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Efficient Synthesis Of Photolabile Alkoxy Benzoin Protecting Groups

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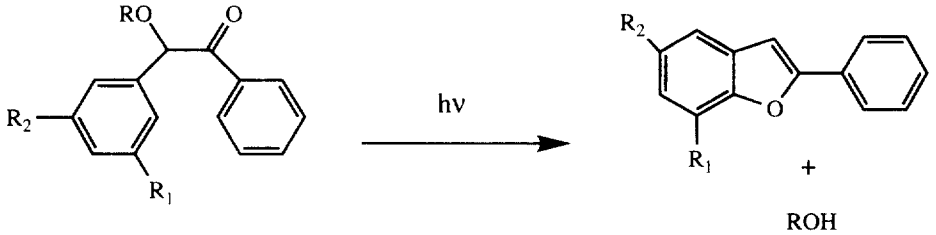
Abstract: *An effective implementation of the Corey-Seebach dithiane addition for the synthesis of photolabile alkoxy benzoin adducts is reported. The method allows for the facile synthesis of photolabile 3',5'-dimethoxybenzoin protected compounds in near quantitative yield and is general in that it can be used for the synthesis of both symmetrical and unsymmetrical benzoins. Importantly, the dithiane intermediate reported is a versatile starting material for the synthesis of many photolabile compounds and should serve as a useful protecting group in complex synthetic schemes requiring multiple orthogonal protecting groups.*

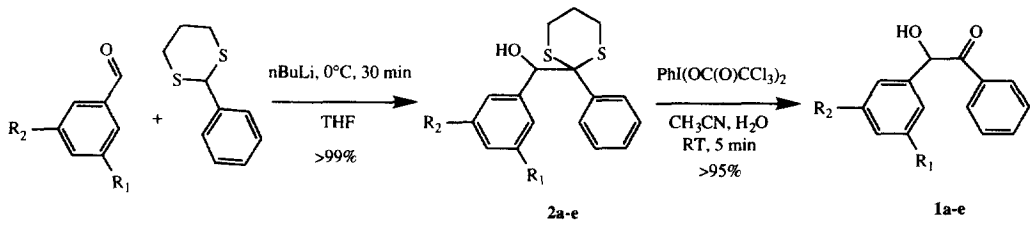
The use of protecting groups in organic synthesis has been invaluable in allowing the complete synthesis of numerous complex organic molecules.[1] A number of protecting groups in organic synthesis have the convenient property that they can be removed photochemically. In an early paper, Woodward described the synthesis and photocleavage properties of a series of substituted nitrobenzyl protecting groups.[2] Subsequently, such protecting groups have played important roles in synthetic strategies, as well as being exploited for use in such diverse fields as semiconductor lithography[3] and the study of rapid enzymatic processes.[4,5]



Eq. 1

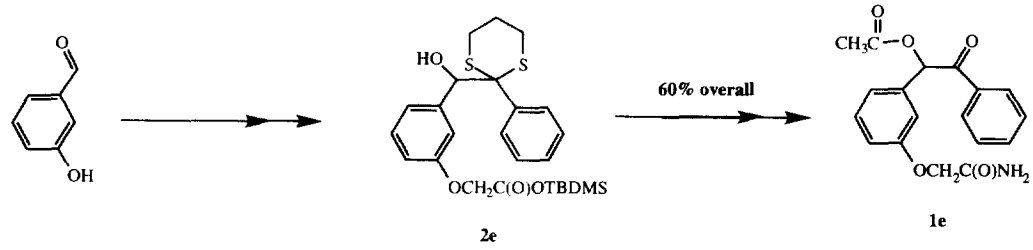
One class of protecting groups that have seen less use are the substituted benzoins **1a-e**, initially reported by Sheehan et al.[6] Of particular interest are the substituted alkoxybenzoins which have quite remarkable photocleavage properties. An example is the 3',5'-dimethoxybenzoin (3',5'-DMB) protecting group which undergoes a photoinitiated cyclization and cleavage, Eq. 1, with a rate constant estimated to be greater than 10^{10} sec^{-1} and a quantum efficiency of 0.64, where R is acetyl. Such a protecting group is of

considerable interest, not only in synthesis, but also for the study of rapid enzyme kinetics and several recent papers have described the use of the 3',5'-DMB as a protecting group in oligonucleotide synthesis,[7] and for 'caged' substrates.[8,9,10] Advantages of the 3',5'-DMB versus substituted nitrobenzyl protecting groups are the rapid release rate, high quantum yield, and the easily detectable, nonreactive, benzofuran photoproduct.



Scheme 1

While the 3',5'-DMB protecting group has many advantages, there are two distinct disadvantages to using such a protecting group. First, while considerable effort has gone into the synthesis of acyloins,[11] many of these methods have proven to be inefficient for a number of targeted acyloins, in particular 3',5'-DMB. Secondly, due to the remarkable photocleavage properties of the 3',5'-DMB protecting group, photolysis occurs in standard laboratory light and samples must be keep in complete darkness, thus making subsequent synthetic transformations cumbersome. Herein we describe the effective implementation of the Corey-Seebach dithiane addition for the synthesis of benzoins (**scheme 1**) via the dithiane protected adduct **2**. As examples, we targeted several benzoins whose synthesis has been reported to give poor or no yield via traditional methods (**2c** and **2d** from ref. 11). We further report that the dithiane adduct **2a** serves as a very convenient synthon for the introduction of the 3',5' DMB photocleavable protecting group. In such a manner, complex protected molecules can be synthesized that remain photochemically stable until the desired conversion of the dithiane moiety to the parent ketone is accomplished. As an example, we synthesized O-acetyl-3'-carbamylmethoxybenzoin (**1e**) in 6 steps, (**scheme 2**) from starting 3-hydroxy benzaldehyde, via the intermediate 3'-TBDMSO-dithiane protected benzoin (**2e**) with an overall isolated yield of 60%.



Scheme 2

In pursuing the synthesis of 3',5' DMB a number of synthetic methods (A-I of Table, see note 17) were attempted.[5,11,12] These methods, while effective, gave poor to moderate yields of the desired benzoin, Table, and were deemed inefficient for our purposes. The final method involves the addition of the 2-phenyl-1,3-dithiane lithium anion (PDLA) to 3,5-dimethoxybenzaldehyde in THF according to the procedures described by Corey and Seebach[13] (Method I). Previous investigators had reported that a similar method gave poor yields of the desired benzoin.[14] In our hands, however, the PDLA readily reacted with the aldehyde to give a quantitative yield of the dithiane adduct **2**. Subsequent deprotection (**scheme 1**) using a variety of standard methods[15] smoothly converts the dithiane adduct to the desired benzoin in near quantitative yields. To demonstrate the utility of this method we have synthesized benzoins **1b-1e** via the dithiane adduct in excellent yields (**Table**).

Table. Synthesis of Benzoins

Benzoin	Method[a]	% Yield Dithiane[b]	%Yield Benzoin	Lit. %Yield (ref 6,8,9,10,11)
3',5' Dimethoxy (**1a**)	A-H (see text)	----	0-55	0-61
same	I (this work)	**>99**	**96**	----
4'-Methoxy (**1b**)	I	**97**	**99**	----
same	A	----	----	50-74
2'-Ethoxy (**1c**)	I	**>99**	**97**	
same	A	----	----	14
2'-Methyl (**1d**)	I	**>99**	**95**	
same	A	----	----	15
3'-TBDMSO (**1e**)	I	**93**	**98**[c]	

a) Cf. text and note 16 **b**) Determined from GC/MS analysis using an HP4100 GCMS equipped with a 10 meter silicon gum column **c**) Yield determined for the O-acetyl-3'-carbamylmethoxybenzoin, see text.

In conclusion, we have demonstrated that the Corey and Seebach dithiane addition is a simple and efficient method for the preparation of both symmetrical and unsymmetrical substituted benzoins. Since most aldehydes can be converted to dithiane adducts using standard methods, it is expected that virtually any set of benzaldehydes may be coupled in this manner to afford the desired benzoin. Furthermore, the stable and nonphotolabile dithiane adducts serve as convenient intermediates in the synthesis of complex molecules incorporating the alkoxy benzoin protecting group (**scheme 2**), which would otherwise be difficult and cumbersome to prepare. The full details of this method and further examples of its utility will be reported elsewhere.[17,18]

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References and Notes

1. Greene, T. W. Protective Groups in Organic Synthesis, John Wiley and Sons, Inc: New York.**1991**.
2. Patchornik, A.; Amit, B.; Woodward, R.B. *J. Am .Chem. Soc.* **1970**, *92*, 6333.
3. Sabomgi, G. J. *Chemical Triggering*, Plenum: **1987**.
4. Gurney, A. M.; Lester, H. A. *Physiol. Rev.* **1987**, *67*, 583.
5. McCray, J. A.; Trentham, D. R. *Annu. Rev. Biophys. Chem.* **1989**, *18*, 239.
6. Sheehan, J. C.; Wilson, R.M.; Oxford, A.W. *J.Am. Chem. Soc.* **1971**, *93*, 7222.
7. Pirrung, M. C.; Bradley, J-C. *J. Org. Chem.* **1995**, *60*, 1116.
8. Baldwin, J. E.; McConnaughie, A. W.; Moloney, M. G.; Pratt, A. J.; Shim, S. B. *Tetrahedron*, **1990**, *46*, 6879.
9. Corrie, J. E. T.; Trentham, D. R. *J. Chem. Soc. Perkin. Trans. 1*, **1992**, 2409.
10. Pirrung, M. C.; Shuey, S. W. *J. Org. Chem.* **1994**, *59*, 3890.
11. Harrison, I. T.; Harrison, S. Compendium of Organic Synthetic Methods, Vol II; John Wiley and Sons, Inc: New York, **1974**; pp 302-307. Hegedus, L.S.; Wade, Jr., L.G.; Compendium of Organic Synthetic Methods, Vol III John Wiley and Sons, Inc: New York, **1977**; pp 366-369. Wade, Jr., L.G.; Compendium of Organic Synthetic Methods, Vol II; John Wiley and Sons, Inc: New York, **1980**; pp 375-379.
12. Krepski, L.R.; Heilmann, S.M.; Rasmussen, J.K. *Tetrahedron Letters*, **1983**, *24*, 38 4075.
13. Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075.
14. Lee, R. A., *U.S. Pat.*, **1984**, 4-469-774.
15. Ibid. ref. 1, pages 203-205.
16. **Method A**: A standard benzoin condensation between 3,5-dimethoxybenzaldehyde and benzaldehyde was unsuccessful in accord with previously reported results, ref 11. **Method B**: Benzoin condensation using phenylmagnesium bromide and the cyanohydrin of the desired aldehyde, yields 12-27%. **Method C**: Synthesis via the corresponding 3',5'-dimethoxydesoxybenzoin was also attempted using a variety of methods. Oxidation with iodosobenzoic acid and hydrolysis of the corresponding epoxide afforded a mixture of diastereomers in 30-50% yield. **Method D**: 3',5'-dimethoxydesoxybenzoin was treated with one equivalent of I_2 in the presence of light, TMSCl, AcOH, or DMAP gave no reaction **Method E**: 3',5'-dimethoxy-desoxybenzoin was treated with 1 equivalent of Br_2 in DCM, a quantitative yield of the ring brominated product was formed. **Method F**: 3',5'-dimethoxydesoxybenzoin was treated with 1.1 equivalents of thionyl chloride at room temp in CCl4. A high yield of the ring halogenated product was isolated. **Method G**: Similar to the method of Krepski et al. (ref. 12) except that the O-TMS cyanohydrin of 3,5-dimethoxybenzaldehyde was generated by treatment of the benzaldehyde with 1.1 equivalents of KCN and TMSCl in CH_3CN at room temperature, yields 34-40%. **Method H**: Procedure was identical to that described by Krepski et al. reference 13, yields 42-55%. **Method I**: A solution of 2-phenyl-1,3-dithiane (390mg, 2mM) in 20mL of dry THF was cooled to 0 C ° and 1.01 equivalents of nBuLi was added dropwise via syringe with rapid stirring. This solution was allowed to stir for 30 min and then 1.0 equivalents of the desired benzaldehyde, dissolved in 1ml dry THF, was added dropwise. The solution was allowed to warm to room temperature and stir for 1 hr. The reaction is quenched by the addition of aqueous NH_4Cl, THF solvent is removed in vacuo and the resultant slurry extracted with dichloromethane. The DCM was washed with 2x20mL of water and solvent removed in vacuo to yield a pale yellow oil. The obtained oils typically crystallize upon standing and are greater than 99% pure based on GC/MS, H^1 NMR and TLC. As such, they can be used for further synthetic transformations without purification .
17. Stowell, M. H. B. et al. manuscript in preparation.
18. Rock, R. S. and Chan, S. I. *J. Org. Chem.* submitted.

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