ORGANIC LETTERS

2012
Vol. 14, No. 15
3842–3845

Intermolecular Radical Reaction of *O*,*Se*-Acetals Generated via Seleno-Pummerer Rearrangement

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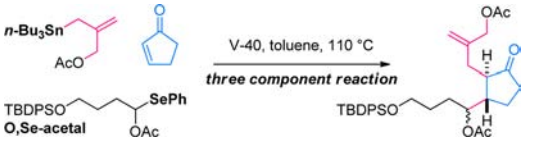
Received May 30, 2012

ABSTRACT



A new general protocol for the synthesis of *O*,*Se*-acetals using the seleno-Pummerer reaction has been developed, and their radical-based two- and three-component coupling reactions were studied. The three-component coupling employed the *O*,*Se*-acetal, cyclopentenone, and an allylstannane derivative, and enabled stereoselective installations of α-acyloxy alkyl and functionalized allyl groups to generate the 2,3-*trans*-disubstituted cyclopentanone in a single operation. The obtained highly functionalized structure was used as an intermediate for facile assembly of the zedoarondiol carboskeleton.

Radical-based carbon−carbon bond formation has long been recognized as a powerful and practical methodology for total synthesis of complex natural products because it exhibits high product yield and chemoselectivity under mild reaction conditions.[1] Among such transformations, we have been particularly interested in three-component radical reactions that enable single-step formation of two new C−C bonds.[2] These multicomponent couplings are suitable for efficient assembly of functionalized carboskeletons, since the reactions maximize the buildup of structural and functional complexity while minimizing the number of synthetic operations.[3]

α-Oxygenated alkyl radicals are extremely useful reactive intermediates for incorporation of oxygen-substituted sp^3 carbon centers onto C=C double bonds and thus are applicable for the construction of multiply oxygenated carboskeletons of natural products. *O*,*Se*-Acetals have been employed as reliable precursors of α-oxygenated radicals, as they are more chemically stable than α-alkoxy alkylhalides (*O*,*X*-acetals, X = Cl, Br, or I) and more reactive than *O*,*S*-acetals. Accordingly, *O*,*Se*-acetals were utilized as versatile substrates for radical cyclizations.[4,5] However, intermolecular reactions of *O*,*Se*-acetals remained unexplored in comparison to their intramolecular counterparts.[6] Here we report the development of a new efficient protocol for synthesis of *O*,*Se*-acetals and their two- and three-component radical reactions. The present three-component reaction allows one-step attachments of

(1) For a recent review, see: Rowlands, G. J. *Tetrahedron* **2010**, *66*, 1593.

(2) Urabe, D.; Yamaguchi, H.; Inoue, M. *Org. Lett.* **2011**, *13*, 4778.

(3) For a recent review, see: Tojino, M.; Ryu, I. Free-radical-mediated Multicomponent Coupling Reactions. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH Verlag: Weinheim, 2005; pp 169−198.

(4) For a recent review on organoselenium compounds, see: Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649.

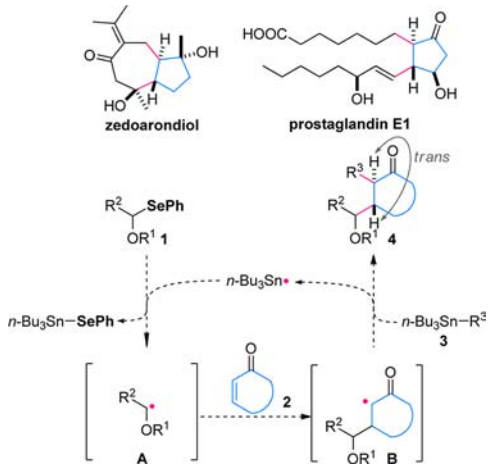
(5) For representative examples of intramolecular radical reactions of *O*,*Se*-acetals: (a) Beckwith, A. L. J.; Pigou, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 85. (b) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 7718. (c) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783. (d) Kumamoto, H.; Ogamino, J.; Tanaka, H.; Suzuki, H.; Haraguchi, K.; Miyasaka, T.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2001**, *57*, 3331. (e) Yamashita, S.; Ishihara, Y.; Morita, H.; Uchiyama, J.; Takeuchi, K.; Inoue, M.; Hirama, M. *J. Nat. Prod.* **2011**, *74*, 357.

(6) For application of intermolecular radical reaction of cyclic *O*,*Se*-acetals in the context of C-glycosylation, see: (a) Abel, S.; Linker, T.; Giese, B. *Synlett* **1991**, 171. (b) Haraguchi, K.; Tanaka, H.; Saito, S.; Yamaguchi, K.; Miyasaka, T. *Tetrahedron Lett.* **1994**, *35*, 9721. (c) SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051. (d) Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870. (e) Liu, Y.; Gallagher, T. *Org. Lett.* **2004**, *6*, 2445. (f) Woodward, H.; Smith, N.; Gallagher, T. *Synlett* **2010**, 869. For a review, see: (g) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700.

10.1021/ol301482f
Published on Web 07/13/2012

two functionalized carbon chains in a stereoselective fashion, and the generated structures will serve as advanced intermediates for synthesis of highly oxygenated natural products.

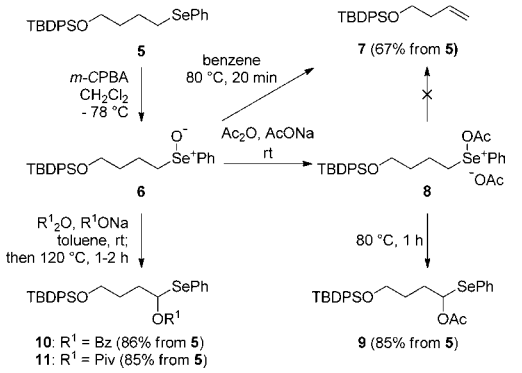
Scheme 1. Plan for Three-Component Coupling Reaction



Our scenario for the three-component reaction between **1**, **2**, and **3** is illustrated in Scheme 1. *O*,*Se*-Acetal **1** would generate alkyl radical **A** by homolytic cleavage of the C–Se bond. The nucleophilic α-oxygenated carbon radical **A** is expected to selectively react with electron-deficient cycloalkenone **2** in the presence of electron-rich tin reagent **3** to generate electron-deficient radical **B**. The R^3 group of **3** would then be introduced from the opposite side of the new carbon chain of **B**, producing *trans*-disubstituted carbocycle **4** in a diastereoselective fashion. Using this methodology, the ring structures of the oxygenated natural products such as zedoarondiol and prostaglandin E1 could be prepared from simple cycloalkenone **2** in a single step. Importantly, this attractive three-component reaction would be realized only when the radical intermediates **A**, **B**, and *n*-$Bu_3Sn^•$ preferentially react with the components **2**, **3**, and **1**, respectively.

To apply *O*,*Se*-acetals to intermolecular reactions, it was a prerequisite for us to develop a concise and general protocol for their preparation (Scheme 2). In this context, we decided to employ a seleno-Pummerer reaction[5d,7,8] because its application would deliver various α-acyloxy phenylselenides from the corresponding phenylselenoxides under neutral conditions. To date, however, seleno-Pummerer reactions have not been fully exploited, mainly due to competing facile olefination of the selenoxide via *syn*-elimination.[9] In fact, selenoxide **6**, which was synthesized from selenide **5** by treatment with *m*-CPBA at −78 °C, underwent elimination at 80 °C within 20 min, clearly demonstrating the thermal instability of **6**. On the other hand, we found that acetylation at room temperature using a reagent mixture of acetic anhydride and sodium acetate completely converted **6** to selenonium salt **8**, which did not undergo *anti*-elimination at 80 °C. Instead, heating of **8** at 80 °C in the same flask resulted in the high-yielding formation of *O*,*Se*-acetal **9** through the desired seleno-Pummerer rearrangement (85% yield from **5**). Reactions of selenoxide **6** with Bz_2O and Piv_2O were also realized without causing elimination, and the obtained selenonium salts were converted to α-benzoyloxy and α-pivaloyloxy phenylselenides **10** (86% yield) and **11** (85% yield), respectively, at 120 °C.

Scheme 2. Seleno-Pummerer Reaction vs *syn*-Elimination



Having optimized the preparative method of the *O*,*Se*-acetals, we demonstrated the high applicability of the seleno-Pummerer reaction using a variety of selenides **12** (Table 1). Acetoxy phenylselenide **13a** was prepared from **12a** without affecting the acid-labile TBS protective group (entry 1). *O*,*Se*-Acetals **13b** and **13c** were generated from homobenzyl selenide **12b** and homoallyl selenide **12c**, respectively (entries 2 and 3), even though *syn*-elimination of the produced selenoxides would afford the stable conjugated olefins.[10] Furthermore, more sterically congested **12d**, **12e**, and **12f** were transformed to **13d**, **13e**, and **13f**, respectively, under the same conditions (entries 4–6). It was practically important that the radical donors **9**, **10**, **11**, and **13a**–**f** were chemically stable upon silica gel purification and irradiation using a desk lamp and necessitated no special precautions in handling.

Next, we explored the intermolecular C–C bond formation between *O*,*Se*-acetals and various electron-deficient

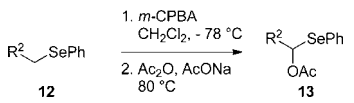
(7) (a) Galambos, G.; Simonidesz, V. *Tetrahedron Lett.* **1982**, *23*, 4371. (b) Fukuyama, T.; Robins, B. D.; Sachleben, R. A. *Tetrahedron Lett.* **1981**, *22*, 4155. (c) Marshall, J. A.; Royce, R. D., Jr. *J. Org. Chem.* **1982**, *47*, 693. (d) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038. (e) Emery, F.; Vogel, P. *Synlett* **1995**, 420.

(8) For selected papers on synthesis of *O*,*Se*-acetals by other methods, see: (a) Dumont, W.; Krief, A. *Angew. Chem., Int. Ed.* **1977**, *16*, 540. (b) Keck, G. E.; Tafesh, A. M. *Synlett* **1990**, 257. (c) Nishiyama, Y.; Yamamoto, H.; Nakata, S.; Ishii, Y. *Chem. Lett.* **1993**, 841. (d) Surowiec, K.; Fuchigami, T. *J. Org. Chem.* **1992**, *57*, 5781. (e) Tingoli, M.; Temperini, A.; Testaferri, L.; Tiecco, M. *Synlett* **1995**, 1129. (f) Myers, A. G.; Gin, D. Y.; Rogers, D. H. *J. Am. Chem. Soc.* **1993**, *115*, 2036. See also refs 5 and 6.

(9) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979.

(10) The low yield of **12c** is attributable to the concomitant formation of 1,3-butadiene, which was not detected due to its volatility.

Table 1. Syntheses of *O*,*Se*-Acetals



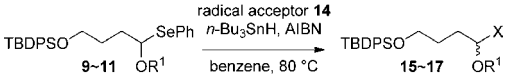
entry	selenide	O,Se-acetal	yield
1	**12a**: $R^2 = (CH_2)_5OTBS$	**13a**	74%
2	**12b**: $R^2 = CH_2Ph$	**13b**	76%
3	**12c**: $R^2 = CH_2CH{=}CH_2$	**13c**	48%
4	**12d**	**13d**	78%
5	**12e**	**13e**	76%[a]
6	**12f**	**13f**	78%

[a] A 1:1 epimeric mixture at the acetoxy-substituted carbon center.

olefins under the reductive conditions (Table 2). The nucleophilic α-acyloxy carbon radicals were effectively generated from Ac (**9**), Bz (**10**), and Piv derivatives (**11**) by treatment with *n*-Bu_3SnH and catalytic AIBN at 80 °C, and all the radicals smoothly reacted with acrylonitrile **14a** to produce **15a**, **16a**, and **17a**, respectively (entries 1−3).[11] In these reactions, slow addition of *n*-Bu_3SnH and AIBN by a syringe pump prevented the direct reduction of the transient α-alkoxy carbon radicals by *n*-Bu_3SnH, and maximized yields of the adducts.[12] Under the same conditions, coupling of **9** with both methyl acrylate **14b** and 1-cyanovinyl acetate **14c** efficiently afforded **15b** and **15c**, respectively (entries 4 and 5). *exo*-Olefin **14d** functioned as a radical acceptor for **9**, leading to 2,3-*trans*-substituted γ-lactone **15d** with complete stereocontrol at C2 (entry 6).[13] Finally, the carbon chain was successfully attached to the cyclic alkenones. Coupling between **9** and cyclopentenone **14e** gave rise to 3-substituted cyclopentanone **15e** in 70% yield (entry 7), while reaction of cyclohexenone **14f** with **9** afforded **15f** in 22% yield (entry 8).

The intermolecular reactions of *O*,*Se*-acetals were then extended to the three-component coupling (Table 3).[14]

Table 2. Intermolecular C−C Bond Formation of *O*,*Se*-Acetals[a,b]



entry	O,Se-acetal	radical acceptor	product and yield
1	**9**	**14a**	**15a**: 86% (R^1 = Ac)
2	**10**	**14a**	**16a**: 72% (R^1 = Bz)
3	**11**	**14a**	**17a**: 80% (R^1 = Piv)
4	**9**	**14b**	**15b**: 72%
5	**9**	**14c**	**15c**: 87%[b]
6	**9**	**14d**	**15d**: 76%[b]
7[c]	**9**	**14e**	**15e**: 70%
8[c]	**9**	**14f**	**15f**: 22%[d]

[a] Conditions: **9**−**11** (1.0 equiv), **14** (1.5 equiv), *n*-Bu_3SnH (2.0 equiv), AIBN (0.4 equiv), benzene (0.02 M), 80 °C. *n*-Bu_3SnH and AIBN (0.2 equiv) were added by syringe pump over 1 h. [b] A 1:1 epimeric mixture at the acetoxy-substituted carbon center. [c] Conditions: **9** (1.0 equiv), **14** (5.0 equiv), *n*-Bu_3SnH (6.0 equiv), AIBN (0.4 equiv), benzene (0.02 M), 80 °C. *n*-Bu_3SnH and AIBN (0.2 equiv) were added by syringe pump over 3 h. [d] Reduced product of **9** was obtained as the major product.

Cyclopentenones **14e** and **14g** were selected as acceptors of the α-oxygenated radicals, and electron-rich allyl tributylstannane derivatives **18**−**20** were used as the trapping agents. Slow addition of allyl tributyltin **18** and AIBN to the refluxing solution of **9** and **14e** in benzene successfully suppressed direct allylation of the α-alkoxy carbon radical and exclusively generated 2,3-*trans*-disubstitued cyclopentanone **21e**[13] in 68% yield (entry 1).

When the radical acceptor **14g** was applied to these conditions (entry 2), 2,3-*trans*-3,4-*trans*-trisubstituted cyclopentanone **21g** was produced (46% yield),[13] indicating that the preexisting stereochemistry of **14g** influenced the selective introduction of the two new stereocenters on the five-membered ring of **21g**. Moreover, functionalized allyl tributyltin derivatives **19**[15] and **20**[16] participated in the three-component reactions. Upon treatment with **9** and **14e** at 110 °C in the presence of V-40, **19** and **20** were transformed to **22e** (68% yield, entry 3) and **23e** (59% yield, entry 4),[13] respectively, both of which have branched carbon chains at C2. Stereoselective formation of the

(11) Reaction of **9** and ethyl vinyl ether, an electron-rich olefin, only gave the reduced product of **9**, indicating nucleophilic character of the α-acyloxy carbon radical.

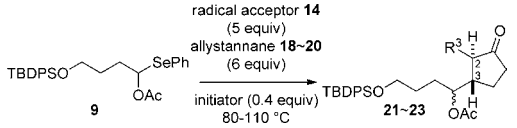
(12) The reaction between **9** and **14a** without using a syring pump afforded **15a** (63% yield) and the reduced product (18% yield).

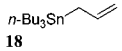
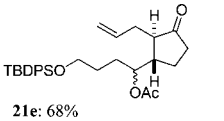
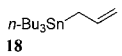
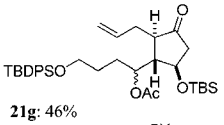
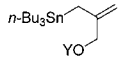
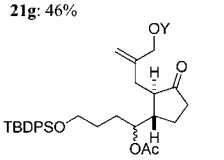
(13) See the Supporting Information for structural determination.

(14) For related examples of three-component radical couplings, see: (a) Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288. (b) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (c) Toru, T.; Watanabe, Y.; Tsusaka, M.; Gautam, R. K.; Tazawa, K.; Bakouetila, M.; Yoneda, T.; Ueno, Y. *Tetrahedron Lett.* **1992**, *33*, 4037. (d) Keck, G. E.; Kordik, C. P. *Tetrahedron Lett.* **1993**, *34*, 6875. (e) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (f) Schaffner, A. P.; Sarkunam, K.; Renaud, P. *Helv. Chim. Acta* **2006**, *89*, 2450.

2,3-*trans*-disubstituted cyclopentanones **21**–**23** proved that the substrates and the radical intermediates reacted in the expected order as depicted in Scheme 1 and demonstrated the efficiency and generality of the present three-component process using *O*,*Se*-acetals.

Table 3. Three-Component Radical-Coupling Reactions[a]

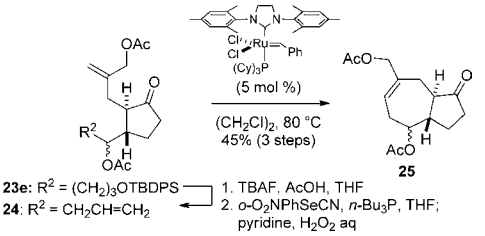


entry	radical acceptor	allystannane	product and yield
1[b]	 **14e**	 *n*-Bu$_3$Sn **18**	 **21e**: 68%
2[c]	 OTBS **14g**	 *n*-Bu$_3$Sn **18**	 **21g**: 46%
3[d] 4[d]	 **14e** **14e**	 **19**: Y = TBDPS **20**: Y = OAc	 **22e**: 68% **23e**: 59%

[a] A 1:1 epimeric mixture at the acetoxy-substituted carbon center. [b] Conditions: **9**, **14e**, **18**, AIBN, benzene (0.1 M), 80 °C. **18** and AIBN (0.2 equiv) were added by syringe pump over 3 h. [c] Conditions: **9**, **14g**, **18**, AIBN, toluene (0.1 M), 110 °C. **18** and AIBN (0.2 equiv) were added by syringe pump over 3 h. [d] Conditions: **9**, **14e**, **19** or **20**, V-40 [1,1′-azobis(cyclohexane-1-carbonitrile)], toluene (0.1 M), 110 °C. **19** or **20** and V-40 (0.2 equiv) were added by syringe pump over 3 h.

By taking advantage of the densely functionalized nature of the three-component adduct **23e**, the *trans*-fused bicyclo[5.3.0]decene structure **25** of anti-inflammatory zedoarondiol[17] (Scheme 1) was constructed in three steps (Scheme 3). Selective removal of the TBDPS group of **23e**, followed by olefin formation through *syn*-elimination of the selenoxide,[18] afforded diene **24**. Finally, the ring closing

Scheme 3. Construction of Bicyclo[5.3.0]decene of Zedoarondiol



metathesis of **24** using the Grubbs' second-generation catalyst[19] gave rise to the tetrasubstituted cycloheptene **25** in 45% yield for three steps.

In conclusion, we developed a general protocol for synthesis of *O*,*Se*-acetals using the seleno-Pummerer rearrangement and demonstrated their mild, yet powerful, radical-based two- and three-component coupling reactions. The α-acyloxy carbon radicals generated from the *O*,*Se*-acetals functioned as nucleophilic radicals, and reliably reacted with electron-deficient olefins, resulting in installation of α-acyloxy alkyl groups. Furthermore, a three-component radical reaction of the *O*,*Se*-acetals, cyclopentenones, and allylstannane derivatives installed two differently functionalized carbon chains in a single step, and was an especially useful method for rapidly increasing complexity of the molecules. The synthetic significance of the three-component reaction was also exemplified by the four-step assembly of the carboskeleton of zedoarondiol from the three simple starting materials. Applications of the developed chemistry to the total synthesis of highly complex natural products are currently underway in our laboratory.

Acknowledgment. This research was financially supported by the Funding Program for Next Generation World-Leading Researchers (JSPS) to M.I. and a Grant-in-Aid for Young Scientists (B) (JSPS) to D.U. We thank T. Ishiyama in our laboratory for synthesis of **14d**.

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

The authors declare no competing financial interest.