

Efficient Synthesis of Medium-Sized Rings Incorporating Indole or Pyrrole Units by Samarium Diiodide Induced Cyclizations

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Samarium diiodide promoted the intramolecular reductive couplings of *N*-alkylated indole and pyrrole derivatives **9–12** and **14** to afford products **15–19** that incorporate seven- and eight-membered rings. They were obtained in good yields and generally with excellent diastereoselectivities. Up to four contiguous stereogenic centres are controlled in this transfor-

mation, which is explained by a highly ordered transition structure with the samarium alcoholate moiety preferring an equatorial position.

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Introduction

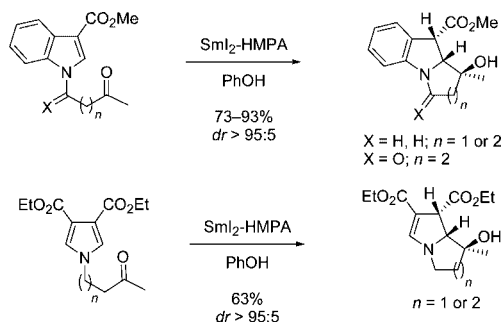
Recent advances in the employment of samarium diiodide^[1] have documented that this coupling reagent effectively promotes a number of important and useful synthetic reactions. Work in our laboratory has so far focused on the stereoselective formation of five- and six-membered rings by samarium ketyl cyclizations of suitably substituted β - or γ -*N*-substituted indole and pyrrole derivatives,^[2] which provided access to novel functionalized bi- and tricyclic compounds (Scheme 1).^[3–5] Herein we report the extension of these studies in order to synthesize seven- and eight-membered rings^[6] incorporating indole and pyrrole units. The general importance of heterocyclic compounds derives from their presence in numerous biologically active compounds. Development of new methods for stereoselective synthesis of heterocycles with complex functional groups is hence of great value. More specifically, the indole and pyrrole sub-

structures are obviously “privileged”^[7] since these heterocycles are present in a myriad of pharmaceutically important compounds.^[8]

Results and Discussion

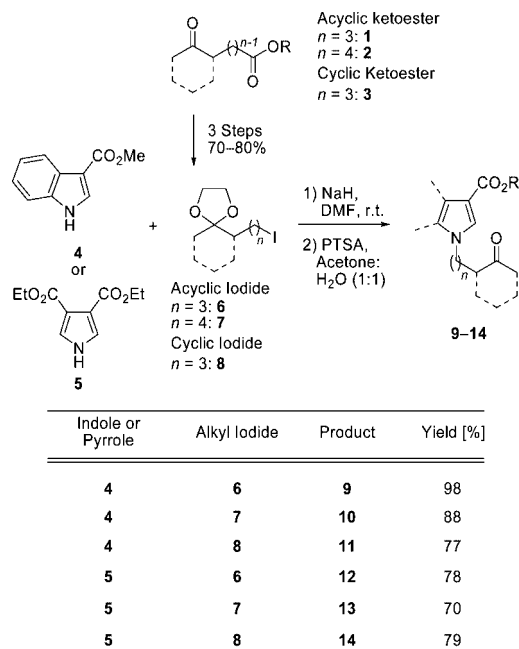
The syntheses of the required precursor indoles or pyrroles started with the *N*-alkylation of commercially available indole or pyrrole derivatives **4** and **5** by employing sodium hydride followed by addition of alkyl iodides **6**, **7** and **8** containing the protected carbonyl group;^[9] these compounds were obtained in three routine steps (ketalization,^[10] reduction^[10] and iodination^[11]) from corresponding esters **1–3**.^[12] Hydrolysis of the ketals in the presence of *p*-toluenesulfonic acid led to desired precursors **9–14** in good overall yields (Scheme 2).^[13]

We then studied the scope and limitations of the samarium diiodide induced ketyl cyclization reactions by examining the feasibility of seven- and eight-membered ring formation with the precursors prepared. Substrates **9–14** were generally subjected to 2.5 equiv. of samarium diiodide in THF along with an excess of HMPA^[14] (10 equiv.) and two equiv. of phenol as a proton source.^[15] The formation of seven-membered rings (Scheme 3) was successful with indole derivative **9** or pyrrole **12**.^[16] Expected bi- and tricyclic products **15** and **16** were obtained in good yields and in a diastereomerically pure form, which demonstrates that this method allows for the generation of three contiguous stereogenic centres with high selectivity. The relative configurations of the products were determined by NOE experiments. The mechanism of this type of reaction is usually described^[2,3] as a sequence of initial electron transfer to the carbonyl group generating a radical anion (samarium ketyl), formation of the new ring by intramolecular addition of the samarium ketyl to the (het)aryl group, a second elec-

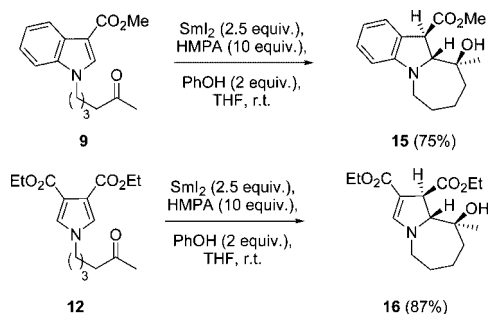


Scheme 1. Samarium diiodide induced cyclizations of hetaryl ketones to bicyclic and tricyclic products containing indole and pyrrole substructures.

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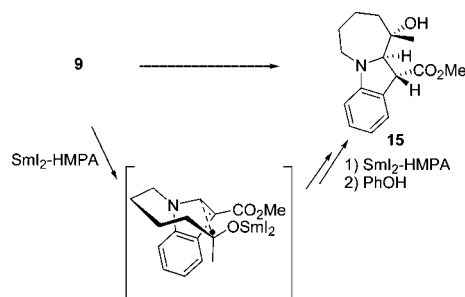

 Scheme 2. Synthesis of precursor indoles **9–11** and pyrroles **12–14**.

tron transfer and subsequent regioselective protonation leading to the corresponding product.^[17]

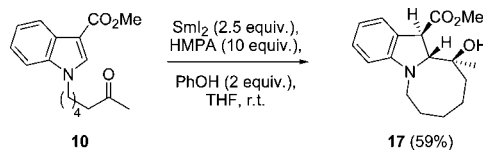

 Scheme 3. Formation of seven-membered heterocyclic compounds **15** and **16** by samarium diiodide induced cyclization of precursors **9** and **12**.

We recently suggested^[1b,2,3] that the high degree of diastereoselectivity for this type of cyclization should be due to a highly ordered cyclic transition structure of the ketyl addition to the (het)aryl ring in which the samarium alkoxide prefers the sterically more favourable equatorial position (Scheme 4). This model nicely explains the relative configuration of the stereogenic centres within the seven-membered ring. For compounds **15** and **16**, the configuration of the carbon bearing the alkoxy carbonyl group seems to be governed by thermodynamic control, which (by deprotonation/protonation) positions this substituent at the convex face of the molecule.^[18]

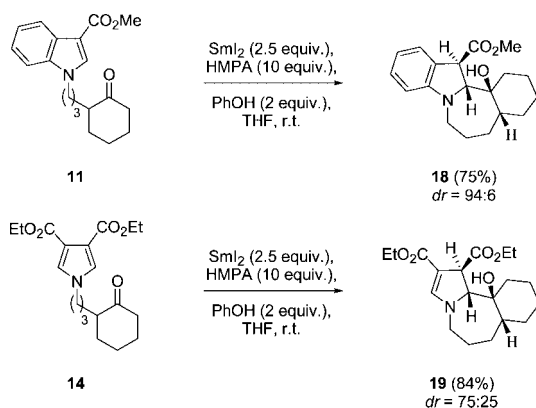
The synthesis of eight-membered rings (Scheme 5) is also possible; however, only indole derivative **10** furnished expected product **17** in moderate yield, whilst pyrrole **13** gave only traces (<5%) of a cyclized product together with small amounts of starting material and unidentified products. We


 Scheme 4. Transition structure of the cyclization of **9** leading to tricyclic product **15** (HMPA ligands are omitted for clarity and simplicity).

also examined the possibility of cyclobutanol formation and therefore prepared a precursor analogous to **9** but with just one methylene group as a spacer unit between the indole nitrogen and the carbonyl group. Not surprisingly, the reaction failed to give the corresponding tricyclic compound with an incorporated four-membered ring and only the corresponding secondary alcohol that was formed by reduction of the carbonyl group was isolated.


 Scheme 5. Conversion of indole derivative **10** into tricyclic product **17** containing an azocin moiety.

The intramolecular samarium diiodide induced ketyl couplings were also examined with precursors containing a cycloalkanone moiety. Compounds **11** and **14** efficiently furnished anticipated polycyclic products **18** and **19** in very good yields (Scheme 6). In the case of indole derivative **18**, four contiguous stereogenic centres were established in a highly selective manner (*dr* = 94:6), whereas the formation of pyrrole derivative **19** proceeded less selectively (*dr* = 75:25). The structural assignments for the major diastereomers as depicted in Scheme 6 are based on NOE ex-


 Scheme 6. Ketyl couplings of cyclohexanone derivatives **11** and **14** leading to products **18** and **19** (only the major diastereomers are depicted, all compounds are racemic).

periments and by analogy considering our earlier ketyl cyclization experiments with cyclohexanone derivatives.^[19] For the major diastereomer of **19**, an X-ray analysis unequivocally proved the constitution and configuration of this compound.^[20] The minor diastereomers of **18** and **19** very likely have *cis*-configuration of the substituents at the two indole carbons; however, these assignments have to be confirmed by additional experiments.

Conclusions

In summary, we have demonstrated that the intramolecular samarium ketyl addition to suitable indole and pyrrole acceptors generates seven- and eight-membered rings containing these heterocycles. Yields are moderate to very good and excellent diastereoselectivities are observed. Up to four contiguous stereogenic centres can be established in a stereoselective fashion. Extension to other substrates to further investigate the scope and limitations of this ring forming process, as well as application of this method to the synthesis of natural products or analogues, are in progress.

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- [13] **Typical Procedure: Synthesis of 9**: To a suspension of NaH (120 mg, 2.96 mmol, 60% suspension in paraffin oil, 1.2 equiv.) in DMF (8 mL) at room temp. was added **4** (432 mg, 2.47 mmol, 1 equiv.). After 30 min of stirring, alkyl iodide **6** (860 mg, 3.20 mmol, 1.3 equiv.) in DMF (2 mL) was added. The mixture was stirred overnight, then diluted with Et₂O (10 mL), washed with water (3 times), the organic phase was dried (MgSO₄) and concentrated under reduced pressure. The resulting oil was dissolved in a mixture of acetone/H₂O (1:1, 8 mL) and PTSA (47 mg, 0.25 mmol, 0.1 equiv.) was added. After completion of the reaction (TLC control), the solution was diluted with Et₂O (10 mL), washed with a saturated aq. NaHCO₃ solution, then the organic layer was dried (MgSO₄) and concentrated. Purification by chromatography on silica gel (hexane/EtOAc, 2:1) gave corresponding ketone **9** (668 mg, 98%) as a colourless oil. ¹H NMR (CDCl₃, 500 MHz): δ = 1.55–1.61 (m, 2 H, CH₂), 1.82–1.88 (m, 2 H, CH₂), 2.08 (s, 3 H, CH₃), 2.41 (t, *J* = 7.1 Hz, 2 H, CH₂), 3.90 (s, 3 H, OCH₃), 4.13 (t, *J* = 7.3 Hz, 2 H, NCH₂), 7.24–7.29 (m, 2 H, Ar), 7.32–7.36 (m, 1 H, Ar), 7.78 (s, 1 H, Ar), 8.15–8.19 (m, 2 H, Ar) ppm. ¹³C NMR (CDCl₃, 126 MHz): δ = 20.8, 29.2 (2 t, CH₂), 29.8 (q, CH₃), 42.7, 46.8 (2 t, CH₂), 50.9 (q, OCH₃), 106.9 (s, Ar), 109.8, 121.7, 121.8, 122.6 (4 d, Ar), 126.7 (s, Ar), 134.0 (d, Ar), 136.3 (s, Ar), 165.4, 207.9 (2 s, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3115, 3055 (=CH), 2995–2890 (CH), 1700 (CO), 1535 (C=C) cm⁻¹. MS (EI, 80 eV, 100 °C): *m/z* (%) = 273 (100) [M]⁺, 242

- (18) $[M - OCH_3]^+$, 188 (74) $[M - CH_3CO(CH_2)_4]^+$, 43 (64) $[CH_3CO]^+$. HRMS (EI, 80 eV, 60 °C): calcd. for $C_{16}H_{19}NO_3$ 273.13651; found 273.13547.
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- [16] **General Procedure for Samarium Diiodide Coupling Reactions:** Samarium (2.7–2.8 equiv.) and 1,2-diiodoethane (2.5–2.6 equiv.) were suspended in freshly distilled anhydrous THF (10 mL per mmol of Sm) under an argon atmosphere and stirred for 2 h at room temp., which provided a dark blue solution of samarium diiodide. The flask was then evacuated, purged with argon and HMPA (10.0 equiv.) was added. After stirring for 30 min., to the freshly prepared deep blue solution of SmI_2 -HMPA, indole or pyrrole derivatives **9–14** (1.0 equiv.) and phenol (3.0 equiv.), dissolved in THF (5 mL) were added in one portion. After 30 min the reaction was quenched with saturated aq. solution of $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvents were evaporated. The resulting crude product was purified by flash chromatography on silica gel by using a hexane/ethyl acetate mixture (4:1). Analytical data for *methyl 10-hydroxy-10-methyl-7,8,9,10,10a,11-hexahydro-6H-azepino[1,2-a]indole-11-carboxylate* (**15**): pale yellow oil. 1H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (s, 3 H, 10- CH_3), 1.41–1.48 (m, 1 H, CH_2), 1.55–1.63 (m, 1 H, CH_2), 1.74–2.05 (m, 4 H, CH_2), 3.17 (ddd, J = 3.6, 5.1, 11.6 Hz, 1 H, 6-H), 3.34 (dt, J = 5.1, 11.6 Hz, 1 H, 6-H), 4.28, 4.19 (AB system, $J_{A,B}$ = 6.6 Hz, 2 H, 10a-H, 11-H), 6.37 (d, J = 7.7 Hz, 1 H, Ar), 6.63 (dt, J = 1.0, 7.7 Hz, 1 H, Ar), 7.10–7.14 (m, 1 H, Ar), 7.25 (d, J = 7.7 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 20.3 (q, CH_3 -10), 23.4, 28.8 (2 t, CH_2), 45.8 (t, C-9), 48.4 (t, C-6), 48.5 (d, C-11), 52.4 (q, OCH_3), 71.7 (d, C-10a), 75.2 (s, C-10), 106.5, 116.7, 124.5 (3 d, Ar), 124.6 (s, Ar), 128.8 (d, Ar), 152.1 (s, Ar), 173.6 (s, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3480 (OH), 3045 (=CH), 2930–2730 (CH), 1740 (C=O), 1600, 1490 (C=C) cm^{-1} . MS (EI, 80 eV, 70 °C): m/z (%) = 275 (54) $[M]^+$, 190 (100), 43 (94) $[C_2H_3O]^+$. HRMS (EI, 80 eV, 70 °C): calcd. for $C_{16}H_{21}NO_3$ 275.15213; found 275.15237.
- Analytical data of *diethyl 9-hydroxy-9-methyl-5,6,7,8,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-1,2-dicarboxylate* (**16**): colourless solid, m.p. 118–120 °C (Et_2O). 1H NMR ($CDCl_3$, 500 MHz): δ = 1.13 (s, 3 H, 9- CH_3), 1.19 (t, J = 7.1 Hz, 3 H, CH_3), 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 1.31–1.41 (m, 1 H, 7-H), 1.50–1.55 (m, 1 H, 8-H), 1.56–1.65 (m, 1 H, 6-H), 1.74–1.88 (m, 3 H, 6-H, 7-H, 8-H), 2.14 (br. s, 1 H, OH), 3.27–3.39 (m, 2 H, 5-H), 3.86 (d, J = 6.4 Hz, 1 H, 9a-H), 3.93 (dd, J = 0.9, 6.4 Hz, 1 H, 1-H), 4.02–4.11 (m, 2 H, OCH_2), 4.15 (q, J = 7.1 Hz, 2 H, OCH_2), 7.07 (d, J = 0.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.1, 14.4 (2 q, CH_3), 20.9 (q, 9- CH_3), 22.3 (t, C-7), 27.3 (t, C-6), 44.2 (t, C-8), 48.7 (d, C-1), 49.1 (t, C-5), 58.9, 61.0 (2 t, OCH_2), 74.3, 74.4 (d, s, C-9a, C-9), 99.4 (s, C-2), 152.2 (d, C-3), 165.3, 174.7 (2 s, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3440 (OH), 3070 (=CH), 2980–2860 (CH), 1740 (C=O), 1730, 1660 (C=O), 1595, 1445, 1375 (C=C) cm^{-1} . MS (EI, 80 eV, 70 °C): m/z (%) = 311 (10) $[M]^+$, 266 (2) $[M - COOH]^+$, 192 (100), 43 (29) $[CH_3CO]^+$. $C_{16}H_{25}NO_5$ (311.2): calcd. C 61.72, H 8.09, N 4.50; found C 61.69, H 8.33, N 4.48.
- [17] For rather electron-deficient hetaryl compounds such as indole and pyrrole derivatives **9–14** as employed in this study we cannot rigorously exclude an alternative mechanism. A Birch-type reduction of the heteroaromatic ring followed by addition of the resulting carbanion to the carbonyl group may also deliver the observed products. For a recent example of the Birch reduction of pyrrole derivatives and subsequent reactions with electrophiles, see: T. J. Donohoe, C. L. Rigby, R. E. Thomas, W. F. Nieuwenhuys, F. L. Bhatti, A. R. Cowley, G. Bhalay, I. D. Linney, *J. Org. Chem.* **2006**, 71, 6298–6301, and references cited here. However, since we observe similar patterns of stereoselectivity for the transformations presented here as for less electron-deficient aryl derivatives, we assume that the product delivering process follows the standard samarium ketyl coupling mechanism.
- [18] This assignment is in contrast to the relative configurations presented in Scheme 1 of ref.^[2] which have also been determined by NOE experiments. We shall discuss and eventually correct the assignment of these compounds in a future full publication.
- [19] For examples, see refs.^[1b,3a,6a]
- [20] I. Brüdgam, H. Hartl, Freie Universität Berlin, unpublished results.

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