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Regiocontrol in the Oxidative Radical Fragmentation of Benzilidene Acetals and Its Mechanistic Implications

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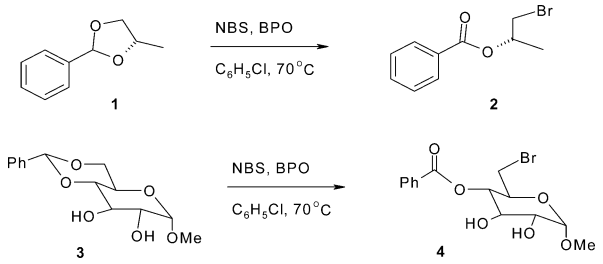
Abstract: The NBS-mediated oxidative fragmentation of benzilidene acetals has been investigated with mechanistic probes **12**, **14**, and **18** designed to discriminate between the possible competitive pathways. Results indicate that fragmentation of the initial benzylic radical **19** does not occur spontaneously but that oxidation proceeds rapidly to give the benzyl bromide **20**, which then fragments via a polar pathway. Reversed regiospecificity in the fragmentation is demonstrated for the first time through the incorporation of an allylic alcohol into the benzilidene acetal.

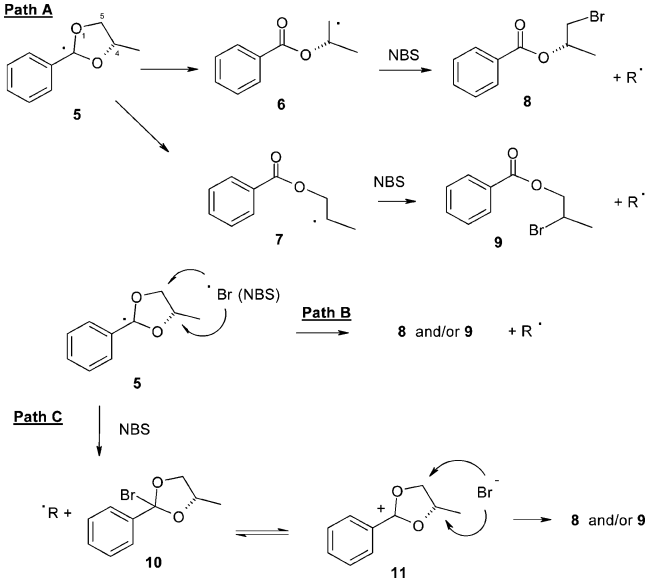
The oxidative fragmentation of benzilidene acetals mediated with *N*-bromosuccinimide (NBS) was described over 50 years ago by Marvell.[1] The overall reaction (Scheme 1) was investigated later by several groups[2] and applied to carbohydrate derivatives by Failla[3] and Hanessian.[4] As shown, simple benzilidene acetals such as the optically active propanediol derivative **1** and the α-methyl-D-gluconopyrano-4,6-benzilidene derivative **3** provide fragments **2** and **4** having the bromine atom on the least hindered position, usually with very high or complete regiocontrol. This result is interesting as it appears radical fragmentation may have occurred via a contra-thermodynamic pathway. The reaction proceeds thermally with the use of NBS alone or, often more efficiently, through the addition of an initiator such as benzoyl peroxide (BPO) or azoisobutyronitrile (AIBN). The reaction is initiated (e.g., from **1**) by H-atom abstraction at the benzilidene position giving the radical **5**, Scheme 2.[2a]

Three different mechanistic pathways, outlined in Scheme 2, have been envisioned for the fate of **5** to account for the products observed. In the original proposal shown as path A,[2a] fragmentation can give two possible radical intermediates **6** and **7** for further propagation with NBS leading to the isomeric bromides **8** and **9**. Alternatively, the radical **5** could be opened by a bromine atom attack at C4 or C5 in a propagation step

SCHEME 1. Reaction of Benzilidene Acetals with NBS



SCHEME 2. Proposed Mechanisms for Benzilidene Acetal Fragmentation with NBS



with NBS (path B), equivalent to the overall free radical process described by Hanessian.[4a] Last, intermediate **5** could be brominated at the benzylic position first via a propagation step followed by an ionic fragmentation pathway (path C). Path A[2a] was initially discounted,[2b] since the products observed from the reaction are usually brominated at the least hindered position which would require radical fragmentation via the contra-thermodynamic pathway. Support in favor of the ionic termination (path C) route was obtained by Hanessian[4c] who isolated products consistent with the trapping of carbocation intermediates by neighboring hydroxyl groups. Despite this, recent evidence from the free-radical-mediated reduction of benzilidene acetals in the presence of thiols is consistent with the direct fragmentation of the initial radical.[5] Due to this apparent contradiction as well as the usefulness of the functionalized products available from this reaction[6] and an appreciation of the large number of radical mediated reactions which have proven

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(2) (a) Huyser, E. S.; Garcia, Z. *J. Org. Chem.* **1962**, *27*, 2716−2719. (b) Prugh, J. D.; McCarthy, W. C. *Tetrahedron Lett.* **1966**, 1351−1356.
(3) Failla, D. L.; Hullar, T. L.; Siskin, S. B. *Chem. Commun.* **1966**, 716−717.
(4) (a) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035−1044. (b) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1045−1053. (c) Hanessian, S.; Plessas, N. R. *J. Org. Chem*, **1969**, 34, 1053−1058.
(5) Roberts, B. P.; Smits, T. M. *Tetrahedron Lett.* **2001**, *42*, 137−140.
(6) (a) Hungerbuhler, E.; Seebach, D.; Wasmuth, D. *Helv. Chem. Acta* **1981**, *64*, 1467−1487. (b) Wood, A. J.; Holt, D. J.; Dominguez, M. C.; Jenkins, P. R. *J. Org. Chem.* **1998**, *63*, 8522−8529.

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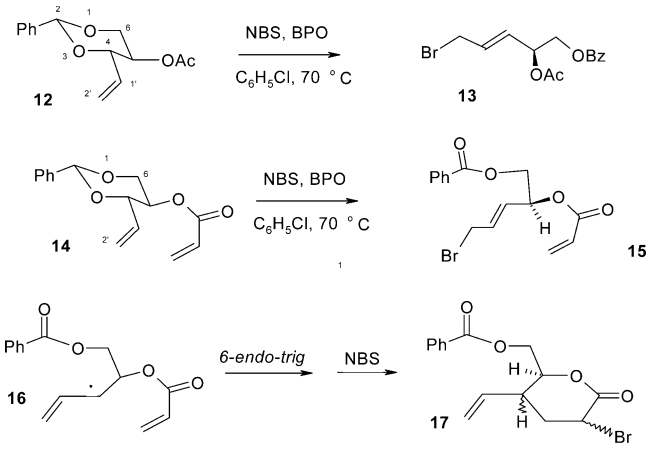
SCHEME 3. Evidence Disfavoring an Open-Chain Radical (Path A)

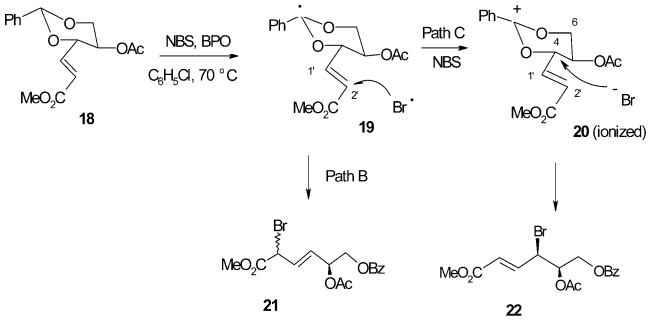


to be of synthetic value,[7] we decided to clarify aspects of the mechanism of this reaction to illuminate its overall scope.[8]

We chose to develop mechanistic probes for the reaction employing substrates derived from the 2,4-benzilidene derivative of D-erythrose, themselves readily available from D-glucose. We first determined that the regioselectivity of the fragmentation was completely reversed by the simple expedient of attaching an olefin allylic to the more hindered position on the acetal, Scheme 3. For example, when **12** was reacted under standard conditions (NBS, BPO(cat.), PhCl, 70 °C, 3 h), the allylic bromide **13** was isolated as the single (*Z*)-isomer. Careful workup and purification gave **13** in 64.2% isolated yield along with 21.5% recovered **12** allowing for 85.7% overall mass balance. No other products were observed; the balance of the material is likely lost to polymerization of starting material and/or product, which is not unexpected. To our knowledge, this is the first time that the regiochemistry of the fragmentation has been altered in this fashion. The reversal of regioselectivity in the opening step mediated by the olefin is likely due to a lowering of the energy of the now allylic σ^* orbital of the O3−C4 bond on the intermediate radical or cation. Product **13** appears to be the result of a concerted bromine radical or bromine anion addition at C2′ on the intermediate benzylic radical or cation respectively in S_N2'-like fashion. The fact that a single olefin is obtained is evidence against an open chain allylic radical (analogous to **7**, path A) through which both allylic isomers as well as possible *E* and *Z* configurational isomers would be expected. This result does not discriminate between the other two substitution pathways outlined (Scheme 2), however.

More definitive evidence against path A was obtained through the second experiment (**14** to **15**) shown in Scheme 3. The acryloyl-substituted olefin **14** was prepared and subjected to our standard fragmentation protocol. If fragmentation of the initial benzylic radical

SCHEME 4. Discriminating Radical Bromine Atom (Path B) or Bromide Anion Mediated Opening (Path C)



to give an open chain radical precedes propagation with NBS (or Br_2), the intermediate radical **16** would be expected to cyclize onto the tethered radicalophile in 6-*endo-trig* or even 8-*endo-trig* fashion, leading to **17** (or isomers). Molecular modeling studies on the fragmented acyclic radical intermediate provide no reasoning why such a cyclization should not occur as either of the radical centers are in close proximity to the β-position of the acrylate. On the other hand, if radical fragmentation does not occur prior to bromine atom or anion attack on the respective intermediate benzylic radical or cation (paths B and C), acyclic substitution products are to be expected. The reaction of substrate **14** proceeded without incident to give a single product readily identified as the allylic bromide **15** (55.2%, 25.3% recovered **14**, 80.5% mass balance). No evidence for any cyclized products was observed; trace polar impurities observed were likely produced through slow hydrolysis of **15**. This result provides strong evidence that under these conditions the initial benzylic radical does not immediately fragment; or at least such fragmentation is considerably slower than the major opening process. The major reaction pathway therefore proceeds through nucleophilic bromine atom or anion opening of the cyclic radical or cation (paths B or C).

Reaction pathways B and C are mechanistically very similar and difficult to unravel, the major difference being whether a bromine atom (propagation with NBS) or bromide anion attacks the activated intermediate. We devised the following experiment to illuminate the subtle difference in reactivity expected in this process for a neutral radical or a polar anion attack on the intermediate. It is well-known that radicals add preferentially to the β-position of enones;[7] however, since they are not subjected to the same electronic constraints as the nucleophilic addition of an anion, they may also add to the α-position of an enone in certain cases where this is mechanistically feasible.[9] Test substrate **18** was prepared (see the Supporting Information) and subjected to the standard reaction, Scheme 4. Given that the propensity for S_N2'-like opening has already been demonstrated, epimeric bromides **21** would be expected (attack at C-2′) if the reaction proceeds through path B. In contrast, if benzylic bromination occurs first following path C and

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(8) Alternative methods for both oxidative and Lewis acid mediated fragmentation of benzilidene acetals have been reported recently; see: (a) Chen, Y.; Wang, P. G. *Tetrahedron Lett.* **2001**, *42*, 4955−4958. (b) Harada, T.; Sekiguchi, K.; Nakamura, T.; Suzuki, J.; Oku, A. *Org. Lett.* **2001**, *3*, 3309−3312.

(9) For an example of radical addition at the α-position of an α,β-unsaturated ester in a cyclic carbohydrate dervivative, see: Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. *Tetrahedron Lett.* **1989**, *30*, 2829−2832.

fragmentation proceeds through the purely ionic path from **20**, then a direct S_N2 displacement of bromide at C4 would be expected giving **22**. In other words, the intrinsic polarity of the unsaturated ester can be used to impede bromide anion attack at the C2′-position. In the event, benzilidene **18** underwent fragmentation under the standard conditions to give bromide **22** (61%, 15.5% recovered **18**, 76.5% mass balance) as a single isomer. Compound **22** is consistent with the direct S_N2-like displacement proceeding with inversion at C4 through bromide anion attack on the cyclic cation, fully supporting the hypothesis that path C is operative here. It is also worth noting that the overall regioselectivity of the opening step is dominated by the presence of the allylic C−O acetal bond as no primary bromide (**20**, bromide attack at C6) was detected in this process.

Overall, taken together with the earlier results of Hannessian,[4] the evidence suggests that the NBS-mediated fragmentation proceeds through path C outlined above terminating through an ion-pair recombination involving a formal *antarafacial* 1,3-bromide shift. The S_N2-like opening is also in accord with earlier studies reported by King[10] in the trapping of similar cations. We conclude that in the presence of NBS, the rate of chain transfer from radical **19** with NBS to give the benzyl bromide **20** is faster than direct fragmentation, whereas in the absence of NBS, the direct radical fragmentation pathway is operative allowing trapping of open-chain radicals.[5] Last, from a synthetic viewpoint, the regiospecific and stereoselective fragmentations described through incorporation of an allylic alcohol into the benzilidene allows for the reversal of regioselectivity in this reaction and the resulting preparation of densely functionalized chirons such as **13**, **15**, and **22** in a few steps from D-glucose.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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