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Alkoxyl radical addition to acceptor-substituted carbon–carbon double bonds

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ABSTRACT

Alkoxyl radicals add 5-*exo*-*trig* selectively to cyano- and methoxycarbonyl-substituted carbon–carbon double bonds, to afford α-acceptor-α-tetrahydrofuryl-2-methyl radicals. Trapping of cyclized radicals by Bu_3SnD furnishes products of site-specific deuterium-labeling in α-position to the acceptor group. In intramolecular competition experiments, alkoxyl radicals add similarly fast to a cyano-substituted double bond than to a terminal alkene, but by a factor >25 faster to an enol ether. The nucleophilic component of alkoxyl radical reactivity opens an interesting new access to tetrahydrofuryl amino acids via C,O-cyclization, as shown by synthesis of a *N*,*O*-protected 5-phenyltetrahydrofuryl-2-methyl glycine.

1. Introduction

The oxygen nucleus attracts an unpaired valence electron in alkoxyl radicals stronger than the carbon nucleus in alkyl radicals. Oxygen radicals therefore attack higher in energy σ- and π-bonds with a reactivity/selectivity profile that is characteristic for many electrophiles.[1,2] Since oxygen forms strong bonds to hydrogen and carbon, the odd electron in alkoxyl radicals gives rise to chemical reactivity that is by orders of magnitude higher than carbon radical reactivity. Typical examples for reactions that take profit from unique alkoxyl radical reactivity are found in metabolic pathways,[3] and in oxidative hydrocarbon degradation, which clear the atmosphere from volatile organic compounds.[4,5]

In spite of enormous reactivity, alkoxyl radicals generally react selectively, following guidelines that allow to apply the intermediates in organic synthesis.[1] A method that has received growing attention for stereoselective synthesis within the past decade is the alkoxyl radical addition to carbon–carbon double bonds.[6–8] The current mechanistic picture shows that alkoxyl radicals add to constitutionally dissymmetric π-bonds with selectivity that often complements additions of alcohols or alkoxides to oxidatively activated alkenes. Additions of oxygen radicals that are too slow to compete with other radical consuming processes, such as β-fragmentation[9–11] or homolytic substitution,[12] generally are accelerated by substituting the carbon double bond with typical donor groups, such as methyl, phenyl, or silyloxy.[13–16] A drawback for pursuing new reactions in alkoxyl radical chemistry in synthesis, however, is the inherent electrophilicity, restricting selectivity control by the polar effect so far exclusively to donor substituents.

The scope of alkoxyl radical chemistry extends, if the intermediates add to Michael-type acceptors. In a communication on alkenoxyl radical generation from *O*-phenylsulfenates for studying stereochemical aspects of 4-pentenoxyl radical cyclization,[17] α-methacrylate-type double bonds were used as *O*-radical acceptors, however, without addressing the role of the polar effect.[18] In view of the potential arising from a nucleophilic component in alkoxyl radical reactivity, we decided to explore in a systematic manner addition to acrylate- and acrylonitrile-type π-bonds, lacking in an activating α-methyl group (Fig. 1). The major results from the study show that 4-pentenoxyl radicals add to the cyano-substituted carbon–carbon double in a rate that compares to the rate of addition to a terminal double bond. The fastest reaction in the series of competition experiments, however, is addition to an enol ether π-bond. From this dichotomic behavior we concluded that alkoxyl radicals are both, electrophiles and nucleophiles, depending on substitution at the π-bond. We used the nucleophilic component of

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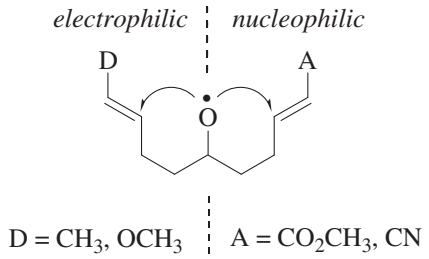


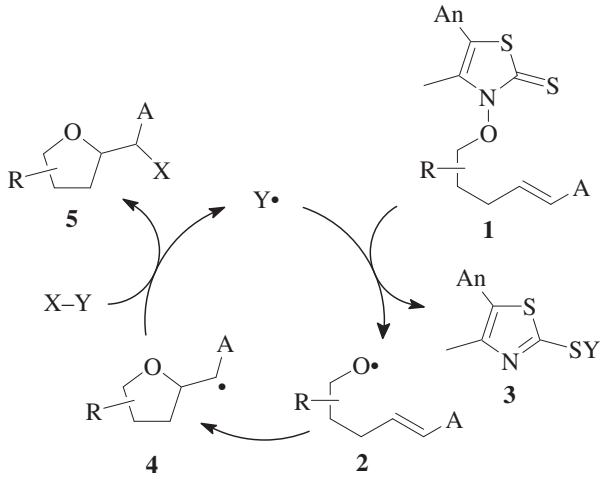
Fig. 1. Structure, substituent effects, and proposed chemical reactivity of alkoxyl radicals used in this study to explore the polar effect in additions to carbon–carbon double bonds.

alkoxyl radical reactivity to develop a new route to synthesis of a *N*,*O*-protected tetrahydrofuryl-2-methyl amino acid via C,O-cyclization.

2. Results and interpretation

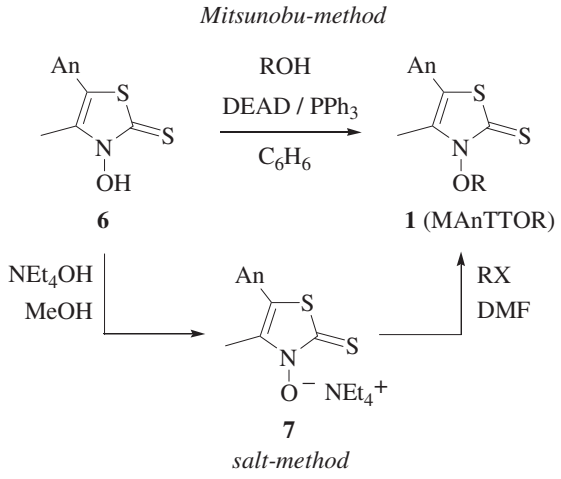
2.1. Alkoxyl radical generation and synthesis of radical precursors

We applied *O*-alkenyl thiohydroxamates of the type **1** in this study as alkoxyl radical progenitors. The compounds add electrophilic radicals Y• at the thione sulfur, which causes the nitrogen–oxygen bond to homolytically break. Radicals used for inducing alkoxyl radical liberation from **1** generally originate from an initiator, such as α,α-azobisisobutyronitrile (AIBN), or from a mediator X–Y in a propagating step of a chain reaction (Scheme 1). Typical mediators X–Y used in this chemistry are tributylstannane, the deuterium derivative Bu_3SnD for isotope labeling, and bromotrichloromethane. An alternative approach to oxygen radical generation from **1** is photochemistry. Excitation of electronic transitions in the molecule, by shining light into the broad electronic band at ~335 nm, selectively induces homolysis of the nitrogen–oxygen bond. The reaction between chain propagating radical Y• and *O*-alkenyl thiohydroxamate **1** thus provides alkenoxyl radical **2** and substituted thiazole **3**.[5,19] For synthesis of tetrahydrofurans (e.g. **5**), bimolecular trapping of alkenoxyl radical **2** by the mediator X–Y must be slower than the cyclization **2**→**4**.[20–23] Trapping of carbon radical **4** by the mediator provides target product **5** and supplies the chain with propagating radical Y•.[5]



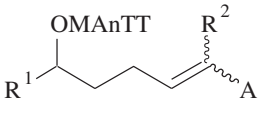
Scheme 1. Steps for alkoxyl radical generation in a chain reaction between *N*-alkoxythiazole-2(3*H*)-thione **1** (R=e.g. CH_3 or Ph; A=e.g. CN, CO_2CH_3; An=*p*-anisyl, i.e. *p*-methoxyphenyl) and a mediator X–Y (Bu_3SnH, Bu_3SnD, or $BrCCl_3$).

For synthesis of alkenyl thiohydroxamates **1a**–**j**, cyclic thiohydroxamic acid **6** was esterified by alkenols using the Mitsunobu-method, or a procedure that we refer to as the *salt-method* (Scheme 2, Supplementary data, and Experimental). Selectivity in the salt-method follows Pearson's principle of hard soft acids and bases. O-Alkylation at the hard oxygen instead of soft sulfur is attainable with a hard carbon electrophile, reacting with a thiohydroxamate anion experiencing no contact from a hard, strongly polarizing cation. This approach is put into practice by converting acid **6** into tetraethylammonium salt **7**, which subsequently is treated in a strongly polar aprotic solvent, such as dimethyl formamide, with an alkenyl chloride (for **1a**–**e**) or a tosylate (for **1i**) (Table 1). In the Mitsunobu-method, the electrophile is generated in situ from an alkenol and the combination of diethyl azodicarboxylate (DEAD) and triphenylphosphine in a solution of benzene, to furnish *O*-alkenyl thiohydroxamates **1f**–**h** and **1j** in yields between 31 and 67% (Fig. 2). After chromatographic purification, the target compounds were received as colorless (**1g**–**i**) to yellow (**1a**–**e**, **1j**) compounds, which are stable for months if stored in a refrigerator. *O*-Alkenyl thiohydroxamates of the type **1** show characteristic electronic spectra having a broad band located at λ=332–338 nm (lg ε ~3.00–3.28 m^2 mol^{-1}, in EtOH for **1a**–**c**, and $CHCl_3$ for **1d**), which allows to photoexcite the molecules for homolytically breaking the nitrogen–oxygen bond (vide supra).



Scheme 2. Methods for synthesis of alkoxyl radical precursors of the type **1** [for yields, see Table 1 and Fig. 2; X=Cl, OTs; R=alkenyl; all reactions were performed at 20–25 °C].

Table 1
Yields of ester- and cyano-substituted *N*-alkenoxythiazolethiones **1a**–**e** prepared from alkenyl chlorides via the salt-method[a]



1a–e

Entry	**1**	R^1	R^2	A	Yield/%	(*E*)/(*Z*)
1	**a**	CH_3	H	CN	36	77:23
2	**b**	C_6H_5	H	CN	49	76:24
3	**c**	CH_3	H	CO_2CH_3	49	>98:2
4	**d**	C_6H_5	H	CO_2CH_3	70	>98:2
5	**e**	C_6H_5	*cyclo*-C_3H_5	CN	73	62:38

[a] (RX=RCl, cf. Scheme 2; MAnTT=5-(4-methoxyphenyl)-4-methyl-2-thiooxo-2,3-dihydrothiazol-3-yl).