

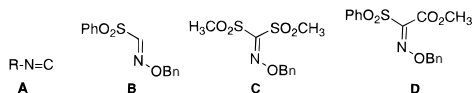
New Radical Cascade Reactions Incorporating Multiple One-Carbon Radical Synthons: A Versatile Synthetic Methodology for Vicinal Singly and Doubly Acylated Oxime Ethers

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Due largely to the extensive efforts of Wasserman and co-workers, vicinal tricarbonyl compounds have found wide applicability as versatile synthetic intermediates for the synthesis of numerous biologically active natural and unnatural compounds.¹ Among many possible approaches for the synthesis of vicinal di- and tricarbonyl compounds,² the sequential coupling of multiple molecules of carbon monoxide, while a direct and straightforward method, has been difficult to achieve. Only restricted examples of the synthesis of aromatic α -keto amides and α -keto esters have been reported thus far in transition-metal catalyzed carbonylation chemistry.³ Radical one-carbon (C1) approaches to di- and tricarbonyl compounds also seem unlikely to provide a viable alternative, since no evidence for double CO trapping was observed during the radical copolymerization of ethylene and CO even at extremely high CO pressures (>1000 atm, ethylene/CO = 3/7).^{4,5} This observation suggests that the addition of an acyl radical to CO occurs only with great difficulty.⁶ To our knowledge, similar free radical transformations using isonitriles **A**, another representative radical C1 synthon,⁴ are also unknown. Thus, the synthesis of vicinal di- and tricarbonyl compounds based on the coupling of multiple radical C1 synthons remains a challenge among possible intermolecular radical cascade reaction strategies.⁷



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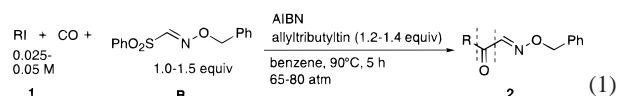
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(6) To our knowledge, no kinetic information about carbonylation of acyl radicals and the reverse process has been reported.

Recently, the Kim group has reported that sulfonyl oxime ethers, such as **B** and **C**, can serve as viable C1 radical acceptor synthons, which serve as latent carbonyl groups, providing novel free radical methods for acylation.⁸ The emergence of these powerful C1 newcomers in radical chemistry led us to attempt a series of unprecedented type of radical cascade reactions leading to vicinal di- and tricarbonyl compounds based on multiple radical C1 synthons: CO and sulfonyl oxime ethers. Herein we report that this new strategy is indeed promising and permits the synthesis of several types of vicinal singly and doubly acylated oxime ethers, which would be precursors of vicinal di- and tricarbonyl compounds.

In the event, the three-component coupling reaction comprised of RX, CO, and phenylsulfonyl oxime ether **B**^{8a} was successfully achieved, providing the desired α -acyl-substituted aldoximes (eq 1). For example, when *n*-octyl iodide (**1a**) was treated with phenylsulfonyl oxime ether **B** in the presence of allyltributyltin, AIBN (catalytic) in a pressurized CO (autoclave) in benzene at 90 °C for 5 h, the anticipated product, *O*-benzyl nonanoyl aldoxime **2a**, was obtained in 80% isolated yield (Table 1, entry 1).⁹ Cyclohexyl iodide **1b** and adamantyl iodide **1c** were converted to the corresponding 2-oxo aldoximes **2b** and **2c**, in 77 and 52% yields, respectively (entries 2 and 3). In entry 4, 5-exo cyclization preceded the consecutive addition to CO and **B**. As indicated in eq 1, these radical reactions were generally conducted by initially pressurizing the reaction vessel (autoclave) with carbon monoxide to 65–80 atm, followed by heating to 90 °C for 5 h. The substrate concentration was 0.025–0.05 M and AIBN was used as radical initiator (20–40 mol%). Unlike simple oxime ethers which exist as a mixture of *syn* and *anti* isomers, α -acylated aldoxime ethers **2** were obtained as a single stereoisomer of *anti*-geometry.¹⁰



In this thermally induced radical chain reaction, allyltributyltin serves as the radical chain carrier which traps benzenesulfonyl radical and generates tributyltin radical. Fortunately, the competing addition of acyl radicals to allyltin, leading to β,γ -unsaturated ketones,¹¹ was negligible, suggesting that the addition of acyl radicals to sulfonyl oxime ether **B** is much more rapid than the addition to allyltin.

Cascade reactions with carbon monoxide and bis-sulfonyl oxime ether **C**^{8c} are found to be useful for the synthesis of 2-oxo and 2,2'-di-oxo ketoximes. Treatment of octyl iodide (**1a**) with one mole equivalent of **C** under CO pressure gave a nonanoyl-substituted sulfonyl oxime ether. Subsequent treatment of the

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(9) Typical procedure: A magnetic stir bar, AIBN (17 mg, 0.1 mmol), a sulfonyl oxime ether **B** (207 mg, 0.7 mmol), allyltributyltin (199 mg, 0.6 mmol), an alkyl iodide **1a** (123 mg, 0.5 mmol), and benzene (20 mL) were placed in a 50-mL stainless steel autoclave lined with a glass liner. The autoclave was purged with carbon monoxide, pressurized with 80 atm of CO, and heated with stirring at 90 °C for 5 h. Excess CO was discharged at room temperature. The crude mixture was washed with ether. After evaporation of the solvent, the residue was subjected to silica gel flash column chromatography (hexane/AcOEt = 19/1) to give the α -keto oxime ether **2a** which contained a small amount of uncarbonylated product. Further purification by recycling by HPLC with a GPC column gave 112 mg of pure **2a** (80% yield).

(10) Recently Naito and co-workers reported that glycoxylic oxime ethers, analogous to **2**, act as alkyl radical acceptors, see: Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174 and references therein.

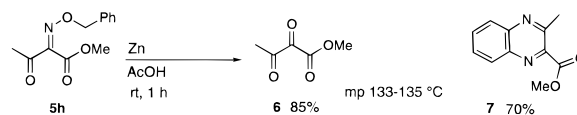
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Table 1. Synthesis of Vicinal Acylated Oxime Ethers by Three-, Four-, and Five-Component Coupling Reactions

entry	RX	C1 synthons conditions ^a	product	yield ^b (isomer ratio) ^{c,d}
1		CO, B 90 °C, 5 h [RI] = 0.025 M		80% (100/0)
2		CO, B 90 °C, 5 h [RI] = 0.025 M		77% (100/0)
3		CO, B 90 °C, 5 h [RI] = 0.025 M		52% (100/0)
4		CO, B 90 °C, 5 h [RI] = 0.050 M		48% (100/0)
5	1a, then	CO, C hv, 15 h, then 10 h [RI] = 0.050 M		47% (100/0) ^e
6		CO, C , CO hv, 24 h [RI] = 0.047 M		70%
7		CO, C , CO 90 °C, 5 h [RI] = 0.025 M		60%
8		CO, D 90 °C, 5 h [RI] = 0.050 M		84% (86/14)
9		CO, D 90 °C, 5 h [RI] = 0.050 M		81% (71/29) 8.6% nOe (for major isomer)
10		CO, D 90 °C, 5 h [RI] = 0.025 M		85% (86/14)
11		CO, D 90 °C, 5 h [RI] = 0.050 M		84% (70/30)
12		CO, D 90 °C, 5 h [RI] = 0.050 M		62% (100/0) ^e
13 ^f		CO, D 90 °C, 5 h [RI] = 0.025 M		51% ^g (82/18)
				19% (76/24)

^a For reaction procedures, see footnote 9 and Supporting Information.^b Isolated yields by silica gel chromatography. For entries 1–4, 6, and 13, preparative HPLC was used for purification. ^c Determined by ¹H NMR. ^d To determine *syn/anti* configurations, nOe experiments were carried out for **2a** and **5b**. ^e The stereochemistry has not yet been determined. ^f Both yield and selectivity are not optimized. ^g Six-membered ring products were formed in small amounts.

crude product with ethyl iodide (**1b**) gave the unsymmetrical product **3a** in 47% yield (entry 5). Remarkably, using 2 equiv of alkyl iodide, a five-component coupling reaction, comprising two molecules of RI, two molecules of CO, and one molecule of **C**, took place efficiently to give doubly acylated oxime ethers in good yields (entries 6 and 7). It should be noted that as can be seen in the examples of the conversion to **3a** and **4a**, irradiation with a xenon lamp through a Pyrex tube also worked well for initiating this allyltin-mediated chain system. As anticipated from

Scheme 1

the well-precedented nucleophilic nature of acyl radicals,¹² sulfonyl oxime ether **D** bearing a methoxycarbonyl group^{8b} served as an efficient acyl radical acceptor. The three-component coupling reaction proceeded quite smoothly to give high yields of the coupling products (entries 8–12). The four-component coupling reaction comprising 4-pentenyl radical, two molecules of CO, and sulfonyl oxime ether **D** was also successful, where the anticipated cyclopentanone **5i** (51%) was obtained along with an uncyclized product **5j** (19%) (entry 13).

Since 2-oxo oximes are useful synthetic intermediates for the synthesis of a variety of nitrogen-containing heterocycles,¹³ including quinoxalines, 2-aminopyrazine *N*-oxides, 4-aminopteridines, etc., it is obvious that the present technique offers a completely new method for the incorporation of two vicinal C1 units in these important compounds. Although several methods for deoxygenation of oximes and oxime ethers have been reported, many of them appeared not applicable to the conversion of vicinal acylated oximes and oxime ethers to the corresponding vicinal di- and tricarbonyl compounds.¹⁴ However, we found that a zinc/AcOH reduction system is particularly useful for the deoxygenation of acylated oximes. For example, when the oxime ether **5h** was treated with zinc powder (3 equiv) in acetic acid (rt, 1 h), the corresponding vicinal tricarboxyl compound **6** was obtained in 85% yield after isolation by silica gel chromatography (hexane/EtOAc = 2/1) (Scheme 1).¹⁵ Treatment of the crude mixture containing **6** with *o*-phenylenediamine gave the corresponding quinoxaline **7** in 70% isolated yield.

In summary, we have shown that a new radical cascade methodology has been achieved, based on multiple radical C1 synthons, which will be a useful addition to radical cascade methodologies. We believe that the extension of this new radical cascade strategy to include C2 synthons holds promise.

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Supporting Information Available: Typical experimental procedures and characterization data for products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) We also found that treatment of **5h** with fresh 10% Pd on C in EtOH/AcOH/H₂O (15:2:1) under an atmosphere of hydrogen for 30 min at room temperature gave a mixture of debenzylated oxime and the target tricarboxyl compound **6** as a ~1:1 mixture in 83% total yield.