ORGANIC LETTERS

2003
Vol. 5, No. 18
3313−3315

Ritter-Type Reactions of *N*-Chlorosaccharin: A Method for the Electrophilic Diamination of Alkenes

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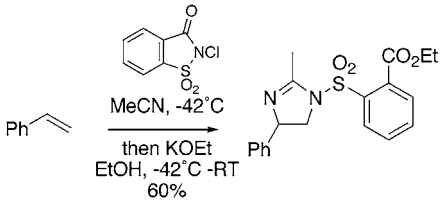
Received July 23, 2003

ABSTRACT



***N*-Chlorosaccharin has been shown to undergo electrophilic Ritter-type reactions with alkenes in acetonitrile. The resulting labile *β*-chloro sulfonylamidines can be ring-opened and cyclized to imidazolines. Overall this provides a one pot method for the electrophilic diamination of alkenes. Competing aziridine formation as well as allylic chlorination are also observed depending on the nature of the alkene used.**

N-Chlorosaccharin (NCSacc, **1**) is a commercially available and relatively inexpensive reagent that is commonly used for a number of reactions where an electrophilic source of chlorine has been required.[1] While exploring the possible generation of saccharin-based nitrogen radicals[2] and their subsequent addition to alkenes, we were surprised to find that acetonitrile solutions of NCSacc reacted with cyclohexene to generate the labile *β*-chloro sulfonylamidine **2** (Scheme 1). Ring opening of the saccharin ring with potassium ethoxide then gave the chloroamidine ester **5** in 66% overall yield. Formation of **2** is most likely to proceed by ring opening of the initially formed cyclohexene chloronium ion **3** with acetonitrile.[3] The resulting nitrilium ion **4** is then intercepted by the saccharin anion in a classic Ritter-type sequence.[4] Repeating the sequence with styrene gave the imidazoline **6** directly by cyclization of the intermediate *β*-chloro sulfonylamidine. Along with **6**, the aziridine **7** is formed, presumably by competing attack of the saccharin anion on the chloronium ion **3** followed by cyclization on ring opening with ethoxide. It is likely that **5** does not form an imidazoline directly due to the steric demands of a trans diaxial conformation that would be required for a nucleophilic cyclization on a cyclohexane ring. However, it was found that cyclization to the imidazoline product **8** could be effected under more forcing conditions by further treatment of **5** with NaH in DMF at room temperature. At this point, we became aware of the similarity of this sequence to the elegant diamination work of Li,[5] which involves the formation of imidazoline directly from electron-deficient alkenes using $TsNCl_2$ under metal catalysis. Li has also reported the formation of diamines using $TsNCl_2$ and MeCN without catalysis.[6] In these reactions, Li proposes Ritter-type reactions proceeding from ring opening of an initially formed aziridinium ion. Intrigued by the differences

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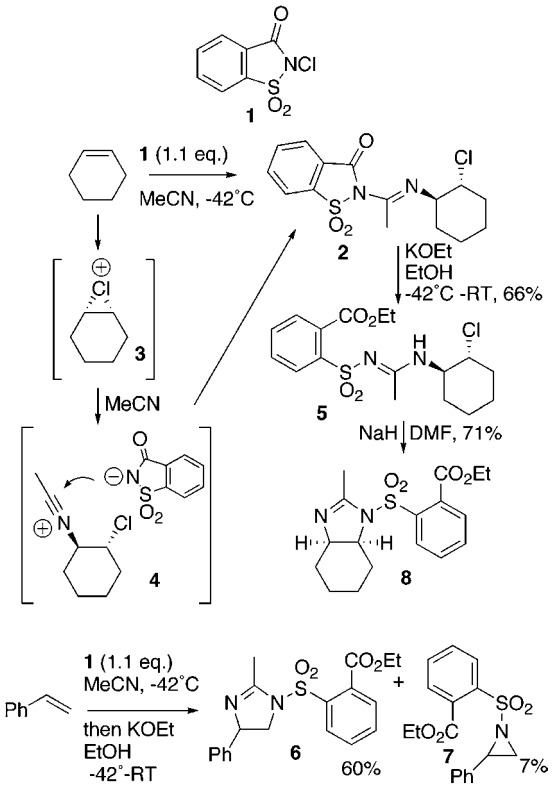
(1) Dawn, H.-S.; Pitman, I. H.; Higuchi, T.; Young, S. *J. Pharm. Sci.* **1970**, *59*, 955.
(2) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.
(3) For chlorination of alkenes with Cl_2 in acetonitrile, see: Cairns, T. L.; Graham, P. J.; Barrick P. L.; Schreiber, R. S. *J. Org. Chem.* **1952**, *17*, 751.
(4) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.

10.1021/ol035374m CCC: $25.00
Published on Web 08/08/2003

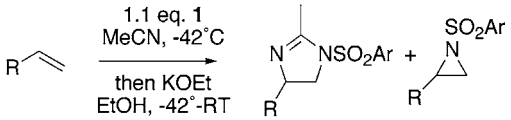
Scheme 1. Reaction of NCSacc with Alkenes



in the likely mechanisms of the Li methodology and our own observations, we set about to explore the scope of the electrophilic diamination of unactivated alkenes with NCSacc.

Initially, we screened a range of styrene derivatives and obtained the corresponding imidazolines in moderate yields. In most cases, aziridine formation was a minor competing pathway. The best conditions found were a one-pot reaction involving the addition of NCSacc to a solution of the alkene at −42 °C followed by the addition of a 24 wt. % solution of EtOK in EtOH to ring open the saccharin ring of the addition products. Warming to room temperature effected in situ cyclization of the β-chloro sulfonylamidines to the imidazoline products. Use of activating aromatic groups produced some interesting results. For example, neither imidazoline nor aziridine products could be isolated from the reaction of 4-methoxy styrene (entry 9) with NCSacc. In this particular case, it is possible that the benzylic chloronium ion (cf. **3**) undergoes ring opening by mesomeric electron release from the methoxy group to give a stabilized cationic intermediate that does not react with either saccharin or acetonitrile nucleophiles. In the case of 4-methyl and 2,4,6-trimethyl styrene, the aziridines were major and exclusive products, respectively (Table 1, entries 7 and 8). This may suggest that the slight inductive effect of the methyl groups makes the benzylic positions less reactive toward acetonitrile. In the case of entry 8, it is also likely that there is a significant steric deactivation of the benzylic position in the chloronium ion that renders it less accessible to the acetonitrile nucleophile.

Table 1. Reaction of NCSacc with Substituted Styrenes



entry	R	imidazoline (%)	aziridine (%)
1	Ph	60	7
2	2-ClC_6H_4−	44	0
3	4-ClC_6H_4−	46	9
4	2-BrC_6H_4−	35	0
5	4-FC_6H_4−	45	13
6	3-MeC_6H_4−	47	10
7	4-MeC_6H_4−	24	23
8	2,4,6-triMeC_6H_4−	0	49
9	4-$MeOC_6H_4$−	0	0

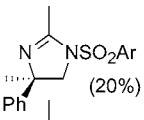
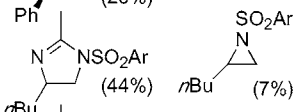
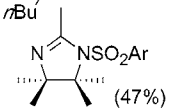
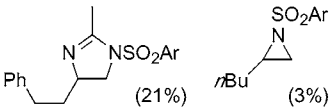
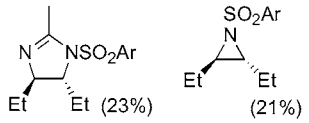
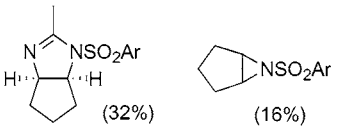
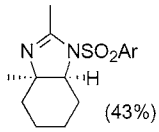
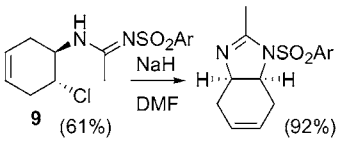
Once the optimal reaction conditions were established for the one-pot conversion of styrenes right through to imidazolines, we then explored the scope of the sequence with a more diverse range of acyclic and cyclic alkenes (Table 2). In most cases, the imidazolines were formed as the major products. In the case of cyclohexadiene (entry 8) and dihydronaphthalene (entry 9), only the uncyclized β-chloro sulfonylamidine adducts **9** and **10**, respectively, were observed.

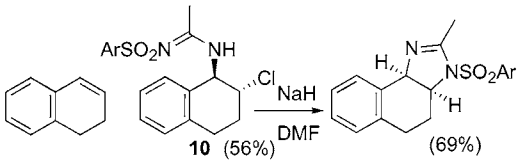
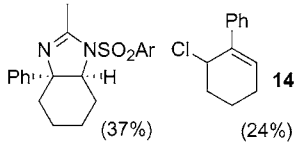
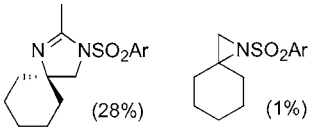
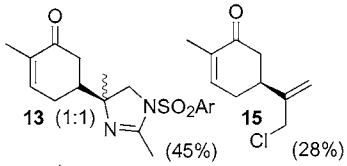
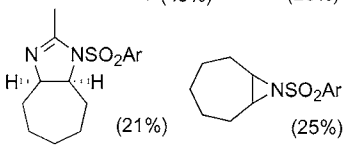
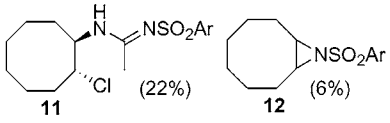
Similarly, cyclooctene gave no imidazoline and only the amidine **11** and the aziridine **12** were isolated (entry 14). These results again are probably indicative of trans diaxial conformational issues in the cyclization of the respective β-chloro sulfonylamidines. It was possible, however, to cyclize these chlorides in DMF solvent by treatment with NaH in a subsequent step (e.g., entries 8 and 9). It is interesting to note that in entries 7 and 10 where the cyclohexene ring contains a substituent, the cyclized imidazolines were formed directly upon ring opening of the saccharin ring. It is likely in these cases that with the extra substituent, the energy barrier to adopting a trans diaxial conformation is much less. In the case of entry 12, (*S*)-carvone reacted with NCSacc to give only imidazoline products **13** resulting from addition across the nonconjugated alkene, thus highlighting the electrophilic nature of the mechanism of this sequence. With entries 10 and 12, the isolation of the allylic chloride products **14** and **15** gave vital information on the significant loss of mass balance observed in many of these reactions. It is likely that elimination of HCl from the intermediate chloronium ions (cf. **3**), possibly by the saccharin anion, leads to allylic chlorides as a major competing pathway in most of these reactions. It is very likely that these products were not observed in the simpler

(5) (a) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem.* **2002**, *67*, 4777. (b) Li, G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277. (c) Li, G.; Wei, H.-X.; Kim, S. H. *Org. Lett.* **2000**, *2*, 2249. (d) Li, G.; Wei, H.-X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395.

(6) Chen, D.; Timmons, C.; Wei, H.-X.; Li, G. *J. Org. Chem.* **2003**, *68*, 5742.

Table 2. Reaction of Various Alkenes with NCSacc in MeCN[a]

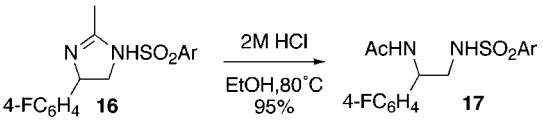
entry	alkene	products (yields)
1	Ph	 (20%)
2	*n*Bu	 (44%) (7%)
3		 (47%)
4	Ph	 (21%) (3%)
5	Et, Et	 (23%) (21%)
6		 (32%) (16%)
7		 (43%)
8		 9 (61%) (92%)

entry	alkene	products (yields)
9		 10 (56%) (69%)
10	Ph	 (37%) 14 (24%)
11		 (28%) (1%)
12		 13 (1:1) (45%) 15 (28%)
13		 (21%) (25%)
14		 11 (22%) 12 (6%)

[a] Ar = 2-$EtO_2CC_6H_4$−.

examples due to product volatility and visualization issues. Overall, this reaction may find use in the synthesis of differentially protected diamines. For example, acid hydrolysis of **16** gave the diamine **17** in excellent yield (Scheme 2).

Scheme 2. Hydrolysis of Imidazolines



In summary, a novel one-pot method for the synthesis of imidazolines from alkenes and NCSacc has been described. The reaction is thought to proceed via a Ritter-type mechanism involving the attack of the saccharin anion on an intermediate nitrilium ion (e.g., **4**), which itself is generated from an alkene-derived chloronium ion (e.g., **3**). The resulting *β*-chloro sulfonylamidines (*eg* **2**) can be cyclized to the imidazolines in situ by treatment with potassium ethoxide solution. The sequence is compromised slightly by the formation of competing aziridine and allylic chloride byproducts. These byproducts are thought to arise from unavoidable side reactions of the initially formed chloronium ions. Although this results in low to moderate overall yields of imidazolines, this methodology does allow rapid access to these complex products from commercially available alkenes in a convenient one-pot reaction. Finally, as this methodology appears to only work with nonactivated alkenes, it compliments the powerful diamination work of Li[5,6] with $TsNCl_2$, which has been mainly limited to the reaction of electron-deficient alkenes.

Acknowledgment. We thank the EPSRC and GlaxoSmithKline for a CASE award.

Supporting Information Available: Experimental procedures and characterization for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035374M