Samarium Diiodide-Induced Diastereoselective Synthesis of Hexahydroquinoline Derivatives

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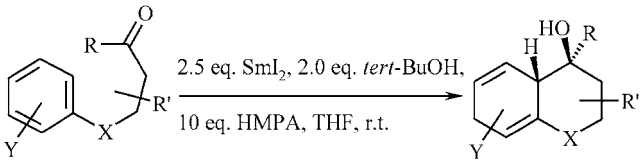
Abstract: Samarium diiodide-induced cyclization of aniline derivatives **5**, **9**, **12**, **14**, and **16** afforded hexahydroquinolines such as **6**, **10**, **13**, **15**, and **17** in moderate to good yields and excellent diastereoselectivities. Phenol was found to be a surprisingly effective proton source in some of these samarium-ketyl cyclizations. The influence of different substituents at nitrogen as well as at the aromatic ring of the aniline moiety was studied. Whereas *para*-donor-substituted aniline derivatives **19** and **21** provided the expected products **20** and **22**, the corresponding *para*-cyano derivatives **23** and **26** took an alternative pathway. *Ipso*-substitution involving spiro intermediates **29** resulted in formation of rearranged products **24** and **28**.

Key words: samarium diiodide, electron transfer, ketyl, radicals, hexahydroquinolines

6-*trig*-Cyclizations of γ-arylketones via ketyl radical addition to the aromatic substituent[1] are of ongoing interest in our group. This method benefits from the remarkable properties of 'Kagan's reagent'[2] samarium diiodide, namely combination of its powerful reduction potential with mild reaction conditions and high chemo- and stereoselectivity. Upon loss of its aromaticity the aryl group serves as a C-6 building block, leading to functionalized hexahydronaphthalene systems (Scheme 1, X = CH_2). Donor- and acceptor-substituted γ-arylketones and naphthyl derivatives were examined.[3,4] The sequence starts with formation of a ketyl radical anion by samarium diiodide-mediated electron transfer to the ketone, followed by 6-*trig*-cyclization to the aromatic ring, resulting in a pentadienyl radical. This is reduced by a second equivalent of samarium diiodide to provide the corresponding pentadienyl anion. Regioselective protonation takes place similarly to the related Birch reaction, furnishing 1,4-cyclohexadiene units.



Scheme 1 X = CH_2, NR

We recently extended the scope of this reaction to aniline derivatives, which yielded hexahydroquinoline derivatives under the aforementioned reductive conditions (Scheme 1, X = NR). Due to the nucleophilic character of the ketyl, we anticipated that relatively electron-poor aniline derivatives should be the most promising candidates for this kind of cyclization reaction, and therefore different substituents were attached to the nitrogen. The required *N*-alkylated anilines were obtained using a palladium(II)-catalyzed addition to methyl vinyl ketone[5] whereas *N*-acylated derivatives were smoothly prepared by Michael addition of aniline to methyl vinyl ketone in refluxing ethanol followed by acylation under standard conditions.

The reductive cyclizations were carried out routinely using 2.5 equivalents of samarium diiodide in the presence of 10 equivalents of HMPA (hexamethylphosphoramide) and 2.0 equivalents of *tert*-butanol in THF at room temperature.[6] The use of HMPA was essential for the success of the reactions since its property as a donor ligand results in drastic enhancement of the reduction potential of samarium(II) species.[7] Scheme 2 summarizes the results of a series in which the *N*-substituent varied from an electron-donating methyl group in **1** via a phenyl substituent with a slight electron-withdrawing mesomeric effect in **3** towards the strongly electron-withdrawing benzyloxycarbonyl and acetyl groups at nitrogen in **5** and **9**.

Compounds **1** and **3** afforded cyclized products with low yield, however, rearomatized derivatives **2** and **4** were isolated instead of the expected hexahydroquinolines. These were probably formed by spontaneous oxidation during work up.[8] Carbamate **5** finally provided the desired cyclization product **6** in moderate yield along with rearomatized **7** and anilide **8**. Compound **8** was most likely generated by base-induced retro-Michael reaction since the anilide anion is a good leaving group in elimination processes. The best result was obtained with substrate **9** yielding 39% of hexahydroquinoline derivative **10**. No rearomatized product was observed, only small amounts of acetanilide **11** and the secondary alcohol **18** generated by reduction of **9** were detected as side products. The newly generated stereogenic centres of **6** and **10** exclusively exhibit the depicted configuration.[9] These first results demonstrate that the anticipated cyclization proceeds in moderate yields with anilides such as **5** and **9**, but even rather electron-rich aniline derivatives **1** and **3** undergo a reaction, although in low yield and followed by rearomatization.

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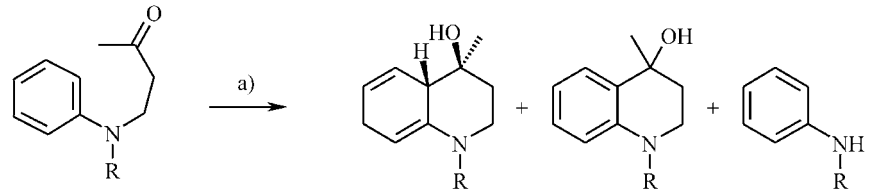
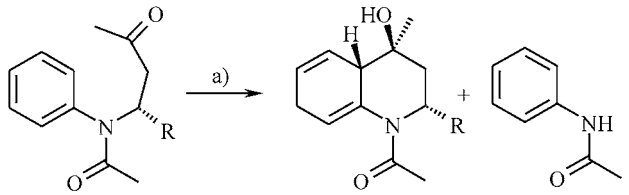


1 R = Me	—	**2** 15 %	—
3 R = Ph	—	**4** 22 %	—
5 R = CO_2Bn	**6** 35 %	**7** 9 %	**8** 10 %
9 R = $COCH_3$	**10** 39 %	—	**11** 7 %[b]

Scheme 2 *Reagents and conditions*: a) 2.5 equiv SmI_2, 2.0 equiv *tert*-BuOH, 10 equiv HMPA, THF, r.t. b) Mixture of acetanilide **11** and secondary alcohol **18**.

We then checked the diastereoselectivity of this novel aryl carbonyl coupling reaction by introducing substituents into the side chain. Syntheses of compounds **12**, **14**, and **16** in Scheme 3 were accomplished by an efficient one-pot method[10] using the corresponding aldehyde, aniline, acetone and a catalytic amount of L-proline in DMSO followed by acylation with acetyl chloride. The samarium diiodide-induced cyclizations of these substrates revealed that even the small methyl substituent of **12** induced an excellent diastereoselectivity (10:1) in synthesis of **13**, and that bulkier substituents such as phenyl in **14** or *iso*-propyl in **16** caused formation of **15** and **17** as single diastereomers. The relative configuration of **17** was unequivocally proven by X-ray analysis.[11]



12 R = CH_3	**13** 50 %[b]	12 %
14 R = Ph	**15** 34 %	39 %
16 R = *iso*-Pr	**17** 63 %	26 %

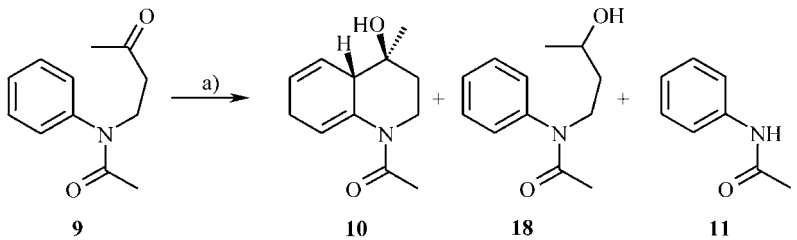
Scheme 3 *Reagents and conditions*: a) 2.5 equiv SmI_2, 2.0 equiv *tert*-BuOH, 10 equiv HMPA, THF, r.t. b) Two diastereomers (10:1).

To generally improve the yield of the cyclizations model substrate **9** was subjected to different reaction conditions (Scheme 4). As mentioned above, use of HMPA is crucial for the reaction but increasing the amount of this additive from 10 to 18 equivalents did not raise the yield significantly. The influence of the proton source was then investigated (Table 1). Entry 1 represents the result under standard conditions. In the absence of a proton source (entry 2) a poor yield was obtained. Water (entry 3) was only a slightly worse proton source compared to *tert*-butanol while methanol (entry 4) yielded almost the same amount of **10** together with side products. Most remarkably, application of phenol (entry 5) dramatically increased the yield of **10** from 39% to 63%, and the amount of side products was reduced to traces. Possibly the generated phenolate anion causes less retro-Michael fragmentation of the starting material due to its lower basicity.[12] In contrast, use of thiophenol (entry 6) led to exclusive isolation of **18**, which indicates that the ketyl radical anion abstracts a hydrogen atom from the thiol rather than adding to the aromatic ring.

Table 1 Influence of the Proton Source on the Cyclization of Compound **9**

Entry	Proton source	**10**	**11**+**18**[a]
1	*tert*-BuOH	39%	7%
2	–	9%	8%
3	H_2O	33%	24%
4	MeOH	38%	3%
5	phenol	63%	< 1%
6	thiophenol	–	85%[b]

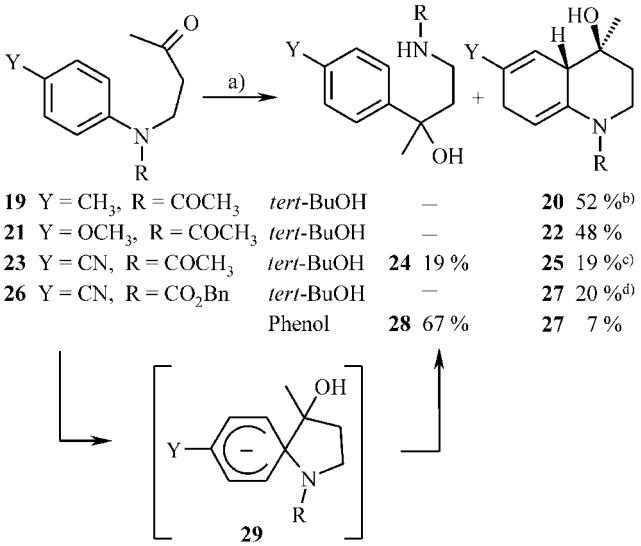
[a] **11** and **18** were isolated as mixtures.
[b] **18** was formed exclusively.



9 **10** **18** **11**

Scheme 4 *Reagents and conditions*: a) 2.5 equiv SmI_2, 2.0 equiv proton source, 10 equiv HMPA, THF, r.t.

The influence of substituents at the aryl group was also investigated. Examples depicted in Scheme 5 demonstrate that electron-donating substituents at the anilide ring are suitable. *Para*-substituted substrates **19** and **21** (Y = CH_3, OCH_3) exclusively afforded the desired bicyclic hexahydroquinolines **20** and **22** in approximately 50% yield.[13] Surprisingly, acceptor-substituents at the anilide complicate the reaction. Compound **23** with a *para*-cyano group led to formation of the expected cyclization product **25** along with *ipso*-substitution product **24**. This evidently arises from a 5-*exo*-*trig* attack to the aromatic ring giving the spirocyclic[14] intermediate **29** in which the negative charge is most favourably stabilized. Elimination of the amide function is promoted by gain of aromaticity and furnishes **24**. The outcome of the reaction of the related compound **26** was strongly dependent on the proton source applied. Treating **26** under standard conditions gave bicyclic product **27** in low yield. However, use of phenol instead of *tert*-butanol furnished the *ipso*-substitution product **28** in good yield.



Scheme 5 *Reagents and conditions*: a) 2.5 equiv SmI_2, 2.0 equiv proton source, 10 equiv HMPA, THF, r.t. b) 4% of secondary alcohol and 5% of acetanilide as side products. c) 14% of acetanilide isolated. d) 69% of benzylalcohol isolated.

These last experiments indicate that a primary *ipso*-attack of the ketyl can not rigorously be ruled out for all cyclization reactions. Spirocycles such as **29** may also be intermediates in other reactions, but their rearrangement by 1,2-shift would finally generate identical products as the direct ketyl addition to the *ortho*-position.

The reductive cyclization reactions presented here reveal a new and stereoselective approach to highly functionalized nitrogen heterocycles. The enamide and alcohol functions allow subsequent synthetic transformations leading to natural product analogue structures. Other *N*-heterocyclic aromatic compounds are currently investigated to further explore scope and limitations of this reductive cyclization method.

Acknowledgment

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(6) **Typical procedure**, cyclization of **16** to **17**: Samarium (0.329 g, 2.19 mmoL) and 1,2-diiodoethane (0.571 g, 2.02 mmol) were suspended in freshly distilled THF (30 mL) under an argon atmosphere and stirred for 2 h at room temperature. To the resulting dark blue solution HMPA (1.45 g, 8.1 mmol) was added. Ketone **16** (200 mg, 0.81 mmol) and *tert*-butanol (0.15 mL, 1.62 mmol), dissolved in THF (20 mL), were then added in one portion to the deep violet solution. After 16 h the reaction was quenched with saturated aqueous solution of sodium bicarbonate, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined ether extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The resulting crude product was purified by flash chromatography on silica gel using hexane–ethyl acetate (5:1 to 1:3) to give **17** (0.128 g, 63%) as a colourless solid. Data for (2*R**,4*S**,4a*S**)-1-acetyl-2-(*iso*-propyl)-4-hydroxy-4-methyl-1,2,3,4,4a,7-hexahydroquinoline (**17**): colourless crystals; mp 164 °C; ^{1}H NMR (C_6D_6, 270 MHz): δ = 0.82, 0.91 (2d, *J* = 6.6 Hz, 3 H each, CH_3), 1.18 (s, 3 H, 4-CH_3), 1.74 (m_c, 2 H, 3-H, 2-CH), 2.05 (s, 3 H, $COCH_3$), 2.05 (m_c, 1 H, 3-H), 2.25 (s, 1 H, br, OH), 2.67 (m_c, 1 H, 4a-H), 2.28 (m_c, 2 H, 7-H), 4.33 (dd, *J* = 6.6, 11.8 Hz, 1 H, 2-H), 5.58 (s, 1 H, br, 8-H), 5.81 (m_c, 2 H, 5-H, 6-H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ = 19.8, 20.3 (2q, CH_3), 21.8 (q, $COCH_3$), 24.4 (q, 4-CH_3), 27.1 (t, C-7), 28.7 (d, 2-CH), 40.4 (t, C-3), 48.9 (d, C-4a), 55.7 (d, C-2), 73.0 (s, C-4), 123.3 (d, C-8), 123.9 (d, C-6), 124.4 (d, C-5), 134.6 (s, C-8a), 169.2 (s, CO); IR (KBr): ν = 3390 (OH), 3030 (=CH), 2975–2820 (CH), 1610 (CO) cm^{-1}; Calcd. for $C_{15}H_{23}NO_2$ (249.4): C 72.23, H 9.30, N 5.62; Found: C 72.49, H 9.10, N 5.50.

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(8) Since samarium(II/III) species are Lewis acids one might assume a simple electrophilic substitution reaction for the formation of **2** and **4**. This possibility was excluded by performing a test reaction with preformed samarium(III) iodide under the same reaction conditions but no cyclization product was observed (in the presence of HMPA as strong donor ligand the Lewis acidity of the samarium salts is effectively reduced).
(9) The relative configuration was determined by NOESY-NMR spectroscopy. For **17** a crystal structure was obtained to prove the relative configuration.
(10) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F. III *Tetrahedron Lett.* **2001**, *42*, 199. (c) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827; Basically, this Mannich reaction leads to optically active compounds with considerable enantioselectivity, but since our interest was focused on the chemo- and diastereoselectivity of the cyclization reaction the enantiomeric excess of these starting materials and the resulting products was so far not determined..
(11) Brüdgam, I.; Hartl, H. Institut für Chemie, FU Berlin, **2002** unpublished results.
(12) When phenol was applied in related SmI_2-induced cyclizations yields were at least equivalent to those with *tert*-butanol as proton source, however, so far no rule is recognizable for which substrates phenol improves the outcome. Other proton sources were also examined (including 2,6-di-*tert*-butylphenol or 2,2,2-trifluoroethanol) but no effect similar to that of phenol was discovered.
(13) The related *ortho*- and *meta*-substituted aromatic compounds generally cyclize with considerably lower efficiency. For cyano-substituted derivatives the yields are particularly low.
(14) For a recent report on related samarium diiodide induced spirocyclizations to electron-deficient aromatic compounds, see: Ohno, H.; Maeda, S.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316.