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β-Alkoxyacrylates in Radical Cyclizations: Remarkably Efficient Oxacycle Synthesis

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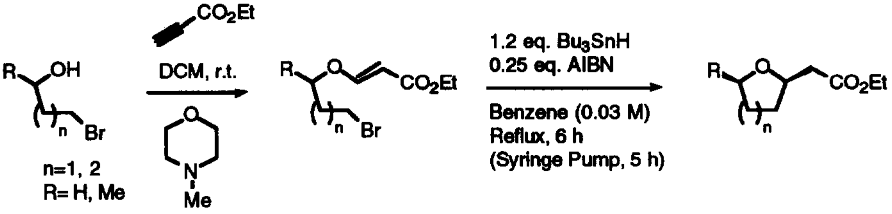
Abstract : β-Alkoxyacrylates were found to be exceptionally efficient radical acceptors in radical-mediated intramolecular cyclizations. For example, reaction of 5-bromo-2-pentanol with ethyl propiolate, tributylstannane-mediated radical cyclization, and hydrolysis yielded (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid, a known component of civet.

Oxacyclic ring systems are widely distributed in a large number of naturally occurring compounds and have been the foci of vigorous synthetic efforts particularly in conjunction with the total synthesis of polyether natural products.[1] Many synthetic schemes are now available[2] for the oxacycle synthesis. Radical-mediated cyclizations[3] were also extensively used for the construction of oxygen-containing ring systems. For example, α-haloacetal cyclization has now become one of the classic methods in synthesis and various α-alkoxy alkyl, vinyl and aryl radicals were also used in oxacycle synthesis.[4] Alkoxy radicals were also used for cyclizations.[5] Cyclization reactions of a variety of oxygen-substituted alkyl radicals were reported recently.[6] Vinyl ethers were used as radical acceptors in cyclic ether synthesis.[7]

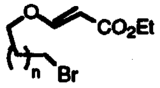
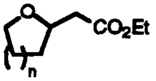
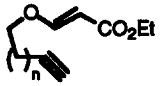
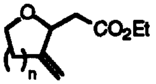
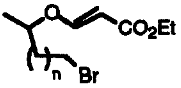
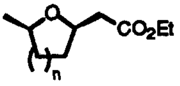
We now wish to report that β-alkoxyacrylates[8] are exceptionally efficient radical acceptors in radical-mediated intramolecular cyclizations and that highly stereoselective synthesis of tetrahydrofurans and tetrahydropyrans is possible in many cases.

Bromoalkanols and alkynols were reacted with ethyl propiolate in the presence of N-methylmorpholine and (*E*)-alkoxyacrylates **1a~6a** were obtained in high yield[9] (Scheme 1). Under the standard high dilution radical cyclization conditions using tributylstannane,[10] five- or six-membered cyclic ether formation was achieved in uniformly high yield employing **1a~6a** as substrates (Table 1). The high efficiency of cyclization and complete preference of *exo* mode of cyclization of alkyl and stannylvinyl radicals ensure the usefulness of β-alkoxyacrylates as radical acceptors. This reactivity and *exo* selectivity reflects the large orbital coefficient at the β-carbon[11] in the LUMO of the β-alkoxyacrylates which is expected to interact with relatively high-energy SOMO of alkyl and stannylvinyl radicals.[12] From the



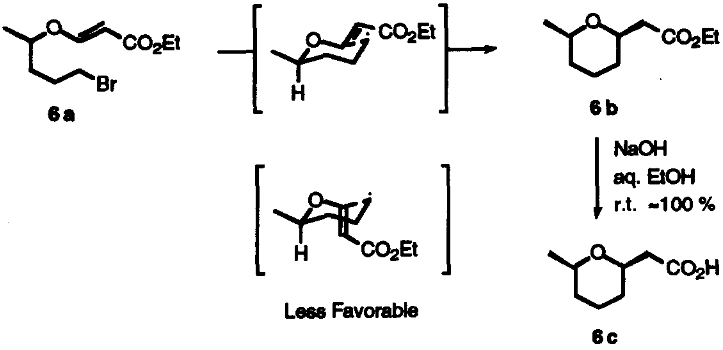
Scheme 1

Table 1

Substrates	Products	Yield (%)
		
1a n=1 **2a** n=2	**1b** n=1 **2b** n=2	95 96
		
3a n=1 **4a** n=2	**3b** n=1 **4b** n=2	98 (69)* 98 (69)
		
5a n=1 **6a** n=2	**5b** n=1 **6b** n=2	98 96

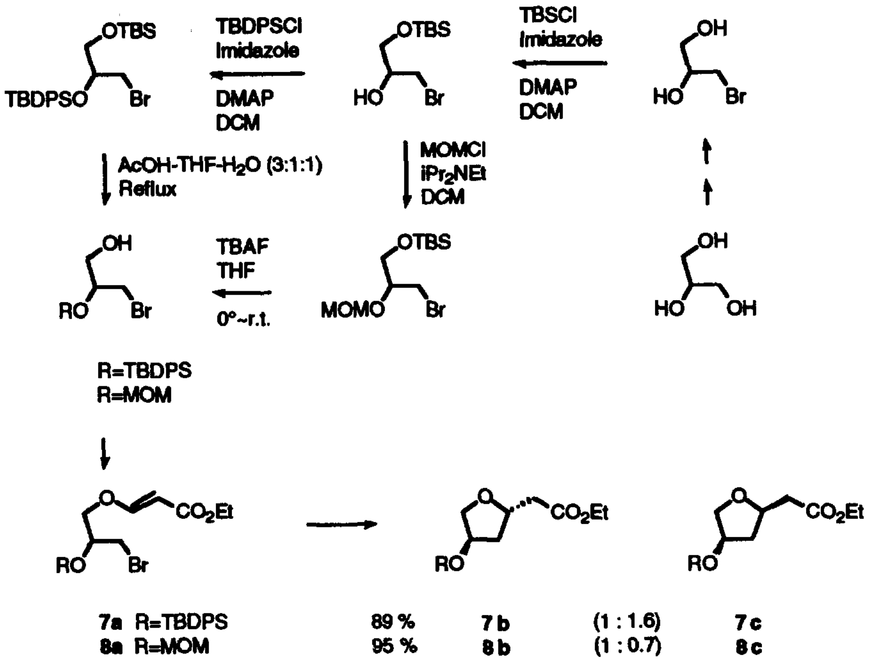
*Isolated yield after acidic destannylation.

synthetic point of view, formation of *cis*-2,5-disubstituted tetrahydrofuran **5b** and *cis*-2,6-disubstituted tetrahydropyran **6b** from **5a** and **6a** is particularly useful and noteworthy.[13] This *cis* selectivity can be explained by chair-like transition state conformations[14] depicted in Scheme 2. The tetrahydropyran **6b** was hydrolyzed to yield (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**6c**)[15] which is the racemic form of a component of civet, the scent gland secretion of civet cat *Viverra civetta*.[16] This is one of the most direct and specific schemes for the synthesis of **6c**.



Scheme 2

The strategy for oxacycle synthesis delineated above can be applied to any systems with more than two hydroxyl groups: one hydroxyl group is needed for transformation into the β-alkoxyacrylate functionality and the carbon carrying the second hydroxyl group serves as the radical center after proper modification. For example, glycerol was converted into 3-bromopropane-1,2-diol via acetonide protection, bromide substitution with carbon tetrabromide and triphenylphosphine, and acidic workup. The primary hydroxyl group was protected as a TBS ether and the secondary hydroxyl group was then converted into a TBDPS or MOM ether. Selective removal of TBS moiety regenerated the primary hydroxyl group in each case. Reaction with ethyl propiolate provided β-alkoxyacrylates **7a** and **8a**, from which tetrahydrofuranyl products were obtained in high yields (Scheme 3). In these cases, both *trans* and *cis* stereoisomers were isolated and it is interesting that opposite stereoselectivity is realized (**7b**<**7c** vs **8b**>**8c**).



Scheme 3

The scheme is well-suited for synthesis of other oxacycles including C-furanosides, which will be the subjects of our future communications.

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10. Best cyclization yields were achieved via slow addition of tributylstannane as specified in Table 1. However, Stork's catalytic tin hydride method can be adopted in a productive manner. For example, **6a** was converted to **6b** in 74 % yield(90 % based on consumed **6a**). See: Stork, G.; Sher, P.M. *J.Am.Chem. Soc.* **1986**, *108*, 303.
11. Acrylates are known to have larger LUMO coefficient at the β-carbon,whereas the α-carbon of vinyl ethers has larger LUMO coefficient. These effects reinforce each other in β-alkoxyacrylates. See Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons: Chichester, **1976**, p 189.
12. See p.15 of the reference 3b.
13. The structure of **6b** was determined by conversion to the known **6c**: see references 14 and 15. The structure of **5b** was confirmed by conversion to *cis*-2-(2'-acetoxyethyl)-5-methyltetrahydrofuran and comparing with the isomeric mixture(*trans/cis*=3:1) formed by treating methyl 3-hydroxy-6-heptenoate with NBS in acetonitrile at room temperature, standard tributylstannane debromination, LAH reduction, and acetylation. The methyl doublet of the *trans* isomer appears at δ 1.20, and the *cis* isomer at δ 1.23.
14. In these structures, the *s-trans* geometry of β-alkoxyacrylate C-O bond was assumed, as the alternative *s-cis* conformation should be destabilized by $A^{(1,3)}$ type allylic strain. In every reaction, this is unfailingly true and leads to the product in a stereospecific manner. For the effect of other substituents in the transition states of radical cyclizations, see:
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15. **6c**: ^{1}H-nmr($CDCl_3$, 200MHz); δ 1.20(d, J=6.3Hz, 3H, CH_3), 1.14-1.85(m, 6H, $(CH_2)_3$), 2.57 and 2.52(A and B parts of ABX system, J_{AB}=15.9Hz, J_{AX}=7.8Hz, J_{BX}=4.6Hz, 2H, CH_2COO), 3.55(m, 1H, HC(6)), 3.78(m, 1H, HC(2)), 10.0(br, COOH). ir(CH_2Cl_2, cm^{-1}); 2400-3400(br), 1725.
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