ORGANIC LETTERS

2003
Vol. 5, No. 23
4305−4307

Novel Stereoselective Syntheses of Highly Functionalized Benzannulated Pyrrolizidines and Indolizidines by Samarium Diiodide Induced Cyclizations of Indole Derivatives

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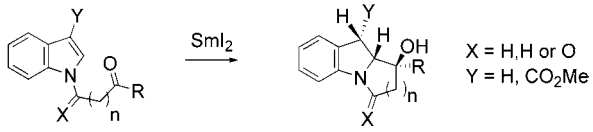
Received August 19, 2003

ABSTRACT



Suitably substituted heteroaromatic compounds such as indole and pyrrole derivatives are excellent acceptor units for intramolecular couplings of samarium ketyls. They furnish highly functionalized indole derivatives with very good diastereoselectivities additionally. Intermediate samarium enolates can be trapped by electrophiles, allowing efficient tandem reactions.

Among natural products and pharmaceutically important compounds, the indole unit belongs to the "privileged structures".[1] Although a variety of methods have been developed to generate derivatives of this heterocycle and to modify its substitution pattern, new methods that stereoselectively provide indole derivatives are still of high interest in synthetic organic chemistry.[2] In this communication we present our recent results demonstrating that suitably substituted indole and pyrrole derivatives are excellent substrates for an intramolecular samarium diiodide induced ketyl cyclization that provides highly functionalized products with mostly excellent diastereoselectivities.[3]

Our recently discovered intramolecular reductive coupling of γ-aryl ketones provides bicyclic compounds where the former aromatic unit is converted into a synthetically very useful 1,4-cyclohexadiene moiety.[4,5] The reactions are promoted by the samarium diiodide−HMPA complex[6] and were previously performed with γ-aryl ketones[4] or their nitrogen

(1) (a) Joule, J. A. *Science of Synthesis* (*Houben-Weyl, Methods of Molecular Transformations*); Georg Thieme Verlag: Stuttgart, 2000; Vol. 10, pp 361−652. (b) Bonjoch, J.; Bosch, J. *Alkaloids* **1996**, *48*, 75−189. (c) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (d) Saxton, J. E. *The Chemistry of Heterocyclic Compounds*; Academic Press: New York, 1994; 25, Part IV.(e) Döpp, H.; Döpp, U.; Langer, U.; Gerding, B. *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1994; Vol. E6b$_1$, pp 546−848; Vol. E6b$_2$. (f) Chadwick, D. J.; Jones, R. A.; Sundberg, R. J. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984; Vol. 4, pp 155−376.

(2) Recent review: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075.

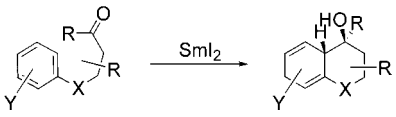
(3) Selected reviews on samarium-promoted chemistry: (a) Banik, B. K. *Eur. J. Org. Chem.* **2002**, 2431−2444. (b) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727−2751. (c) Hölemann, A. *Synlett* **2001**, 1497−1498. (d) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745−777. (e) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (f) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (g) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (h) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573−6614.

(4) (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem.* **1999**, *111*, 874−876; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 789−791. (b) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267−4277. (c) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290−1292.

(5) For related aryl carbonyl couplings see: (a) Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643−4649. (b) Kuo, C.-W.; Fang, J.-M. *Synth. Commun.* **2001**, *31*, 877−892. (c) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem.* **1995**, *107*, 2597−2599; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2383. (d) Ohno, H.; Maeda, S.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316−317. (e) Ohno, H.; Wakayama, R.; Maeda, S.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909−5916.

10.1021/ol0355581 CCC: $25.00
Published on Web 10/23/2003

Scheme 1

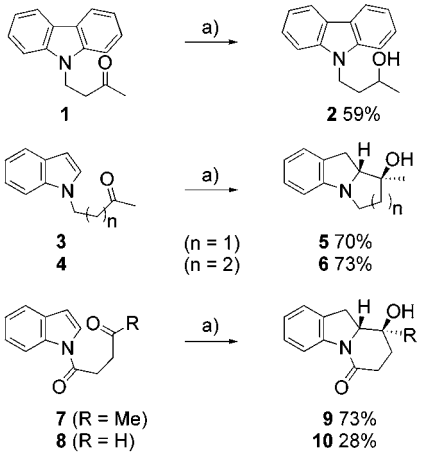


analogues prepared from aniline derivatives (Scheme 1).[7] They afford either functionalized hexahydronaphthalenes or hexahydroquinolines with moderate to good yields and excellent diastereoselectivities.

The samarium diiodide−HMPA complex transfers an electron to the carbonyl group, thus generating a radical anion (samarium ketyl) that forms a new six-membered ring by intramolecular addition to the aryl substituent. A second electron transfer and the regioselective protonation finally lead to bicyclic products. Similarities of the last steps with the well-known Birch reduction are obvious.

Because of the mentioned importance of indole derivatives we turned our interest from aniline derivatives to the cyclizations of precursors with indole or pyrrole units. It was not clear at all whether these electron-rich aromatic compounds would be suitable acceptors of samarium ketyls.[8] We employed 2.5 equiv of samarium diiodide in THF along with an excess of HMPA (10 equiv) and 2.0 equiv of phenol as proton source, which has beneficial effects as demonstrated earlier.[7] Carbazole derivative **1** served as the first model substrate but failed to cyclize and furnished only secondary alcohol **2** under standard conditions (Scheme 2). However,

Scheme 2 [a]



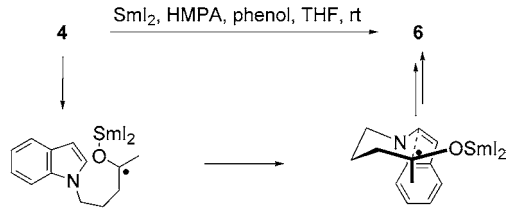
[a] (a) 2.5 equiv of SmI_2, THF, 10 equiv of HMPA, 2.0 equiv of phenol, rt.

treatment of the *N*-alkylated indole derivatives **3** and **4** resulted in formation of diastereomerically pure benzpyrrolizidine **5** and benzindolizidine **6** in good yield. Along with **5** a small quantity (6%) of the uncyclized secondary alcohol was isolated.

Similarly, two *N*-acylated substrates **7** and **8** furnished tricyclic compounds **9** and **10**. Whereas methyl ketone **7** smoothly cyclized to **9**, the corresponding aldehyde **8** provided **10** only in low yield. Aldehydes are generally less reliable starting materials for ketyl cyclizations and usually do not provide the expected products in the intramolecular ketyl aryl coupling.[9]

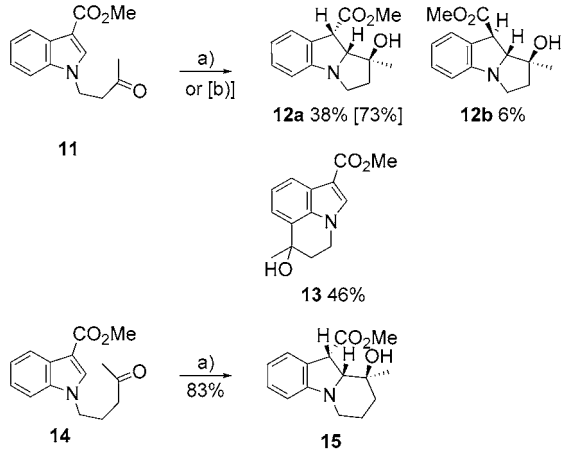
The high degree of diastereoselectivity for these and the following cyclizations may be explained by assumption of a highly ordered cyclic transition state during ketyl addition to the aromatic system (Scheme 3).[4a] For steric and electronic reasons the samarium alcoholate favors an equatorial position.[10] The relative configuration was proven by two-dimensional NOESY−NMR spectroscopy.

Scheme 3



3-Methoxycarbonyl-substituted indole derivatives **11** and **14** were subjected to the general procedure (Scheme 4)

Scheme 4 [a]



[a] (a) 2.5 equiv of SmI_2, THF, 10 equiv of HMPA, 2.0 equiv of phenol, rt. (b) 2.5 equiv of SmI_2, THF, 2.0 equiv of phenol. rt.

because electron-withdrawing groups at aryl substituents usually have a beneficial effect on these cyclization reactions.[4c,9]

(6) The use of HMPA as additive strongly raises the reducing ability of samarium diiodide and is required for many ketyl coupling reactions. See: (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485−1486. (b) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6895−6899.

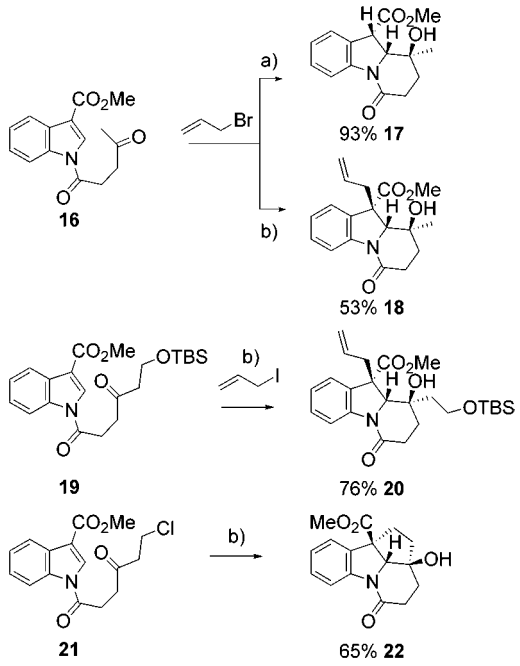
(7) Gross, S.; Reissig, H.-U. *Synlett* **2002**, 2027−2030.

(8) A few inter- and intramolecular indole carbonyl coupling reactions have been reported: Lin, S.-C.; Yang, F.-D.; Shiue, J.-S.; Yang, S.-M.; Fang, J.-M. *J. Org. Chem.* **1998**, *63*, 2909−2917. However, no dihydroindole derivatives were isolated but the corresponding reoxidized indoles.

Surprisingly, the cyclization of **11** provides **13** as the slightly favored product arising from an addition to the benzene ring rather than to the apparently activated 2-position of the indole. Aromatized compound **13** was most probably formed by spontaneous oxidation during aqueous workup from the corresponding dihydro derivative.[4c,7,9] The expected products **12a** and **12b** were isolated as a mixture of diastereomers. Even more surprisingly, compound **12a** was isolated as exclusive product in 73% yield, when the reaction was performed *in the absence of HMPA*. Apparently, the regioselectivity is dramatically altered if samarium diiodide is employed without this additive, which generally increases the reactivity of SmI_2. The 6-*exo-trig* cyclization of the chain-elongated derivative **14** formed tricyclic compound **15** as single diastereomer with excellent yield. No experiment without HMPA has so far been performed with this substrate.

With even more electron-deficient *N*-acylated indole derivatives **16**, **19**, and **21** the cyclizations have generally been executed without HMPA. Polycyclic products **17**, **18**, **20**, and **22** were formed with essentially perfect diastereoselectivity and good to excellent yields (Scheme 5).

Scheme 5 [a]

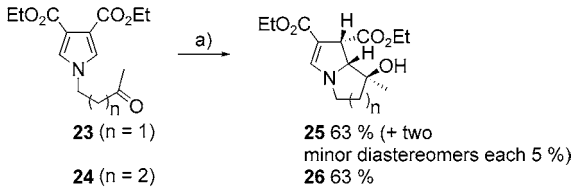


[a] (a) 2.5 equiv of SmI_2, THF, 2.0 equiv of phenol, rt. (b) 2.5 equiv of SmI_2, THF, rt.

Intermediate samarium enolates derived from **16** or **19** could stereoselectively be trapped with allyl halides, leading to **18** and **20**. The intramolecular alkylation by the chloroalkyl terminus of **21** led to tetracyclic compound **22** with satisfactory efficiency.[11] These cascade reactions selectively generate three continuous stereogenic centers, including a quarternary carbon atom at the 3-position of the dihydroindole moiety, a structural motif of many indole alkaloids. On the basis of the established reductive coupling, syntheses of natural products such as strychnine alkaloids and mitomycin derivatives may be possible.

To explore further the scope and limitations of these samarium diiodide induced cyclizations with heteroaromatic compounds, pyrrole derivatives **23** and **24** were examined (Scheme 6). These two substrates cyclized as anticipated,

Scheme 6 [a]



[a] (a) 2.5 equiv of SmI_2, THF, 10 equiv of HMPA, 2.0 equiv of phenol, rt.

furnishing pyrrolizidine and indolizidine derivatives **25** and **26** with good yields and stereoselectivities. Reactions without HMPA have so far not been examined.

In conclusion, a novel and fairly general protocol for the formation of highly functionalized and substituted heterocycles has been found by samarium diiodide induced cyclizations with indole derivatives as precursor compounds.[12] Benzannulated pyrrolizidine and indolizidine derivatives are accessible with high diastereoselectivity and in good to excellent yields. The applicability of sequential reactions has been demonstrated employing inter- and intramolecular alkylations as subsequent steps. The obtained polycyclic compounds should be of high interest for the synthesis of natural products and pharmaceutically important heterocyclic compounds.

Acknowledgment. Support of this work by the Ernst Schering Research Foundation and the Volkswagen-Stiftung is gratefully acknowledged. We also thank the Fonds der Chemischen Industrie and the Schering AG for general support.

Supporting Information Available: Detailed description of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Berndt, M.; Reissig, H.-U. Unpublished results. Berndt, M. Ph.D. Dissertation, Freie Universität Berlin, 2003.

(10) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073−3100. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974.

(11) The rather electron-deficient double bond attacked during cyclizations of indole derivatives **16**, **19**, and **21** may be regarded as β-amidoacrylates. For samarium(II) diiodide induced intramolecular couplings to simple urethane acrylates, see: MacDonald, S. J. F.; Mills, K.; Spooner, J. E.; Upton, R. J.; Dowle, M. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3931−3936.

(12) In analogy to the indole derivative described in this communication, γ-naphthyl ketones are excellent substrates for the samarium diiodide induced coupling (first example in ref 4a, many further examples will be published in a future report, ref 9).