Radicals in Synthesis

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Radical Alkylation of Bis(silyloxy)enamine Derivatives of Organic Nitro Compounds**

*Jin Young Lee, Young-Taek Hong, and Sunggak Kim**

Organic nitro compounds are valuable intermediates in organic synthesis that undergo a variety of carbon–carbon bond-forming reactions. The alkylation of primary and secondary alkyl nitro compounds proceeds via dianion species to yield α- and β-alkylated nitro compounds, respectively.[1] The conjugate addition and nitroaldol reaction of organic nitro compounds have also found wide application in synthesis.[2] Despite the great synthetic importance of the nitro

[*] J. Y. Lee, Y.-T. Hong, Prof. Dr. S. Kim
Center for Molecular Design & Synthesis and
Department of Chemistry
School of Molecular Science
Korea Advanced Institute of Science and Technology
Daejeon 305-701 (Korea)
Fax: (+82) 42-869-8370
E-mail: skim@kaist.ac.kr

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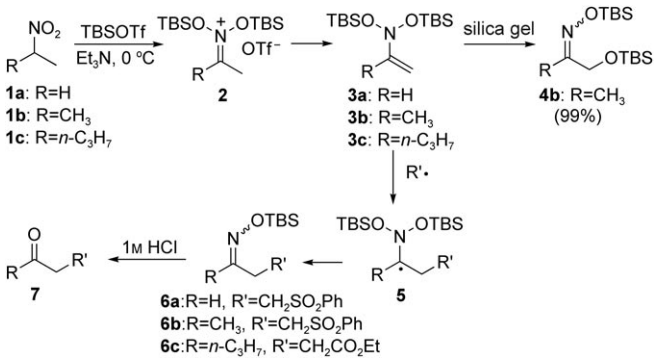
group, radical-mediated reactions of this functional group have not been well studied. Previously reported chain processes via radical anion intermediates nicely complement standard enolate alkylations, as they give good results with tertiary alkyl and aryl halides.[3,4] The nitroalkylation of alkyl iodides via silyl nitronates[5] has also been described, as well as the previously known reduction of tertiary nitro groups with Bu_3SnH/2,2′-azobisisobutyronitrile (AIBN).[6]

Our approach for the radical alkylation of organic nitro compounds is outlined in Scheme 1. It involves the addition of an alkyl radical to a bis(silyloxy)enamine **3** and subsequent homolytic cleavage of one N–O bond to yield an oxime ether **6**. Thus, this approach would enable alkylation at the β position to the nitro group together with the conversion of the nitro group into the synthetically important oxime ether group. We began our study with 2-nitropropane (**1b**). The treatment of **1b** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 2.0 equiv) and triethylamine (2.2 equiv) afforded the bis(silyloxy)enamine **3b** via **2**.[7] Since **3b** underwent rearrangement into **4b** when passed through a column of silica gel,[7c] the remaining reactions were carried out with the crude product after an aqueous workup. Irradiation of a solution of **3b**, iodomethyl phenyl sulfone, and hexamethylditin in benzene at 300 nm for 9 h afforded

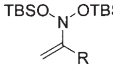
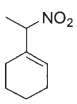
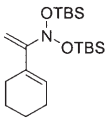
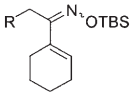
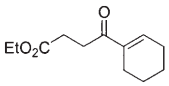
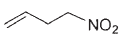
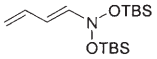
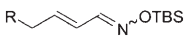
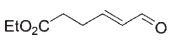
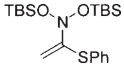
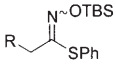
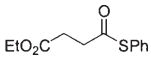
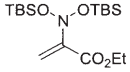
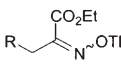
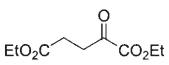


Scheme 1. Radical alkylation of the organic nitro compound **1**.

the oxime ether **6b** in 71 % yield. The hydrolysis of **6b** with 1M HCl then gave the ketone **7b** in 91 % yield. Furthermore, the oxime ether group can be converted into an amino[8] or nitro group.[9] When **1c** was treated with TBSOTf and triethylamine under similar conditions, the deprotonation of **2c** by triethylamine occurred at the less-substituted carbon atom, thereby yielding **3c** in a regioselective manner.

Our experimental results are summarized in Table 1. The radical reaction of the conjugated bis(silyloxy)enamine **3e**,

Table 1: Radical alkylation of organic nitro compounds.[a]

Nitro compound		Enamine		Oxime ether		Yield [%]	Carbonyl compound		Yield [%]
									
1a	R = H	**3a**	R = H	**6a**	R = H R′ = CH_2SO_2Ph	85	**7a**	R = H R′ = CH_2SO_2Ph	86
1b	R = CH_3	**3b**	R = CH_3	**6b**	R = CH_3 R′ = CH_2SO_2Ph	71	**7b**	R = CH_3 R′ = CH_2SO_2Ph	91
1c	R = *n*-C_3H_7	**3c**	R = *n*-C_3H_7	**6c**	R = *n*-C_3H_7 R′ = CH_2CO_2Et	70	**7c**	R = *n*-C_3H_7 R′ = CH_2CO_2Et	85
1d	R = Ph	**3d**	R = Ph	**6d**	R = Ph R′ = CH_2CO_2Et	82	**7d**	R = Ph R′ = CH_2CO_2Et	93
									
1e		**3e**		**6e**	R = CH_2SO_2Ph	79	**7e**		85
				6f	R = CH_2CO_2Et	72			
									
1f		**3f**		**6g**	R = CH_2CO_2Et	65	**7f**		93
				6h	R = CH_2SO_2Ph	62			
									
1g		**3g**		**6i**	R = CH_2CO_2Et	76	**7g**		73
				6j	R = CH_2SO_2Ph	79			
									
1h		**3h**		**6k**	R = CH_2CO_2Et	70	**7h**		88

[a] Reaction conditions: $(Me_3Sn)_2$ (1 equiv), benzene, 300 nm.

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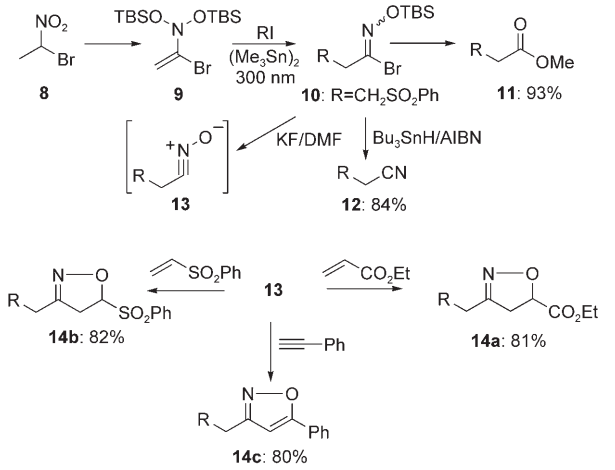
derived from the allylic nitro compound **1e**, with iodomethyl phenyl sulfone gave the conjugated oxime ether **6e** in 79% yield. When a benzene solution of ethyl iodoacetate and the conjugated enamine **3f**, derived from 4-nitro-1-butene (**1f**), was subjected to the standard reaction conditions, **7f** was isolated after acidic hydrolysis of the oxime ether **6g**. The successful synthesis of **7f** indicates that the procedure is useful for the preparation of γ-alkylated enals from γ,δ-unsaturated nitro compounds.

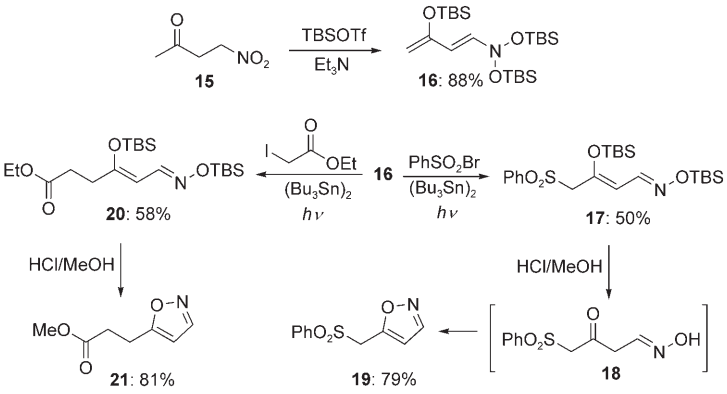
This method can be further extended to other α-substituted nitro compounds to yield several types of synthetically useful carbonyl derivatives. For example, the radical reaction of **3g** under the same conditions, followed by acidic hydrolysis, afforded the thiol ester **7g** in good yield. Furthermore, the radical reaction of **3h** afforded the oxime ester **6k**, which underwent acidic hydrolysis to give the synthetically important α-ketoester **7h**.

Oxime ether **10** was obtained by radical alkylation of the bromo-substituted enamine **9** under similar conditions. The acidic hydrolysis of **10** in methanolic HCl at reflux gave the corresponding methyl ester **11** in 93% yield, whereas the radical reaction of **10** with Bu_3SnH/AIBN in refluxing benzene provided the nitrile **12** in 84% yield. Furthermore, **10** underwent 1,3-dipolar cycloaddition upon treatment with potassium fluoride in *N*,*N*-dimethylformamide (DMF) in the presence of polarophiles via the nitrile oxide **13** generated in situ. An acrylic ester, a vinyl sulfone, and phenylacetylene underwent smooth 1,3-dipolar cycloadditions with **13** to give the corresponding isoxazolines **14a** and **14b**, and isoxazole **14c** (Scheme 2).[10]



Scheme 2. Radical alkylation of **9** followed by 1,3-dipolar cycloaddition.

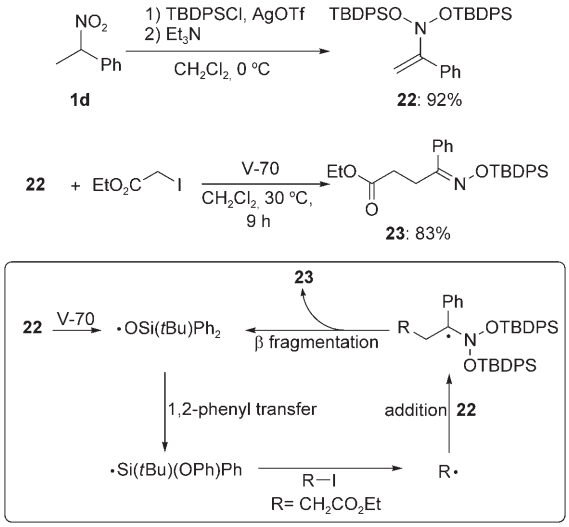
Isoxazole derivatives can also be prepared by the radical alkylation of **15**. The radical reaction of **16** with phenyl sulfonyl bromide under similar conditions afforded the oxime ether **17** in 50% yield. When **17** was subjected to hydrolysis in HCl/MeOH at reflux for 1 h, the isoxazole **19** was obtained in 79% yield.[11] Similarly, the use of ethyl iodoacetate as an alkylating agent provided the isoxazole **21** after transesterification of **20** under acidic conditions (Scheme 3).



Scheme 3. Synthesis of isoxazoles by radical reactions of **16**.

Tin-based reagents are not always convenient because of the inherent toxicity of organotin derivatives and the difficulties often encountered in removing tin residues from the product.[12] For a tin-free approach,[13] we implemented the findings of our previous studies on the radical rearrangement of silyloxy radicals into the corresponding silyl radicals.[14] Thus, the treatment of **1d** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and triethylamine in the presence of silver triflate in dichloromethane afforded the bis-(silyloxy)enamine **22** in 92% yield. When the radical reaction was carried out with **22** and ethyl iodoacetate in the presence of 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) as the initiator in dichloromethane at 30 °C for 9 h, the oxime ether **23** was isolated in 83% yield (Scheme 4). To determine the efficiency and the scope of the present method, additional experiments were carried out with **22** and several different alkyl halides. As shown in Table 2, alkyl iodides with an electron-withdrawing substituent at the α position underwent clean radical alkylation reactions under tin-free conditions.

In conclusion, we have developed a novel radical alkylation reaction of organic nitro derivatives via bis-(silyloxy)enamines. The method enables not only alkylation



Scheme 4. Tin-free radical alkylation of **1d** via **22**.

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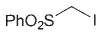
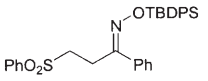
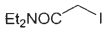
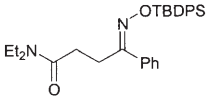
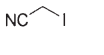
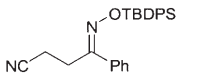
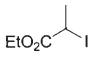
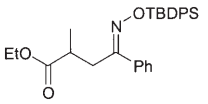
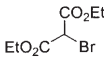
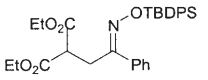
Table 2: Tin-free radical alkylation of the organic nitro compound **1d**.[a]

Entry	Substrate	Product	Yield [%]
1			61
2			63
3			68
4			72
5			75

[a] Reaction conditions: V-70, CH_2Cl_2, 30 °C, 9 h.

β to the nitro group, but also the conversion of the nitro group into an oxime ether functionality. Furthermore, the radical alkylation can be carried out under tin-free conditions.

Experimental Section

Typical procedure A: A solution of iodomethyl phenyl sulfone (56 mg, 0.2 mmol), **3b** (95 mg, 0.3 mmol), and hexamethylditin (65 mg, 0.2 mmol) in benzene (1 mL; 0.2 M in iodide) was purged with nitrogen for 10 min and then irradiated in a photochemical reactor at 300 nm for 9 h. The solvent was then evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc/hexane (1:5) as the eluent to give **6b** (49 mg, 71%, *E*/*Z* 5:1 (ratio calculated from the ^{1}H NMR spectrum)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ(*E* isomer) = 0.04 (s, 6H), 0.79 (s, 9H), 1.85 (s, 3H), 2.61–2.66 (m, 2H), 3.22–3.26 (m, 2H), 7.53–7.57 (m, 2H), 7.62–7.64 (m, 1H), 7.87–7.90 ppm (m, 2H); δ(*Z* isomer) = 0.07 (s, 6H), 0.86 (s, 9H), 1.80 (s, 3H), 2.52–2.57 (m, 2H), 3.30–3.35 (m, 2H), 7.53–7.57 (m, 2H), 7.62–7.64 (m, 1H), 7.87–7.90 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ(*E* isomer) = −5.3 (2C), 17.8, 20.2, 23.5, 25.9 (3C), 51.7, 128.1, 129.3, 133.8, 138.6, 157.4 ppm; IR (polymer): $\tilde{\nu}$ = 784, 839, 938, 1155, 1253, 1309, 1654, 2859, 2933 cm^{-1}; HRMS: calcd for $C_{16}H_{27}NO_3SSi$ [M^+]: 341.1481; found: 341.1430.

Typical procedure B (tin-free conditions): A solution of ethyl iodoacetate (45 mg, 0.2 mmol), **22** (188 mg, 0.3 mmol), and V-70 (12 mg, 0.04 mmol) in dichloromethane (1 mL; 0.2 M in iodide) was purged with nitrogen for 10 min and then stirred at 30 °C under nitrogen for 9 h. The solvent was then evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc/hexane (1:20) as the eluent to give **23** (82 mg, 83%, *E*/*Z* 3.3:1 (ratio calculated from the ^{1}H NMR spectrum)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ(*E* isomer) = 1.14 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.66–2.70 (m, 2H), 3.23–3.27 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 7.31–7.40 (m, 10H), 7.61–7.62 (m, 2H), 7.71–7.73 ppm (m, 3H); δ(*Z* isomer) = 1.00 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.50–2.54 (m, 2H), 2.84–2.88 (m, 2H), 3.91 (q, *J* = 7.1 Hz, 2H), 7.31–7.40 (m, 10H), 7.61–7.62 (m, 2H), 7.71–7.73 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ(*E* isomer) = 14.1, 19.4, 22.2, 27.2 (3C), 31.0, 60.6, 126.4, 127.4, 127.5 (2C), 127.9, 128.4, 129.3, 129.6, 133.7, 135.1, 135.5 (2C), 161.5, 172.6 ppm; IR (polymer): $\tilde{\nu}$ = 704, 744, 1114, 1528, 1566, 1690, 1732, 2859, 2934 cm^{-1}; HRMS: calcd for $C_{28}H_{33}NO_3Si$ [M^+]: 459.2230; found: 459.2231.

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