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Diastereoselective Free Radical Halogenation, Azidation, and Rearrangement of β-Silyl Barton Esters

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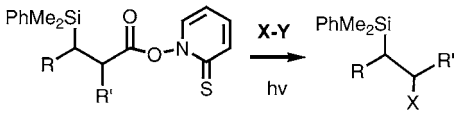
ABSTRACT

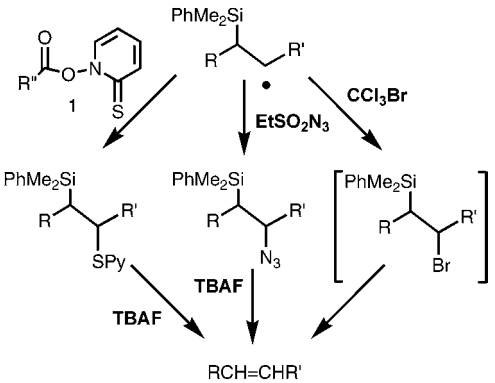


Barton esters of β-silylcarboxylic acids were decomposed by photolysis alone in organic solvents or in the presence of ethanesulfonyl azide or bromotrichloromethane. Products of the reaction, β-silylthiopyridyl ethers, β-silyl azides, or alkenes, were formed with significant control of stereochemistry.

The attention to free radical chemistry over the past decade has been due in part to the functional group tolerance of free radical reactions and to the ability to control stereochemistry in radical transformations.[1,2] Recently we reported on the stereoselective formation and elimination of β-bromosilanes in Lewis acid promoted atom transfer additions to branched allylsilanes.[3] The resulting β-bromosilanes underwent a nonradical elimination process that gave the thermodynamically less stable cis olefins in good yield. The configuration of the product olefins in these reactions allowed for the analysis of the stereochemical outcome in the atom transfer reaction. Anti-elimination of bromosilane[4] yields cis olefin products when the β-bromosilane has a threo configuration, a result of stereochemical control in the bromine atom transfer.

Thiohydroxamate esters, **1**, (Barton esters) are widely used as sources of alkyl radicals[5,6] because they are easily prepared and provide ready entry to a variety of radical precursors from activated carboxylic acids. Reactions of Barton esters are typically initiated by photolysis, thus providing a mild source of the desired alkyl radical species. We report here that β-silyl Barton esters can be readily prepared and used in free radical halogenation, azidation, and thiopyridyl rearrangement reactions with moderate to excellent diastereocontrol and yield (Scheme 1).

Scheme 1



The thiohydroxamate esters were readily prepared by reaction of activated and appropriately substituted β-silyl carboxylic acids with the sodium salt of 2-mercaptopyridine-*N*-oxide.[7] The carboxylic acids were prepared using Flem-

(1) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082.
(2) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
(3) Porter, N. A.; Zhang, G.; Reed, A. D. *Tetrahedron Lett.* **2000**, *41*, 5773−5777.
(4) Jarvie, A. W. P.; Holt, A.; Thompson, J. *J. Chem. Soc. B* **1969**, 852−855.
(5) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675−684.
(6) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733−2740.

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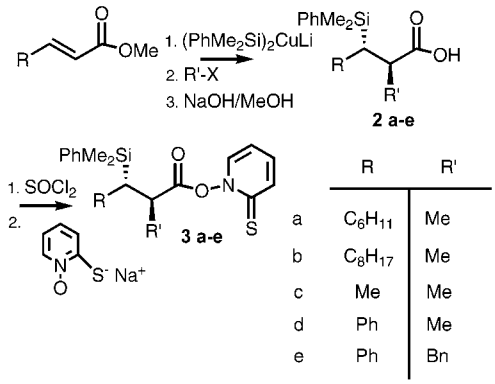
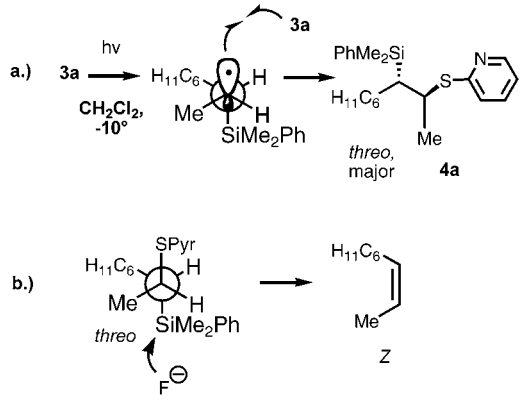
Scheme 2



ing's procedure as outlined in Scheme 2.[8] Acids **2a**−**e** were transformed to the corresponding thiohydroxamate esters by conversion to the acid chloride followed by reaction with the 2-mercaptopyridine-*N*-oxide salt in methylene chloride (reaction, workup, and purification were performed in the dark) (Scheme 2). Compounds **3a**−**e** were obtained in good crude yields and were isolated by recrystallization or column chromatography (SiO_2) diastereomerically pure as judged by NMR.

We chose the thiopyridyl rearrangement[9] reaction of **3a**−**e**, as illustrated in Scheme 3 for **3a**, as an initial test of

Scheme 3



diastereocontrol. A methylene chloride solution of the Barton ester was irradiated until the solution became practically colorless (usually 3−4 h irradiation time). The solvent was then removed under reduced pressure, the thiopyridyl products were isolated by preparative TLC, and NMR analysis was conducted to determine the diastereomeric ratio of the resulting products. In most cases, the diastereomeric ratio was >80:20 (Table 1). When **4a** was treated with a solution of TBAF, elimination took place, which smoothly produced olefins, whose E/Z ratio (GC) was in excellent agreement with the diastereomeric ratio of the thiopyridyl products as determined by NMR. The olefin mixture was compared to authentic samples and the Z isomer was found

Table 1. Formation of Thiopyridyls from Barton Esters

entry	substrate[a]	**4** *dr*[b,c]	alkene[d] *E*/*Z*[e]
1	**3a**	80:20	24:76
2	**3b**	80:20	16:84
3	**3c**	72:28	nd[f]
4	**3d**	87:13	90:10
5	**3d**	83:17[g]	90:10
6	**3e**	91:9[h]	79:21

[a] Reaction of **3** at −10 °C in CH_2Cl_2 initiated by light. [b] Diastereomeric product ratio determined by ^1H NMR of the crude product mixture. [c] Isolated yields by preparative TLC, 40% for reactions at −10 °C. [d] Prepared by TBAF/THF treatment of the diastereomeric product mixture **4** at room temperature. [e] Determined by gas chromatography by comparison with authentic standards. [f] Not determined because of the volatility of alkene products. [g] Reaction at room temperature, isolated yield by preparative TLC, 80%. [h] Isolated yield, 20% by TLC.

to be the major geometrical isomer present (Table 1, entries 1 and 2). Formation of the Z isomer can be rationalized assuming an *E2* elimination pathway for the TBAF-induced elimination process from *threo*-**4a** (Scheme 3b).

When the R group in **3** was a simple alkyl group (entries 2 and 3) or cycloalkyl (entry 1), the diastereomeric ratio (dr) of the thiopyridyl products was on the order of 80:20. Isolated yields were generally poor to moderate for this transformation, 30−40%, for the reactions carried out at −10 °C. When R in **3** was a phenyl group (**3d** and **3e** in Table 1, entries 4−6), the *dr* observed for **4** is greater than that observed when R is alkyl or cycloalkyl. When **3d** was irradiated at room temperature, an isolated yield of **4d** of 80% was obtained for the thiopyridyl product. Stereoselectivity for this transformation dropped from 87:13 at −10 °C to 83:17 at room temperature. The highest level of diastereoselectivity was achieved with **3e**, which gave a *dr* of 91:9 at −10 °C (entry 6) but a poor yield of 20%.

When the thiopyridyl products **4d** and **4e** were subjected to TBAF elimination, the *E* isomer was the major olefin formed. This suggests that either the stereochemical course for reaction of **3d** and **3e** differed from the other compounds studied or that the TBAF elimination did not proceed by a strict *E2* elimination process.[10] To address this point, the major and minor diastereomers of **4d** were isolated by chromatography. The isolated isomers were then separately subjected to TBAF elimination, and the olefin products were analyzed by GC and compared with authentic samples. The products derived from the minor isomer of **4d** were a >99:1 *E*/*Z* olefin mixture, and the olefins obtained from the major (threo) isomer of **4d** were an 82:18 *E*/*Z* mixture. This result can be rationalized by an *E1cb* mechanism[11] for the TBAF-induced elimination from **4d** and **4e**, a conclusion consistent

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(8) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318−321.
(9) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 8050−8059.
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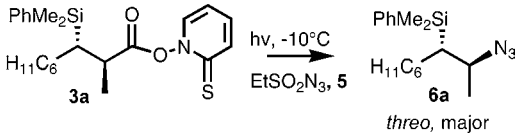
(11) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987.

with observations reported by Fleming.[10] We conclude that the results from all of the transformations are consistent; threo is the major product formed in every case.

Attempts were made to promote an *E2* elimination process from **4d** and **4e**. The use of a nonpolar solvent (hexane) and lower reaction temperatures (−10 and −78 °C) in the elimination reaction gave an increase in Z olefin compared to reactions carried out at room temperature in THF, but the olefin *dr* never approached the ratio expected for an *E2* process.

Free radical azidation of alkyl iodides takes place readily in the presence of ethanesulfonyl azide (**5**) to give good yields of alkyl azides.[12,13] To date, there have been no studies of acyclic stereocontrol in these free radical azidation processes, and we used **3a**−**e** to explore the formation of alkyl azides where stereochemistry was an issue (Scheme 4).

Scheme 4



The azidation of **3a**−**e** was performed in a manner as reported for alkyl iodides[12,13] except that no external initiator was employed. A methylene chloride solution of the thiohydroxamate ester was irradiated in the presence of 3−5 equiv of **5** under an inert atmosphere until the solution became practically colorless. The resulting mixture was concentrated, and the residue was purified by preparative TLC. Table 2 shows that the course of the azidation of **3a**−**e** appears to be highly substrate-dependent. Thus, **3a** gave a mixture of alkyl azides **6a** with a *dr* of 60:40 (Table 2 entry 1), and when this product diastereomer mixture was subjected to treatment with TBAF, elimination of the elements of silyl azide took place with the resulting alkenes being produced in an *E*/*Z* ratio of 42:58. The excellent agreement between the GC analysis of the olefins and the NMR analysis of the azide mixture **6a** allowed the TBAF elimination to be used as a diagnostic tool for the determination of relative configuration of the product alkyl azides. Diastereoselectivities for the reaction improved substantially for **3d** and **3e** as illustrated in entries 4 and 5 of Table 2. Azidation of **3d** gave an alkyl azide mixture with a *dr* of 92:8, and **3e** provided an alkyl azide mixture with a *dr* of 91:9. As was the case with the thiopyridyl products **4d** and **4e**, the azides **6d** and **6e** did not produce olefins whose isomeric composition was consistent with that of the parent azides. The TBAF elimination results for substrates **6d** and **6e** suggest an *E1cb* elimination mechanism, a result that is consistent with the elimination reaction of thiopyridyls **4d** and **4e.**

^{1}H NMR analysis of the crude reaction mixtures showed that, in addition to azide products **6**, a substantial amount of thiopyridyl rearrangement product, **4**, was produced in the reactions with ethanesulfonyl azide. For **3d**, NMR indicated a 56% yield of azide **6d** with the thiopyridyl products **4d** being formed in 40%. Significant quantities of thiopyridyl products are formed in all of the azidation reactions, and product accountability is generally in excess of 80%.

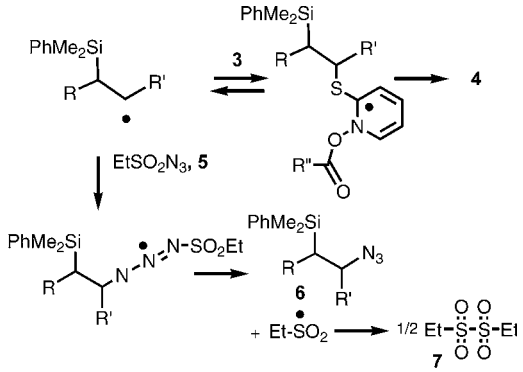
Table 2. Formation of Azides from Barton Esters

entry	substrate[a]	**6** *dr*[b,c]	olefin[d] *E*/*Z*[e]
1	**3a**	60:40[f]	42:58
2	**3b**	76:24[g]	24:76
3	**3c**	67:33	nd[h]
4	**3d**	92:8[i]	81:19
5	**3e**	91:9	89:11

[a] Reaction of **3** at −10 °C in CH_2Cl_2 initiated by light. [b] Diastereomeric product ratio determined by ^{1}H NMR of the crude product mixture. [c] Isolated yields by preparative TLC, 30−45% for reactions at −10 °C. [d] Prepared by TBAF treatment of the diastereomeric product mixture **6**. [e] Determined by gas chromatography by comparison with authentic standards. [f] Yield of 44% determined by ^{1}H NMR of crude product compared to an internal standard. [g] Ratio determined by TBAF elimination because of overlap of signals in the NMR. [h] Not determined because of volatility of alkene products. [i] Yield of 56% determined by ^{1}H NMR of crude product compared to an internal standard. Yield of 66% by the slow infusion method described in Supporting Information.

It is likely that at lower reaction temperatures, the extrusion of SO_2 from the ethylsulfonyl radical is slow. This assumption is supported by the observation that NMR and GC−MS analysis showed that no 2-ethylthiopyridine was produced, as expected if ethyl radical chain propagation had occurred. Because both azide and thiopyridyl products are observed, we suggest a mechanism for the transformation as shown in Scheme 5.

Scheme 5



NMR and mass spectral analysis of the crude reaction mixtures indicated the presence of ethyl disulfone **7** (Scheme 5), a product that is formed in yields comparable to that of the azide. The presence of **7** and the absence of the 2-ethylthiopyridine in the product mixtures indicates that ethyl radicals are not available for chain propagation. When the azidation of **3d** was initiated with Et_3B/O_2, both azide and thiopyridyl products were observed in a ca. 1:1 ratio along with substantial amounts of 2-ethylthiopyridine.

(12) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496−6497.
(13) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717−4727.

Table 3. Formation of Alkenes from Reaction of Barton Esters with $BrCCl_3$

entry	substrate[a,b]	olefin E/Z[c]
1	**3a**	38:62
2	**3b**	33:67
3	**3d**	92:8
4	**3e**	95:5

[a] Reaction of **3** at −10 °C in CCl_3Br/CH_2Cl_2 initiated by light. [b] Yields were 60−80% by isolation or determined by gas chromatography with *p*-xylene internal standard. [c] Determined by gas chromatography and comparison with authentic samples.

β-Halosilanes undergo anti-elimination of silylhalide to produce olefins in moderate to excellent yields,[3,4] and we sought entry to these halosilanes via **3a**−**e**. Free radical halogenation was performed by irradiating the thiohydroxamate ester in a 1:1 mixture of $CH_2Cl_2/CBrCl_3$ until the mixture became practically colorless, and the crude reaction mixture was immediately analyzed by GC. The results from the halogenation reaction are presented in Table 3. The halogenation and elimination of **3a** (Table 3 entry 1) resulted in an olefin E/Z ratio of 38:62, and a similar E/Z ratio (33:67) was obtained in the halogenation and elimination of substrate **3b**. Substrate **3d** and **3e** gave olefin with high E selectivity (E/Z = 92:8 and 95:5) with excellent product yields (80%). We suspect that substrates **3d** and **3e** when halogenated may undergo a stepwise elimination of $PhMe_2SiBr$, accounting for the E selectivity in these reactions.

The results obtained for halogenation, azidation, and thiopyridyl formation from β-silyl radicals show that considerable levels of diastereocontrol can be achieved for a variety of substrates. A preliminary discussion of stereocontrol in radical reactions similar to the ones described here is given in the accompanying Letter by Chabaud et al. The transformations described may prove to be useful in a variety of synthetic transformations.

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Supporting Information Available: Detailed descriptions of experimental procedures and spectral information and analyses for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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