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Synthesis of dibromoolefins via a tandem ozonolysis-dibromoolefination reaction

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ABSTRACT

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Keywords: Ozonolysis Dibromoolefination Aldehydes Corey-Fuchs reaction In this Letter we outline the synthesis of a variety of dibromoolefins (DBOs) from a series of alkenes by coupling an oxidative cleavage and a reaction with a phosphorous ylide. This approach strategically avoids isolation of reactive aldehyde intermediates and presents one of the few examples coupling carbon-carbon bond formation with ozonolysis.

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Aldehydes are reactive functional groups that are useful handles for many chemical transformations. One of the most useful examples of this is their reaction with phosphorus ylides to produce alkenes: the Wittig reaction.¹ This reactivity has also been expanded to the synthesis of alkynes,² and dibromoolefins.³ In addition to being employed in the synthesis of terminal alkynes,³ dibromoolefins (DBOs) can be used in the preparation of bromoalkynes-an important starting material for the Cadiot-Chodkiewicz reaction.⁴ DBOs are also used as starting materials in the Suzuki-Miyaura and Stille couplings,⁵ as well as Fritch-Buttenberg-Wiechell rearrangements.6

As part of our ongoing studies to investigate the chemical manipulation of fatty acid methyl esters, we aimed to synthesise 1,1-dibromodecene, 3a, from methyl oleate, 1. The first of two steps (Scheme 1) in our proposed reaction was oxidative cleavage of the carbon-carbon double bond to generate nonanal. 2a. We chose to employ ozonolysis as the preferred oxidative cleavage method because of its relative simplicity, and low toxicity.⁷ However, ozonolysis produces ozonides and hydroperoxyacetals that must be reduced to form the desired aldehyde. Unfortunately, these particular intermediates are unstable and potentially hazardous.⁸ To limit the formation of these undesired products, 1 equiv of *N*-methylmorpholine-*N*-oxide (NMO) can be added to the reaction mixture to form the target aldehydes by reacting with the carbonyl oxide.⁹ We found that this approach was successful in cleaving methyl oleate and producing the desired aldehydes. We also found

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Scheme 1. Synthesis of 1,1-dibromodecene from methyl oleate.

3a

that reducing the amount of NMO from the 3 equiv used by Dussault et al. to 1 equiv did not impact the yield. ¹H NMR analysis of the crude reaction products showed the presence of a peak at 9.77 ppm, consistent with an aldehyde proton and no evidence of a signal consistent with the starting alkene protons. Unfortunately, isolation and subsequent separation of the aldehydes proved impossible. The major product isolated by flash column chromatography (FCC) was nonanoic acid, 4 (Fig. 1). Another product





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Figure 1. Competing products in the isolation of nonanal (2a).

observed when trying to obtain pure nonanal was the nonyl non-anoate, **5** (Fig. 1).¹⁰

To avoid this complication, we chose to explore the possibility of bypassing isolation of the aldehyde and performing ozonolysis and dibromoolefination in one step. Similar strategies have proven successful in the synthesis of alkenes and alkynes from primary alcohols,¹¹ but few examples have been published demonstrating this kind of carbon–carbon bond formation performed in tandem with ozonolysis.¹² A recent publication from Willand–Charnley and Dussault demonstrating tandem ozonolysis and carbon–carbon bond formation highlights the importance of the findings we report here.¹³ To date, all reports of tandem reactions of this type have been limited to terminal olefins and enolates. Here we demonstrate an effective cleavage of internal olefins.

As a model system for this reaction, we investigated the reactions of *trans*-stilbene. It was chosen because, as a symmetric alkene, only a single product would be produced. Furthermore, being relatively electron-rich, it was expected to proceed smoothly through the ozonolysis procedure.

Using 2.0 equiv of each Zn, CBr₄, and PPh₃ (Z/C/P) for each equivalent of aldehyde produced, the reaction was not complete after six days (Table 1, entry 1), as indicated by the presence of two compounds clearly separable using TLC (R_f = 0.35 and 0.62 in 8:1 hexanes:ethyl acetate) as well as a downfield peak in the ¹H NMR at 10.06 ppm, consistent with the presence of benzaldehyde. Of important note, there was no evidence of the *trans*-stilbene starting material in either the TLC or the ¹H NMR analyses.¹⁴ These observations are suggestive of the alkene proceeding efficiently through the ozonolysis and the delay in reaction is likely occurring

in the dibromoolefination. It is also worth noting the ¹H NMR shows no evidence of dimerisation or over-oxidation to benzoic acid.

To reduce the reaction time, the Z/C/P mixture was reacted for 6 h in refluxing dichloromethane (DCM) before addition of the ozonolysis mixture (Table 1, entry 2). After over 7 days of reaction, no dibromoolefin was detected by TLC and the reaction was stopped.

To facilitate a more efficient reaction, the relative proportions of Z/C/P were increased from 2.0 to 2.5 equiv per equivalent of aldehyde (Table 1, entry 3). The yield increased to 79%, and though there was no evidence of an unreacted aldehyde or starting material in the product, the reaction time required for this conversion remained quite long, at 120 h. Increasing the Z/C/P concentrations to 3.0 equiv per equivalent of aldehyde resulted in conversion to dibromoolefin in only 3 h, and the reaction yield increased to 85% (Table 1, entry 8). The resulting product, 1,1-dibromo-2-phenylethene, was isolated as a light yellow oil and required no further purification.

With the reaction conditions optimised, we applied this method to a variety of alkenes to evaluate the generality of the approach (See: Table 2). 3.0 equiv of each Zn, CBr₄, and PPh₃ for each equivalent of aldehyde was reacted for 24 h, after which the alkene was ozonolysed and added to the reaction mixture. The reactions were monitored by TLC and ¹H NMR. It was immediately evident that yields had dropped compared to reaction with *trans*-stilbene; however, they are comparable to the literature yields when a two-step process is employed. No further purification was required for entries 1–4.

Unexpected results were obtained when the starting material was *trans*-4-stilbenemethanol (Table 2, entry 5). Conspicuously absent from the ¹H NMR spectrum were peaks arising from benzylic methylene protons at about δ = 4.8 ppm. The crude ¹H NMR showed the expected peaks associated with 1,1-dibromo-2-phenylethene, as well as an unexpected singlet at δ = 7.57 ppm. To separate this unknown impurity from 1,1-dibromo-2-phenylethene, it was selectively precipitated as a cream-coloured solid at low tem-

Table 1

Reaction conditions used in the synthesis of 1,1-dibromo-2-phenylethene^a

$\begin{array}{c} & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\$				
Entry	Zn/CBr ₄ /PPh ₃ ^b (equiv)	Reaction time ^c (h)	Total time ^d (h)	Yield ^e (%)
1	4.0 ^f	120	146	58
2	4.0 ^{f,g}	_	_	0
3	5.0 ^h	120	167	79
4	6.0 ⁱ	120	165	83
5	6.0 ⁱ	72	118	75
6	6.0 ⁱ	24	48	74
7	6.0 ⁱ	3	26	84
8	6 0 ⁱ	3	27	85

^a General procedure: Zn, CBr₄, PPh₃ were added to an argon filled, flame-dried round bottom flask and then suspended in DCM (0.3 M). The mixture was stirred between 23 and 48 h followed by addition of the post-ozonoylsis mixture by canula. The reaction was stirred until complete, as determined by TLC.

^b Number of equivalents for each Zn, CBr₄, and PPh₃.

^c Reaction time following addition of ozonolysis mixture.

^d Total reaction time including time for reacting the Zn/CBr₄/PPh₃.

^e All yields are for isolated product.

^f 2.0 equiv of each Zn, CBr₄, PPh₃ for 1.0 equiv of aldehyde produced.

^g Zn/CBr₄/PPh₃ was reacted in refluxing DCM.

^h 2.5 equiv of each Zn/CBr₄/PPh₃ for 1.0 equiv of aldehyde produced.

ⁱ 3.0 equiv of each Zn/CBr₄/PPh₃ for 1.0 equiv of aldehyde produced.

Table 2

Tandem ozonolysis-dibromoolefination on alkenes



^a Isolated yields.

perature $(-20-0 \,^{\circ}\text{C})$ in a minimum amount of hexanes. The ¹H NMR showed only two singlets: δ = 7.57 ppm (4H) and δ = 7.49 ppm (2H). The IR spectrum of the sample did not show signals consistent with O–H or sp³ C–H functional groups and the mass spectrum provides a molecular formula of C₁₀H₆Br₄. Based on this data we assert this product is **7** (Scheme 2). Oxidation of the benzylic alcohol during ozonolysis could result in the formation of **6**, which reacts with the excess Z/C/P to form **7**.¹⁵

Having established appropriate conditions for effective tandem ozonolysis–dibromoolefination, we revisited the synthesis of **3** (Table 2, entry 6). The two resulting dibromoolefins, **3a** and **3b**, were separated using flash column chromatography. The large difference between the R_f values of **3a** and **3b**, (0.73 and 0.44, respectively) allowed for effective isolation of the two products. While yields were remained lower than those observed for the *trans*-stilbene reaction (66% for **3a**, 54% for **3b**) they are substantially

higher than those obtained when we employed the two-step procedure. Importantly, this new tandem approach provides the desired products with no evidence of oxidation, degradation, or dimerisation.

In summary, we have shown oxidative alkene cleavage by ozonolysis that can be coupled to a Corey–Fuchs type dibromoolefination and have successfully generated synthetically valuable dibromoolefins. This was achieved while realising good yields without isolating the reactive aldehyde intermediate. We have shown that this method can be applied successfully to a variety of alkenes and that it avoids the potential for concentrating ozonolysis mixtures that still contain ozonides.

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Supplementary data

Supplementary data (experimental details and full characterisation data on all compounds along with the ¹H and ¹³C NMR for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.121.

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Scheme 2. Proposed formation of the unexpected product obtained for reaction with trans-4-stilbenemethanol.

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- For further discussion on oxidation of benzyl ethers see Godfrey, C. R. A. Comprehensive Organic Synthesis–Selectivity, Strategy and Efficiency in Modern Organic Chemistry In Trost, B. M., Fleming, I., Eds.; Elsevier, 1991. Vol. 7.