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TANDEM ALKYNE INSERTION AND ALLYL SULFONIUM YLIDE REARRANGEMENT OF γ,δ–ALKYNYL-α'-DIAZOKETONES

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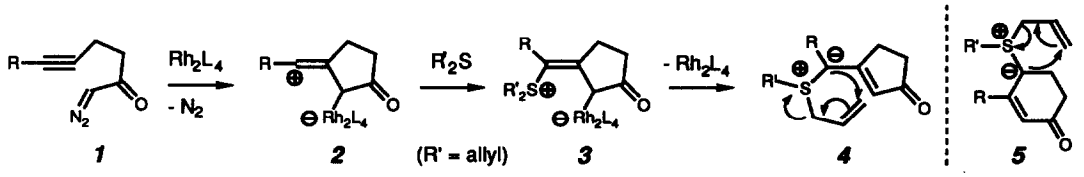
Summary: *Acetylenic α-diazoketones **1**, when treated with catalytic rhodium carboxylate dimer and diallylsulfide (1.1 equiv), undergo sequential alkyne insertion/ylide formation/sigmatropic rearrangement to give γ-allylthio cyclic enones. This transformation was used to probe the influence of alkyne substituents on 5-exo vs. 6-endo cyclization selectivity in the alkyne insertion event.*

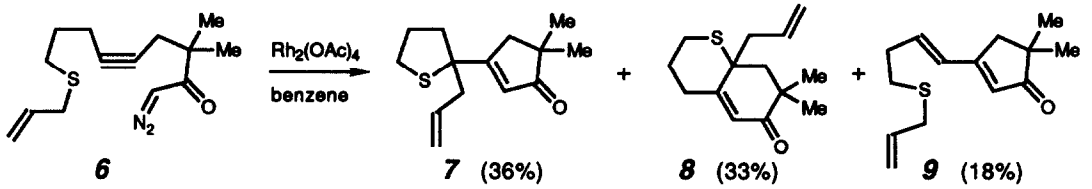
The metal-catalyzed generation of ylides from α-diazocarbonyl compounds and heteroatom-bearing molecules has been widely studied.[2] It is believed that nucleophilic addition to a reactive electrophilic α-ketometallocarbene intermediate is followed by dissociation of the catalyst and free ylide. An analogous process would involve addition of a heteroatom (e.g., S) to a vinylogous metallocarbene (e.g., **2**), generated from **1** by 5-exo electrophilic attack of the initial metallocarbene at an appropriately tethered alkyne unit. This mode of "alkyne insertion" and ylide formation would result in intermediate **4** (perhaps via **3**), while the parallel 6-endo cyclization pathway would result in its isomer **5**. A variety of methods for trapping transient species like **2** has been studied,[3] but only oxygen nucleophiles have been employed for formation of ylide intermediates derived from **2** thus far.[3a-d]



1 *2* *3* *4* *5*

Doyle has demonstrated that the allyl sulfur ylide rearrangement provides a useful indirect method for detecting transient metallocarbene complexes in the metal catalyzed reaction of ethyl diazoacetate and allyl methyl sulfide.[2c] In this paper we report the results of a similar strategy to identify *regioisomeric* carbene intermediates in the alkyne insertion reaction. We have found that sulfur ylide formation readily occurs to give intermediates **4** or **5** which spontaneously undergo [2,3]-sigmatropic rearrangement[4] to isolable compounds. The ratio of products arising from **4** and **5** and, thus, the regioselectivity of the cyclization of **1** is highly dependent on the alkyne substituent R.

Scheme 1

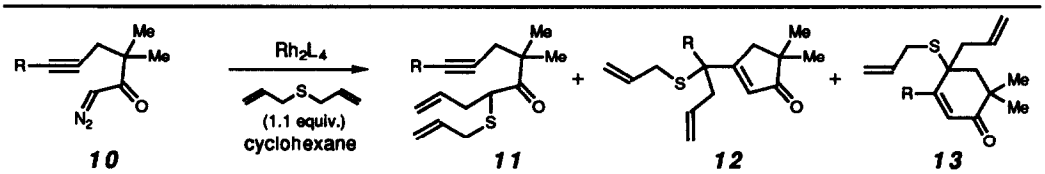


6 **7** (36%) **8** (33%) **9** (18%)

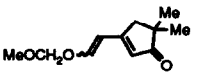
The high efficiency with which sulfide traps vinylogous carbene intermediates was first demonstrated by the catalytic decomposition of **6** (0.04 M in benzene, 5 mol% $Rh_2(OAc)_4$, 70 °C, 4 h) to give the heterocycles **7** and **8** as well as the 1,2-hydrogen migration product **9** in good overall yield after SiO_2 chromatography.[5] The lack of significant byproducts in this intramolecular cyclization prompted us to explore bimolecular versions, which are described in Table 1. For example, a solution of the methyl substituted alkyne **10a** (entry 1) and 1.1 molar equivalents of diallylsulfide in cyclohexane (0.10 M) was treated with 5 mol% $Rh_2(OAc)_4$ at room temperature for 22 hours. Filtration of the resultant pink solution through a short plug of SiO_2 and concentration gave the crude material which was chromatographed to provide uncyclized sulfide **11a** and equal portions of cyclopentenone **12a** and cyclohexenone **13a**.

The low regioselectivity in cyclizations with R = alkyl group is dramatically increased in reactions of the 6-endo selective terminal alkyne **10b** and the 5-exo selective phenyl alkyne **10c** (entries 2 and 3). Diazoketone

Table 1[a] Rh(II) Induced Bimolecular Alkyne Insertion/Allyl Sulfur Ylide Rearrangements of Diazoketones **10**.



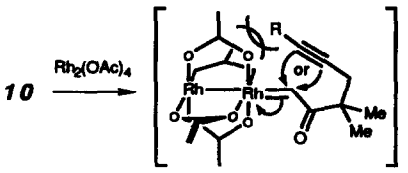
10 **11** **12** **13**

Entry	R(in 10-13)	[10]	Yield, %[b]		
1	***a*** R = Me	(0.10 M)	10 %	33 %	31 %
2	***b*** R = H	(0.15 M)	*c*	*c*	80 %
3	***c*** R = Ph	(0.09 M)	15 %	71 %	*c*
4	***c*** R = Ph	(0.50 M)	(26 %)[d]	(60 %)[d]	*c*
5	***c*** R = Ph	(0.05 M)	(8 %)[d]	(78 %)[d]	*c*
6	***c*** R = Ph	(0.02 M)	(2 %)[d]	(83 %)[d]	*c*
7	***d*** R = CH_2OMOM	(0.11 M)	19 %	 **14** 42 %	36 %

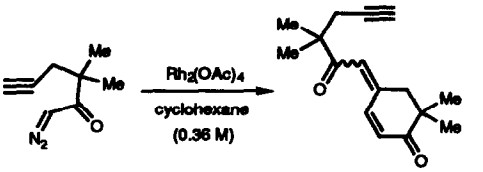
[a]All reactions were run using ~5 mol% $Rh_2(OAc)_4$ (entries 1-3) or $Rh_2(O_2CC_7H_{15})_4$ (entries 4-7) and 1.1 equiv. of diallylsulfide at 25 °C for ~20 h under N_2 at the indicated [10]. [b]Yields not in parentheses refer to isolated material after MPLC on SiO_2. [c]Product not observed, therefore <1 % yield. [d]Parallel experiments, yields estimated by gc analysis.

10b underwent conversion solely to cyclo*hex*enone **13b** in 80% yield. The absence of acyclic sulfide **11b** from this reaction (entry 2) likely illustrates the enhanced rate of cyclization when R = H over compounds with other (bulkier) substituents. This is consistent with the presence of a destabilizing steric interaction between the R group and the carboxylate ligands of the catalyst in the presumed intermediate geometry required for nucleophilic addition by the alkyne onto the electron-deficient carbene center[3e] (Scheme 2). In the absence of

Scheme 2



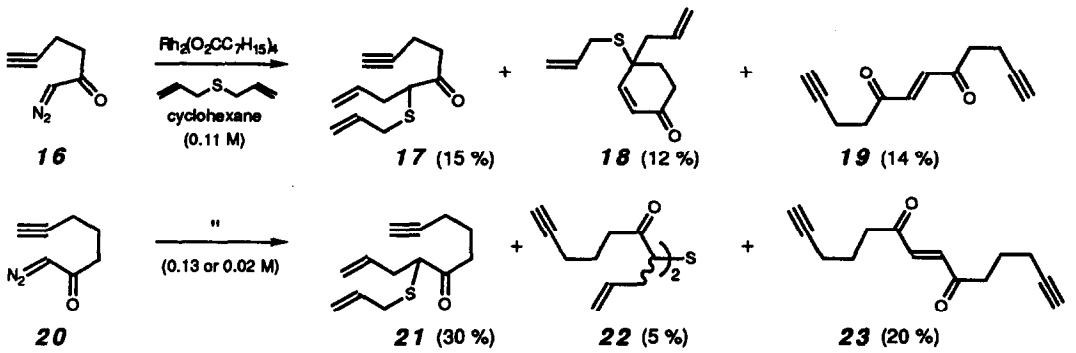
Scheme 3



diallylsulfide, $Rh_2(OAc)_4$ induced a regio- and stereospecific dimerization of **10b** to give **15** (Scheme 3). No symmetrical, acyclic carbene dimer was observed (gc-ms). Again cyclization preceded bimolecular trapping (in this case by another diazoketone molecule) even at relatively high concentration. The phenyl-substituted alkyne **10c** (entry 3) gave the cyclo*pent*enone **12c** and the acyclic isomer **11c** in ratios inversely related to the reaction concentration (entries 4-6). Thus, sulfonium ylide formation *prior* to alkyne insertion was reduced to an acceptable level by simply decreasing the molarity of the reactants to 0.02 M (entry 6). The alkoxymethyl substituted alkyne **10d** exhibited only slight preference for 5-exo cyclization (entry 7), but 1,2-migration of the O-activated hydrogen to yield *E*- and *Z*-**14**[6] competed effectively with ylide formation. The 5-exo vs. 6-endo selectivity in these reactions is probably derived from a combination of steric interactions between R and the catalyst (Scheme 2) and the ability of the R group to stabilize cyclic vinylogous carbene intermediates like **2**.[3e]

The reaction of **16** (Scheme 4) illustrates the important role of the geminal α-methyl substituents in substrates **10**. Although the same cyclization regiospecificity was observed as with **10b**, uncyclized sulfide **17** and uncyclized dimer **19** comprised the majority of the isolated material. This reduced rate of cyclization relative to **10b** can probably be attributed to the absence of the Thorpe-Ingold effect[7] and the enhanced steric accessibility of the initial acyclic carbene intermediate from **16**. Reaction of the one carbon homolog **20** led only to acyclic products **21**-**23**. Presumably, the unusual dimer **22** (mixture of diastereomers) arose via ylide formation between **20** and **21** and subsequent [2,3]-sigmatropic rearrangement.

Scheme 4



The results described here indicate that both 5-exo and 6-endo specific alkyne insertions can occur, and that sulfonium ylide formation *after* cyclization can be induced with high efficiency. We are currently investigating rearrangements and other applications of similarly generated sulfur ylide intermediates.

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References and Notes

1) Graduate Fellow of the ACS Division of Organic Chemistry, sponsored by Glaxo Research Laboratories, 1990-1991.

2) Reviews: a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. Allylthio-α-diazocarbonyl decompositions: c) Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, 860. d) Tamblyn, W. H.; Hoffmann, S. R.; Doyle, M. P. *J. Organomet. Chem.* **1981**, *216*, C64. e) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1988**, *29*, 6005.

3) a) Padwa, A.; Krumpe, K. E.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 2633. b) Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J. M.; Krumpe, K. E.; Schofftstall, A. M. *J. Org. Chem.* **1990**, *55*, 414. c) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518. d) Padwa, A.; Krumpe, K. E.; Garreau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523. e) Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4343. f) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, *32*, 3755.

4) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.*, **1979**, *18*, 563.

5) The spectroscopic properties of all compounds are in full agreement with the assigned structures.[8] Yields are not optimized.

6) Isolated as a mixture of isomers, 4:1::*E*:*Z*. This *E*-stereoselectivity (see also 9) is consistent with previously observed 1,2-hydrogen migrations *after alkyne insertion*.[3b-e] See ref 3e for mechanistic discussion and comparison with C-H insertions of carbene complexes derived from simple α-diazoketones.

7) a) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505. b) Jung, M. E. *Synlett* **1990**, 186.

8) Selected characterization data for compounds; **7**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.93 (dd, J = 1.5 and 1.5 Hz, C<u>H</u>CO), 5.62 (dddd; J = 17.5, 10.4, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.07 (bd, J = 17.5 Hz, CH=H$_E$H$_Z$), 5.06 (bd, J = 10.4 Hz, CH=H$_E$H$_Z$), 2.92-2.97 (m, C<u>H</u>$_2$S), 2.65 (dddd; J = 15.0, 7.0, 1.2, and 1 Hz; C<u>H</u>$_a$H$_b$CH=CH$_2$), 2.64 (dddd; J = 15.0, 7.0, 1.2, and 1 Hz; CH$_a$H$_b$CH=CH$_2$), 2.56 (dd, J = 17.9 and 1.5 Hz, C<u>H</u>$_a$H$_b$CMe$_2$), 2.44 (dd, J = 17.9 and 1.5 Hz, CH$_a$H$_b$CMe$_2$), 2.1-2.21 (m, 2H), 1.91-2.1 (m, 2H), 1.09 (s, C<u>H</u>$_3$), and 1.11 (s, C<u>H</u>$_3$). IR ($CDCl_3$): ν(C=O) 1690 cm^{-1}. GC/MS (EI): m/z 236 (M$^{\oplus}$, 2), 195 (100). **8**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.78 (dd, J = 1 and 1 Hz, C<u>H</u>CO), 5.71 (dddd; J = 17, 10.8, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.16 (dddd; J = 10.8, 1, 1, and 1 Hz; CH=H$_E$H$_Z$), 5.14 (dddd; J = 17, 1, 1, and 1 Hz; CH=H$_E$H$_Z$), 3.11 (dd, J = 12.9 and 3 Hz, C<u>H</u>$_a$H$_b$S), 3.05 (dd, J = 12.9 and 2.5 Hz, CH$_a$H$_b$S), 2.76 (dddd; J = 13.9, 7.0, 1, and 1 Hz; C<u>H</u>$_a$H$_b$CH=CH$_2$), 2.65 (dddd; J = 13.9, 7.0, 1, and 1 Hz; CH$_a$H$_b$CH=CH$_2$), 2.15-2.54 (m, 3H), 2.11 (d, J = 15.2, Hz, C<u>H</u>$_a$H$_b$CMe$_2$), 1.93 (m, 1H), 1.59 (d, J = 15.2, Hz, CH$_a$H$_b$CMe$_2$), 1.27 (s, C<u>H</u>$_3$), and 1.09 (s, C<u>H</u>$_3$). IR ($CDCl_3$): ν(C=O) 1660 cm^{-1}. GC/MS (EI): m/z 236 (M$^{\oplus}$, 12), 195 (100). **11c**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35-7.40 (m, 2 ArH), 7.27-7.30 (m, 3 ArH), 5.76 (dddd; J = 17.1, 10.0, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.73 (dddd; J = 17.1, 10.0, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.14 (bd, J = 17.1 Hz, CH=CH$_E$H$_Z$), 4.98-5.10 [m, (CH=H$_E$H$_Z$) and (CH=CH$_E$H$_Z$)$_2$], 3.76 (dd, J = 8.3 and 6.4 Hz, C<u>H</u>S), 3.22 (bdd, J = 13.2 and 7.0 Hz, SCH$_a$H$_b$), 3.08 (bdd, J = 13.2 and 7.0 Hz, SCH$_a$H$_b$), 2.69 (bddd; J = 13.9, 8.3, and 7.0 Hz; CHC<u>H</u>$_a$H$_b$CH=CH$_2$), 2.66 (s, C≡CC<u>H</u>$_2$), 2.44 (bddd; J = 13.9, 7.0, and 6.4 Hz; CHCH$_a$H$_b$CH=CH$_2$), 1.39 (s, C<u>H</u>$_3$), and 1.35 (s, C<u>H</u>$_3$). IR ($CDCl_3$): ν(C=O) 1693 cm^{-1}. HRMS (CI, isobutane): Anal. calcd for $C_{20}H_{24}OS$ 312.1523. Found 312.1548. **12c**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.26-7.36 (m, 5 ArH), 6.10 (dd, J = 1.6 and 1.6 Hz, C<u>H</u>CO), 5.73 (dddd; J = 17.0, 9.9, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.64 (dddd; J = 17.0, 10.2, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.12 (bd, J = 17 Hz, CH=CH$_E$H$_Z$), 4.96-5.05 [m, (CH=H$_E$H$_Z$) and (CH=CH$_E$H$_Z$)$_2$], 2.89 [bd, J = 7.0 Hz, (C<u>H</u>$_2$CH=CH$_2$)$_2$], 2.55 (dd, J = 18.3 and 1.6 Hz, C<u>H</u>$_a$H$_b$CMe$_2$), 2.37 (dd, J = 18.3 and 1.6 Hz, CH$_a$H$_b$CMe$_2$), 1.08 (s, C<u>H</u>$_3$), and 1.06 (s, C<u>H</u>$_3$). IR ($CDCl_3$): ν(C=O) 1695 cm^{-1}. Anal. calcd for $C_{20}H_{24}OS$: C, 76.88; H, 7.74. Found C, 77.07; H, 7.76. **13b**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.65 (d, J = 10.1 Hz, C<u>H</u>=CH), 5.90 (d, J = 10.1 Hz, CH=C<u>H</u>), 5.89 (dddd; J = 17.0, 10.3, 7.1, and 7.1 Hz; C<u>H</u>=CH$_2$), 5.83 (dddd; J = 17.0, 9.9, 7.0, and 7.0 Hz; C<u>H</u>=CH$_2$), 5.06-5.23 [m, (CH=C<u>H</u>$_2$)$_2$], 3.20 (ddd; J = 7.0, 1, and 1 Hz; SC<u>H</u>$_2$), 2.56 (bd, J = 7.1 Hz, CC<u>H</u>$_2$CH=CH$_2$), 2.09 (d, J = 15.2 Hz, C<u>H</u>$_a$H$_b$CMe$_2$), 2.02 (d, J = 15.2 Hz, CH$_a$H$_b$CMe$_2$), 1.25 (s, C<u>H</u>$_3$), and 1.16 (s, C<u>H</u>$_3$). IR ($CDCl_3$): ν(C=O) 1675 cm^{-1}. HRMS (CI, NH_3): Anal. calcd for $C_{14}H_{20}OS+H^{\oplus}$ 237.1313. Found 237.1329.

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