JOC Notes

Stannous Chloride-Mediated Reductive Cyclization−Rearrangement of Nitroarenyl Ketones†

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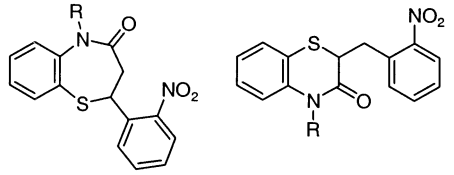
Abstract: Cyclization products are produced in excellent yields from using standard reaction conditions for nitroarene reduction to aminoarene with $SnCl_2$. Thus, 4-methyl-2-(2-nitrobenzyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (**2b)** upon treatment with $SnCl_2$ in ethanol did not produce the expected aniline derivative. Instead, 6-methyl-11a, 12-dihydro-6*H*-quino[3,2-*b*][1,4]benzothiazine (**3**) was produced in excellent yield, presumably via novel Sn (IV)-mediated amidine formation from the initial aniline reduction product. Under identical reaction conditions, 2-(2-nitrophenyl)-thiochroman-4-one (**6**) produces ethyl 5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin-11-ylacetate (**7**). A novel semipinacol rearrangement is proposed to account for this extensive skeletal rearrangement. Aniline derivative (**14**) (from **6** treated with $FeSO_4 \cdot 7H_2O$) forms 12-ethoxy-11,12-dihydro-6*H*-6,12-methanodibenzo[*b*,*f*][1,5]thiazocine (**15)** upon treatment with $SnCl_2$ in ethanol. Thiophene analogues of **6** and **14** (**18** and **19**, respectively**)** react similarly, forming the analogous thiazepine (**20**) and cyclic *N*,*O*-acetals (**21**), respectively.

Stannous chloride in concentrated hydrochloric acid is one of the classic reagents for reduction of nitroarenes to the corresponding aminoarene.[1] More recent modifications use water or ethanol as solvent with no added acid.[2] Reduction of the nitro group followed (*in situ*) by interaction of a reduction intermediate with functionality in an ortho-substituted arene is a well-trodden pathway to heterocyclic compounds. In addition to examples of cyclization of fully reduced aniline species such as the Reissert sequence (*o*-nitrotoluene condensation with ethyl oxalate followed by reduction to ethyl indole-2-carboxylate),[3] intramolecular capture of an intermediate hydroxylamine is also a well-established process. For instance, heterocyclic nitrones[4] or hydroxamic acids[5] are available from suitably substituted nitroarenes. Mechanistically related intramolecular reactions with esters,[6] anhydrides,[7] and nitriles[4c,8] are also reported to produce a variety of heterocycles.

While investigating routes to novel precursors for the sulfoxide electrophilic sulfenylation (SES) reaction,[9] we observed some unusual and synthetically useful reactions of nitroarenes in the presence of stannous chloride in hot alcoholic solvents which we report here.

Formation of Cyclic Amidines. Reaction of *o*-aminothiophenol with *o*-nitrocinnamic acid has been reported to produce benzothiazepinone **1a** as the sole product.[10] However, we obtained not only the desired seven-membered-ring product **1a**, but also benzothiazinone **2a**. The two isomeric products could be cleanly separated by column chromatography. The degree of conversion of reactants and the ratio of the two products varied with reaction conditions. Although not practical synthetically, one run left for several months at room temperature (after an initial 24 h at reflux in toluene) gave a combined yield of 82% with **1a** and **2a** formed in a 1:1.3 ratio. By comparison, after 24 h at reflux in toluene containing piperidine, the yield was only 28% and the **1a** to **2a** ratio was 1:2.6. Since the melting point of neither compound matched the value of compound **1a** reported in the literature (lit.[10] mp 176−178 °C, **1a** mp 212−213 °C, **2a** mp 184−186 °C), we examined these compounds[11] and the literature[12] more closely and conclude the structure assignments for **1** and **2** shown below are correct.



1 a R = H
b R= Me

2 a R = H
b R = Me

Methylation of **1a** and **2a** utilizing Gaino's method[14] yielded **1b** and **2b**, respectively. Reduction of **2b** using Bellamy's procedure[15] ($SnCl_2$ in hot ethanol) did not

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† A portion of this work was presented at the 221th National Meeting of the American Chemical Society, San Diego, CA, April 1-5, 2001; ORGN-180. Structures for **7** and **20** were assigned incorrectly in this presentation.

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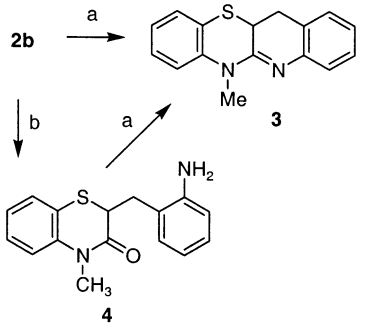
SCHEME 1[a]

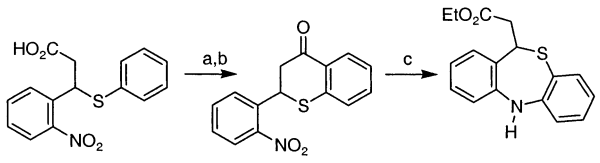


[a] Reagents: (a) 5 equiv of $SnCl_2$, EtOH, reflux, 2 h; (b) 10 equiv of $FeSO_4 \cdot 7H_2O$, MeOH/H_2O, reflux, 1.5 h.

produce the corresponding aniline as expected. Instead, cyclic amidine **3** was isolated in nearly quantitative yield (Scheme 1).[16]

Formation of amidines by reaction of amines and amides with prior amide activation by electrophilic reagents is a very common synthetic protocol,[17] but formation from nitroarene reduction or from reaction of an amide and an amine in the presence of $SnCl_2$ is novel.[18] No reaction takes place in the absence of $SnCl_2$. In this case amidine formation from the intermediate aniline product under tin catalysis, perhaps in the form of a tin amidate, could account for the product. The intermediacy of aniline **4** in this process is supported by reduction of **2b** using $FeSO_4 \cdot 7H_2O$ in refluxing MeOH/H_2O.[19] This reaction provided the aniline derivative (**4**) in excellent yield as the sole product. Exposure of **4** to $SnCl_2$ in hot ethanol produces **3** in 92% yield.

SCHEME 2[a]



[a] Reagents: (a) $(CO)_2Cl_2$, CH_2Cl_2; (b) $SnCl_4$, CH_2Cl_2 (70%, 2 steps); (c) 5 equiv of $SnCl_2$, EtOH, reflux (>97%).

Treatment of benzothiazepinone **1b** with $SnCl_2$ produced only a very poorly soluble solid, which could not be characterized. This reaction was not pursued further.

A Novel Semipinacol Rearrangement and Related *N,O*-Acetal Formation. To explore this unexpected chemistry further we prepared the thiochromanone analogue of **2** (i.e., **6**) using the general procedure of Ponticello (Scheme 2).[20]

Treatment of **6** with $SnCl_2$ in refluxing ethanol reproducibly gave a single product in nearly quantitative yield. However, the product was not an aniline or an amidine, as expected from the results obtained from **2b**. NMR spectral data show incorporation of an ethoxy group and the presence of an ester carbonyl and an exchangeable hydrogen. An apparent triplet at δ 4.57 is attributed to the proton attached to a methine carbon adjacent to the sulfur atom. This triplet signal is coupled to nonequivalent hydrogen atoms on an adjacent methylene group (δ 2.77 and 2.70). Further NMR analysis ($^1H-^1H$ COSY, $^1H-^{13}C$ COSY, DEPT, and HMBC) as well as interpretation of the IR and LRMS suggests the product is **7**.

(11) Additional structural confirmation was obtained from the ^{13}C chemical shifts of methine and methylene carbon atoms in seven- and six-membered ring compounds **1a**, **1b**, **2a**, **2b**, and **4**. Seven-membered ring compounds show a CH peak at δ 45−46 and a CH_2 peak at δ 39−40 [$^1H-^{13}C$ COSY correlation to methine and methylene protons at δ 5.51 and δ 2.84−2.98, respectively, in **1a**]. Six-membered-ring compounds show a CH peak at δ 42−43 and a CH_2 peak at δ 31−33 [$^1H-^{13}C$ COSY correlation to methine and methylene protons at δ 3.71 and δ 2.70/3.20 (AB quartet), respectively, in **4**]. These ^{13}C chemical shifts are in accord with the assignment of seven- and six-membered-ring skeletons to **1** and **2**, respectively.

(12) There is only one report of **1a** in the literature (ref 10) and no reports of **2a**. The benzothiazepinone skeleton is generally prepared by reacting *o*-aminobenzenethiol with an α,β-unsaturated carboxylic acid (e.g., cinnamic acid) at high temperature (160−180 °C) for several hours[10,12a] while the benzothiazinone skeleton is generally prepared from an α-bromoacid (e.g., 2-bromo-3-phenylpropanoic acid).[12b,c] As a product of initial direct Michael addition, **1** is expected to be the kinetic product. However, after **1** has formed and under conditions allowing equilibration through retro-Michael addition, even though anti-Michael addition product **2** is disfavored kinetically it could begin to appear in the reaction mixture since it may be favored thermodynamically. This analysis is consistent with the **1a**:**2a** ratio observed in our reactions. Also, the rate of anti-Michael addition is enhanced with Michael acceptors containing a β-group capable of stabilizing a negative charge.[12d,e] All of this may mean that some compounds assigned the benzothiazepinone skeleton in the literature may in fact be the corresponding benzothiazinone analogue (especially when the phenyl ring is replaced by 2-nitrophenyl, a pyridine ring or other π-deficient heteroaromatic moieties). This is an important point because many of the reports of applications of these reactions discuss the products as potential therapeutic targets.[10,12c,13] (a) Mills, W. H.; Whitworth, J. B. *J. Chem. Soc.* **1927**, 2738−2753. (b) Unger, R.; Graf, G. *Chem. Ber.* **1897**, *30*, 2387. (c) Trapani, G.; Latrofa, A.; Franco, M.; Liso, G. *Farmaco* **1995**, *50*, 107−112. (d) Martin, V.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1992**, *57*, 5530−5532. (e) Klumpp, G. W.; Mierop, A. J.; Vrielink, J. J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, *107*, 6740−6742.

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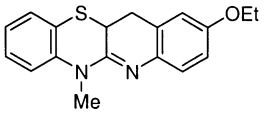
(16) Confirmation of structure **3** by X-ray diffraction will be reported separately. The only impurity isolated (in very small quantity) is **i**,



i

perhaps formed from an acid- or tin-catalyzed attack of ethanol on the intermediate hydroxylamine (with loss of water) followed by amidine formation from the derived aniline derivative. For physical and spectral properties of **i** see the Experimental Section.

(17) (a) Via imidoyl triflates: Charette, A. B.; M. Grenon *Tetrahedron Lett.* **2000**, *41*, 1677−1680. (b) Via imidoyl chlorides: Kraft. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 705−714. Benincori, T.; Sannicolo, F. *J. Heterocycl. Chem.* **1988**, *25*, 1029−1033. (c) Via imidoesters: Roger, R.; Neilson, D. G. In *The Chemistry of Imidates*; Patai, S., Ed.; Wiley: New York, 1960; p 179.

(18) Amidine formation in a one-pot reductive cyclization of nitroarenes containing a cyano group is known: see refs 4c and 8. Amidines from addition of amines to nitriles are well-known: Ogonor, J. I. *Tetrahedron* **1981**, *37*, 2909−2910.

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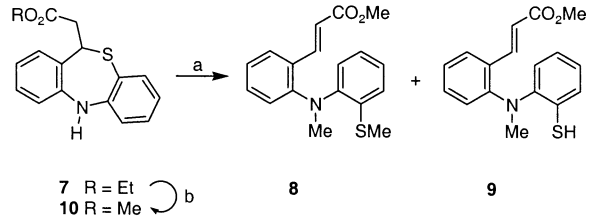
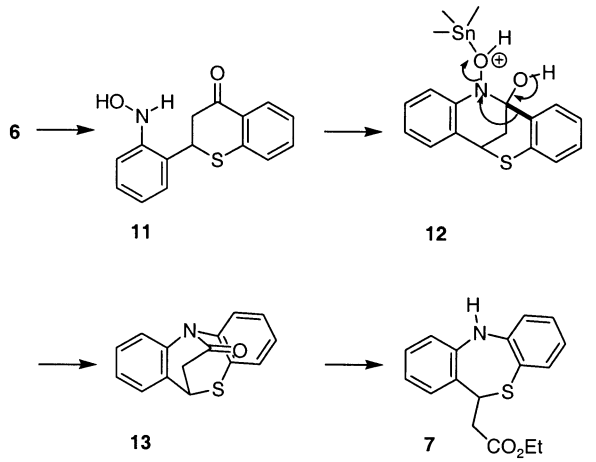
SCHEME 3[a]

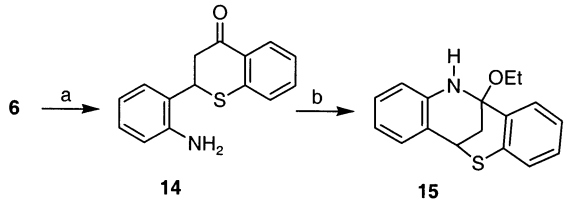


[a] Reagents: (a) MeI (5 equiv), *t*-BuOK (2.2 equiv), THF, rt, 19 h; (b) NaOMe (2 equiv), MeOH, reflux, 15 h.

SCHEME 4



SCHEME 5[a]



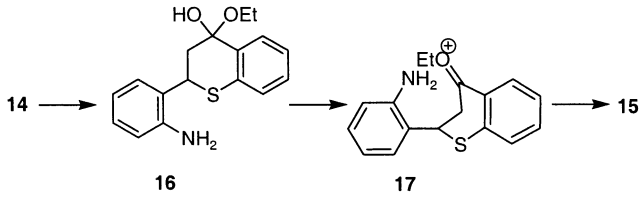
[a] Reagents: (a) 10 equiv of $FeSO_4 \cdot 7H_2O$, $MeOH/H_2O$, reflux, 2 h (>98%); (b) 5 equiv of $SnCl_2$, EtOH, reflux, 2 h (>99%).

Chemical evidence also supports structure **7**. Treatment of compound **7** with *t*-BuOK and MeI in THF both *N*-methylates the nitrogen atom and induces retro-Michael addition giving products **8** and **9** (Scheme 3). Interestingly, under these reaction conditions the ethyl ester is replaced by a methyl ester. Ethyl ester **7** could also be converted to the corresponding methyl ester (**10**) by MeONa in refluxing MeOH, but under these conditions no retro-Michael product was isolated.

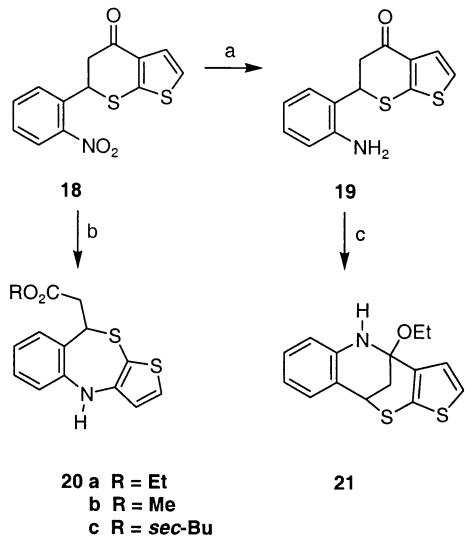
The mechanism of formation of **7** most likely involves an intermediate hydroxylamine (**11**) (Scheme 4). Nucleophilic addition of the hydroxylamine to the ketonic carbonyl leads to **12**, which may undergo a tin-mediated pinacol-type rearrangement with preferred migration of the phenyl substituent to produce amide **13**. Ethanolysis of the amide generates the observed product (**7**).[21] Such a semipinacol rearrangement[22] of an *N*-hydroxyhemiaminal has not been reported previously.

Reduction of nitroarene **6** by $FeSO_4 \cdot 7H_2O$ in refluxing $MeOH/H_2O$ was uneventful, producing the corresponding aniline derivative (**14**) as a mixture of conformers (7:3 ratio) in excellent yield (Scheme 5). Treatment of **14** with $SnCl_2$ in refluxing ethanol produced a single compound in nearly quantitative yield to which we assign structure **15**.[23]

SCHEME 6



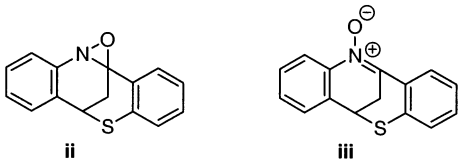
SCHEME 7[a]



[a] Reagents: (a) 10 equiv of $FeSO_4 \cdot 7H_2O$, $MeOH/H_2O$, reflux, 2 h (98%); (b) 5 equiv of $SnCl_2$, ROH, reflux, 2 h (98%); (c) 5 equiv of $SnCl_2$, EtOH, reflux, 2 h (99%).

Formation of **15** may be mechanistically similar to formation of **7**. With the reduced nucleophilicity of the nitrogen atom in **14** (compared to the α-effect enhanced **11**), the reaction pathway could proceed slightly differ-

(21) Less strained analogues of **12** (Scheme 4) are intermediates in the standard route to nitrones. Nitrones and oxaziranes equilibrate photochemically or thermally (ref 4). In this case, **ii/iii**



could form from attack of the hemiaminal hydroxyl at nitrogen with Sn-assisted displacement of the *N*-hydroxyl group. Although rearrangement of oxaziranes to amides is a well-know process, this pathway to **13** seems less likely due to steric strain in the intermediates: (a) Just, G.; Cunningham, M. *Tetrahedron Lett.* **1972**, 1151−1153. (b) Hamar, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473−495. (c) Umezawa, B. *Chem. Pharm. Bull. Jpn.* **1960**, *8*, 967−975. (d) Bonnett, R.; Clark, V. M.; Todd, A. *J. Chem. Soc.* **1959**, 2102−2104. (e) Krimm, H. *Chem. Ber.* **1958**, *91*, 1057−1068. (f) Kroehnke, F. *Ann.* **1957**, *604*, 203−207.

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(23) *N*,*O*-Acetal formation catalyzed by $SnCl_2$ has some precedence: 2,3-dimethylindole reacts with benzaldehydes in the presence of $SnCl_2$ in ethanol-stabilized dicholoromethane to form *N*,*O*-acetals (Pindur, U.; Schiffl, E. *Monatsh. Chem.* **1986**, *117*, 1461−1463).

ently, providing initially the hemiacetal **16**, by attack of ethanol rather than the proximate amino group. Under Sn catalysis **16** could form an oxenium ion (**17**) with subsequent intramolecular attack providing *N*,*O*-acetal **15** (Scheme 6). In the absence of $SnCl_2$, no reaction takes place.

To begin to investigate the generality of these reactions, thiophene analogues **18** and **19** were prepared as described above for **6** and **14**, respectively. Reduction of **18** with $SnCl_2$ in hot ethanol gave the benzothienothiazepine **20a** in excellent yield (Scheme 7). Changing the alcohol used as the reaction solvent to methanol or 2-butanol provided the corresponding methyl and *sec*-butyl esters **20b** and **20c**, respectively. Treatment of **19** with $SnCl_2$ in ethanol gave *N*,*O*-acetal **21** in excellent yield.

In conclusion, three reaction pathways for intermediates in processes in which tin may serve as a reducing agent or Lewis acid, or both, are reported. One of these pathways, a novel semipinacol rearrangement, may be useful for the preparation of novel heterocycles not readily available by other approaches.

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Supporting Information Available: Full experimental details, characterization of new compounds, and ^1H and ^{13}C spectra of compounds **1ab**, **2ab**, **3**−**10**, **14**, **15**, **18**, **19**, **20a**,**b**,**c**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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