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N,Se-Acetals: Easy Preparation and Application to Radical Mediated EPC Synthesis

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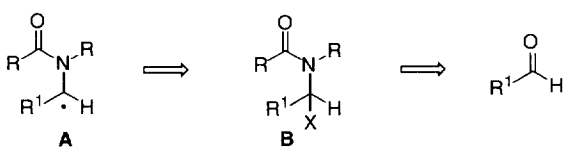
Abstract: A facile synthesis of N,S- and N,Se-acetals starting from aldehydes and primary amines is presented. These acetals are used as precursors for radical reactions. The stereoselectivity of the reactions depends on the radical trap used.

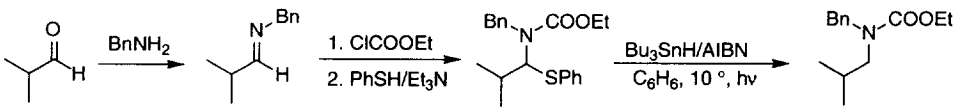
1-Amidoalkyl radicals (**A**) are promising reactive intermediates which can be used for the synthesis of alkaloids and unusual amino acids.[1] Their use is still sparse because of the lack of a general method of generation. The homolysis of a C-halogen (**B**) bond represents the most straightforward method, however, this approach is strongly limited by the instability of the precursors when X = halide.[2] Sulfides and selenides are good substitutes to halides, however, up to now, the preparation of N,S- and N,Se-acetals from carbonyl compounds is limited to highly reactive aldehydes such as formaldehyde[3] and glyoxylates.[4] Arya[5] has developed a more general method by converting carbonyl compounds into thiazolidine derivatives, this method suffers from the presence of a substituted ethyl residue at nitrogen which cannot be easily removed after the radical reaction. We report here our investigations about the conversion of aldehydes into N,S- and N,Se-acetals and preliminary results of their use in stereoselective radical reactions and in EPC synthesis (= synthesis of enantiomerically pure compounds) .



A **B**

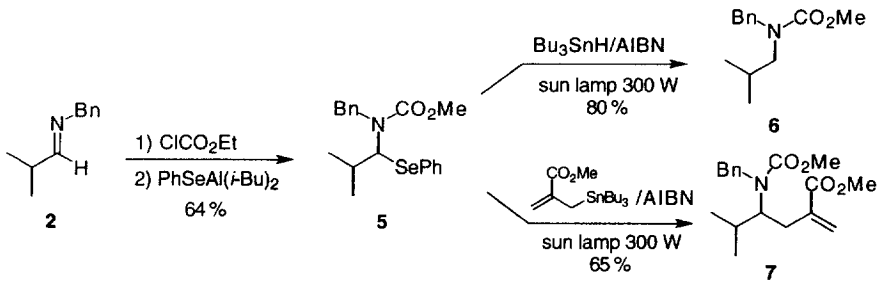
The first strategy investigated is based on the formation of intermediate N,O-acetals[6] which can be easily transformed into N,S-acetals according to literature procedures[7]. N,O-acetals can be obtained from aldehydes by the procedure of Böhme and Hartke:[8] the aldehyde is first converted into an imine which gives an N,O-acetal upon treatment with ethyl chloroformate and methanol/Et_3N. Preliminary experiments with isobutyraldehyde **1** show that the isolation of the intermediate N,O

-acetal is not necessary. Direct treatment of the imine **2** with ethyl chloroformate and thiophenol gives the N,S-acetal **3** in 40 % yield.



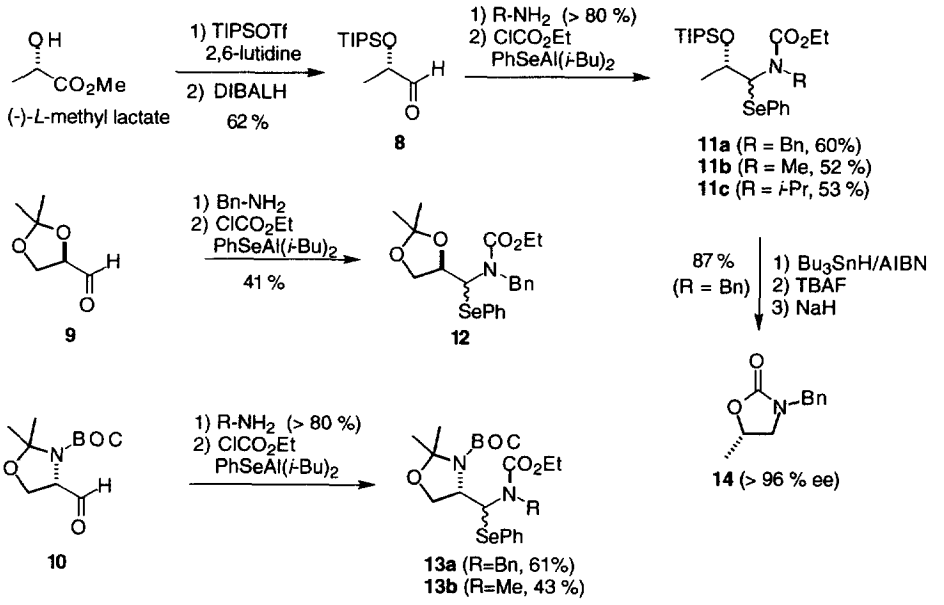
1 **2** **3** **4**

Irradiation of **3** with a 300 W sun lamp in the presence of Bu_3SnH/AIBN gives the desulfurized **4** in 86 % yield proving that N,S-acetals are suitable precursors for radical generation. However, the reduction is very slow (12 h) and the radical precursor **3** is not suitable for the formation of C-C bonds using the Pereyre/Keck allylation procedure.[9] This problem can be overcome by using an N,Se-acetal as a radical precursor. Reaction of **2** with ClCOOEt followed by PhSeH/Et_3N gives the expected N,Se-acetal **5**. Better results are obtained when diisobutylaluminum benzeneselenolate (PhSeAl*i*-Bu_2), prepared by reduction of diphenyldiselenide with DIBALH,[10] is used as a nucleophile. N,Se-Acetal **5** is isolated in 64 % yield. Reduction of **5** in the presence of Bu_3SnH/AIBN is fast (1 h) and gives carbamate **6** in good yield. The reaction of **5** with 2-(methoxycarbonyl)propenyltributylstannane is now possible and provides **7** in 65 % yield.

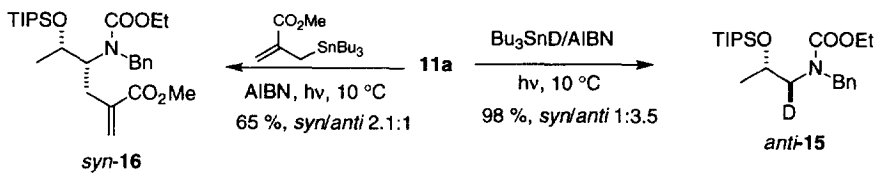


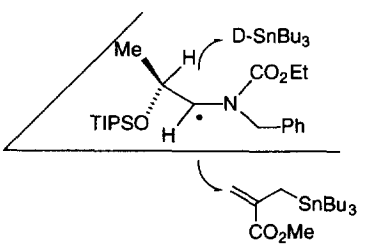
2 **5** **6** **7**

Next, we turn our attention to precursors derived from chiral aldehydes **8** (prepared from *L*-lactic acid), **9** and **10**. In all cases, the N,Se-acetals are obtained with satisfactory yields and different amines have been successfully used.[11] After reduction of **11a** (Bu_3SnH/AIBN) and straightforward transformation into the oxazolidinone **14**, we have shown by capillary gas chromatography on a chiral column (30 % *diacetoxygamma* in *OV-1701*) that the optical purity of the final product is preserved (over 95 % ee).



The stereoselectivity of the radical reactions using **11-13** is actually under investigation. The first results have shown an interesting dependence on the nature of the radical trap suggesting that stereoelectronic effects play an important role. For instance, **11a** is preferentially reduced with Bu_3SnD to *anti*-**15** (98 % yield, *syn/anti* 1:3.5). On the other hand, reaction of **11a** with [2-(methoxycarbonyl)propenyl]tributylstannane gives preferentially *syn*-**16** (62 %, *syn/anti* 2.1:1).[12]





minimum energy conformation of the radical

The selectivity for the deuteration reaction can be explained with the $A^{1,3}$ strain model,[13] where the radical reaction occurs *anti* to the bulky triisopropylsilyloxy group. The reversed selectivity for the

allylation reaction is not clear at the moment, however stereoelectronic effects (attack *anti* to the C-Me bond) and steric interactions with the benzyl protective group, which can be out of the plane of the radical, seem to be involved.

In conclusion we have presented a general method for the synthesis of N,S- and N,Se-acetals starting from aldehydes. The N,Se-acetals are excellent precursors for radical reactions. Almost no racemization occurs during the synthesis of these acetals which subsequently makes them promising precursors for EPC synthesis.

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REFERENCES AND NOTES

1. For a recent review on 1-amino and 1-amidoalkyl radicals see: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913-926.
2. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689-2692.
3. See for exemple: Nedugov, A. N.; Pavlova, N. N.; Usmanova, Z. R. *Zh. Org. Khim.* **1994**, *30*, 70-72. Anciaux, A.; Eman, A.; Dumont, W.; Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1975**, 1613-1616. Pollak, I. E.; Grillot, G. F. *J. Org. Chem.* **1966**, *31*, 3514-3516. Grillot, G. F.; Felton, H. R.; Garrett, B. R.; Greenberg, H.; Green, R.; Clementi, R.; Moskowitz, M. *J. Am. Chem. Soc.* **1954**, *76*, 3969-3971.
4. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2693-2694.
5. Arya, P.; Wayner, D. D. M. *Tetrahedron Lett.* **1991**, *32*, 6265-6268. Arya, P.; Lesage, M.; Wayner, D. D. M. *Tetrahedron Lett.* **1991**, *32*, 2853-2856.
6. N,O-acetals can also be obtained from amides by electrochemical oxidation: Shono, T. *Electrochemistry as a New Tool in Organic Synthesis*; Springer: Berlin, 1984. The efficiency of this approach is however weakend by the formation of regioisomers when unsymmetric secondary amines are employed.
7. See for exemple: Burnett, D. A.; Choi, J. K.; Hart, D. J.; Tsai, Y. M. *J. Am. Chem. Soc.* **1984**, *106*, 8201-8209 and references cited therein.
8. Böhme, H.; Hartke, K. *Chem. Ber.* **1963**, *96*, 600-603.
9. Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *61*, C33-C35. Keck, G.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079-4094.
10. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831-2843.
11. General procedure: the imine (5.0 mmol) in dry Et_2O (5 ml) was cooled to 0° under N_2. A soln. of ethyl chloformate (5.0 mmol) in dry Et_2O (5 ml) was added dropwise. The reaction mixture was stirred for 3 to 6 h at r.t. and was then cooled to -10°. A 1M solution of diisobutylaluminum benzeneselenolate in toluene (5.5 ml, prepared from 1M DIBALH (5.5 ml) and diphenyldiselenide (2.75 mmol)) was added dropwise and the clear yellow soln. was stirred at -10° for 1 h. The reaction mixture was treated with MeOH/H_2O (1:2.5, 0.8 ml) and the solution was filtered through Celite . The Celite was washed with Et_2O and the filtrate was washed with water and brine. Drying ($MgSO_4$), concentration and chromatography of the crude product on silica gel afforded the desired N,Se-acetals.
12. For a typical procedure, see: Renaud, P.; Stojanovic, A. *Tetrahedron Lett.* **1996**, *37*, 2569-2572.
13. For a recent review on the $A^{1,3}$ strain model in radical chemistry see: Giese, B.; Damm, W.; Batra, R. *Chemtracts: Org. Chem.* **1994**, *7*, 355-370. For examles with amino substituted radicals, see ref. 12 and: Damm, W.; Hoffmann, U.; Macko, L.; Neuburger, M.; Zehnder, M.; Giese, B. *Tetrahedron* **1994**, *50*, 7029-7048. Lesage, M.; Arya, P. *Synlett* **1996**, 237-238.

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