JOC Notes

Nucleophilic Substitution by Grignard Reagents on Sulfur Mustards

Antonella Converso, Pierre-Loïc Saaidi,[1] K. Barry Sharpless, and M. G. Finn*

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

mgfinn@scripps.edu

Received June 17, 2004

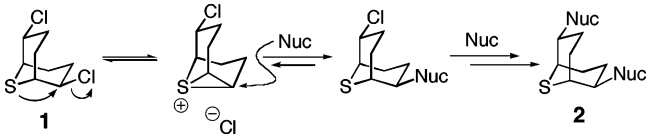
Abstract: With proper activation of the leaving group, sulfur mustards react with Grignard reagents with neighboring group participation of the sulfur atom. 2,6-Dichloro-9-thiabicyclo[3.3.1]nonane is especially useful in this regard, providing clean reactivity with organomagnesium nucleophiles on a topologically constrained scaffold.

The chemistry of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane, **1**, provides a good illustration of the power of anchimeric assistance in organic chemistry.[2,3] The reactivity of this compound is enhanced by the central heteroatom, which engages the β-chlorinated centers to facilitate nucleophilic substitution via a highly reactive episulfonium ion (Scheme 1). The double inversion process preserves stereochemistry in substitution reactions with a broad range of heteroatom nucleophiles.

Compound **1** and its disubstituted derivatives **2** are chiral, C_2-symmetric structures. The C−Cl/Nuc axes describe two vectors with a dihedral angle of 84°, and the electrophilic carbon centers are quite sterically hindered. The latter point has been most clearly demonstrated by the fact that chloride in **1** cannot be displaced by NMe_3 or NEt_3, whereas the weaker but less sterically demanding nucleophile pyridine forms very stable adducts.[3] The parent dichloride and several disubstituted derivatives can be prepared in enantiomerically enriched form either by chiral HPLC or by substitution of a diastereomerically enriched bis(brucine) adduct.[3] The system therefore lends itself to the display of functionality in chiral form, as may be found in chiral ligands for metals, chiral acids or bases, and components of chiral polymers.

To realize certain examples of these types of structures, new carbon−carbon bonds must be made with mustard-type electrophiles such as **1**. The literature contains very few well-characterized examples of anchimeric assistance in substitution by such activated carbon nucleophiles as

SCHEME 1



magnesium, cuprate, and silyl reagents.[4] The only known example with **1** is a brief report of the use of trialkylaluminum compounds.[5] It should be noted that by "anchimeric assistance" we do not mean the tethering of a reactive organometallic to the electrophile by means of a pendant heteroatom,[6] which renders the C−C bond-forming event intramolecular and has occasionally been given the anchimeric assistance label. Rather, we refer to the stereochemically distinct double inversion process, in which the electrophile is activated by intramolecular interaction with a nucleophilic component and is subsequently captured by external nucleophile. We report here that **1** engages in clean substitution with retention in reactions with a variety of Grignard reagents, presumably via the neighboring group participation of sulfur as shown in Scheme 1. Precedents include the chemistry of β-chloro-β-alkoxythioether compounds derived from the addition of arylsulfenyl chlorides to vinyl ethers,[4] applications to the synthesis of *C*-glycosides,[7] and substitution reactions of *N*-(α-haloalkyl)benzotriazoles.[8]

Alkyl- and aryllithium reagents were found to promote elimination in preference to substitution, although disubstituted products from **1** were observed in trace amounts (Scheme 2A). Grignard reagents, which are more polarizable than lithium compounds and are therefore expected to be less prone toward proton abstraction, gave intractable mixtures at 0 °C in ethereal solvents. Such mixtures contained <10% of the desired compounds, along with olefins derived from elimination and other compounds. However, the use of Grignard reagents at room temperature or above provided disubstitution of **1** with retention of configuration in good to excellent yields for aromatic, acetylenic, and primary alkylmagnesium bromides (Scheme 2B, Table 1). All compounds described here were prepared in racemic form.

(1) Present address: Laboratoire de Chimie, UMR-5182 CNRS/ENS, Ecole Normale Supérieure de Lyon, France.

(2) Weil, E. D.; Smith, K. J.; Gruber, R. J. *J. Org. Chem.* **1966**, *31*, 1669−1679.

(3) Converso, A.; Burow, K.; Marzinzik, A.; Sharpless, K. B.; Finn, M. G. *J. Org. Chem.* **2001**, *66*, 4386-4392.

(4) Smoliakova, I. P.; Caple, R.; Brenny, J. W.; Smit, W. A.; Kryschenko, Y. K.; Shashkov, A. S.; Chizhov, O. S.; Krimer, M. Z.; Morar, G. V.; Kalyan, Y. B. *Synlett* **1995**, 275−276 and references therein.

(5) Tolstikov, G. A.; Kantyukova, R. G.; Spirikhin, L. V. *Zh. Org. Kim.* **1980**, *16*, 1408−1418.

(6) (a) Examples include the following: (i) Fuji, K.; Tanaka, K.; Ahn, M.; Mizuchi, M. *Chem. Pharm. Bull.* **1994**, *42*, 957−959. (ii) Calo, V.; De Nitti, C.; Lopez, L.; Scilimati, A. *Tetrahedron* **1992**, *48*, 6051−6058. (iii) Oliva, M.; Safont, V. S.; Andres, J.; Castillo, R.; Moliner, V. *Int. J. Quantum Chem.* **1997**, *65*, 719−728. (b) An ambiguous case is provided by: Marot, C.; Philipp, C.; Rollin, P. *Tetrahedron Lett.* **1992**, *33*, 4575−4578. It is not clear which phenomenon − tethered reactivity or true anchimeric assistance − is operative in the examples described.

(7) (a) Smoliakova, I. P.; Han, M. M.; Gong, J. C. *Tetrahedron* **1999**, *55*, 4559−4572. (b) Han, M. M.; Smoliakova, I. P.; Koikov, L. N. *Carbohydr. Res.* **2000**, *323*, 202−207. (c) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589−608. (d) Liu, H.; Smoliakova, I. P. *Tetrahedron* **2001**, *57*, 2973−2980.

(8) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Belyakov, S. A. *Synthesis* **1999**, Supplment, 1437−1440.

10.1021/jo0489869 CCC: $27.50
Published on Web 09/14/2004

SCHEME 2

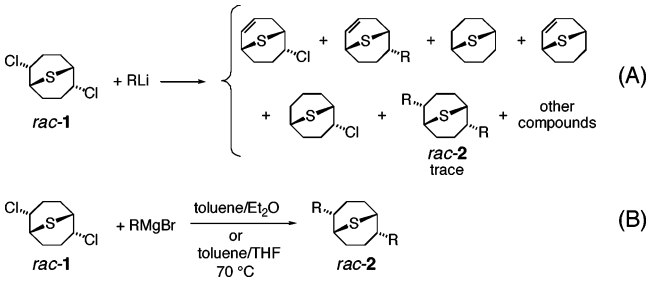


TABLE 1. Isolated Yields and Characteristic Infrared Bands of Disubstituted Products from Reactions of 1 with Grignard Reagents at 70 °C in Toluene (Scheme 2B)

RMgX	yield, %	product	ν_{C-H}[a]	δ_{C-H}[b]
PhMgBr	99	**2a**	2977	1490
o-tolyl-MgBr	98	**2b**	2990	1483
2-Me-1-naphthyl-MgBr	62	**2c**	2974	1480
vinyl-MgBr	69	**2d**	2973	1480
allyl-MgBr	90	**2e**	2981	1483
$CH_3C{\equiv}C-MgBr$	97	**2f**	2983	1477
$HC{\equiv}C-MgBr$	30	**2g**	2980	1483
n-pentyl-MgBr	99	**2h**	2955	1479
MeMgBr	85	**2i**	2951	1480

[a] "Anomalous" stretching band for axial C3−H and C7−H bonds, cm^{-1}. [b] "Anomalous" bending band for axial C3−H and C7−H bonds, cm^{-1}.

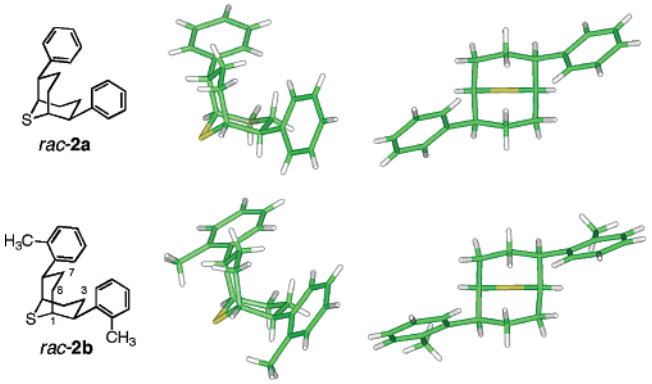


FIGURE 1. X-ray crystal structures of **2a** and **2b**. (Middle) View showing the chair/chair conformation of the bicyclononane core. (Right) View down the C_2 symmetry axis. Relevant carbon position numbers are shown on the sketch of **2b**.

Assignment of retention of configuration, and therefore firm evidence for a pathway of neighboring group participation, was obtained by X-ray crystallography of **2a** and **2b** (Figure 1). The trans orientation of sulfur and substituent centers in both compounds was accompanied by characteristic coupling constants in the ^1H NMR spectrum and C−H stretching and bending bands in the IR spectrum at uniquely high frequencies (Table 1) due to congestion of axial C−H bonds at the 3 and 7 positions of the chair/chair conformation favored for the 2,6-disubstituted-9-thiabicyclo[3.3.1] core.[2,9] These spectroscopic signatures were found in each of the remaining substitution products **2c**−**i**, allowing us to extend the assignment of retention beyond the two cases characterized in the solid state.

The conformation of aryl groups in **2b**, in which the *o*-methyl substituents are found on the "sulfur" side of the structure, is consistent with molecular mechanics calculations showing this to be the most stable rotameric form by approximately 5 kcal/mol. Rotation about the C−aryl bond is restricted, with severe steric interactions between the aromatic ortho positions and the axial C3−H and equatorial C8−H atoms of the thiabicyclo[3.3.1]-nonane core. To escape these interactions, the ortho substituent of 2-substituted aryl fragments must be placed away from the thiabicyclononane core, and such compounds are locked at room temperature with respect to rotation about the C2−aryl bond axis. Compound **2c**, derived from 1-bromo-2-methylnaphthalene, displays the expected hindered rotation about the equivalent C2 positions in solution, giving rise to a broadened NMR spectrum. Heating to 70 °C causes the signals to sharpen to a single set, indicative of faster rotation around these bonds on the NMR time scale at elevated temperature. The stereochemical control exemplified by **2b** and the hindered bond rotation of **2c** are potentially useful in the design of chiral ligands and polymeric materials.

For the reactions described above, donor solvents were found to be detrimental to the purity of the final product: both diethyl ether and tetrahydrofuran, commonly used in Grignard preparation, promote elimination, albeit to a modest extent at room temperature (≤10% of the product mixture). Elimination can be minimized if the ether or THF is removed by evaporation prior to addition of **1**, but this may occur at the expense of Grignard reagent solubility and therefore of yield. The use of dichloromethane[10] instead of toluene further suppressed elimination. However, it proved to be most convenient to perform the reactions in toluene at 70 °C without pre-evaporation of ethereal cosolvent. Under these conditions, diethyl ether is carried away from the mixture and the low-temperature elimination pathway is further disfavored. If it is required to perform the reaction at room temperature, the best performance is usually obtained in dichloromethane with prior removal of ether or THF from the Grignard mixture. In most cases, poorer results are achieved if the Grignard reagent concentration is less than 0.2 M. Diethynyl compound **2f** was isolated in low yield due to the formation of bridging acetylide dimers and higher oligomers. Secondary magnesium bromides gave mixtures of elimination and reduction products, whereas *t*-BuMgCl induced mostly reduction.

No substitution was observed for several cases in which the magnesium reagents were prepared from aryl bromides by activation of Mg^0 with 1,2-dibromoethane (20% relative to **1**). In these cases, the dibromide adduct **4** was the only product observed in addition to recovered **1**; an example is shown in Scheme 3. (Activation of metallic Mg with catalytic amounts of iodine, rather than dibromoethane, works well; compound **2c** was prepared in this manner.) Since the formation of $MgBr_2$ would be expected from dibromoethane and Mg^0, the response of a standard reaction to the addition of $MgBr_2$ was tested. When 20% $MgBr_2$ was added to commercially available PhMgBr, which otherwise performs well, significantly poorer re-

(9) Brown, W. A. C.; Eglinton, G.; Martin, J.; Parker, W.; Sim, G. A. *Proc. Chem. Soc.* **1964**, 57−58.

(10) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417−420.

SCHEME 3

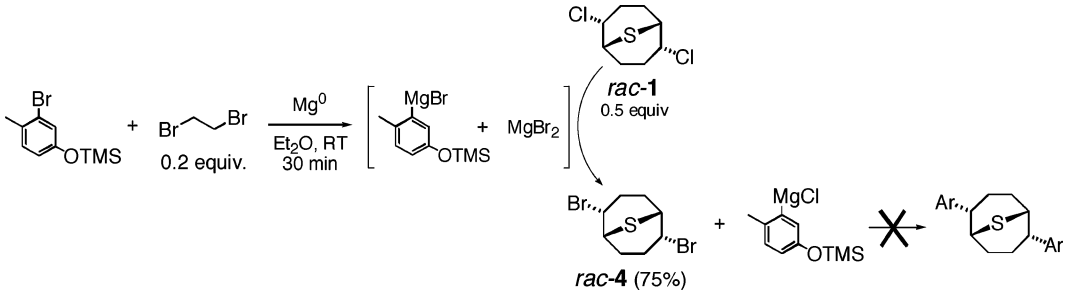
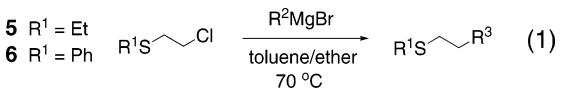


TABLE 2. Reactions of Grignard Nucleophiles with 2-Chloroethyl Ethyl Sulfides 5 and 6 (Eq 1)



(1)

entry	R^1	R^2	R^3	product	yield, %
1	Et	*n*-pentyl	*n*-pentyl	**7**	26
2	Et	cyclopentyl	H	**8**	91
3	Et	Ph	Ph	**9**	82
4	Ph	*n*-pentyl	Br	**10**	60
5	Ph	cyclopentyl	Br	**10**	51
6	Ph	Ph	Ph	**11**	98
7	Ph	Me	Br, Me	**10**, **12**	70, 30

sults were obtained (lower and variable substitution yields and approximately 10% of olefins derived from elimination of HCl from **1**).

These observations suggest that Br-for-Cl substitution is enhanced by $MgBr_2$. Furthermore, either the bromide adduct **4** is a much poorer electrophile than **1** toward Grignard nucleophiles or the organomagnesium byproduct of the Br-for-Cl substitution is a poor nucleophile. The former possibility was discounted by comparisons between **1** and **4** in reactions with a standard amine nucleophile (benzylamine, acetonitrile solution, room temperature) and with PhMgBr (toluene, 70 °C). In the first case, **4** was found to be at least 10 times more reactive than **1**, whereas in the second case, both electrophiles were consumed within a very short time. Thus, **4** can be expected to be reactive with bona fide Grignard nucleophiles. It must therefore be the case that RMgCl is produced from the reaction of **1**, RMgBr, and $MgBr_2$ in an inactive or poorly active form. It is perhaps worthwhile to note in this context that commercially available organomagnesium bromides were found to be superior to chlorides in terms of overall yield and the formation of unwanted byproducts, whereas iodides gave little or no substitution. For example, MeMgBr gave **2i** in 85% yield (Table 1) while MeMgCl provided **2i** in approximately 42% yield, along with 7% of unreacted **1** and approximately 4% of material containing the olefinic products of elimination.

To compare **1** to simple sulfur mustard electrophiles, a series of reactions was performed on the *S*-ethyl- and *S*-phenyl *β*-chlorothioether electrophiles **5** and **6** (eq 1, Table 2). The former is presumed to react with participation of the alkylthioether group, while the latter is known to eschew anchimeric assistance in favor of direct substitution of halide nucleophiles.[11] For both **5** and **6**, PhMgBr gave phenyl substitution in high yield. In contrast, *n*-pentyl-MgBr provided alkyl attack with **5**, but bromide attack with **6**. Cyclopentylmagnesium bromide also deposited bromine on **6**, and gave reduction with **5**. A mixture of methyl and bromine substitution products was observed for MeMgBr with **6**. It therefore appears that, without anchimeric assistance (compound **6**), treatment with Grignard reagents results largely in substitution by bromide and not alkyl. When an episulfonium intermediate is accessible (as with **5**), alkyl attack and elimination are more favored. The clean reactivity of PhMgBr may result from its weaker basicity, more Lewis acidic Mg^{2+} center, or different aggregation state compared to alkylmagnesium reagents.

The nature of the optimal solvent is obviously different for the Grignard reactions of **1** (best performed in toluene) and its wide-ranging substitution chemistry with heteroatom nucleophiles (done in water or acetonitrile).[3] While the distribution of potential magnesium species (RMgBr, MgR_2, and oligomeric variations) is affected by the reaction conditions,[12] we suggest that the solvent exerts its most important influence on the electrophile.[13] In a nonpolar medium, the reactive episulfonium ion intermediate that drives the chemistry of this system is highly disfavored. This charged species is of course destabilized by a mismatch with a nonpolar environment, but more importantly, aprotic solvents provide no protic solvation to the outgoing chloride ion.[14] Lewis acidic magnesium complexes can overcome this problem by assisting the departure of chloride to promote episulfonium ion formation (Figure 2), but only when nucleophilic solvents such as ether and THF (which might otherwise compete for binding to the metal ion) are absent. (Lewis acids have been used for the generation of α-alkoxyepisulfonium ions from the corresponding *β*-chlorothioethers.[7d]) The delivery of the carbon nucleophile to the episulfonium ion may occur from within the proposed intermediate ion pair, as shown in Figure 2, or may occur from a different organomagnesium center.

Substitution reactions of simple alkyl halides with Grignard reagents are surprisingly rare.[15] One reason may be the complex interplay between factors such as

(11) McManus, S. P.; Karaman, R. M.; Sedaghat-Herati, R.; Harris, J. M. *J. Org. Chem.* **1995**, *60*, 4764−4766.

(12) RMgBr has been shown to be favored at higher temperatures and MgR_2 is favored by precipitation of $MgBr_2$ in nonpolar solvents. In addition, the best reaction conditions (high concentration in nonpolar solvent) lend themselves to the formation of oligomers, which are less basic than monomeric Grignard reagents. See: Silverman, G. S. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker Inc.: New York, 1996; pp 307−353.

(13) Krow, G. R.; Lin, G.; Rapolu, D.; Fang, Y.; Lester, W. S.; Herzon, S. B.; Sonnet, P. E. *J. Org. Chem.* **2003**, *68*, 5292−5299.

(14) Gajewski, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 10877−10883.

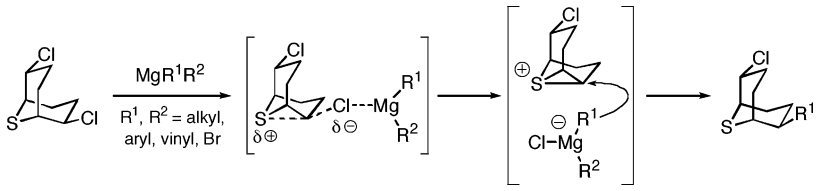


FIGURE 2. Proposed Lewis acid assisted formation and alkylation of episulfonium ion from 2,6-dichloro-9-thiabicyclo[3.3.1]-nonane.

solvent, counterion, and leaving group, which contributes to variable outcomes as described above. Alternative strategies, such as transition metal catalysis,[16] are usually required. As shown here, anchimeric assistance, engineered with the proper combination of Lewis acid and solvent, provides another powerful activating mechanism for such transformations.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences, the National Institutes of Health (GM 28384), the National Science Foundation (CHE-9985553), the W. M. Keck Foundation, and the Skaggs Institute for Chemical Biology. P.-L.S. thanks the Ecole Normale Supérieure de Lyon for a scholarship. We are grateful to Dr. Michal Sabat (University of Virginia) for X-ray crystal structures.

Supporting Information Available: Experimental procedures and characterization data for the products, and crystallographic details for **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0489869

(15) (a) Ganellin, C. R.; Hollyman, D. R.; Ridley, H. F. *J. Chem. Soc. C* **1967**, 2220−2225. (b) Ring opening of aziridinium electrophiles with Grignard reagents has been reported, in a two-step sequence rather than as a case of anchimeric assistance: Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W.; Vater, E. J.; Guenter, F.; Mergelsberg, I.; Scherer, D. *Org. Proc. Res. Dev.* **1998**, *2*, 175−185.

(16) (a) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056−4059. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (c) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297−1299. (d) Scheiper, B.; Bonnekessel, M.; Krause, H.; Furstner, A. *J. Org. Chem.* **2004**, *69*, 3943−3949. (e) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461−1463. (f) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646−5647. (g) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137−4139. (h) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222−4223. (i) Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871−2873. (j) Shimizu, R.; Yoneda, E.; Fuchikami, T. *Tetrahedron Lett.* **1996**, *37*, 5557−5560. (k) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.