New Thiochromans via Reductive Cyclization of Thiophenol Derivatives

André Niermann, Janine E. Grössel, Hans-Ulrich Reissig*

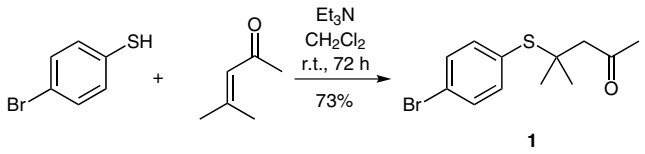
Freie Universität Berlin, Institut für Chemie und Biochemie, Takustrasse 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

Received: 01.11.2012; Accepted after revision: 23.11.2012

Abstract: Reductive cyclization of sulfur-containing substrates **1** and **5** with samarium diiodide afforded the corresponding thiochroman derivatives with excellent diastereoselectivities. Cyclization of **1** is facilitated by geminal dimethyl substitution, which accelerates the reductive coupling and prevents samarium diiodide induced dehalogenation. Bromo-substituted dihydrothiochroman derivative **8** was further functionalized in subsequent reactions. Analogously, bromo-substituted hexahydroquinoline derivative **10** was diastereoselectively prepared in satisfying yield.

Key words: samarium diiodide, radical, cyclization, thiochroman, geminal disubstitution, γ-aryl ketone

Samarium diiodide is known as a very efficient reagent in organic synthesis triggering the formation of new carbon–carbon bonds.[1] Our group is interested in the application of samarium diiodide in the reductive cyclizations of (hetero)aryl ketones that deliver functionalized dearomatized products with excellent diastereoselectivity.[1e,i] A broad spectrum of substrates such as ketones with (substituted) phenyl,[2,3] naphthyl,[4] aniline,[5] indole, pyrrole[6] and quinoline[7] moieties in γ-position were successfully used as precursors. In the course of these studies we also investigated the influence of geminal disubstitution on these reductive cyclizations of (substituted) phenyl ketones[2h,i] and now present our results applying substrates containing a sulfur or nitrogen atom in the linker unit. Compounds such as **1** are easily prepared by conjugate addition of the corresponding thiophenol derivative to mesityl oxide (Scheme 1)[8] and they are excellent precursors for the preparation of unusually substituted thiochroman derivatives.[9]



1

Scheme 1 Preparation of bromo-substituted γ-aryl ketone **1** by conjugate addition

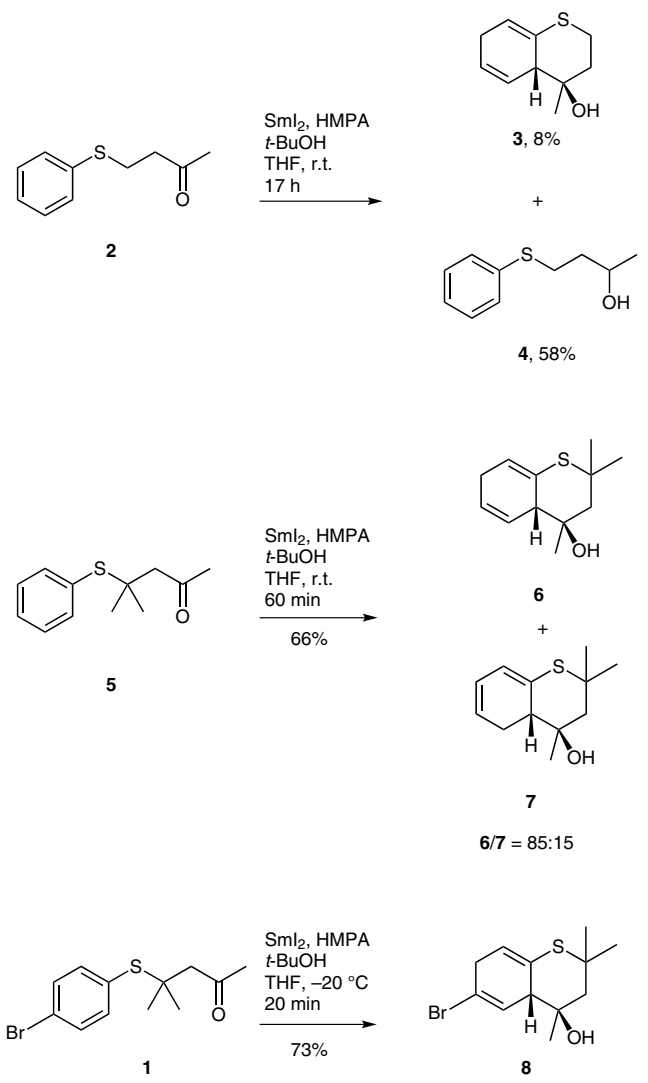
Scheme 2 summarizes our results on reductive cyclizations.[10] The attempted reductive cyclization of ketone **2**, bearing a thioether in the linker but no geminal dimethyl unit, did not lead to a satisfying conversion. Along with small amounts of bicyclic product **3** we mainly isolated secondary alcohol **4** as a result of samarium diiodide mediated reduction of the carbonyl group. In contrast, precursor **5** bearing two methyl groups in the linker unit underwent smooth reductive cyclization and furnished a mixture of the desired bicyclic compound **6** and the conjugated diene **7** in satisfying yield. It should be noted that similar mixtures of regioisomers are regularly isolated when substrates without additional substituents at the phenyl ring are applied as precursors.[2g,h] The origin of the low regioselectivity is still under investigation, but preliminary results indicate that a kinetically controlled unselective protonation of an anionic intermediate is responsible for the generation of product mixtures.[11] The relative configuration of these compounds was established by NMR spectroscopy and is analogous to that of cyclization products previously reported.[2,5,6]

Comparison of the results of precursors **2** and **5** suggests that geminal dialkyl substitution is very beneficial for efficient cyclizations. We therefore examined the conversion of *para*-bromo-substituted precursor **1** and were delighted to observe that the cyclization proceeds cleanly and rapidly even at a lower temperature affording bromo-substituted thiochroman derivative **8** in good yield.[12] No evidence was found for the generation of compounds **6** or **7**, possible products of a reductive removal of the bromo substituent. Thus, for the first time a bromo-substituted aryl ketone was successfully applied in the samarium diiodide induced ketyl–aryl coupling process. Previous investigations towards cyclization of aryl ketones with a *para*-chloro substituent predominantly led to dechlorinated products due to a fast reduction of the carbon–halogen bond.[2g] Apparently, the geminal dimethyl substitution of compound **1** strongly accelerates the cyclization and dehalogenation does not occur.

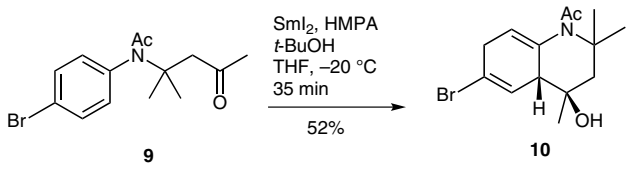
We also explored the related *para*-bromoaniline-derived ketone **9** as substrate and smoothly obtained hexahydroquinoline derivative **10** albeit in moderate yield (Scheme 3). Substrates without a bromo substituent and without the dimethyl unit had been investigated previously and furnished cyclization products in excellent diastereoselectivities.[5] An attempt to cyclize the iodo analogue of **9** led to a more complex product mixture containing only small amounts of the desired cyclization products.[11,13] The related precursors with an oxygen atom in the linker unit were not suitable with the reductive ketyl–aryl coupling as only small amounts of cyclization products could be obtained.

Thiochroman derivatives such as **8** are promising candidates for subsequent transformations, e.g. transition-met-

SYNLETT 2013, 24, 0177–0180
Advanced online publication: 11.12.2012
DOI: 10.1055/s-0032-1317922; Art ID: ST-2012-D0935-L

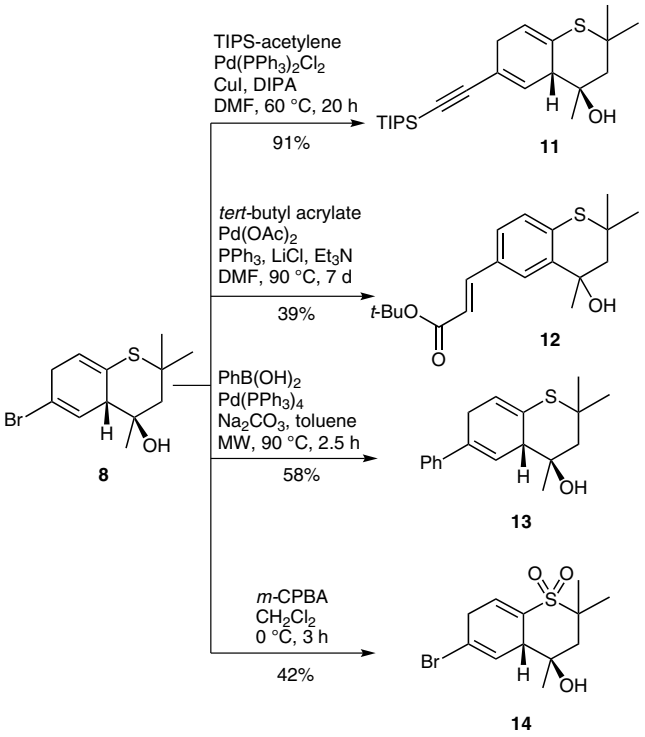


Scheme 2 Samarium diiodide induced cyclizations of sulfur-containing γ-aryl ketones with different substitution patterns



Scheme 3 Samarium diiodide induced cyclization of aniline-derived γ-aryl ketone **9**

al-catalyzed cross couplings or oxidations at the sulfur atom. Our exemplary results are illustrated in Scheme 4. Sonogashira reaction of **8** with TIPS–acetylene as coupling partner afforded alkyne **11** in very good yield, whereas a Heck coupling with *tert*-butyl acrylate required high temperatures and long reaction times to furnish re-aromatized thiochroman derivative **12** in modest yield. Suzuki–Miyaura coupling of **8** and phenyl boronic acid under standard conditions afforded compound **13** in moderate yield. Sulfone **14** was obtained by oxidation of **8** with *m*-CPBA under mild conditions with no evidence for the generation of epoxides.[14] Nevertheless, the low yield for this transformation indicates the formation of side products.



Scheme 4 Subsequent transformations of bromo-substituted compound **8** leading to new thiochroman derivatives **11**–**14**

In summary, we could demonstrate that the samarium diiodide induced cyclization of sulfur-containing precursors constitutes a new and valuable approach to thiochroman derivatives which are formed diastereoselectively. We again could show that geminal dialkyl substitution of the linker unit is essential to attain acceptable yields. This allows the use of bromo-substituted precursors and hence subsequent transformations utilizing this functional group leading to a variety of new highly substituted thiochroman derivatives.

Acknowledgment

We thank the Deutsche Forschungsgemeinschaft and BayerHealthcare for generous financial support. We gratefully acknowledge the assistance of Dr. R. Zimmer during preparation of this manuscript.

References and Notes

(1) For selected reviews, see: (a) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (c) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (d) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (e) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422. (f) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (g) Nicolaou, K. C.; Ellery, S.; Chen, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140; *Angew. Chem.* **2009**, *121*, 7276.

(h) Procter, D. J.; Flowers, R. A. II.; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry: Cambridge, **2010**.
(i) Beemelmanns, C.; Reissig, H.-U. *Chem. Soc. Rev.* **2011**, *40*, 2199. (j) Harb, H. Y.; Procter, D. J. *Synlett* **2012**, *23*, 6.

(2) (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **1999**, *38*, 789; *Angew. Chem.* **1999**, *111*, 874. (b) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267. (c) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290. (d) Ohno, H.; Maeda, S.-I.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316. (e) Ohno, H.; Wakayama, R.; Maeda, S.-I.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909. (f) Ohno, H.; Okumura, M.; Maeda, S.-I.; Iwasaki, H.; Wakayama, R.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 7722. (g) Wefelscheid, U. K.; Berndt, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 3635. (h) Niermann, A.; Reissig, H.-U. *Synlett* **2011**, 525. (i) Berndt, M.; Hölemann, A.; Niermann, A.; Bentz, C.; Zimmer, R.; Reissig, H.-U. *Eur. J. Org. Chem.* **2012**, 1299.

(3) For related ketyl–aryl couplings, see: (a) Kise, N.; Suzumoto, T.; Shono, T. *J. Org. Chem.* **1994**, *59*, 1407. (b) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2383; *Angew. Chem.* **1995**, *107*, 2597 . (c) Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643. (d) Heimann, J.; Schäfer, H. J.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2003**, 2919.

(4) (a) Berndt, M.; Hlobilova, I.; Reissig, H.-U. *Org. Lett.* **2004**, *6*, 957. (b) Aulenta, F.; Berndt, M.; Brüdgam, I.; Hartl, H.; Sörgel, S.; Reissig, H.-U. *Chem. Eur. J.* **2007**, *13*, 6047. (c) Wefelscheid, U. K.; Reissig, H.-U. *Adv. Synth. Catal.* **2008**, *350*, 65. (d) Wefelscheid, U. K.; Reissig, H.-U. *Tetrahedron: Asymmetry* **2010**, *21*, 1601.

(5) (a) Gross, S.; Reissig, H.-U. *Synlett* **2002**, 2027. (b) Kumaran, R. S.; Brüdgam, I.; Reissig, H.-U. *Synlett* **2008**, 991.

(6) (a) Gross, S.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 4305. (b) Blot, V.; Reissig, H.-U. *Synlett* **2006**, 2763. (c) Blot, V.; Reissig, H.-U. *Eur. J. Org. Chem.* **2006**, 4989. (d) Beemelmanns, C.; Reissig, H.-U. *Org. Biomol. Chem.* **2009**, *7*, 4475. (e) Beemelmanns, C.; Blot, V.; Gross, S.; Lentz, D.; Reissig, H.-U. *Eur. J. Org. Chem.* **2010**, 2716. (f) Beemelmanns, C.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2010**, *49*, 8021; *Angew. Chem.* **2010**, *122*, 8195 . (g) For a related electrochemical cyclization, see: Kise, N.; Mano, T.; Sakurai, T. *Org. Lett.* **2008**, *10*, 4617.

(7) Aulenta, F.; Wefelscheid, U. K.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 2325.

(8) Spruce, L. W.; Gale, J. B.; Berlin, K. D.; Verma, A. K.; Breitman, T. R.; Ji, X.; Van der Helm, D. *J. Med. Chem.* **1991**, *34*, 430.

(9) For selected publications dealing with the synthesis of thiochroman derivatives, see: (a) Takido, T.; Itabashi, K.; Takagi, Y. *J. Heterocycl. Chem.* **1995**, *32*, 687. (b) Nenajdenko, V.; Sanin, A.; Churakov, A.; Howard, J.; Balenkova, E. *Chem. Heterocycl. Compd.* **1999**, *35*, 549. (c) Kumar, P.; Bodas, M. S. *Tetrahedron* **2001**, *57*, 9755. (d) Katritzky, A. R.; Button, M. A. C. *J. Org. Chem.* **2001**, *66*, 5595. (e) Bath, S.; Laso, N. M.; Lopez-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2003**, 204. (f) Saito, T.; Horikoshi, T.; Otani, T.; Matsuda, Y.; Karakasa, T. *Tetrahedron Lett.* **2003**, *44*, 6513. (g) Liepa, A. J.; Nguyen, O.; Saubern, S. *Aust. J. Chem.* **2005**, *58*, 864. (h) Jafarzadeh, M.; Amani, K.; Nikpour, F. *Tetrahedron Lett.* **2005**, *46*, 7567. (i) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (j) Guha, C.; Pal, R.; Mallik, A. K. *ARKIVOC* **2012**, *(ix)*, 85; and references cited in this article.

(10) **General Procedure for Samarium Diiodide Induced Cyclizations of Aryl Ketones**: HMPA (10 equiv) was added to a previously prepared stock solution of SmI_2 in THF (0.1 M, 2.05 equiv) under argon and the solution was stirred for 20 min. During this time the solution turned from dark blue to dark violet. In a separate flask, the substrate (1 equiv) and *t*-BuOH (2 equiv) were dissolved in THF (10 mL/mmol cyclization precursor) under argon. Argon was bubbled through the solution for 20 min. The substrate solution was then transferred with a syringe to the samarium diiodide solution and the resulting mixture was stirred at r.t. or –20 °C until the color changed from violet to grey. Saturated aq Na-K-tartrate solution was added, the organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$ and the solvents were removed under reduced pressure to give the crude product, which still contained small amounts of HMPA. Flash chromatography with aluminum oxide (activity grade III) yielded the cyclization products.

(11) Niermann, A. *Dissertation*; Freie Universität Berlin, **2012**.

(12) **Cyclization of Compound 1**: According to the general procedure, the samarium diiodide solution in THF (27.2 mL, 2.59 mmol), HMPA (2.21 mL, 12.6 mmol), **1** (0.361 g, 1.26 mmol), and *t*-BuOH (0.187 g, 2.52 mmol) afforded after purification by flash chromatography (hexane–EtOAc, 9:1) compound **8** in 73% yield (265 mg) as a colorless oil. Analytical data of **(4*R**,4a*S**)-6-Bromo-2,2,4-trimethyl-3,4,4a,7-tetrahydro-2*H*-thiochromen-4-ol** (**8**): ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.21, 1.30, 1.37 (3 × s, 3 H each, CH_3), 1.57 (br s, 1 H, OH), 1.99, 2.02 (AB system, J_{AB} = 13.4 Hz, 1 H each, 3-H), 3.02 (m_c, 1 H, 4a-H), 3.07 (dddd, *J* = 1.2, 3.8, 7.5, 22.4 Hz, 1 H, 7-H), 3.17 (dddd, *J* = 1.9, 3.4, 7.4, 22.4 Hz, 1 H, 7-H), 5.96 (ddd, *J* = 1.3, 3.4, 3.8 Hz, 1 H, 8-H), 6.30 (ddd, *J* = 1.2, 1.9, 3.5 Hz, 1 H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.6, 30.6, 32.7 (3 × q, CH_3), 37.2 (t, C-7), 43.6 (s, C-2), 53.7 (d, C-4a), 56.8 (t, C-3), 73.6 (s, C-4), 119.6 (s, C-6), 126.2 (d, C-5), 126.9 (d, C-8), 129.3 (s, C-8a). IR (film): 3400 (O–H), 3010–2850 (=C–H, C–H), 1665 (C=C) cm^{-1}. Anal. Calcd for $C_{12}H_{17}BrOS$ (289.2): C, 49.83; H, 5.92. Found: C, 49.78; H, 5.77.

(13) Large amounts of dehalogenated compounds were isolated indicating that the increase in rate due to geminal dimethyl substitution cannot compensate the very fast samarium diiodide mediated deiodination.

(14) **Oxidation of Compound 8 with *m*-CPBA**: *m*-CPBA (0.313 g, 1.82 mmol) was added to a solution of alkenyl bromide **8** (0.150 g, 0.52 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After stirring for 3 h at 0 °C, the solvent was removed under reduced pressure and the crude material was subjected to column chromatography on silica gel (hexane–EtOAc, 7:3). Sulfone **14** was isolated as a colorless solid (70 mg, 42%). Analytical data of **(4*R**,4a*S**)-6-Bromo-2,2,4-trimethyl-1,1-dioxo-3,4,4a,7-tetrahydro-2*H*-benzo-thiopyran-4-ol (14)**: mp 160–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24, 1.34, 1.41 (3 × s, 3 H each, CH_3), 1.83 (br s, 1 H, OH), 1.88, 2.38 (2 × d, *J* = 14.4 Hz, 1 H each, 3-H), 3.26 (dddd, *J* = 1.3, 3.9, 7.8, 23.6 Hz, 1 H, 7-H), 3.36 (dddd, *J* = 2.0, 3.1, 7.5, 23.6 Hz, 1 H, 7-H), 3.63 (m_c, 1 H, 4a-H), 6.29 (m_c, 1 H, 5-H), 6.78 (m_c, 1 H, 8-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.0, 22.8, 24.5 (3 × q, Me), 36.0 (t, C-7), 49.7 (d, C-4a),

51.9 (t, C-3), 57.2 (s, C-2), 72.9 (s, C-4), 118.8 (s, C-6), 125.5 (d, C-5), 132.8 (s, C-8a), 135.2 (d, C-8). IR (film): 3480 (O–H), 2990–2855 (=C–H, C–H), 1130 (S=O) cm^{-1}.

HRMS (ESI–TOF–MS): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{17}BrO_3SNa$: 342.9979; found: 342.9977.

