Unusual Medium Effect on the Distribution of 1,2,3-Selenadiazole Regioisomers in the Reaction of *N*-Benzyl-4-homopiperidinone Semicarbazone with Selenium Dioxide

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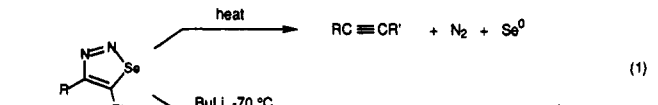
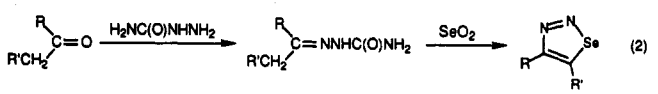
Four 7-membered-ring, unsymmetrical semicarbazones (1, 4–6) were reacted with selenium dioxide to give 1,2,3-selenadiazole products. Special interest was directed to the regiochemical control obtained. Carbocycle 6 and carbamate 4 provided slightly more "proximal" isomer (**a**; ca. 70%) than "distal" isomer (**b**; ca. 30%), and the ratios were unaffected by the presence of water. Thioether 5 showed a significant bias toward the proximal isomer (**8a:8b** = ca. 7:1); again, there was essentially no water dependence. Amino compound 1 behaved like 4 and 6 in relatively nonpolar solvents, but the proximal isomer **2a** was much more prevalent (75 to >96%) in polar, protic media. For the case of 1, water dramatically amplified the amount of proximal isomer **2a** in ether solvents, from 60–65 to 90–95%, and HOAc (at 23 °C) gave **2a** almost exclusively. When the HCl salt of 1 was reacted with selenium dioxide in anhydrous ether solvents, an enhancement of proximal isomer **2a** (from 60–65 to ca. 85%) was experienced, but water now had little effect on the isomer ratio. ^{77}Se NMR measurements were employed to distinguish and quantitate selenadiazole regioisomers.

1,2,3-Selenadiazoles are useful synthetically because they can fragment under relatively mild thermolysis conditions (ca. 150 °C) or on treatment with butyllithium at low temperature to acetylene derivatives, with concomitant extrusion of nitrogen and selenium (eq 1).[1] Over the years,



(1)



(2)

this reaction has proved especially fruitful as a source of unusual and highly strained acetylenes (as well as their adducts with trapping reagents) from aldehyde or ketone precursors that possess at least one α-methylene group.[1-3] The overall process simply involves conversion of the carbonyl compound to a semicarbazone derivative, which is then treated with selenium dioxide to generate the requisite 1,2,3-selenadiazole (eq 2).

In the case of an unsymmetrical semicarbazone with two available α-methylenes, a pair of selenadiazole products is possible. The regiochemistry of this ring closure has been addressed in the literature from time to time,[3,4] along with the effect of various structural features on the distribution of regioisomers. However, there has been no mention of the ability of other reaction parameters to exert a significant influence on regiocontrol. We now report that the oxidation of semicarbazone 1 to selenadiazoles **2a** and **2b** is subject to an unprecedented solvent dependence.

Results and Discussion

Selenium Dioxide Reactions. Reaction of amino ketone 3 with semicarbazide gave a mixture of *Z* and *E* semicarbazones (1; *Z*:*E* = 1:1), which crystallized as a 1:9 mixture of *Z*/*E* isomers.[5] Oxidation of *E*-rich 1 (*Z*:*E* = 10:90) with selenium dioxide in aqueous dioxane[3f] produced "proximal" selenadiazole **2a** preferentially (Table I, entries 2 and 3). The outcome was similar when a mixture of 1 containing about 50% of *Z*-1 was subjected to these conditions, albeit formation of **2a** was now slightly enhanced

Table I. Reaction of Semicarbazone Derivatives with SeO_2[a]

entry	substrate	reaction medium	product ratio[b]
1	1 (*Z*/*E* = 1:1)	dioxane/water (5:1)	**2a:2b** = 20:1[c]
2	1	dioxane/water (5:1)	**2a:2b** = 9.5:1[d]
3	1	dioxane/water (1:5)	**2a:2b** = 9:1
4	1	dioxane	**2a:2b** = 1.5:1
5	1	HOAc/water (1.3:1)	**2a:2b** = 7:1
6	1	HOAc	**2a:2b** = >25:1[e]
7[f]	1	HOAc	**2a:2b** = 3.4:1
8	1	DMF-d_7	**2a:2b** = 5:1
9	1	CD_3CN	**2a:2b** = 4:1
10	1	$CDCl_3$	**2a:2b** = 3.7:1
11	1	$CHCl_3$	**2a:2b** = 3:1
12	1	CD_2Cl_2	**2a:2b** = 2:1
13	1	*t*-BuOH	**2a:2b** = 2.6:1
14	1	THF/water (5:1)	**2a:2b** = 9:1
15	1	THF	**2a:2b** = 2:1[g]
16[h]	1	THF	**2a:2b** = 2:1
17	1	THF-d_8	**2a:2b** = 1.2:1
18	1·HCl	dioxane/water (5:1)	**2a:2b** = 6:1
19	1·HCl	HOAc	**2a:2b** = >25:1
20	1·HCl	THF	**2a:2b** = 5:1[i]
21	4	dioxane/water (5:1)	**7a:7b** = 2:1[j]
22	4	HOAc	**7a:7b** = 2.9:1
23[f]	4	HOAc	**7a:7b** = 1.5:1[k]
24	4	THF	**7a:7b** = 2:1[j]
25	5	dioxane/water (5:1)	**8a:8b** = 7:1[l]
26	5	THF	**8a:8b** = 6.7:1
27	6	dioxane/water (5:1)	**9a:9b** = 2.4:1
28	6	THF	**9a:9b** = 2.5:1
29	6	dioxane	**9a:9b** = 2.6:1

[a] Reactions were conducted at 23 °C with 2 molar equiv of SeO_2, unless indicated otherwise. Compound 1 is enriched in *E* isomer (*Z*:*E* = 10:90), unless indicated otherwise; 4 and 6 are solely the *E* isomer; 5 is solely the *Z* isomer. [b] Ratios reported in this table are based on ^{1}H NMR integration data. [c] Isolated crude yield of mixture was 100%. [d] Isolated crude yield of mixture was 80%. [e] No **2a** was detected by 400-MHz ^{1}H NMR, although a trace was seen by TLC; isolated yield was 58%. The same ratio of **2a:2b** was obtained with 1 molar equiv of SeO_2 in HOAc at 23 °C. [f] Reaction was carried out at reflux with 1 molar equiv of SeO_2. [g] Isolated yield of mixture was 48%. [h] Freshly sublimed SeO_2 (260–280 °C (0.1 Torr)) was used. [i] Other unidentified components were present. [j] Isolated yield of mixture was 18%. [k] Isolated yield of mixture was 40%. [l] Average of two separate experiments with ratios of 6:1 and 8:1.

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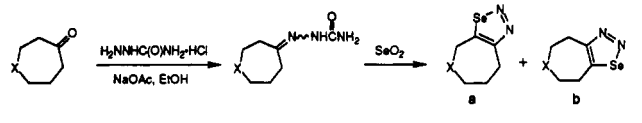
Scheme I



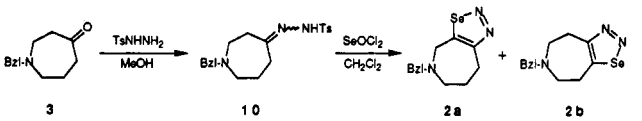
1 X = NCH_2Ph
4 X = $NCO_2C_2H_5$
5 X = S
6 X = CMe_2
11 X = CHEt

2 X = NCH_2Ph
7 X = $NCO_2C_2H_5$
8 X = S
9 X = CMe_2
12 X = CHEt

(entry 1). Likewise, a mixture of *Z*-rich 1 (*Z*:*E* = 90:10) predominantly furnished **2a**. Thus, the semicarbazone *Z*/*E* ratio has little bearing on the regiochemistry, as was realized earlier by Zimmer and Meier for a different cyclic semicarbazone derivative.[3f] Since the ratio of **2a**/**2b** did not change significantly over the course of the reaction, as monitored by TLC, we can rule out selective decomposition of one isomer to give the observed high selectivity.

Interestingly, on changing the solvent to anhydrous dioxane the proportion of "distal" selenadiazole **2b** was greatly enhanced, such that the product ratio became **2a**:**2b** = 1.5:1 (entry 4). The selenium dioxide cyclization of 1 (*Z*:*E* = 10:90) was examined under a variety of conditions, and the results are presented in Table I. Overall, the mixture of selenadiazoles varied according to the medium employed on a fairly wide spectrum, from >25:1 in HOAc at 23 °C (entry 6) and 20:1 in aqueous dioxane (entry 1) to 1.2:1 in anhydrous THF-d_8 (entry 17). The regioselectivity observed for the cyclization of 1 in ether solvents seems to be especially sensitive to the presence or absence of water in the medium. When 1 was subjected to selenium dioxide oxidation in anhydrous tetrahydrofuran (THF), the ratio of **2a**/**2b** was the same as that for anhydrous dioxane (entries 15 and 4); in the former case, freshly sublimed selenium dioxide gave an identical result (entry 16). By the same token, cyclization in aqueous THF mimicked the results for aqueous dioxane (entries 2 and 14; with 1 molar equiv of water in THF, the amount of proximal isomer increased slightly, **2a**:**2b** = 3.5:1). The reactions at 23 °C generally required 2 molar equiv of selenium dioxide for complete conversion to products; with

Scheme II



3 10 **2a** **2b**

1 molar equiv, the reaction stopped at 50% conversion. A requirement for 2 molar equiv of selenium dioxide may be related to the insolubility of elemental selenium formed during the course of reaction in the solvent media at room temperature. With acetic acid solutions, in which the elemental selenium is better dissolved, 1 molar equiv of selenium dioxide sufficed to drive the reaction of 1 and 4 to completion (entries 7 and 23). Surprisingly, although refluxing HOAc afforded a modest regioselectivity for proximal isomer **2a** (entry 7), HOAc at room temperature afforded a very high selectivity (>25:1) for **2a** (entry 6). It turned out that addition of water to the acetic acid reaction in this situation actually detracted from the high proximal selectivity (entry 5).

It was reasonable to suppose that the basic amino functionality within the homopiperidine ring is somehow responsible for the unprecedented solvent effect on regiochemistry. Protonation of the nitrogen of 1 (1·HCl) caused the ratio in aqueous dioxane to change from 20:1 to 6:1 (cf. entries 1 and 18) and that in THF to change from 2:1 to 5:1 (cf. entries 15 and 20). Thus, the extraordinary regioselectivity with HOAc may be related more to a medium effect than to protonation on nitrogen (cf. entries 6 and 19).

Extending this approach, we conducted selenium dioxide oxidation experiments at two ends of the solvent spectrum with semicarbazone derivatives **4**–**6**, in which the basic nitrogen is now replaced by an amide nitrogen, a sulfur, or a carbon, respectively (Scheme I). We intended for these compounds to serve as model substrates and as links to regiochemical results already in the literature (vide infra).[3] With **4** in either aqueous dioxane or anhydrous THF, the regioselectivity was low and virtually the same, selenadiazoles **7a** and **7b** being formed in a ratio of 2:1 (entries 21 and 24). By the same token, reaction of **5** in aqueous dioxane (entry 25) or anhydrous THF (entry 26) afforded similar ratios for **8a** and **8b** (ca. 7:1). The reaction of **6** in aqueous dioxane (entry 27) or anhydrous ethers (entries 28 and 29) showed virtually no selectivity and similar ratios of **9a** and **9b** (ca. 2.5:1).[6] Although each semicarbazone **4**–**6** engendered a different ratio of selenadiazole regioisomers, the sensitivity to solvent appears to be absent for these reactions. Thus, the results with amine 1 do represent a special phenomenon.

Reactions with $SeOCl_2$. Grandi and Vivarelli prepared selenadiazoles from various tosylhydrazones by oxidizing them with selenoyl dichloride in methylene chloride at low temperature (−15 °C).[4] The regiochemistry they observed with tosylhydrazones of unsymmetrical aliphatic methyl ketones was highly biased to one selenadiazole, the internal one derived from the thermodynamically more favored enehydrazine. Since this regiochemistry is opposite to that for selenium dioxide reactions with such systems,[3a,f] which are biased to the terminal product, we decided to examine this reagent. With selenoyl dichloride under the published conditions, tosylhydrazone **10** yielded **2a** and **2b** in a 5.7:1 ratio (Scheme II). Applying the same reaction to semi-

(1) (a) Lalezari, I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 352–354. (b) Lalezari, I.; Shafiee, A.; Yalpani, M. *Adv. Heterocycl. Chem.* **1979**, *24*, 127. (c) Meier, H.; Hanold, N.; Molz, T.; Bissinger, H. J.; Kolshorn, H.; Zountas, J. *Tetrahedron* **1986**, *42*, 1711 and references cited therein. (d) Hevesi, L.; Krief, A. In *Organoselenium Chemistry I*; Springer-Verlag: Berlin, 1988; pp 170–177.

(2) (a) Hanold, N.; Meier, H. *Chem. Ber.* **1985**, *118*, 198. (b) Gleiter, R.; Karcher, M.; Jahn, R.; Irngartinger, H. *Ibid.* **1988**, *121*, 735. (c) Meier, H.; Molz, T.; Merkle, U.; Echter, T.; Lorch, M. *Liebigs Ann. Chem.* **1982**, 914. (d) Bissinger, H.-J.; Detert, H.; Meier, H. *Ibid.* **1988**, 221. (e) Gleiter, R.; Kratz, D.; Schehlmann, V. *Tetrahedron Lett.* **1988**, *29*, 2813. (f) Tokitoh, N.; Ishizuka, H.; Ando, W. *Chem. Lett.* **1988**, 657. (g) Meier, H.; Petersen, H. *Synthesis* **1978**, 596.

(3) (a) Lalezari, I.; Shafiee, A.; Yalpani, M. *J. Org. Chem.* **1971**, *36*, 2836. (b) Shafiee, A.; Toghraie, S.; Aria, F.; Mortezaei-Zandjani, G. *J. Heterocycl. Chem.* **1982**, *19*, 1305. (c) Petersen, H.; Meier, H. *Chem. Ber.* **1980**, *113*, 2383. (d) Meier, H.; Layer, M.; Combrink, W.; Schniepp, S. *Ibid.* **1976**, *109*, 1650. (e) Meier, H.; Mayer, W.; Kolshorn, H. *Ibid.* **1987**, *120*, 685. (f) Zimmer, O.; Meier, H. *Ibid.* **1981**, *114*, 2938. (g) Stavirdou, E.; Schuhmacher, H.; Meier, H. *Liebigs Ann. Chem.* **1989**, 435. (h) Meier, H.; Antony-Mayer, C.; Schulz-Popitz, C.; Zerban, G. *Ibid.* **1987**, 1087. (i) Meier, H.; Stavirdou, E.; Storek, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 809.

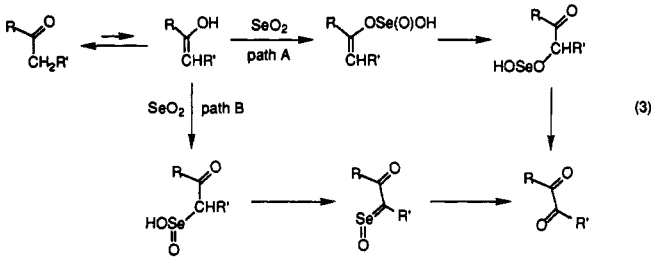
(4) For a study of regiochemistry in the formation of 1,2,3-selenadiazoles from tosylhydrazones and $SeOCl_2$, see: Grandi, R.; Vivarelli, P. *J. Chem. Res., Synop.* **1989**, 186.

(5) When the reaction was complete (0.5 h), the *Z*/*E* ratio was approximately 1:1 (TLC). However, over several hours the crude reaction mixture equilibrated at room temperature, resulting in material with a *Z*/*E* ratio of 1:9. The product crystallized from ethanol as a 1:9 mixture of *Z*/*E* isomers (TLC, ^1H NMR, MS). The pure semicarbazone isomers, separated by preparative TLC, were found to maintain their stereochemical integrity after standing in methanol at 23 °C for 48 h.

(6) An identical study was conducted on the corresponding cycloheptanone system with X = CHEt (viz. 11). Although the ratio of selenadiazole regioisomers could not be ascertained by ^1H NMR, even by using two-dimensional techniques (because of the complexity of the spectra), we found a 1.1:1 ratio of **12a**:**12b** by using ^{77}Se NMR (vide infra).

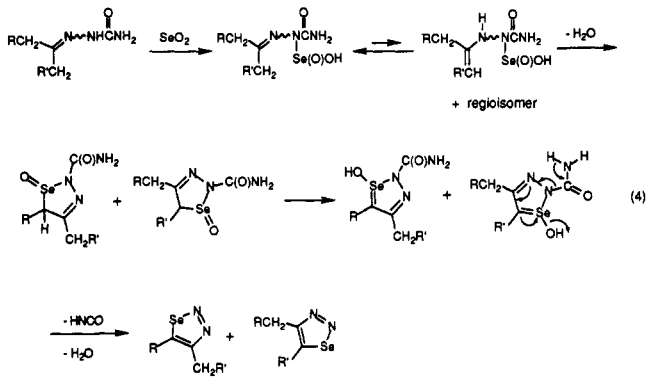
carbazone 1 yielded **2a** and **2b** in a 2:1 ratio, which mimics our result for the oxidation of 1 with selenium dioxide in CD_2Cl_2.

Regiochemistry for Selenadiazole Formation and the Unusual Behavior of 1. The α-oxidation of aldehydes and ketones with selenium dioxide to yield 1,2-dicarbonyl products is a well-known process, and two related mechanisms have been proposed. Corey and Schaefer[7] suggested initial formation of a selenate ester with the oxygen of the enol form, followed by rearrangement to an α-keto selenolate and elimination of water and elemental selenium (eq 3, path A). More recently, Sharpless and



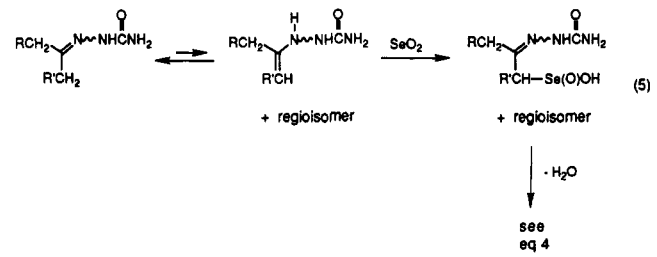
(3)

Gordon[8] offered a sound argument for a mechanism involving direct attack by electrophilic selenium on the carbon–carbon double bond of the enol tautomer, followed by dehydration of the keto seleninic acid and elimination of elemental selenium (eq 3, path B). It is reasonable to suppose that semicarbazones would be prone to similar reactivity with selenium dioxide, in which case a related enehydrazine would be crucial. For the case of a ketone semicarbazone, mechanisms have been proposed that entail initial selenamide formation on the sp^3 nitrogen,[1a,9] in a manner related to the Corey–Schaefer mechanism (eq 4).



(4)

This intermediate then tautomerizes to an enehydrazine, which suffers attack on the carbon–carbon double bond by the electrophilic selenium to give a dihydroselenadiazole *Se*-oxide (with loss of water). A tautomer of this species loses water and hydrocyanic acid (which readily combine to form ammonium bicarbonate) to afford the final selenadiazole(s). A mechanism involving direct attack on the 2-position of the enehydrazine to generate an unstable hydrazone seleninic acid, according to Sharpless and Gordon, is also plausible (eq 5). This species could cyclize to a 5-membered heterocycle, thereby capturing the selenium. The rest of the route to selenadiazole(s) would proceed according to eq 4. As far as regiochemistry is concerned, the critical point of either mechanism would seem to be the relative ease of formation and/or relative reactivities of the two enehydrazines.



(5)

How might this pertain to our studies? With carbocycle model **6**, we obtained similar amounts of the two possible regioisomers, and the distribution was independent of the presence of water. Surprisingly, carbamate **4** provided analogous results. On the other hand, thio ether **5** showed a much greater bias for selenium introduction at the carbon more *proximate* to the endocyclic sulfur atom; again, there was no water dependence. Presumably, the enehydrazine in this "proximal" orientation is formed more easily and/or is more reactive than the "distal" one. Interestingly, for the case of an α-thio ether (in comparison to our β-thio ether **5**) Meier and co-workers observed complete regiochemical preference for the proximal isomer.[3g,i] The enehydrazine for this direction would be expected to form more easily because of enhanced acidity at that α-carbon of the hydrazone. Shafiee et al. reported similar α-carbon reactivity for thio and seleno ethers; however, ethers reacted in the opposite sense.[3b] β,γ-Conjugative groups (like vinyl, cyclopropyl, phenyl, and carbethoxy) also directed cyclization to the proximate carbon.[3c,d,f,h] However, an equal proportion of regioisomers was found with a γ,δ-alkene group,[3c] comparable to what we observed with **6**. By contrast, a γ,δ-epoxide gave mostly the proximal isomer,[3e] and a γ-bromo substituent gave a moderate preference for the proximal isomer, as well.[3f]

The behavior of amino compound **1** in relatively nonpolar solvents is similar to that seen with **4** and **6**, rather than with **5** (Table I). The proximal isomer is more prevalent in polar solvents and highly preferred (>90%) in ether/water mixtures or HOAc at 23 °C. Although water has a dramatic effect on amplifying the amount of proximal isomer in ether solvents, it has little effect in acetic acid. In this respect, compound **1** falls into a class by itself. When **1** is protonated as an independent salt in anhydrous ether solvent, an enhancement of the proximal isomer is experienced; however, water now has little effect on the regiochemistry.

To explain these results, one could suggest that the β-amino group, when it is protonated and/or strongly hydrogen bonded, either allows the proximal enehydrazine intermediate to form more readily or enhances the reactivity of this intermediate. As the latter seems a less likely possibility to us, we suggest that ease of enehydrazine formation may be the critical factor.[10] At this juncture, one cannot reach a more concrete conclusion on this issue.

Selenium-77 NMR of Selenadiazoles. We found ^1H NMR spectroscopy to be useful for determining ratios of selenadiazole regioisomers in most instances. However, in the case of carbamate **7** we had to warm the NMR sample to ca. 75 °C to increase the rate of interconversion of the amide rotamers relative to the NMR time scale. Otherwise, the spectrum represented four different species and was too complex to evaluate. We also had difficulty

(7) Corey, E. J.; Schaefer, J. P. *J. Am. Chem. Soc.* **1960**, *82*, 918.
(8) Sharpless, K. B.; Gordon, K. M. *J. Am. Chem. Soc.* **1976**, *98*, 300.
(9) (a) Lalezari, I.; Shafiee, A.; Yalpani, M. *Tetrahedron Lett.* **1969**, 5105. (b) Meier, H.; Voigt, E. *Tetrahedron* **1972**, *28*, 187.

(10) There is really no way at this time to get a handle on the effect of β-heteroatom-containing groups on the enolization of semicarbazone species. In fact, this area is still not well understood for enolization of ketones, see: Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965. Pratt, N. E.; Albizati, K. F. *J. Org. Chem.* **1990**, *55*, 770 and references therein.

in using ^{1}H NMR data to quantitate the regioisomers of 12 (formed from 11).[6]

The selenadiazoles all contain a selenium-77 nucleus that could be used as a probe to determine regioisomer ratios. This is a spin = $^1/_2$ nucleus with a reasonable natural abundance (7.5%), a usable sensitivity (ca. 3 times that of ^{13}C), and an enormous chemical shift dispersion in the range of 3000 ppm.[11] The utility of ^{77}Se NMR for sensing minor structural differences was impressively illustrated by the work of Silks et al. on diastereomeric pairs of 1,3-oxazolidine-2-selones with remote stereogenic centers.[12] Thus, we were confident that the selenadiazole regioisomers would be assayable by this method.[13] Indeed, two clean signals for the isomers of **2**, **8**, **9**, and **12** were easily distinguished and quantitated by integration. Moreover, in the case of **7**, *four* signals, accounting for the *Z* and *E* amide rotamers of each regioisomer, were nicely discerned. *As the selenium atom is rather remote from the sites of change in 7, this auspicious outcome serves to underscore the resolving power of ^{77}Se NMR.* The NMR results are as follows: **2a**:**2b** = 9.5:1 (δ 1550.7/1538.3), **7a**:**7a'**:**7b**:**7b'** = 2.9:2.4:1.2:1 (δ 1539.7/1544.0/1557.1/1557.3), **8a**:**8b** = 7:1 (δ 1541.5/1560.0), **9a**:**9b** = 2.2:1 (δ 1549.5/1534.6), and **12a**:**12b** = 1.1:1 (δ 1539.8/1532.3). The isomer ratios for **2** and **7**–**9** were consistent with those determined by ^{1}H NMR (**12** could not be evaluated by ^{1}H NMR). From this brief investigation, it appears that ^{77}Se NMR is an effective method for differentiating and quantitating selenadiazole regioisomers. However, there is one important caveat to note: since the order of chemical shifts for pairs of selenadiazole regioisomers can be unpredictable, one cannot rely solely on ^{77}Se NMR to make unambiguous structural assignments.

Conclusion

The distribution of selenadiazole regioisomers in the reaction of semicarbazones with selenium dioxide, from our work and that of others,[3] can be influenced by substituents at α-, β-, and γ-positions relative to the hydrazone carbon. In several cases, the "proximal" regioisomer is substantially enhanced.[3] With the saturated 7-membered-ring system, a "desymmetrization node" of quaternary carbon or amide nitrogen gave little regiochemical bias, while a divalent sulfur atom gave a respectable bias for the proximal isomer. A tertiary amino nitrogen (in **1**) gave little-to-moderate bias for the proximal isomer in neutral organic solvents, unless water was added, in which case a high proportion of proximal product (85–95%) was realized. With this amino substrate, acetic acid at room temperature resulted in a remarkably high bias for the proximal isomer (>96%). While this report is the first to demonstrate the effect of solvent on the regiochemistry of selenadiazole formation, more importantly it reveals the unexpectedly impressive influence of polar solvent media, such as aqueous ethers or HOAc.

Our results with ^{77}Se NMR underscore the significance of this nucleus as a structural "reporter" in organic molecules.[12] It is particularly remarkable that the ^{77}Se nucleus in **7b** is able to sense the two amide rotamers ($\Delta\delta$ = 0.2 ppm) even though it is five bonds away and lies close to the symmetry axis defined by the amide C–N bond.

Experimental Section

General Procedures. Proton NMR spectra were recorded on either a Bruker AM-400 spectrometer or a Bruker AM-360 spectrometer with $CDCl_3$ as solvent and Me_4Si as an internal standard, unless otherwise indicated. NMR abbreviations are as follows: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; dist = distorted. ^{77}Se NMR spectra were obtained at 68.7 MHz on a Bruker AM-360 spectrometer in $CDCl_3$ at ambient probe temperature (ca. 25 °C); the measurements were conducted without heteronuclear proton decoupling to avoid temperature gradients in the samples and without spinning the NMR sample in the probe. The ^{77}Se chemical shifts were referenced to 60% $(CH_3)_2Se$/40% $CDCl_3$ at δ 0 as recommended by Luthra et al.[14] ^{77}Se T_1 values were determined to be in the range of 0.75–1.0 s by the standard inversion-recovery technique. This allowed for reliable quantitation of regioisomer ratios through integration. High-resolution mass spectra were obtained on a Finnigan-MAT 8230 double-focusing spectrometer with FC43 as standard. TLC separations were conducted on 250-μm silica plates with visualizations by UV fluorescence and iodine staining. Preparative TLC was performed with tapered silica gel plates (300–1700 μm). Flash chromatography was done with flash-column silica gel (32–63 μm). Melting points were determined on a Thomas-Hoover apparatus calibrated by a set of melting point standards.

Materials. Commercially available reagents were generally used without further purification. The following ketones were prepared by the ring-expansion method of Finney and Riley[15] with a modification in that oxalic acid, water, and 2-propanol were used in place of aqueous HCl for the decarboxylation step: *N*-carbethoxyhexahydro-4*H*-azepin-4-one[15] [70% yield; ^{1}H NMR δ 1.25 (t, 3 H, *J* = 7 Hz), 1.75–1.85 (m, 2 H), 2.6–2.7 (m, 4 H), 3.55–3.65 (m, 4 H), 4.13 (q, 2 H, *J* = 7 Hz)]; 4-thiepanone[16] [75%; ^{1}H NMR δ 2.0–2.1 (m, 2 H), 2.55–2.60 (m, 2 H), 2.75–2.9 (m, 6 H)]; 4,4-dimethylcycloheptanone[17] [74%; ^{1}H NMR δ 0.9 (s, 6 H), 1.45–1.48 (m, 2 H), 1.55–1.58 (m, 2 H), 1.68–1.72 (m, 2 H), 2.43–2.47 (m, 4 H)]; 4-ethylcycloheptanone[18] [87%; ^{1}H NMR δ 0.90 (t, 3 H, *J* = 2 Hz), 1.15–1.40 (m, 6 H), 1.59–1.65 (m, 1 H), 1.8–2.0 (m, 3 H), 2.45–2.5 (m, 3 H)]. *N*-Benzylhexahydro-4*H*-azepin-4-one hydrochloride (**3**) was prepared by a modification of the procedure of Yokoo and Morosawa,[19] in which potassium *tert*-butoxide in toluene was substituted for NaOEt in xylene [46%; mp 191–192 °C (lit.[19] mp 186–187 °C); ^{1}H NMR δ 2.0–2.1 (m, 1 H), 2.45–2.9 (m, 6 H), 3.55–3.65 (m, 1 H), 3.65–3.8 (m, 1 H), 3.85–3.95 (m, 1 H), 4.25 (d, 2 H, *J* = 4 Hz), 7.45–7.5 (m, 3 H), 7.63–7.65 (m, 2 H)].

The following semicarbazones were prepared by the method of Meier et al.:[3e] *N*-benzylhexahydro-4*H*-azepin-4-one semicarbazone (**1**) [72% yield; 1:9 mixture of *Z*/*E* isomers; mp 179–181 °C; ^{1}H NMR (DMSO-d_6) δ 1.6–1.65 (m, 2 H, *Z* isomer), 1.65–1.8 (m, 2 H, *E* isomer), 2.3–2.4 (m, 2 H, *E* isomer), 2.45–2.5 (m, 2 H, *Z* isomer), 2.5–2.6 (m, 6 H, *E* isomer), 2.6–2.7 (m, 6 H, *Z* isomer), 3.55 (s, 2 H, *E* isomer), 3.59 (s, 2 H, *Z* isomer), 6.20 (s, 2 H), 7.2–7.4 (m, 5 H), 8.77 (s, 1 H)]; *N*-carbethoxyhexahydro-4*H*-azepin-4-one semicarbazone (**4**) [91%; *E* isomer; mp 184.5–186 °C; ^{1}H NMR (DMSO-d_6) δ 1.1–1.25 (m, 3 H), 1.5–1.6 (br s, 2 H), 2.5–2.6 (m, 2 H), 3.3–3.4 (br s, 2 H), 3.41 (d, *J* = 4 Hz, 2 H), 3.48 (d, *J* = 5 Hz, 2 H), 3.95–4.10 (dist q, *J* = 7 Hz, 2 H), 6.1–6.3 (br s, 2 H), 8.85–8.95 (br s, 1 H)]; 4-thiepanone semicarbazone (**5**) [63%; *Z* isomer; mp 168–169.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.8–1.9 (m, 2 H), 2.35–2.45 (m, 2 H), 2.55–2.65 (m, 4 H), 2.75–2.8 (m, 2 H), 6.2–6.3 (br s, 2 H), 8.85–8.95 (br s, 1 H)]; 4,4-dimethylcycloheptanone semicarbazone (**6**) [56%; *E* isomer; mp 174–176 °C;

(11) For reviews on ^{77}Se NMR, see: (a) Lardon, M. A. In *Organic Selenium Compounds: Their Chemistry and Biology*, Klayman, D. L., Günther, W. H. H., Eds.; Wiley-Interscience: New York, 1973; pp 933–939. (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986, pp 17–21.

(12) Silks, L. A., III; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979. Also, see: Silks, L. A., III; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkin Trans. I*, in press. (We thank Dr. Silks for a preprint of this paper.)

(13) During the course of our work, the first (to our knowledge) ^{77}Se NMR data on selenadiazoles were reported: Duddeck, H.; Wagner, P.; Müller, D.; Jászberényi, J. C. *Magn. Reson. Chem.* **1990**, *28*, 549.

(14) Luthra, N. P.; Dunlap, R. B.; Odom, J. D. *J. Magn. Reson.* **1983**, *52*, 318.

(15) Finney, Z.; Riley, T. *J. Med. Chem.* **1980**, *23*, 895.

(16) Johnson, P.; Berchtold, G. *J. Org. Chem.* **1970**, *35*, 584.

(17) Glazer, E.; Knorr, R.; Ganter, C.; Roberts, J. *J. Am. Chem. Soc.* **1972**, *94*, 6026.

(18) Adamson, D. W.; Kenner, J. *J. Chem. Soc.*, **1939**, 181.

(19) Yokoo, A.; Morosawa, S. *Bull. Chem. Soc. Jpn.* **1956**, *29*, 631.

^{1}H NMR (DMSO-d_6) δ 0.84 (s, 3 H), 0.91 (s, 3 H), 1.3–1.4 (m, 3 H), 1.45–1.6 (m, 3 H), 2.23–2.28 (m, 2 H), 2.29–2.32 (m, 2 H), 6.17 (br s, 2 H), 8.67 (d, J = 13 Hz, 1 H)]; 4-ethylcycloheptanone semicarbazone[18] (11) [37%; ca. 1:1 mixture of Z/E isomers by ^{13}C NMR; mp 128–130 °C (lit.[18] mp 125–127 °C); ^{1}H NMR δ 0.89 (t, J = 2 Hz, 3 H), 1.1–1.4 (m, 4 H), 1.4–1.5 (m, 1 H), 1.55–1.7 (m, 1 H), 1.7–1.95 (m, 3 H), 2.1–2.2 (m, 1 H), 2.3–2.35 (m, 2 H), 2.35–2.5 (m, 1 H), the NH signals were very broad]. The geometries of the semicarbazones were determined by proton homonuclear decoupling and ^{1}H NMR NOE experiments.

Selenium Dioxide Oxidation of Semicarbazones. A. General Procedure. The semicarbazone (0.1 mmol), selenium dioxide (22 mg, 0.2 mmol), and 1 mL of solvent were combined and stirred for 1–5 days. The reaction mixture was passed through filter aid, and the filter cake was washed well with methylene chloride or chloroform. The combined filtrate and washings were dried (K_2CO_3) and evaporated in vacuo at room temperature. The residue was examined directly by ^{1}H NMR or purified by preparative TLC with preservation of the original isomer composition and examined by NMR. The yields of crude organic products, which contained some TLC origin material, generally ranged between 50 and 100%; purification in several experiments indicated that around half the crude product was the desired selenadiazoles.

B. Example. Selenadiazoles 2a and 2b. A 1:9 Z/E mixture of semicarbazone 1 (2.18 g, 8.4 mmol) in 40 mL of anhydrous tetrahydrofuran was treated with selenium dioxide (1.85 g, 16.8 mmol) and stirred for 72 h under nitrogen. The reaction mixture was passed through Dicalite, and the cake was washed well with methylene chloride. Concentration of the filtrate and washings supplied a brown oil, which was triturated three times with hot ethyl acetate/hexane (1:6) and then with ethyl acetate. The supernatants were combined and evaporated in vacuo to give a mixture of selenadiazoles **2a** and **2b** as an orange oil (1.64 g, 66%). Flash chromatography with ethyl acetate/hexanes (gradient 1:6, 1:4, and 1:1) gave 0.78 g (32%) of pure **2a** as a yellow oil that solidified on standing [^{1}H NMR δ 1.85–1.9 (m, 2 H), 3.25–3.3 (m, 2 H), 3.50–3.55 (m, 2 H), 3.66 (s, 2 H), 4.15 (s, 2 H), 7.25–7.35 (m, 5 H)] and 0.38 g (16%) of pure **2b** as an orange oil [^{1}H NMR δ 2.79–2.82 (m, 2 H), 2.85–2.9 (m, 2 H), 3.20–3.22 (m, 2 H), 3.49–3.52 (m, 2 H), 3.77 (s, 2 H), 7.3–7.4 (m, 5 H)]. An analytical sample of **2a** was obtained by two recrystallizations from diethyl ether/hexanes as yellow plates, mp 77–78 °C. Anal. Calcd for $C_{13}H_{15}N_3Se$: C, 53.43; H, 5.17; N, 14.38. Found: C, 53.76; H, 4.95; N, 14.14.

Analytical Data for Selenadiazoles 7–9. The regioisomers of selenadiazoles **7–9** could not be separated by liquid chromatography or crystallization; hence, they were analyzed as mixtures.[20] **7a:7b** (purified as an oil; 40% yield): ^{1}H NMR (DMSO-d_6 at 77 °C) δ 1.12 (t, J = 7 Hz, 3 H, **7a**), 1.21 (t, J = 7 Hz, 2.3 H, **7b**), 1.8–1.95 (m, 2 H, **7a**), 3.26–3.28 (m, 1.53 H, **7b**), 3.35–3.45 (m, 2 H, **7a**), 3.45–3.55 (m, 1.53 H, **7b**), 3.6–3.75 (m, 6.6 H, **7a** and **7b**), 4.00 (q, J = 7 Hz, 2 H, **7a**), 4.10 (q, J = 7 Hz, 1.53 H, **7b**), 4.85 (s, 2 H, **7a**); HR-CI-MS (2-methylpropane) m/z calcd 276.0251, found 276.0230.

8a:8b (purified as off-white plates, 40% yield): mp 41–52 °C; ^{1}H NMR δ 2.03–2.08 (m, 2 H, **8a**), 2.8–2.85 (m, 0.33 H, **8b**), 3.08–3.11 (m, 2 H, **8a**), 3.50–3.53 (m, 2 H, **8a**), 3.55–3.58 (m, 0.33 H, **8b**), 3.63–3.66 (m, 0.33 H, **8b**), 3.85–3.88 (m, 0.33 H, **8b**), 4.11 (s, 2 H, **8a**). Anal. Calcd for $C_6H_8N_2SSe$: C, 32.88; H, 3.67; N, 12.78. Found: C, 33.25; H, 3.77; N, 12.70.[20]

9a:9b (purified as an oil, 42% yield): ^{1}H NMR δ 0.94 (s, 6 H, **9a**), 1.05 (s, 2.5 H, **9b**), 1.55–1.65 (m, 1.6 H, **9b**), 1.7–1.8 (m, 4 H, **9a**), 2.96 (s, 2 H, **9a**), 3.05–3.08 (m, 0.8 H, **9b**), 3.3–3.35 (m, 2.8 H, **9a** and **9b**); HR-CI-MS (2-methylpropane) m/z calcd 231.0399, found 231.0381.

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Registry No. (*E*)-1, 134390-80-0; (*Z*)-1, 134390-79-7; **2a**, 134390-85-5; **2b**, 134390-86-6; **3**, 1208-76-0; (*E*)-**4**, 134418-63-6; **4** ketone, 56515-89-0; (*Z*)-**5**, 134390-81-1; **5** ketone, 22072-22-6; (*E*)-**6**, 134390-82-2; **6** ketone, 35099-49-1; **7a**, 134390-87-7; **7b**, 134390-88-8; **8a**, 134390-89-9; **8b**, 134390-90-2; **9a**, 134390-91-3; **9b**, 134390-92-4; (*E*)-**10**, 134390-96-8; (*Z*)-**10**, 134390-95-7; (*E*)-**11**, 134390-84-4; (*Z*)-**11**, 134390-83-3; **11** ketone, 134390-78-6; **12a**, 134390-93-5; **12b**, 134390-94-6.

(20) **Note added in proof:** Eventually, **8a** was obtained alone by recrystallizing the mixture of **8a:8b** from ether/hexane to give off-white platelets, mp 76–78 °C.

Notes

Selenium-Promoted Conversion of β-Diketones and β-Keto Esters into α,α-Dimethoxy β-Diketones and α,α-Dimethoxy β-Keto Esters

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We have recently reported that the reaction of diphenyl diselenide with ammonium peroxydisulfate produces phenylselenenyl sulfate, which acts as a strong phenylselenenylating agent for unsaturated compounds.[1] We have also observed that ammonium peroxydisulfate reacts with phenyl alkyl selenides to give the deselenenylation products, regenerating the phenylselenium electrophilic species. Thus, by use of an excess of ammonium peroxydisulfate and catalytic amounts of diphenyl diselenide, in a nucleophilic solvent like methanol, it was possible to effect in one pot the production of the phenylselenenylating agent, the alkoxyselenenylation of the unsaturated compounds, and the alkoxydeselenenylation of the addition products. This procedure has been used to effect useful conversions of alkenes into 1,1- and 1,2-dialkoxyalkanes,[2] methyl ketones into α-keto acetals,[3] and terminal and internal alkynes into α-keto acetals and α-keto ketals, re-

(1) (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Bartoli, D. *Tetrahedron Lett.* **1989**, *30*, 1417. (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *Tetrahedron* **1989**, *45*, 6819. (c) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Bartoli, D.; *Tetrahedron* **1988**, *44*, 2261. (d) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429.

(2) (a) Tiecco, M.; Testaferri, L.; Tingoli, M. *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer Academic: Dordrecht, 1989; p 253. (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Bartoli, D. *Tetrahedron* **1988**, *44*, 2273.

(3) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *J. Org. Chem.* **1990**, *55*, 4523.

0022-3263/91/1956-5207$02.50/0