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Carbenoid-mediated elimination of sulfides and selenides. A mild and efficient method for introducing α,β-double bonds to electron-withdrawing substituents

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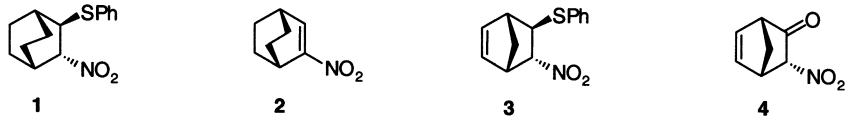
Abstract—Cycloalkanes bearing both an electron-withdrawing group and an arylsulfenyl or arylselenenyl function in β-position are shown to react with 2 equiv. of a carbenoid species to generate the corresponding Michael acceptor. The reaction occurs under very mild conditions and affords the products in good to excellent yields. The process constitutes a useful alternative to the oxidation/*syn*-elimination sequence. © 2002 Elsevier Science Ltd. All rights reserved.

Converting an alkyl chain substituted by an electron-withdrawing substituent into the α,β-unsaturated analogue has often been a key transformation in the construction of complex molecules. Indeed such a functional modification opens the door to utilizing several of the major reactions of organic chemistry (e.g. the Michael addition and the cycloaddition reactions). A large number of methods are nowadays available to achieve this and the development of organoselenium chemistry in the late 1970s, for example, was partly due to the need of having a milder counterpart to the thermal *syn*-elimination of sulfenic acids from sulfoxides.[1]

In the course of developing a new synthetic approach to building polycyclic skeletons, we were confronted with the need for converting β-arylthio- and β-arylselenonitrocycloalkanes into the corresponding nitrocycloalkenes.[2] Application of the classical oxidation/*syn*-elimination sequence of reactions to **1**, under a variety of conditions, led only to complex, untreatable mixtures of compounds (Fig. 1).[3] Treatment of the substrates with different bases in the hope of eliminating a thiol or a selenol led, at best, to epimerization of the compounds. Thus, for example, treating **1** with triethylamine gave all possible diastereomers and no nitroalkene **2**. The use of potassium *tert*-butanolate on **3** in THF furnished only ketone **4** in 77% isolated yield, upon hydrolysis. While this result clearly indicates the formation of a nitronate (the first step of the Nef reaction[4]), the epimerization and decomposition processes described above indicate the high reactivity of the desired products towards nucleophilic addition and polymerisation reactions.[5] These data induced a search for a milder method.

We surmised that in situ transformation of the thioether or selenoether into a sulfonium or selenonium group would (i) facilitate elimination under basic conditions, and (ii) reduce the ability of the thereby-formed sulfur or selenium by-product to add onto the newly formed activated alkene. In this context, the use of a carbene or a carbenoid species would generate a sulfur or selenium ylide able to act as an internal base, the *cis* stereochemical relationship between this group and the acidic, α-nitro hydrogen favoring the deprotonation step.



1 **2** **3** **4**

Figure 1.

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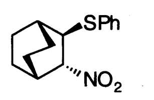
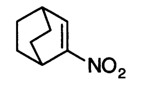
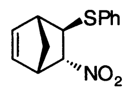
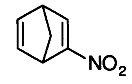
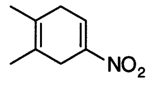
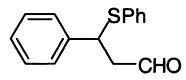
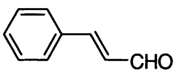
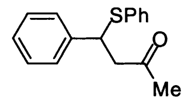
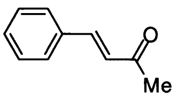
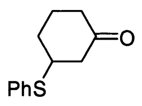
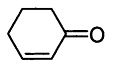
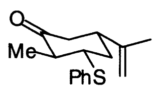
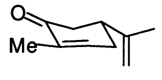
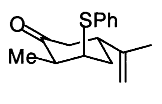
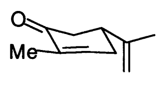
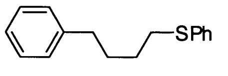
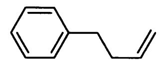
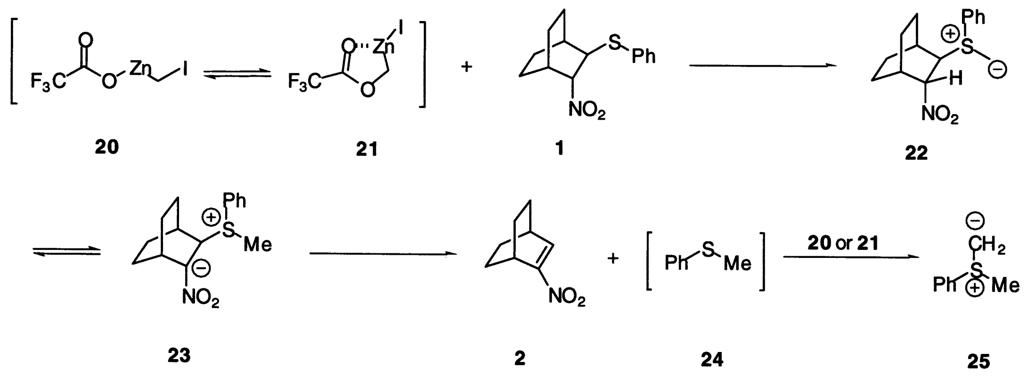
Interacting the substrates with a zinc carbenoid entity, according to the Furukawa procedure, led only to tarry mixtures.[6] Application of Shi's superior protocol to **1** furnished a mixture containing some thioanisole as well as the desired product **2** and starting material (a circa 1:1 mixture).[7] Increasing the amount of carbenoid precursor and reagents to 2 equiv. *cleanly*, *quantitatively and within minutes* converted the substrate into the desired nitroalkene **2**, isolated in 79% yield after chromatography on silica.

The scope and limits of this new organochemical transformation were then explored by submitting different substrates to the hereabove conditions (Table 1). Substrate **3** was devoid of reactivity under these conditions, and this behavior can be attributed to the strain in bicycle **5**.[2] β-Selenoether nitroalkanes are also converted into the desired nitroalkenes, as exemplified by the case of substrate **6**. Worthy of note is the fact that compound **7** is obtained without a trace of 3,4-dimethylnitrobenzene, thus illustrating the gentleness of the procedure. *trans*-Cinnamaldehyde is also produced under similar conditions (entry 4). The use of ketone **10** resulted in the formation of *cis*- and *trans*-4-phenylbut-3-en-2-one (**11**), isolated in 95% yield and identical to every respect to an authentic sample, while 3-phenylthiocyclohexanone (**12**) led to cyclohexenone. Both diastereomers of *R*-(−)-carvone derivatives (**14** and **16**, respectively) delivered *R*-(−)-carvone. Especially enlightening is the fact that no cyclopropanation reaction occurred on the isolated carbon–carbon double bond, the result of a much faster reaction between the carbenoid and the thioether group.[8] An electron-withdrawing substituent seems, however, necessary for the reaction to occur under mild conditions. When sulfide **18** was subjected to the procedure, not a trace of alkene **19** could be detected, the starting material being left untouched.

Table 1. Transformation of substrates to electron-poor alkene via the method depicted in Scheme 1

Entry	substrate		Product[a]		Yield (%)[b]
1		**1**		**2**	79
2		**3**		**5**	0
3		**6**		**7**	50
4		**8**		**9**	97[c]
5		**10**		**11**	95[d]
6		**12**		**13**	58
7		**14**		**15**	65
8		**16**		**17**	63
9		**18**		**19**	0

a. The reaction was conducted under anoxic conditions. b. Yields are for isolated, pure compounds[10]. c. Determined by gas chromatography using *n*-tetradecane as internal standard. d. Isolated as a 1:1 mixture of *E* and *Z* isomers.



Scheme 1.

A likely mechanism is depicted in Scheme 1. Charrette has suggested that Shi's carbenoid is best represented by an equilibrium between **20** and **21**.[9] Reaction of this entity with **1** would deliver ylid **22**, in a way reminiscent of the reaction between allyl sulfides and carbenoid species generated under a somewhat different procedure.[8] Intermediate **22** could then act as an internal base to pick up the proton α to the nitro group to form zwitterion **23**. This would thereafter produce the desired product **2** by eliminating thioanisole; this by-product would subsequently be transformed into the water-soluble sulfur ylid **25**. The *trans* stereochemical relationship between the thioether group and the hydrogen α to the ketone in substrate **16** demonstrates that the process may also follow an intermolecular pathway. The fact that sulfide **18** was unreactive under the reaction conditions, or even under reflux, seems to indicate that the process involves the intermediacy of a nitronate or an enolate. Indeed, comparison of the mean pK_a values for hydrogen atoms in α position to nitro, aldehyde and keto groups (10, 20 and 20, respectively) with that of sulfonium or selenonium salts (around 25) indicates that the equilibrium is displaced towards the right.[11]

A typical procedure is as follows. Diethyl zinc (10 mL of a 1.0 M solution in hexane) was added to dichloromethane (10 mL) under argon. The reaction mixture was cooled to 0°C and a solution of trifluoroacetic acid (1.14 g, 10.0 mmol) in dichloromethane (5 mL) was added over a 45 min period of time, using a syringe pump. The resultant whitish solution was stirred for an additional 10 min and diiodomethane (2.68 g; 10.0 mmol) in dichloromethane (5 mL) was added dropwise. After 10 more min of stirring, a solution of **1** (1.315 g; 5.0 mmol) in dichloromethane (5 mL) was added. Upon completion of the addition, the reaction mixture was quenched with aqueous saturated ammonium chloride (25 mL). The solution was extracted with pentane (2×20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. Purification of the crude material over a small path of silica gel using first pentane, then pentane/ether (95/5) as eluents yields 604 mg of colorless, oily **2** (79% yield).[12]

Acknowledgements

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References

1. Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986; pp. 132–142.
2. Deléens, R.; Gautier, A.; Piettre, S. R. *Tetrahedron Lett.* **2002**, *43*, 4963–4968.
3. These conditions included $NaIO_4$, *m*-CPBA and H_2O_2 under a variety of conditions (solvents, heating).
4. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; pp. 159–166.
5. Thiols and selenols (or their salts) are known to add onto nitroalkenes, see: Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; pp. 70–84.
6. (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58; (b) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647–2659; (c) Nishimura, J.; Furukawa, J.; Kawabata, N.; Kitayama, M. *Tetrahedron* **1971**, *27*, 1799–1806.
7. Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621–8624.
8. Such a selectivity has already been observed in the past, see: Cohen, T.; Kosarych, Z. *Tetrahedron Lett.* **1982**, *23*, 3019–3022.
9. Charrette, A. B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* **2001**, *123*, 8139–8140.
10. All compounds displayed analytical data in accordance with the structures depicted in the paper.
11. (a) Tapuhi, E.; Jencks, W. P. *J. Am. Chem. Chem.* **1982**, *104*, 5758–5763; (b) Guthrie, J. P.; Cossar, J.; Klym, A. *J. Am. Chem. Chem.* **1984**, *106*, 1351–1360; (c) Johnson, C. R. In *Comprehensive Organic Chemistry*; Barton,

D. H. R.; Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, pp. 247–260; (d) Cheng, J.-P.; Liu, B.; Zhao, Y.; Sun, Y.; Zhang, X.-M.; Lu, Y. *J. Org. Chem.* **1999**, *64*, 604–610.

12. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (dd, 1H, N-C=C$\underline{H}$, $^3J=2.28, 7.53$ Hz), 3.55 (m, 1H, N-C-C$\underline{H}$), 2.92 (m, 1H, N-C=CH-C$\underline{H}$), 1.76–1.54 (m, 4H, 2×N-C-CH-C$\underline{H}_2$), 1.52–1.19 ppm (m, 4H, 2×N-C-CH-CH$_2$-C$\underline{H}_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.02, 66.31, 31.91, 29.58, 26.12, 25.17 ppm.