Polycyclic Amines

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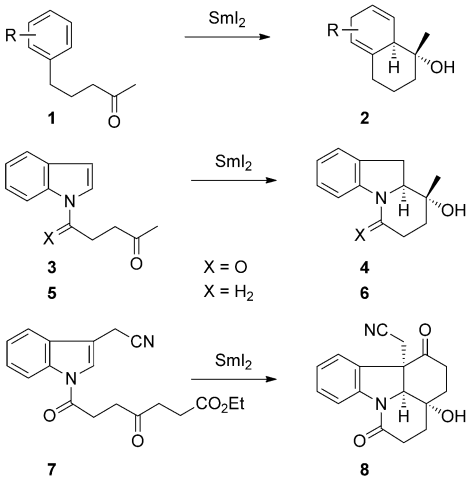
Synthesis of Polycyclic Tertiary Carbinamines by Samarium Diiodide Mediated Cyclizations of Indolyl Sulfinyl Imines**

*Chintada Nageswara Rao, Dieter Lentz, and Hans-Ulrich Reissig**

Dedicated to Professor Johann Mulzer on the occasion of his 70th birthday

Abstract: *Samarium diiodide mediated cyclizations of N-acylated indole derivatives bearing sulfinyl imine moieties afforded polycyclic tertiary carbinamines with moderate to excellent diastereoselectivities. Lithium bromide and water turned out to be the best additives to achieve these transformations in good yields. Using enantiopure sulfinyl imines the outcome strongly depends on the reactivity of the indole moiety. Whereas with unactivated indole derivatives desulfinylation and formation of racemic products was observed, indoles bearing electron-withdrawing substituents at C-3 afforded the polycyclic products with intact N-sulfinyl groups and with excellent diastereoselectivity, finally allowing the preparation of enantiopure tertiary carbinamines. The mechanisms of these processes are discussed.*

Samarium diiodide mediated reactions find wide application in organic synthesis.[1] Many selective and unique transformations are possible[2] and quite a number of natural-product syntheses witnesses the usefulness of this electron-transfer reagent.[3] Our group discovered and explored samarium-ketyl/aryl cyclizations that convert simple or complex (hetero)aryl ketones, such as **1**, into dearomatized products **2** with excellent diastereoselectivity (Scheme 1).[4] The method proved to be particularly useful in reactions of *N*-acylated or *N*-alkylated indolyl ketones of type **3** or **5** that provided tricyclic compounds **4** and **6**, respectively.[5] This approach to functionalized indoline derivatives could be further extended to cascade reactions employing precursors such as **7**. This compound was smoothly converted into tetracyclic compound **8** that is an ideal intermediate of one of the shortest syntheses of the alkaloid strychnine reported to date.[6] Whereas the cyclizations of ketones were investigated in detail, demonstrating scope and limitations, the related imine derivatives have not been studied so far.[7,8] With the objective of developing an enantioselective synthesis of cyclic



Scheme 1. Samarium diiodide mediated cyclizations of γ-arylketones **1**, *N*-acylated and *N*-alkylated indole derivatives **3**, **5**, and **7** leading to bi- and tricyclic tertiary alcohols **2**, **4**, **6**, or to tetracyclic strychnine precursor **8**.

products similar to **8** we started to study samarium diiodide promoted reactions of indole-derived sulfinyl imines derivatives.[9] We selected indoles because of their excellent behavior in the ketone cyclizations and because of our interest in the expected indolinyl-substituted tertiary carbinamines[10] that are of relevance for the synthesis of natural products or their analogues.

We started our investigations with the sulfinyl imine **10** that is easily available by $Ti(OEt)_4$-promoted condensation of *N*-acylated indole derivative **3** with racemic *tert*-butylsulfinamide **9**.[11] Treatment of compound **10** with 2.4 equivalents of SmI_2 under standard conditions used for ketone cyclizations in the presence of hexamethyl phosphoramide (HMPA)[12] and *tert*-butanol provided the expected cyclization product **11** only in around 5% yield and mainly led to decomposition (Scheme 2). We therefore examined alternative conditions and finally found that the cyclization proceeds in excellent yield within 5 min if SmI_2 (6 equiv) was employed in the presence of lithium bromide (72 equiv) and water (72 equiv) as additives.[8,13,14] The two diastereomers **11a** and **11b** were isolated in a 67:33 ratio in 90% yield. The cyclization also occurs with slightly diminished yields when only LiBr (67% yield) or only H_2O (60% yield) were used as additives. Under all conditions examined the primary amines were isolated and not the expected the *N*-sulfinylated amines. The two diaste-

[*] Dr. C. N. Rao, Prof. Dr. D. Lentz, Prof. Dr. H.-U. Reissig
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
E-mail: hans.reissig@chemie.fu-berlin.de

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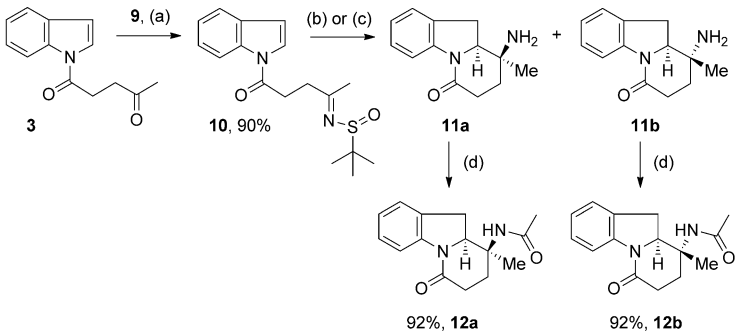
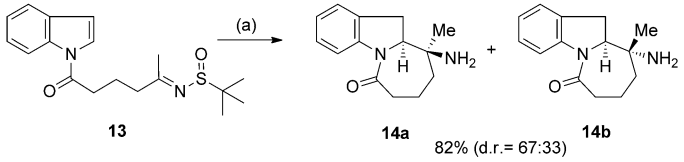
Supporting information for this article (experimental details, compound characterization of all new compounds, and additional information) is available on the WWW under http://dx.doi.org/10.1002/anie.201408324.



Scheme 2. Reagents and conditions: a) **9** = (*rac*)-*tert*-butylsulfinamide, $Ti(OEt)_4$, THF, reflux, 36 h; b) SmI_2 (2.4 equiv), HMPA (10 equiv), *t*BuOH (10 equiv), THF, room temperature, 7 h, ca. 5% (d.r. ca. 75:25); c) SmI_2 (6.0 equiv), LiBr (72 equiv), H_2O (72 equiv), THF, room temperature, < 5 min, 90% (d.r. = 67:33); d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 16 h.

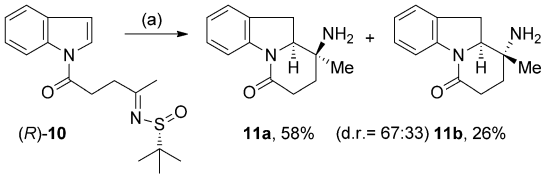
reomers **11a** and **11b** were separated and *N*-acylated with acetic acid anhydride to afford compounds **12a** and **12b**. The constitution and relative configuration of **12a** was determined by an X-ray crystal-structure analysis (see Supporting Information).[15] This result unequivocally demonstrates that starting from the sulfinyl imines the slightly favored diastereomer **11a** shows a *trans*-relationship of the amino group and the bridgehead hydrogen whilst for ketone cyclizations the opposite relative configuration was observed exclusively (see transformation **3** to **4** in Scheme 1).

The cyclization of the homologous *N*-sulfinyl imine **13** under the conditions described above furnished the expected products **14a** and **14b** with a newly generated seven-membered ring in good yield and low diastereoselectivity (Scheme 3). The configurations are assigned in analogy to **11** since the NMR spectroscopic data are similar.



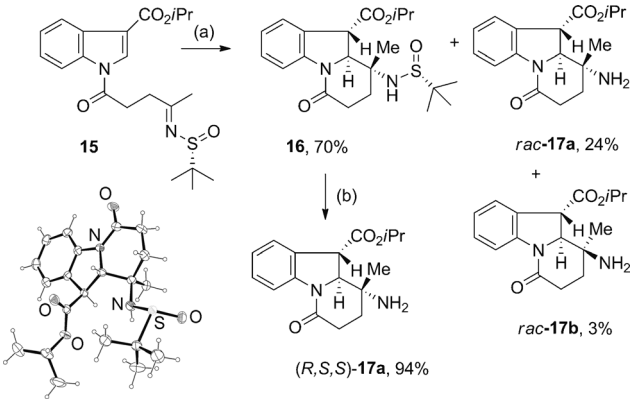
Scheme 3. Reagents and conditions: a) SmI_2, LiBr, H_2O, THF, room temperature, 30 min.

The observed desulfinylation made us skeptical whether an enantiopure sulfur auxiliary will have any influence on the cyclization. The *N*-sulfinyl imine (*R*)-**10** (Scheme 4), generated from compound **3** and (*R*)-*tert*-butylsulfinamide (*R*)-**9**, furnished the cyclization products **11a** and **11b**, but as suspected both isomers were racemic as shown by their conversion to Mosher amides (see Supporting Information). This result indicates that the N–S bond is very likely cleaved before the cyclization occurs and hence the chiral auxiliary has no influence on the C–C bond forming step.



Scheme 4. Reagents and conditions: a) SmI_2, LiBr, H_2O, THF, room temperature, < 5 min.

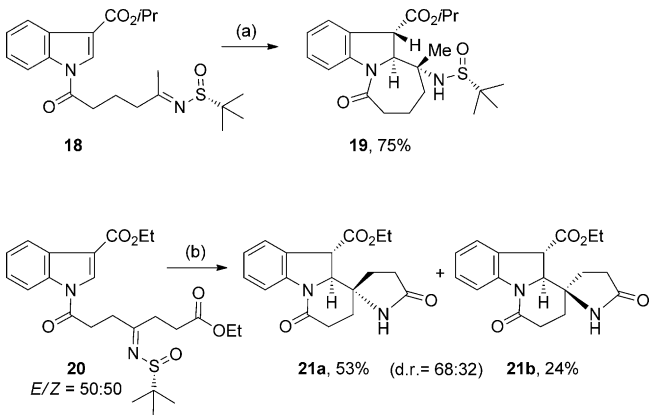
Gratifyingly, the reaction of indole derivative **15** (Scheme 5) bearing an electron-withdrawing group at C-3 exhibits a different behavior. The majority of the cyclization products still bear the *N*-sulfinyl group and compound **16** was formed as a single diastereomer. As racemic by-products the desulfinylated compounds **17a** and **17b** were formed. The constitution and configuration of the tricyclic product **16** was established by an X-ray crystal-structure analysis.[15,16] Compound **16** was smoothly desulfinylated by treatment with 1N hydrochloric acid to give (*R*,*S*,*S*)-**17a** in excellent yield.



Scheme 5. Reagents and conditions: a) SmI_2, LiBr, H_2O, THF, 10–12 °C, syringe-pump addition to **15** for 30 min; b) 1N HCl, MeOH, room temperature, 20 h. Molecular structure (ORTEP)[16] of compound **16** (thermal ellipsoid at 50% probability).

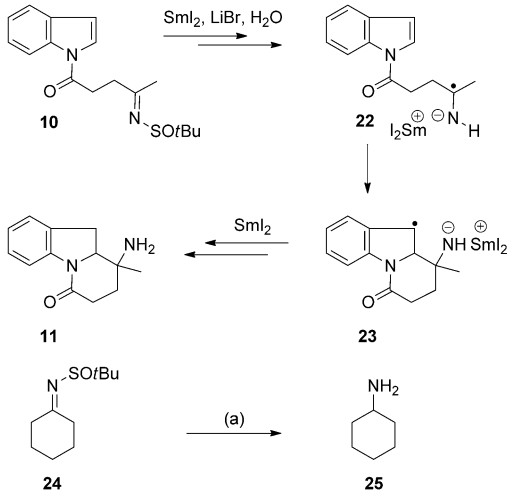
The homologous sulfinyl imine **18** (Scheme 6) afforded the tricyclic indoline derivative **19** in higher yield as a single diastereomer (configuration proposed in analogy to **16**) demonstrating that precursors of type **15** and **18** allow the preparation of tricyclic amines in high enantiopurity (e.r. > 97:3). In contrast, imino ester **20** furnished two desulfinylated spiro compounds **21a** and **21b** (77% yield, d.r. 68:32). Since the two products did not show any optical rotation we assume that they are racemic. The two examples in Scheme 6 reveal that a subtle influence of the structure of precursors decides the outcome of these reductive cyclizations.

Altogether, the examples of Schemes 2–6 demonstrate that the cyclizations of sulfinyl imines with the indole moiety proceed smoothly providing tertiary carbinamines with good yields and varying diastereoselectivities. Two competing mechanisms are apparently operating depending on the substitution pattern of the indole unit. Without an electron-withdrawing group, a desulfinylation reaction occurs at the imine unit that provides a species undergoing the intra-



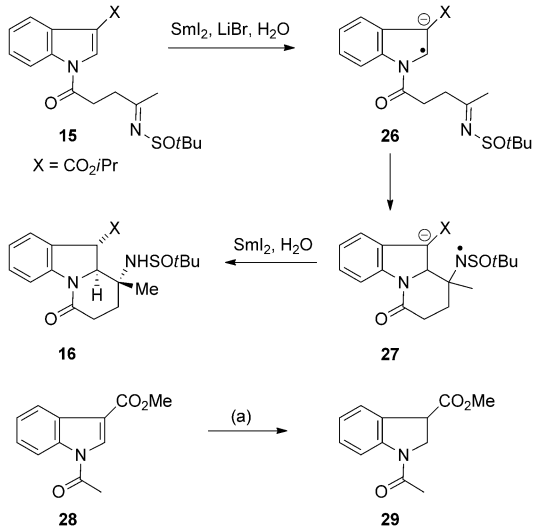
Scheme 6. Reagents and conditions: a) SmI_2, LiBr, H_2O, THF, 10–12 °C, syringe-pump addition to **18** for 30 min; b) SmI_2, LiBr, H_2O, THF, 18 °C, syringe-pump addition to **20** for 45 min.

molecular addition to C-2 of the indole derivative. Hence the chiral sulfur auxiliary has no influence on the stereochemical outcome of this step (see example presented in Scheme 4). That the *N*-desulfinylation very likely occurs at the imine stage and not after the cyclization is also shown by the stability of *N*-sulfinyl amines, such as **16** or **19**, under the reaction conditions despite of an excess of samarium diiodide. A possible mechanism for this pathway is depicted in Scheme 7 involving formation of an azaketyl intermediate **22**.[17] This species adds to the indole unit to deliver **23** that after a further electron transfer and protonation affords cyclization product **11**. Since the cyclization of **22** to **23** proceeds only with a 2:1 diastereoselectivity, a discussion of this aspect seems not to be appropriate at the moment. To our knowledge the desulfinylation of *N*-sulfinyl imines has not been reported to date.[18] The feasibility of this process was demonstrated by the smooth transformation of cyclohexanone-derived ketimine **24** into amine **25**.



Scheme 7. Proposed "imine-first mechanism" for the cyclization of unactivated indole derivatives and samarium diiodide promoted reduction of *N*-sulfinyl imine **24** to **25**; reagents and conditions: a) SmI_2, LiBr, H_2O, THF, room temperature, <1 min.

If, on the other hand, an electron-withdrawing group activates the indole derivative, an electron transfer to this moiety is more likely.[19] The generated radical anion **26** (Scheme 8) subsequently adds to the imine still bearing the chiral auxiliary to provide intermediate **27**.[20] A second electron transfer and subsequent protonation affords product **16**. High diastereoselectivity is observed in this case and the



Scheme 8. Proposed "indole-first" mechanism for the cyclization of activated indole derivatives and samarium diiodide promoted reduction of indole **28** to **29**: reagents and conditions: a) SmI_2, LiBr, H_2O, THF, room temperature, 10 min; (in addition, 4% of the compound with reduced *N*-acetyl group of **28** was isolated, see Supporting Information).

configuration at the carbon atom adjacent to the amino group can be explained by the models suggested for the additions of nucleophiles to *tert*-butylsulfinyl imines. In general, nucleophiles preferentially attack the *Si*-face of ketimines which have an *R*-configured sulfur auxiliary.[21] The plausibility of a fast electron transfer to activated indoles is demonstrated by the immediate reduction of model compound **28** to indoline **29** under the reaction conditions.[22]

In conclusion, our results present two seemingly similar cyclization processes leading to tertiary carbinamines in good yield and moderate to excellent diastereoselectivity. A closer look reveals mechanistic differences and only activated indole derivatives allow the preparation of enantiopure compounds. Nevertheless, the procedures described allow an entry to interesting molecular skeletons incorporating indoline moieties not available by other methods. A new samarium diiodide promoted desulfination of sulfinyl imines was discovered during this investigation.

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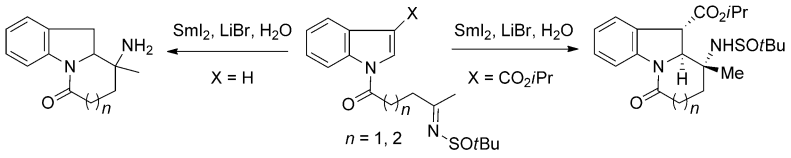
Communications

Polycyclic Amines

C. N. Rao, D. Lentz, H.-U. Reissig* ——— ■■■–■■■

Synthesis of Polycyclic Tertiary Carbinamines by Samarium Diiodide Mediated Cyclizations of Indolyl Sulfinyl Imines



Two ways to three rings: Indolyl sulfinyl imines undergo smooth SmI_2-mediated cyclizations and provide polycyclic tertiary carbinamines in good yield. *N*-Sulfinyl imines with unactivated indole units (X = H) undergo an *N*-desulfinylation—a previously unknown reaction—and then the cyclization. In contrast, activated indoles ($X = CO_2R$) undergo cyclization with intact *N*-sulfinyl imine moiety leading to the formation of enantiomerically pure tricyclic products.