

Synthesis of New Sulfonyloximes and Their Use in Free-Radical Olefin Carbo-oximation

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S Supporting Information

ABSTRACT: New bifunctional reagents for free-radical carbo-oximation of olefins have been developed. In this process, a single reagent can act both as a trap for nucleophilic radicals as well as a source of electrophilic radical via an α -scission of an alkylsulfonyl radical. This strategy involving the addition of a C-centered electrophilic radical and an oxime across the double bond of an electron-rich alkene is initiated with a *t*-BuO radical following an unusual mechanism, supported by both experiments and density functional theory calculations.



Addition of C-centered radicals to sulfonyloximes such as **1** (Figure 1) constitutes a straightforward one-carbon chain elongation strategy and an efficient manner to incorporate a masked aldehyde group. This methodology, first reported by Kim and co-workers in 1996,¹ has since been applied to various transformations,² including multicomponent carbonylation reactions.³ Sulfonyloxime **1** was also used as a radical trap in the carbo-oximation of olefins, leading to new functionalized oximes such as **2** (Figure 1).⁴ This methodology allows the incorporation of two new functional groups on the carbon backbone of a large variety of olefins with the formation of two σ -bonds. The carbo-oximation reaction relies on the addition of an electrophilic radical species **I**, generated from a xanthate or an alkyl halide, to the less hindered end of an electron-rich olefin, generating a nucleophilic radical **II**, which can then be trapped by the electrophilic sulfonyl acceptor **1**. The PhSO_2 radical released during the addition– β -elimination sequence does not fragment under the above reaction conditions (80 °C) to furnish a phenyl radical which could sustain the radical chain. Hexabutyltin is thus added and upon reaction with the PhSO_2 radical generates a tin radical, which is able to propagate the chain. Unlike arylsulfonyl radicals, certain alkylsulfonyl radicals can undergo (reversibly) an α -scission to afford an alkyl radical and SO_2 .⁵ Zard et al. have elegantly used this property to develop tin-free allylation and vinylation of alkyl iodides and xanthates.⁶ Based on these premises, Renaud and co-workers⁷ recently developed an efficient carboazidation of olefins using ethyl-2-(azidosulfonyl)ethanoate. This reagent was reported to transfer to the olefin both an azido group and an electrophilic radical of type **I** (electron-withdrawing group (EWG) = CO_2Me) generated upon α -scission of the corresponding alkylsulfonyl radical. To overcome the use of a stoichiometric amount of hexabutyltin required in the three-component olefin carbo-oximation depicted in Figure 1, it was envisioned to develop bifunctional sulfones such as **3** (Scheme 1), which would incorporate both an alkylsulfonyl group and an oxime. Addition of a nucleophilic radical onto **3** would afford the desired carbo-oximation product along with an alkylsulfonyl radical, precursor of the electrophilic radical **I**. Herein, we

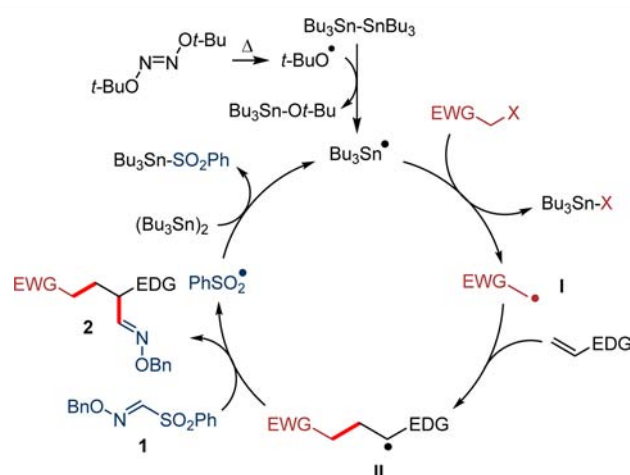
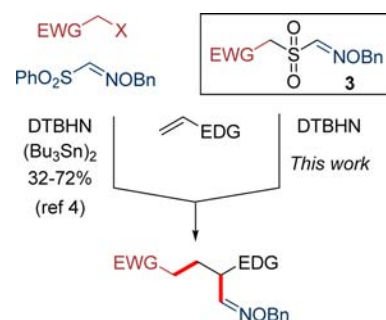


Figure 1. Free-radical three-component carbo-oximation of olefins.

Scheme 1. Bifunctional Sulfonyloximes for Olefin Carbo-oximation Reactions



report on the synthesis of sulfones **3** and their reactions with olefins under free-radical conditions. The scope and limitation

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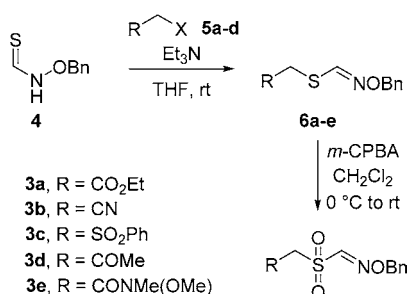
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of the methodology has been studied, and a mechanism, which includes an unusual initiation process supported by experimental evidence and density functional theory (DFT) calculations, is discussed.

The preparation of bifunctional sulfones was first carried out extending Kim's methodology,¹ which includes a sulfanylation of a chloro-oxime with a thiol, followed by the oxidation of the corresponding thioether into the desired sulfone **3a**.⁸ However, while this approach was reliable to access **3a** (EWG = CO₂Et; see Supporting Information), it was found to be difficult to generalize to other sulfones as the required thiols are not readily available.

An alternative strategy was thus devised based on the alkylation of *O*-benzylthiohydroxamate **4**, with commercially available alkyl halides **5a–d** (Table 1). Compound **4** was easily

Table 1. Preparation of Bifunctional Sulfonyloximes 3a–e



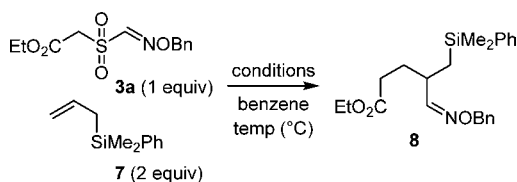
entry	sulfone	alkylation yield ^a (%)	oxidation yield ^a (%)
1	3b	80	50
2	3c	32 ^b	58
3	3d	75	45
4	3e	75	74

^aIsolated yields. ^bConditions: K₂CO₃, TBAI, THF, 60 °C.

prepared by treatment of the corresponding *O*-benzylthiohydroxamate with Lawesson's reagent (THF, reflux, 1 h, 90%; see Supporting Information). Alkylation of **4** led to the desired sulfanyloximes **6a–e**, which were then oxidized with *m*-CPBA into the desired bifunctional sulfonyloximes **3a–e** in moderate to good overall yields.

Preliminary carbo-oxidation experiments were carried out using sulfonyloxime **3a** (1 equiv) and allylsilane **7** (2 equiv) as the olefinic partner (Table 2). Initiation was first performed

Table 2. Olefin Carbo-oxidation: Preliminary Studies



entry	initiator	equiv	temp (°C)	additives	yield ^a (%)
1	DTBD	2 × 0.05	reflux		0
2	Et ₃ B/O ₂	3 × 0.1	20		0
3	DLP	2 × 0.1	reflux		39
4	DLP	2 × 0.1	reflux	Xanth ^{b,c}	50
5	DTBHN	0.15	70		34
6	DTBHN	3 × 0.05	70		60
7	DTBHN	3 × 0.05	70	(Bu ₃ Sn) ₂ ^c	79

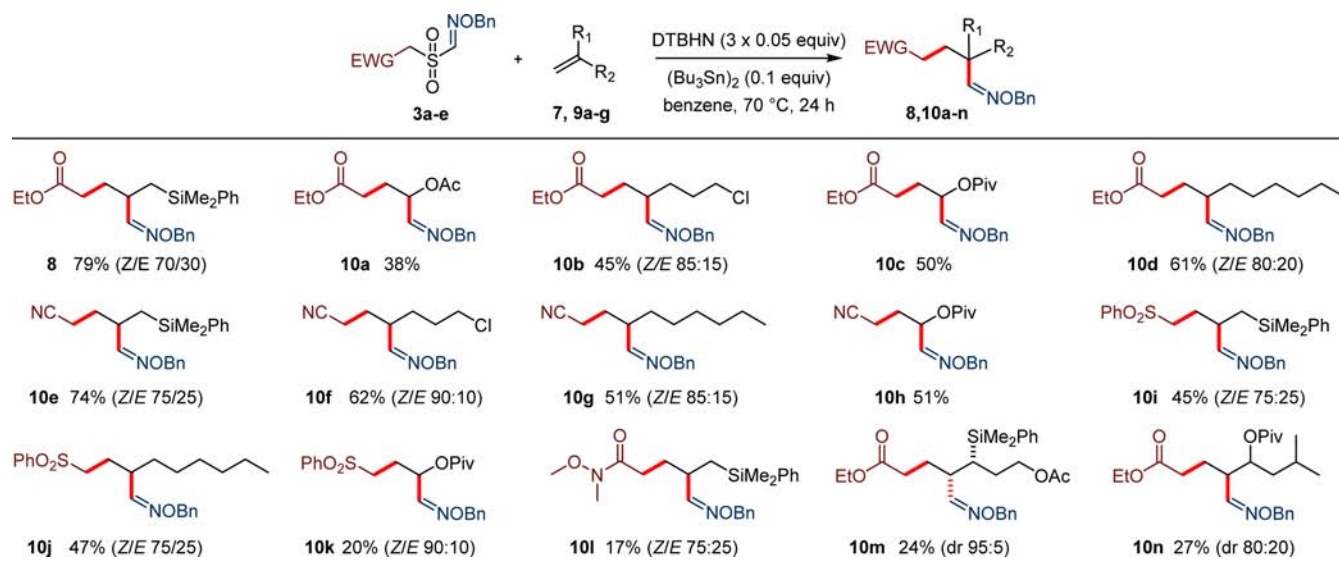
^aIsolated yields. ^bXanth: EtO₂CCH₂S(C=S)OEt. ^c10 mol %.

using nucleophilic alkyl radicals, generated from di-*tert*-butyldiazene (DTBD) or dilauroyl peroxide (DLP). Surprisingly, while the former was reported to be very efficient in the carboazidation reaction,⁷ no trace of the desired compound **8** was observed (Table 2, entry 1). Similarly, the ethyl radical produced upon reaction of Et₃B with oxygen was unable to initiate the process.⁹ More encouraging results were obtained with DLP leading to **8**, albeit in moderate yield (entry 3). A catalytic amount (10 mol %) of an ethyl xanthate was then added with DLP to generate the electrophilic radical precursor **I** (EWG = CO₂Et) (entry 4).¹⁰ The yield was effectively improved compared to the same reaction without xanthate (entry 3), but our efforts to further increase the reaction yield unfortunately failed. Surprisingly, when the reaction was achieved in the presence of di-*tert*-butyl hyponitrite (DTBHN) (0.15 equiv), a source of electrophilic alkoxy radicals, the oxime was totally consumed after only 3 h and the carbo-oxidation product **8** was formed, albeit with a modest yield (entry 5). To avoid excessive consumption of reagent **3a**, 0.05 equiv of DTBHN was added first at 70 °C, with two additional portions later (2 × 0.05). This effectively improved the yield of **8**, indicating that the bifunctional oxime **3a** was able to propagate the radical chain (entry 6). Addition of a catalytic amount of ditin (10 mol %) was also tested to increase the chain length.¹¹ Under these conditions, **8** was obtained in good yield (entry 7). These conditions, although not tin-free, were considered optimal, the purification of the product being much easier than in the original three-component process which required 1.5 equiv of (Bu₃Sn)₂ and 5 equiv of olefin.⁴

With the optimized experimental conditions in hand, various olefins **9** were submitted to the carbo-oxidation process in the presence of acceptors **3a–e** (Scheme 2). The reactions were carried out starting from 1 equiv of oximes **3a–e** and 2 equiv of olefins **9**, in the presence of 0.15 equiv of DTBHN in benzene (Scheme 2). Oximes **3a** and **3b**, leading to electrophilic radicals, generally led to reasonable yields, although a slightly lower efficiency was observed with less activated olefins, emphasizing the role of polar effects in these reactions.^{3b} In contrast, yields dropped dramatically with oximes **3c** and **3e**, which may be related to the lower rate for the α -scission of the sulfonyl radical in these cases. C-centered radicals α to a sulfonyl or a Weinreb amide group were found to add efficiently onto electron-rich olefins in three-component processes,^{4b} so that the poor yields here cannot be associated with their low reactivity. The process was also found to be sensitive to steric hindrance, as indicated by the modest yields observed for **10m** and **10n** issued from the corresponding sterically congested allylsilane and allylic ester.

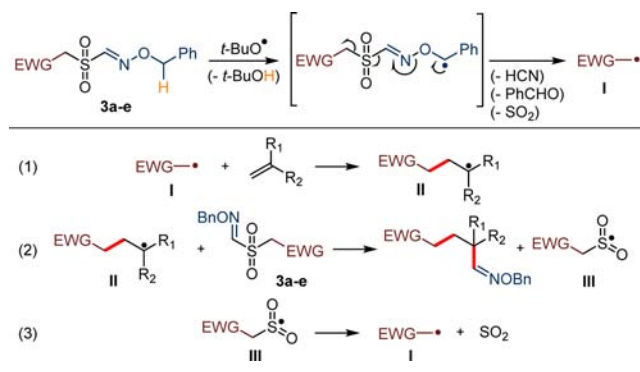
Finally, in contrast with the three-component process,⁴ which affords exclusively the (*Z*)-oxime, a mixture of *Z/E* isomers, in the favor of the former, is observed here. A tentative reaction mechanism, closely related to that proposed by Renaud for the carboazidation process,⁷ was proposed, as depicted in Scheme 3. This would involve an attack of the electrophilic radical species **I** onto the olefin to generate a new nucleophilic radical **II** (1), which could then add onto the sulfonyloximes **3a–e** to afford the desired product, along with an alkylsulfonyl radical **III** (2), which after α -scission would regenerate **I** and SO₂ (3). Although this mechanism appeared plausible, the nature of the initiation step remained obscure. Propagation of the radical chain was found to be effective without tin additive and in the presence of a low amount of initiator. The low efficiency of alkyl radicals generated from DTBD, DLP, and Et₃B in the initiation step may be attributed

Scheme 2. Scope and Limitations of the Carbo-oximation Reaction between Oximes 3a–e and Olefins 9



to both steric and electronic effects. The absence of reactivity of nucleophilic *t*-butyl radicals generated from DTBD may result from the important steric hindrance around the oxime carbon center, as suggested by the low yields obtained with sterically congested olefins (e.g., **10m,n**). In parallel, the low reactivity of less nucleophilic primary alkyl radicals may be explained by the low electrophilicity of oxime ethers (vide infra). In contrast, the reactivity of DTBHN releasing an electrophilic alkoxy radical was somehow surprising as 0.15 equiv of DTBHN is sufficient to promote the reaction (Table 2, entry 6). *t*-BuO radicals are known to decompose at high temperature (140 °C) into acetone and methyl radical.¹² Although our reactions are performed at 70 °C, one cannot totally rule out an initiation step resulting from a nucleophilic attack of a small amount of reactive methyl radical onto oximes 3. However, identification of traces of benzaldehyde from the crude ¹H NMR and by GC-MS analysis led us to propose an alternative (or concomitant) mechanism where benzylic hydrogens of the oxime ether would be abstracted first by a *t*-BuO radical (Scheme 3).¹³ The

Scheme 3. Tentative Mechanism



resulting benzylic radical would then β -fragment, releasing benzaldehyde, cyanhydric acid, and SO₂ to generate the electrophilic radical I. To get better insights into this initiation step, DFT calculations at the M062X/6-31G+(d,p) level were carried out using oxime 3a and *t*-BuO radical as model substrate and reagent respectively. Several pathways were envisioned, and the energies are depicted in Figure 2.

From these computational studies, two kinetically favored pathways emerged, leading to intermediates with the lowest energy. The most favored route (blue) involved the formation of a benzylic radical *i'* resulting from the abstraction of a hydrogen of 3a by the *t*-BuO radical. The second route (green) resulted from an addition of the alkoxy radical onto the oxime 3a, generating an alkoxyaminyl radical *i*. This pathway, which is only slightly more energetic, was less predictable but suggests that oxime ethers are also prone to react with electrophilic radical species as they form highly stabilized alkoxyaminyl radicals.¹⁴ Three other possible pathways involving a hydrogen abstraction of 3a by the *t*-BuO radical were considered to be too high in energy and thus were discarded. The benzylic radical *i'* then led to benzaldehyde along with an iminyl radical *ii'*, which upon fragmentation led to HCN and the radical species III. In the alternative route, the alkoxyaminyl radical *i* afforded III and an alkoxyoxime *ii* through a single step, exhibiting a very low energy barrier. The observation of benzaldehyde in our experiments suggests that the initiation pathway proposed in Scheme 3 and supported by the calculations below is likely the favored one. However, although the alkoxyoxime *ii* could not be detected, the second more favorable (green) route is on the computation error margin and cannot be totally ruled out based on our calculations. The role of the catalytic amount of tin is not yet clear, but an attack of the nucleophilic Bu₃Sn radical onto the sulfonyl oxime, followed by a β -fragmentation step, appears to be an additional and plausible pathway to generate radical III then I.

In summary, we have developed efficient access to new bifunctional sulfonyloximes that exhibit moderate to good reactivity in radical olefin carbo-oximation reactions. This strategy allows such processes to be carried out with only a catalytic amount of tin and only 2 equiv of olefin, thus facilitating final product purification. An original initiation pathway was also discovered, which was supported by the isolation of a fragmentation product and DFT calculations. Further investigations on this unusual initiation process are under scrutiny in our laboratory and will be reported in due course.

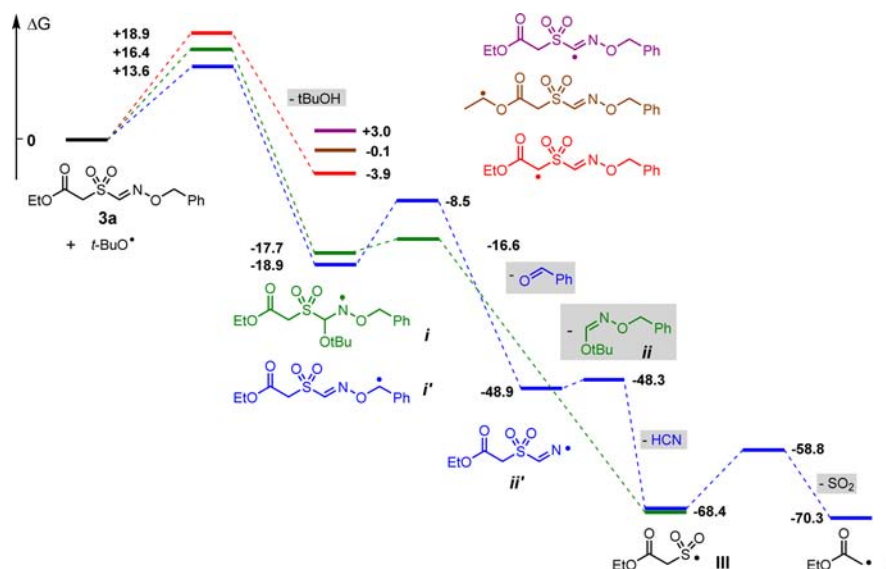


Figure 2. Computational studies on the initiation step at the M062X/6-31G+(d,p) level.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and product characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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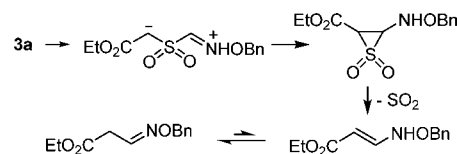
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