to room temperature and stirred overnight (12 h). Entry 6 required reflux due to the hindered nature of phosphorane **3**.

All reactions delivered good yields of dienoates **9**–**14** with entry 6 affording a trisubstituted (2*E*,4*E*)-dienoate. The *E*/*Z* geometric isomers were separable by chromatography. While it is known that stabilized phosphoranes are stereoselective for the *E* isomer in the Wittig reaction, we turned our attention to the Horner–Wadsworth–Emmons (HWE) reaction in order to (1) increase

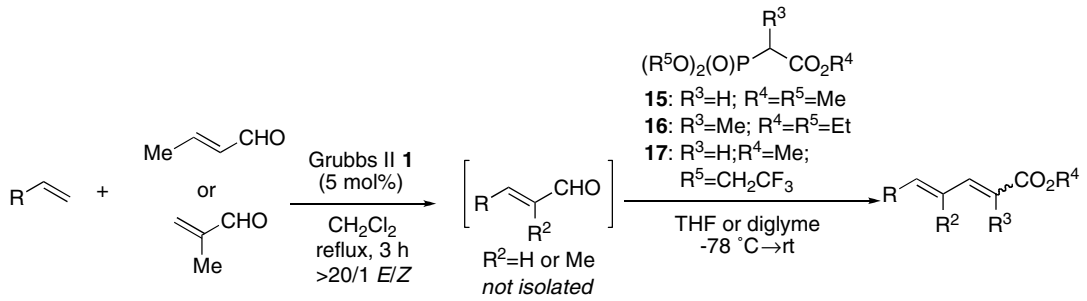
Table 1. One-pot CM/Wittig olefination for the stereoselective synthesis of (2*E*,4*E*)-dienoates



Entry	Olefin	Phosphorane	Product	Yield[a,b] (ratio: 2*E*/2*Z*)[c]
1	 **4**	**2**	 **9**	77% (9:1)
2	 **5**	**2**	 **10**	57% (9:1)
3	 **6**	**2**	 **11**	60% (8:1)
4	 **7**	**2**	 **12**	73% (9:1)
5	 **8**	**2**	 **13**	48% (11:1)
6	 **5**	**3**	 **14**	50% (5:1)

[a] Yields refer to the average of two runs.
[b] Isolated yield of separable *E*/*Z* mixture.
[c] Ratio determined by ^{1}H NMR.

Table 2. Tandem CM/HWE olefination for the stereoselective synthesis of (2*E*,4*E*)-or (2*Z*,4*E*)-dienoates



Entry	Olefin	Aldehyde (3 equiv)	Phosphonate	Product	Yield[a,b] (ratio: 2*E*/2*Z*)[c]
1	TBSO, **4**	Me, CHO	**16**	TBSO, CO_2Et, Me, **18**	83% (20.1)
2	TBSO, **4**	CHO, Me	**15**	TBSO, CO_2Me, Me, **19**	81% (20:1)
3	**8**	Me, CHO	**15**	CO_2Me, **13**	55% (18:1)
4	**8**	Me, CHO	**17**	**20**, CO_2Me	63% (1:6.5)
5	MeO_2C, **5**	Me, CHO	**16**	MeO_2C, CO_2Et, Me, **14**	69% (5:1)

[a] Yields refer to the average of two runs.
[b] Isolated yield of separable *E*/*Z* mixture.
[c] Ratio determined by ^1H NMR.

the stereoselectivity of the olefination step and (2) access the *Z*-enoate by recruiting the Still and Gennari[13] phosphonate **17** (vide infra). Towards this end, we repeated the CM sequence with the olefin substrates albeit in a tandem fashion as HWE reactions are performed in ethereal solvents (e.g., THF or diglyme).[14] The results are summarized in Table 2.[15]

Operationally, the reaction mixtures were concentrated following the CM step and added to phosphonate anions corresponding to **15**–**17** at −78 °C. Yields ranged from 55% (entry 3) to 83% (entry 1), showing the synthetic viability of this tandem sequence. The Still–Gennari olefination with phosphonate **17** delivered (2*Z*,4*E*)-dienoate **20** in 63% yield with a good *Z*/*E* ratio (6.5:1).

In order to expand the scope of this methodology, we wanted to study what other α,β-unsaturated aldehydes could be used in the sequence. While (*E*)-2-methyl-2-butenal failed to react after 12 h under reflux, recourse to methacrolein (3 equiv) resulted in a favourable reaction (entry 2). Olefination with trimethyl phosphonoacetate (**16**) yielded 81% of dienoate **19** with excellent 2*E*,2*Z* selectivity (20:1). Finally, tandem CM/HWE with phosphonopropionate **16** afforded dienedioate **14** in 69% with good 2*E*,2*Z* selectivity (5:1), which was also prepared via the one-pot CM/Wittig (see Table 1, entry 6) albeit in lower yield (50%).

3. Conclusion

We have developed an efficient olefin cross-metathesis/phosphorus-based olefination method either in a one-pot (Wittig) or sequential (HWE) fashion wherein the latter allows ready access to (2*Z*,4*E*)-dienoates in good yield and with good diastereoselectivity. This process streamlines traditional reaction sequences to readily access useful 2,4-dienoates in a stereoselective fashion. We are currently investigating other tandem and one-pot sequences featuring olefin cross-metathesis and those results will be reported in due course.

4. Experimental

4.1. One-pot CM/Witig sequence (Table 1)

Crotonaldehyde (101 mg, 1.45 mmol) dissolved in deaerated CH_2Cl_2 (2.2 mL) was added to a solution of olefin (0.48 mmol) in deaerated CH_2Cl_2 (1.0 mL). Grubbs second-generation catalyst **1** (20 mg, 5 mol %) was added, and the reaction mixture was heated to 40 °C under an

Ar atmosphere for 3 h. The reaction mixture was cooled to 0 °C, and phosphorane **2** (194 mg, 0.58 mmol) was added. The reaction mixture was stirred at rt for 15 h (for entries **2** and **6**, reaction mixture was refluxed for 1 h), concentrated under reduced pressure and purified by flash column chromatography eluting with 2–10% ethyl acetate/hexanes.

4.2. Tandem CM/HWE sequence (Table 2—entries 1, 2 and 5)

NaH (28 mg, 0.69 mmol) was added to a solution of phosphonate (0.69 mmol) in THF or diglyme (5.0 mL) at 0 °C. The reaction mixture was stirred for 30 min. The crude enal (0.48 mmol) derived from the cross-metathesis step (see above experimental) was dissolved in THF or diglyme (3.0 mL) and added to the phosphonate solution. The reaction mixture was warmed to rt and stirred for 15 h. Diethyl ether (10 mL) was added, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with water (2×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 2–10% ethyl acetate/hexanes.

4.3. Tandem CM/HWE sequence (Table 2—entries 3 and 4)

KHMDS (1.06 mL, 0.5 M in toluene, 0.53 mmol) was added to a solution of phosphonate (0.53 mmol) in THF (5.0 mL) at −78 °C. The reaction mixture was stirred for 30 min. The crude enal (0.48 mmol) derived from the cross-metathesis step (see above experimental) was dissolved in THF (3.0 mL) and added to the phosphonate solution. The reaction mixture was stirred at −78 °C for 4 h. Diethyl ether (10 mL) was added, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with water (2×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 2–10% ethyl acetate/hexanes.

Acknowledgements

Financial support of this work by the Department of Chemistry at Temple University is gratefully acknowledged. We thank Dr. Yann Schrodi (Materia, Inc.) for the generous donation of Grubbs II catalyst **1**.

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11. During the review of this manuscript, Snapper published an article concerning the ruthenium-catalyzed tandem cross-metathesis/Wittig olefination of terminal olefins for the synthesis of (2*E*,4*E*)-dienoates: Murelli, R. P.; Snapper, M. L. *Org. Lett.* **2007**, *9*, 1749.
12. Spectral data (^1H and ^{13}C NMR) were in agreement for the following known compounds: Compound **9**: Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Belanger, F. *J. Am. Chem. Soc.* **2004**, *126*, 9926; Compound **10**: Xuan, J. X.; Fry, A. J. *Tetrahedron Lett.* **2001**, *42*, 3275; Compound **11**: Montserrat, C.; de March, P.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron* **1997**, *53*, 16803; Compound **12**: Horsham, M. A.; Class, T. J.; Johnston, J. J.; Casida, J. E. J. *Agric. Food Chem.* **1989**, *37*, 777; Compound **13**: Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, *70*, 5376, Compound **14**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, $J = 11.2$ Hz, 1H), 6.42–6.35 (m, 1H), 6.07–6.00 (m, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.67 (s, 3H), 2.50 (t, $J = 6.4$ Hz, 2H), 2.47–2.43 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 168.4, 139.7, 137.8, 127.0, 126.2, 60.4, 51.6, 33.3, 28.3, 14.2, 12.5; IR (neat): 2982, 2953, 1739, 1703 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{18}O_4 + H^+$, 227.1283; found, 227.1277.
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14. Attempts at transferring a solution of crude enal in dichloromethane from the CM step to an ethereal solution of the appropriate phosphonate anion resulted in lower product yields.
15. Spectral data (^1H and ^{13}C NMR) were in agreement for the following known compounds: Compound **13**: see Ref. 11; Compound **20**: Touchard, F. P. *Tetrahedron Lett.* **2004**, *45*, 5519, Compound **18**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, $J = 11.2$ Hz, 1H), 6.38–6.31 (m, 1H), 6.10–6.00 (m, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.61 (t, $J = 6.0$ Hz, 2H), 2.25 (q, $J = 7.2$ Hz, 2H), 1.91 (s, 3H), 1.68–1.61 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 142.4, 138.4, 126.3, 125.2, 62.2, 60.4, 32.0, 29.6, 25.9, 18.3, 14.3, 12.5, −5.3. IR (neat): 2953, 2930, 1706 cm^{-1}.; HRMS (FAB) calcd for $C_{17}H_{32}O_3Si + H^+$, 313.2199; found, 313.2210. Compound **19**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, $J = 15.6$ Hz, 1H), 5.89 (t, $J = 7.2$ Hz, 1H), 5.78 (d, $J = 15.6$ Hz, 1H), 3.73 (s, 3H), 3.58 (t, $J = 6.8$ Hz, 2H), 2.26 (q, $J = 8.0$ Hz, 2H), 1.76 (s, 3H) 1.65–1.58 (m, 3H), 0.88 (s, 9H), 0.34 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 149.8, 141.8, 133.1, 115.1, 62.3, 51.4, 32.1, 25.9, 25.2, 18.3, 12.0, −5.3; IR (neat): 2952, 2930, 1726 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{30}O_3Si + H^+$, 299.2043; found, 299.2056.