Novel Radical Reaction of Phenylsulfonyl Oxime Ethers. A Free Radical Acylation Approach

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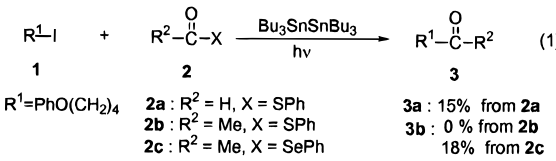
Although acylation represents one of the most useful and thoroughly studied reactions in organic chemistry,[1] a successful free radical-mediated acylation is not presently available. Only a few examples, involving highly activated carbonyls such as biacetyl[2] and acyl aldoximes,[3] have appeared to date.[4] It is also noteworthy that free radical carbonylation has recently been reported.[5] This reaction allows the introdution of carbonyl groups to organic halides.

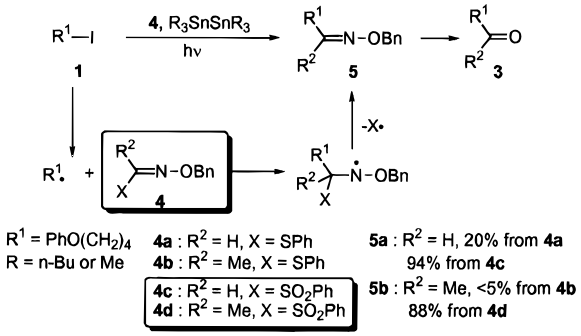
In order to examine the feasibility of radical-mediated acylation reactions, we began our study with thiol esters as radical acceptors (eq 1).[6,7] When 4-phenoxybutyl iodide **1** was



(1)

irradiated in the presence of *S*-phenyl thioformate **2a** and bis-(tributyltin) (1.2 equiv) in benzene (0.2M in iodide) using Neumann's method,[8] aldehyde **3a** was obtained in 15% yield.[9] The use of *S*-phenyl thioacetate **2b** did not give **3b**, but the selenol ester **2c** gave **3b** in 18% yield. We conceived that the unsuccessful outcome might be due to the reversibility of the additions of alkyl radicals to C═O bonds and the higher π bond strengths of C═O bonds.[10] Thus, a fundamentally new acylation approach was sought, and we now report a conceptually simple solution to this problem, wherein an oxime ether **4** can be used as a carbonyl equivalent radical acceptor in addition reactions of alkyl radicals. This concept is based on the fact that alkyl radicals undergo facile additions to C═N bonds such as oxime ethers[11,12] and hydrazones.[13] As shown in Scheme 1, our approach involves additions of alkyl radicals to C═N bonds and subsequent β-exclusion of phenyl thio radicals which react with bis(trialkyl)tin to propagate a chain. However, initial attempts to employ this strategy were disappointing, since the use of **4a** under the similar conditions afforded **5a** in 20% yield,[14] whereas the use of **4b** afforded only a small amount of **5b** (<5%).

Scheme 1



We next examined phenylsulfonyl oxime ethers since the phenylsulfonyl group would be expected to lower the energy of the LUMO of a radical acceptor, thereby increasing the rate of addition of alkyl radicals to **4c** and **4d** by reducing the SOMO−LUMO difference.[15] As predicted, the phenylsulfonyl oxime ethers **4c** and **4d** appeared to be highly effective and synthetically useful reagents for radical-mediated acylations under mild conditions. Reagents **4c** and **4d** were prepared by MCPBA oxidation of **4a** and **4b**, respectively, and obtained as stable crystalline solids.[16] When **1** was treated with $Bu_3SnSnBu_3$ (1.2 equiv), **4c** (2.0 equiv), and acetone (5 equiv) as a sensitizer in benzene (0.3 M in iodide) at 300 nm for 4 h, O-benzyl aldoxime **5a** was obtained in 94% yield. This product was hydrolyzed to aldehyde **3a** in 90% yield using a 30% HCHO solution in THF (1:3) in the presence of a catalytic amount of

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(4) Indirect approaches for formylation include additions of alkyl radicals to isonitriles and sulfonyl cyanides. (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (b) Barton, D. H. R.; Ozbalik, N.; Vacher, B. *Tetrahedron* **1988**, *44*, 3501. (c) Fang, J.-M.; Chen, M.-Y. *Tetrahedron Lett.* **1987**, *28*, 2853. (d) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *Tetrahedron Lett.* **1991**, *32*, 3321. (e) Leopez, J. C.; Gomez, A. M.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 3871.

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(8) Harendza, M.; Junggebauer, J.; Lebmann, K.; Neuman, W. P.; Tews, H. *Synlett* **1993**, 286.

(9) In addition to **3a**, *S*-phenyl 4-phenoxypentanethioate (6%) was isolated along with recovery of **2a** (40%).

(10) (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (c) Walton, R.; Fraser- Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791. (d) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954.

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(12) According to our kinetic and competition studies on the rate constant for 5- *exo* and 6-*exo* cyclization of primary alkyl radicals to the O-benzyl oxime ethers, C═N bonds in oxime ethers seem to be much better radical acceptors than C═C and C═O bonds. Kim, Y. J. Unpublished results.

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(14) The use of the hydrazone ($HC(SPh)═NNMe_2$) gave $PhO(CH_2)_4$-$CH═NNMe_2$ in 26% yield.

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Table 1. Preparation of Oxime Ethers from Alkyl Halides with **4c** and **4d**[21]

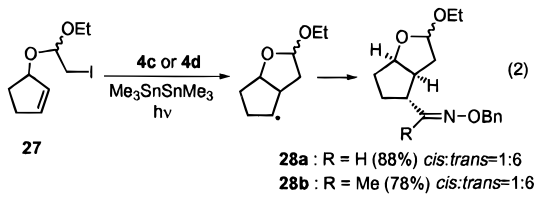
substrate	product (yield, %)[a]
THP–O–(CH$_2$)$_2$–I (**6**)	THP–O–(CH$_2$)$_2$–CH=N–OBn (**7** (93%))
I (**8**)	R–C(=N–OBn)–H (**9a** : R = H (91%); **9b** : R = Me (87%))
I–(CH$_2$)$_3$–CH(I)–CH$_3$ (**10**)	(CH$_2$)$_3$–C(=N–OBn)–R (**11a** : R = H (85%); **11b** : R = Me (76%))
I–C(CH$_3$)$_3$ (**12**)	C(CH$_3$)$_3$–C(=N–OBn)–R (**13a** : R = H (85%); **13b** : R = Me (15%))
MeO$_2$C–(CH$_2$)$_9$–X (**14** (X = I); **16** (X = Br))	MeO$_2$C–(CH$_2$)$_9$–C(=N–OBn)–R (**15a** : R = H (92%); **15b** : R = Me (84%)[b] = Me (65%)[c])
HO–(CH$_2$)$_2$–Br (**17**)	HO–(CH$_2$)$_2$–C(=N–OBn)–Me (**18** (61%)[d])
(CH$_2$)$_7$–O–C(=O)–CH$_2$–I (**19**)	(CH$_2$)$_7$–O–C(=O)–CH$_2$–C(=N–OBn)–H (**20** (72%)[d])
t-Bu–C$_6$H$_4$–CH$_2$–Br (**21**)	t-Bu–C$_6$H$_4$–CH$_2$–C(=N–OBn)–Me (**22** (40%)[e])
BnO–C$_6$H$_6$O$_3$(Br)(OBn)$_2$ (**23**)	BnO–C$_6$H$_6$O$_3$(C(=N–OBn)–R)(OBn)$_2$ (**24a** : R = H (64%); **24b** : R = Me (53%))
N(Boc)–CH$_2$–CH$_2$–I (**25**)	N(Boc)–CH$_2$–CH$_2$–CH=N–OBn (**26** (95%))

[a] All yield are uncorrected for recovery of starting material. [b] **14** was used. [c] **16** (20%) was recovered. [d] The direct reduction product (20%) was also isolated. [e] 4,4′-*tert*-butyldibenzyl (40%) was isolated.

HCl.[17] In addition a small amount of O-benzyl *n*-pentanaldoxime (12−20%) was isolated as a result of the homolytic bond cleavage of the Sn−*n*-C_4H_9 bond under the photochemical conditions used. The use of hexamethylditin obviates the problem of the formation of aldoxime byproduct, and the remaining reactions were carried out with this reagent (1.2 equiv).[18] Thermal initiation with AIBN was also investigated with **1** and **4c**. However, the reaction was incomplete even after 12 h, and the yield was considerably lower (40%).

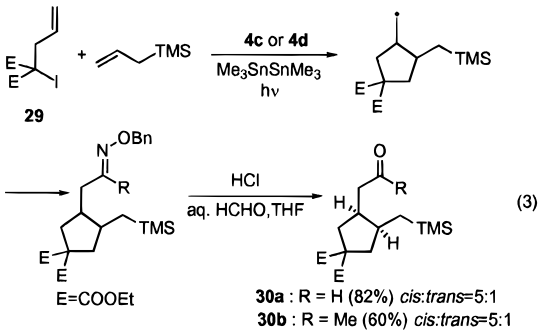
Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method. For most of the cases observed, the reaction was complete within 4 h with alkyl iodides and afforded the O-benzyl oxime ethers in high yield. However, sterically hindered *tert*-butyl iodide did not work well with **4d**. The reaction was successful with alkyl bromides, although longer reaction times were required and yields were lower. In the reaction with benzylic bromide, the desired oxime ether was obtained in low yield (40%) along with the dimeric product (40%) because of the relatively low reactivity of the stable benzylic radical. Acetal, ester, alcohol, and carbamate moieties are all tolerated, as would be expected from the nature of the radical reaction. The reaction was successfully applied to a carbohydrate in which acylations were achieved at the anomeric center, thus providing facile routes to highly functionalized *C*-glycosyl derivatives.

Encouraged by the success of this acylation approach, we have studied the feasibility of the cyclization−acylation sequence, which cannot be achieved using conventional synthetic methods (eq 2). When a mixture of **27**, $Me_3SnSnMe_3$ (1.2



equiv), **4c** (2.0 equiv), and acetone (5 equiv) in benzene (0.3 M in the iodide) was irradiated at 300 nm for 4 h, **28a** was isolated in 88% yield.[19]

We have also studied three-component coupling reactions involving an intermolecular addition, cyclization, and acylation sequence (eq 3).[20] Treatment of **29** with $Me_3SnSnMe_3$ (1.2



equiv), **4c** (2.0 equiv), and acetone (5.0 equiv) in benzene (0.3 M in **29**) and irradiation at 300 nm for 6 h, followed by hydrolysis of the O-benzyl oxime ether group, afforded **30a** in 82% yield, demonstrating the synthetic usefulness of the present method. A similar result was also obtained with **4d**, although a lower yield was obtained.

In conclusion, we have discovered the first successful radical acylation approach which we believe has great synthetic potential because it succeeds in complex molecules, where more conventional synthetic methods would be inappropriate. Further studies on the synthetic utility of this method with several other functionalized phenylsulfonyl oxime ethers are in progress, and the results will be reported in the future.

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Supporting Information Available: Experimental procedures for the preparation of **4c**, **4d**, and **5a** as well as spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) for the reaction products (9 pages). Ordering information is given on any current masthead page.

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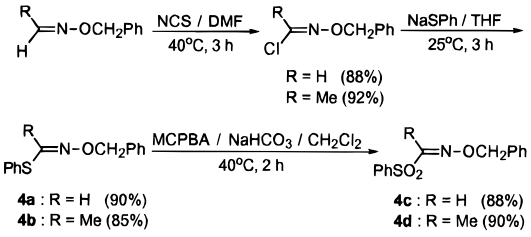
(16) The preparation of **4c** (mp 51−52 °C) and **4d** (mp 45−46 °C) is as follows.



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(18) The use of bis(tributyltin) gave similar yields in most cases. However, separation of the product from O-benzyl pentanaldoxime was difficult in several cases.

(19) The ratio of *cis*-/*trans*-isomer was determined by analysis of the ^{1}H NMR spectrum of the corresponding ketones after deprotection of O-benzyl oxime ether group.

(20) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872.

(21) The reaction was carried out with $Me_3SnSnMe_3$ (1.2 equiv), **4c** or **4d** (2.0 equiv), and acetone (5.0 equiv) in benzene (0.3 M in substrate) at 300 nm for 4 h (alkyl iodides) and for 12 h (alkyl bromides).