JOC The Journal of Organic Chemistry

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Thia-, Aza-, and Selena[3.3.1]bicyclononane Dichlorides: Rates vs Internal Nucleophile in Anchimeric Assistance

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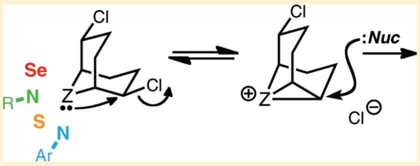
S Supporting Information

ABSTRACT: Sulfur-, selenium-, and nitrogen-containing compounds bearing leaving groups in the β-position undergo facile substitution chemistry enabled by anchimeric assistance. Here we provide direct comparisons between such systems in the rigid bicyclo[3.3.1]nonane framework easily derived from 1,5-cyclooctadiene. For a series of dichloride electrophiles of this type, the relative reactivities were found to be Se $\gg$ (alkyl)N $>$ S $\geq$ (propargyl)N $>$ (phenyl)N, with the reaction rates at the two extremes differing by more than 3 orders of magnitude. For the *N*-alkyl case, substitution rates were largely independent of the trapping nucleophile but were strongly dependent on solvent, showing that the process is controlled by the formation of the high-energy three-membered cationic intermediate.



■ INTRODUCTION

The transannular addition of sulfur dichloride to *cis,cis*-1,5-cyclooctadiene (1,5-COD) gives the 9-thiabicyclo[3.3.1]dichloride **1**, as shown in Figure 1A. This process was first reported in 1966 independently by Weil (Hooker Chemical Co.),[1] Corey (Harvard Univeristy),[2] and Lautenschlaeger (Dunlop Corp.),[3] listed in order of submission dates of their respective papers, inaugurating or continuing work in all three groups on substitution chemistry by anchimeric assistance. In recognition of these seminal contributions, we designate such 1,5-COD-derived species bearing a donor atom in the 9-position and leaving groups β to the donor as "WCL" electrophiles.

Polymer cross-linking by sulfenium ion reactions with $C{=}C$ double bonds is one of the key mechanisms for the vulcanization of rubber.[4] Each of the pioneering WCL investigators noted that similar reactions of SCl_2 with other cyclic dienes gave polymeric products unless conducted at high dilution but that the cyclooctadiene-derived material did not. The resistance of 1,5-COD to polymerization is due to the favorable torsional properties of the dual-chair bicyclo[3.3.1] skeleton, which is one vertex and two bonds short of an adamantyl framework.[5] While the facile substitution chemistry of this species was noted by all of the pioneers, its scope and limitations were not explored.

We have previously described the highly reliable bond-forming ability of sulfur WCL electrophiles with heteroatom[6] and Grignard nucleophiles[7] and their reversibility when the nucleophile also constitutes a good leaving group, such as halide, isothiocyanate, and most importantly, tertiary or heterocyclic amine.[6a,8] The WCL motif also constitutes a conformationally constrained and therefore well-controlled test bed for the fundamental study of anchimeric assistance (closely related to the homoanomeric effect in the case of a β-disposition between interacting groups).[9] Since we are interested in a variety of applications of this potential "click" reaction,[10] we wished to survey analogues containing three of the most active internal nucleophilic centers—nitrogen, sulfur, and selenium—in order to learn what range of reactivities might be accessible.

■ RESULTS AND DISCUSSION

Selenium dichloride and dibromide can be generated from elemental selenium and sulfuryl chloride or bromine in chloroform.[11] When freshly prepared they are practically pure compounds which can be used for the synthesis of organoselenium adducts.[11] Thus, the addition of $SeCl_2$ to 1,5-COD was found to proceed smoothly in chloroform to furnish adduct **2** in >95% yield more rapidly than the analogous sulfur reaction (Figure 1A). Compound **2** was previously prepared from Se_2Cl_2 and 1,5-COD by Lautenschlaeger[12] but was not characterized.

Nitrogen analogues **3** were synthesized by a stepwise procedure that is more general than a previously reported route using *N*-halosuccinimide.[13] Catalytic oxidation[14] of 1,5-COD to *cis*-diepoxide **4** was followed by ring-opening with four different amines to provide 9-azabicyclo[3.3.1]- and [4.2.1]nonanediols **5a**−**d** (Figure 1B). Heating each mixture with thionyl or methanesulfonyl chloride provided the 9-azabicyclo[3.3.1]nonane dichlorides **3a**−**d** as the hydrochloride salts.

The formation of the most stable bicyclo[3.3.1]nonane isomer in each case shows that reversible addition/elimination of chloride occurs for sulfur, selenium, and both aliphatic and

Received: December 10, 2010
Published: May 05, 2011

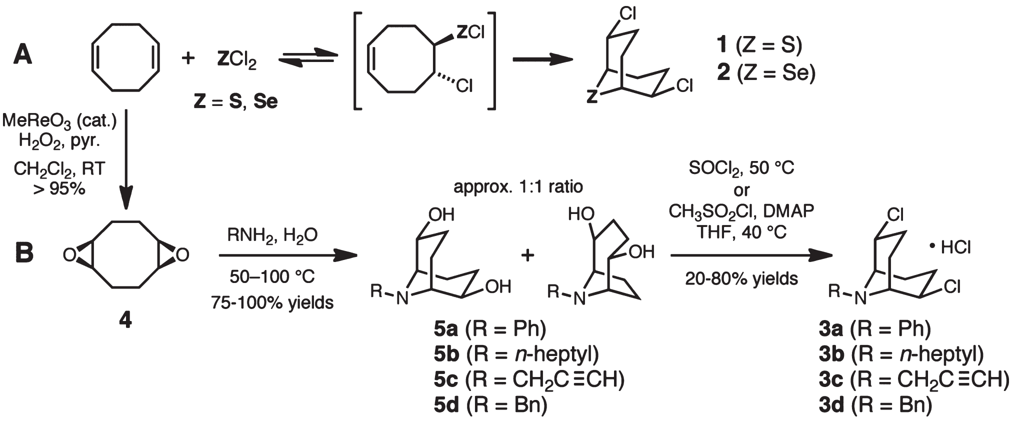
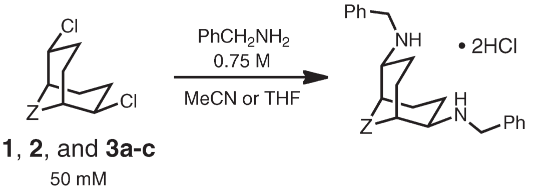


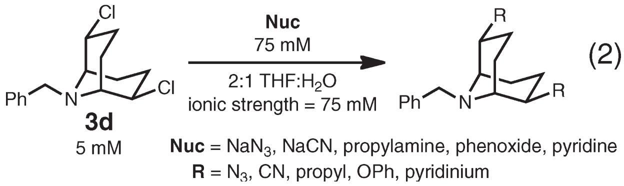
Figure 1. (A) Synthesis of sulfur and selenium dichloride electrophiles **1** and **2**. (B) Synthesis of aza analogues **3a**−**d**. Compound **3a** was isolated as a 91:9 mixture of [3.3.1] and [4.2.1] isomers, the only dichloride to show such a distribution (Supporting Information).

aromatic amine congeners. The involvement of anchimeric assistance throughout the series is similarly indicated by the substitution chemistry of each of its members, which occurs with retention and is dependent on the presence of an atom with active lone pairs in the bridging position,[6a] but no comparison of the relative reactivities of these WCL electrophiles has been described.

A pilot study by ^{1}H NMR determined that the sulfur dichloride electrophile **1** was at least 15 times more reactive with benzylamine than the aniline derivative **3a** and that the disubstituted products (eq 1) were exclusively formed in both cases (data not shown). However, the NMR method was too cumbersome for the determination of absolute rates. Instead, the reactions were analyzed by following the disappearance of each electrophile using quantitative GC−MS in the presence of excess benzylamine and an internal standard, in either dry acetonitrile or dry THF. Alcohol or water additives were avoided in order to eliminate the possibility of solvolysis rather than substitution by the desired amine nucleophile. The disubstituted products precipitated under these conditions and were therefore not analyzed during the kinetics experiments, but were confirmed as the predominant products (>90% yield) by independent reactions on a larger scale. The only exceptions were adducts of **2**, which were prone to decomposition upon storage and chromatography. Intermediate monosubstitution products were not detected by GC−MS, suggesting that the second substitution reaction goes faster than the first, but their absence has not been rigorously established other than for the sulfur electrophile (**1**),[6a] and other reports have shown the opposite trend.[15] For the desired purpose —determining the influence of the central heteroatom nucleophile on reactivity—we therefore followed the disappearance of the starting dichlorides as the simplest possible comparison applicable to all cases.



(1)



(2)

Table 1. Observed First-Order Rate Constants for the Substitution Reactions Shown in eq 1

entry	elec (Z)[a]	nuc[b]	k_{obs}[c] (min^{-1})	k_{rel}[d]	$t_{1/2}$ (min)
		solvent = acetonitrile			
1	**1** (S)	$BnNH_2$	$1.45 \pm 0.02 \times 10^{-2}$	112	47.7 ± 0.5
2	**2** (Se)	$BnNH_2$	not measured	fast	not measured
3	**3a** (NPh)	$BnNH_2$	$1.30 \pm 0.04 \times 10^{-4}$	1[c]	5320 ± 140
4	**3b** (*N*-*n*-heptyl)	$BnNH_2$	$1.15 \pm 0.02 \times 10^{-1}$	881	6.0 ± 0.1
5	**3c** (*N*-propargyl)	$BnNH_2$	$3.27 \pm 0.11 \times 10^{-3}$	25	212 ± 7
		solvent = THF			
6	**1** (S)	$BnNH_2$	$1.52 \pm 0.10 \times 10^{-4}$	1[c]	4550 ± 310
7	**2** (Se)	$BnNH_2$	$6.39 \pm 0.15 \times 10^{-3}$	42	109 ± 3
8	**3a** (NPh)	$BnNH_2$	not measured	slow	not measured
9	**3b** (*N*-*n*-heptyl)	$BnNH_2$	$9.32 \pm 0.71 \times 10^{-4}$	6	744 ± 60
10	**3c** (*N*-propargyl)	$BnNH_2$	$3.56 \pm 0.18 \times 10^{-4}$	2	1950 ± 100
		solvent = 2:1 THF:H_2O			
11	**3d** (NBn)	C_3H_7N	$3.51 \pm 0.36 \times 10^{-2}$	1.3	19.8 ± 2
12	**3d** (NBn)	NaN_3	$6.31 \pm 0.41 \times 10^{-2}$	2.4	11.0 ± 0.7
13	**3d** (NBn)	NaCN	$3.35 \pm 0.11 \times 10^{-2}$	1.3	20.7 ± 0.7
14	**3d** (NBn)	pyridine	$2.66 \pm 0.18 \times 10^{-2}$	1[c]	26.0 ± 1.8
15	**3d** (NBn)	phenoxide	$6.13 \pm 0.14 \times 10^{-2}$	2.3	11.3 ± 0.3

[a] WCL electrophile; the bridging group at the 9-position is shown in parentheses. [b] Capturing nucleophile used in 15-fold excess concentration relative to electrophile. [c] Rate constants for each entry are reported as the average of three separate experiments with the indicated standard deviations. [d] k_{rel} is designated as 1.0 for the slowest rate constant observed in each solvent system.

The reactions were performed under pseudo-first-order conditions, giving the observed rate constants shown in Table 1. The substitution reaction of selenium WCL electrophile **2** was too fast to measure in acetonitrile, being largely complete before the first aliquot could be taken. The remaining four electrophiles were found to exhibit relative reactivities in the order **3b** > **1** > **3c** > **3a**. The nature of the 9-aza substituent therefore contributes substantially to the reaction rate in the expected order of nucleophilicity, *N*-heptyl > *N*-propargyl > *N*-phenyl, with a difference in rate of more than 800-fold between the slowest and fastest cases. In order to measure the reaction rate of **2**, the experiments were

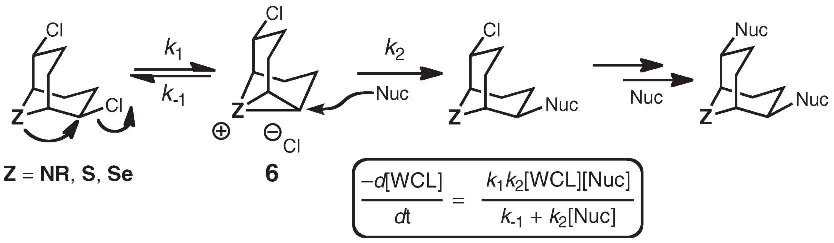


Figure 2. Mechanism of anchimeric assistance for compounds of the WCL class.

performed in THF under otherwise identical conditions, slowing the reactions by providing a less polar environment. The order of reactivity was almost the same as in acetonitrile (**2** > **3b** > **3c** > **1** > **3a**), but in this case **3c** was observed to be slightly faster than **1**. The selenium WCL compound **2** was approximately seven times more reactive than its next closest competitor, heptylamine-bridged **3b**.

The effect of nucleophile identity was examined by comparing the rates of chloride substitution with five different nucleophiles (eq 2), using benzylamine-bridged hydrochloride salt **3d** as a representative WCL electrophile that is easily detected by UV−vis spectroscopy and reacts with similar rates to **3c** (data not shown). To ensure that compound **3d** existed primarily as the free base during the kinetic study, 5 equiv of triethylamine was added to the mixture at the beginning of each experiment. These reactions were performed in a 2:1 THF/water mixture in order to provide a common medium that dissolves all of the nucleophiles, giving rise to substantially faster substitution than under non-aqueous conditions, presumably because of enhanced support for the formation of the high-energy charged aziridinium intermediate. Accordingly, initial concentrations were reduced 10-fold to slow the overall process to an easily measurable time frame. Ionic strength was equalized by the addition of $NaPF_6$ to the reactions of the uncharged nucleophiles (propylamine and pyridine; see the Experimental Section). Rates were again observed by following the disappearance of starting material, this time by HPLC. Entries 11−15 of Table 1 show that the process is largely insensitive to the nature of the differing nucleophiles, which are expected to be of very different activity.

The above data are consistent with a two-step mechanism involving reversible formation of a cationic intermediate followed by interception of this species with a nucleophile as shown in Figure 2. We draw the key intermediate as a three-membered ring (aziridinium, episulfonium, or episelenenium; structure **6**) because of the very strong preference for stereochemical retention exhibited by all of these substitution reactions, but it is also possible that hyperconjugative stabilization of the carbon-centered cation takes place.[16] In either event, when nucleophilic trapping of is much faster than its formation ($k_2[\mathrm{Nuc}] \gg k_{-1}$), the reaction will appear to be first order with rate-limiting formation of the strained intermediate. If, however, concentrations are lowered so that the bimolecular capture rate is slowed (in the extreme, $k_2[\mathrm{Nuc}] \ll k_{-1}$), then the reaction should have second-order character. The observed rates did vary as a function of capturing nucleophile (Table 1, entries 11−15; a factor of 2.4 overall), but to a much smaller degree than as a function of the internal nucleophile (Table 1, entries 1−5 and 6−10; factors of hundreds to about 1000). This suggests that the reactions may have a small amount of second-order character under the conditions used (50 mM electrophile, large excess of nucleophile) but are dominated by the first-order pathway. When trapping nucleophile is omitted in aqueous THF, the reactions are much slower, showing that the k_{-1} step is competitive with trapping by water.

The observed solvent effects are also consistent with rate-determining internal displacement of chloride, with reactions in acetonitrile and aqueous THF being much faster than in THF alone. Thus, the reactions of benzylamine with **1** and **3b** are approximately 90 and 120 times faster, respectively, in acetonitrile (Table 1, entry 1 vs 6 and 4 vs 9). *N*-Propargyl electrophile **3c** reacts only nine times faster in acetonitrile than in THF, for reasons that we cannot yet explain, and the selenium- and aniline-based reagents **2** and **3a** could not be quantitatively compared but also react much faster in acetonitrile. This solvent is more polar and better able to solvate chloride ion, both factors favoring formation of the electrophilic intermediate.[17] The order of effectiveness of the internal nucleophile (Se > heptylamine > S ≥ propargylamine > aniline) suggests that a combination of factors are at work, including ability to stabilize a positive charge (Se > S > N) and basicity (*N*-alkyl > *N*-aryl).

To the comparisons between internal nucleophiles that have appeared previously (for example, sulfur vs selenium,[16] oxygen vs nitrogen,[18] and halogen vs oxygen vs nitrogen vs sulfur[19]), the results reported here add the first quantitative comparison of the activating abilities of nitrogen, sulfur, and selenium atoms in an otherwise identical and well-defined anchimeric assistance process. The rate differences are substantial, amounting to more than a factor of 1000. This allows us to tune reactivity in a predictable way for linkage formation and destruction, providing a versatile tool for the synthesis of functional small molecules and polymers.

■ EXPERIMENTAL SECTION

Compound **1** was prepared as previously described.[6b] The selenium analogue **2** was prepared by reaction of $SeCl_2$ with 1,5-cyclooctadiene, and the amine WCL electrophiles **3** were prepared from *cis*-1,5-cyclooctadiene diepoxide as outlined above. These procedures and characterization data are provided in the Supporting Information.

Kinetics experiments as a function of electrophile (Table 1, entries 1−10) were performed at room temperature on 50 mM solutions of each dichloride in dry THF or acetonitrile containing an internal standard. Similar kinetics measurements were performed at room temperature as a function of nucleophile (Table 1, entries 11−15) on 2:1 THF/water solutions of **3d** (5 mM), NEt_3 (25 mM, 5.0 equiv.), an internal standard, and added $NaPF_6$ to equalize ionic strength when necessary. The reactions were initiated by the addition of 15 equiv of nucleophile to the rapidly stirred solutions and were followed by GC or HPLC analysis of aliquots removed and quenched at certain times. Experimental details are provided in the Supporting Information.

ASSOCIATED CONTENT

Ⓢ Supporting Information. Details of syntheses, compound characterization, kinetics procedures, and representative kinetics plots for results shown in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank the Skaggs Institute for Chemical Biology, the National Science Foundation (1011796), and the Russian Academy of Sciences (Program 5.1.8) for support of this work. We are grateful to Dr. David Díaz and Dr. Bunpei Hatano of the Sharpless laboratory for early syntheses of compounds **1** and **3b**, to Dr. Andrew Vaino for early experiments along these lines, and to Dr. Laura Pasternack for helpful expertise in NMR spectroscopy.

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