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Samarium(II)–Mediated Linker Cleavage–Cyclization in Fluorous Synthesis: Reactions of Samarium Enolates

Karen M. James,[†] Nigel Willetts,[‡] and David J. Procter*,[†]

The School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, and Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, U.K.

david.j.procter@manchester.ac.uk

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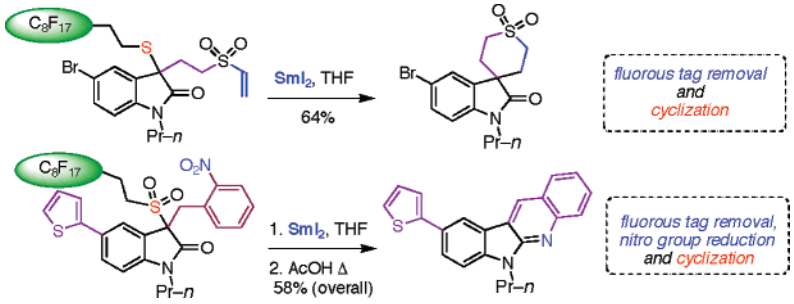
ABSTRACT



SmI_2 has been used to cleave a sulfur linker and trigger cyclizations in strategies for the traceless fluorous synthesis of N-heterocycles. The studies give further insights into the reactivity of samarium enolates.

Samarium(II) iodide (SmI_2) is a one-electron reducing agent that has found widespread use in organic synthesis.[1] The reagent has been used to mediate many processes ranging from functional group interconversions to complex carbon−carbon bond-forming sequences.[1] Cyclization reactions are among the most useful transformations mediated by SmI_2, and these have been used extensively in natural product synthesis.[1j]

The development of versatile linker designs is important for continued advancements in high-throughput synthesis.[2] We have previously described a traceless linker strategy for phase tag-assisted synthesis where the link to the tag is cleaved using SmI_2[3] and have illustrated the utility of the

[†] University of Manchester.
[‡] Syngenta, Jealott's Hill International Research Centre.

(1) For reviews on the use of SmI_2 in organic synthesis: (a) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A. *Org. React.* **1994**, *46*, 211. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (e) Molander, G. A.; Harris C. R. *Tetrahedron* **1998**, *54*, 3321. (f) Kagan, H.; Namy, J. L. *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; p 155. (g) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (h) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (i) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (j) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (k) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393.

(2) For reviews on linkers and cleavage strategies for solid-phase organic synthesis, see: (a) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (b) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (c) Bräse, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899. (d) McAllister, L. A.; McCormick, R. A.; Procter, D. J. *Tetrahedron* **2005**, *61*, 11527. (e) Scott, P. J. H.; Steel, P. G. *Eur. J. Org. Chem.* **2006**, 2251.

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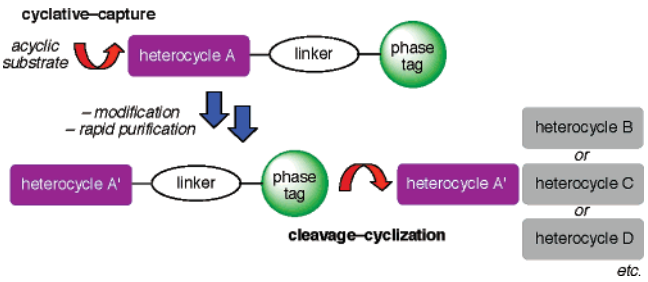
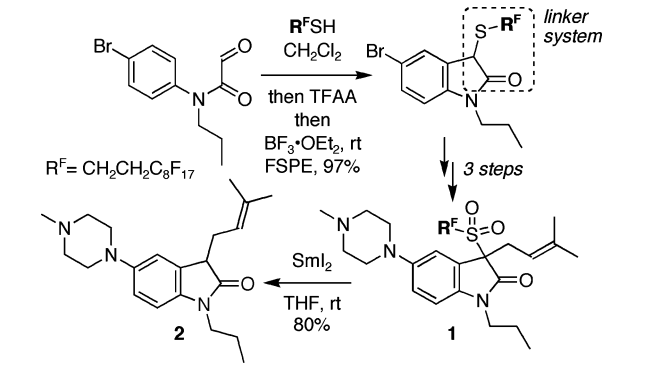
linker for the solid phase[3a−e] and fluorous[3f−h] synthesis of N-heterocycles. In phase tag-assisted synthesis, extra steps to introduce and remove the phase tag are unavoidable. It is desirable to gain more synthetic value from these steps by using the construction of the linker and its cleavage to trigger other reactions that result in the construction of valuable motifs such as heterocyclic rings (Scheme 1).

Scheme 1



For example, in our fluorous[4] approach, we have developed a Pummerer-type process[5] that allows the fluorous tag to be introduced, a heterocycle to be constructed, and the linker system to be established in a one-pot reaction (Scheme 2). After modification of the heterocyclic scaffold, treatment

Scheme 2



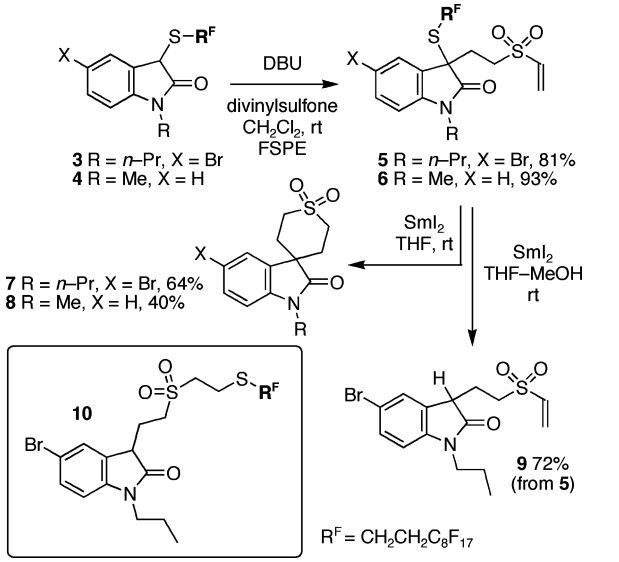
of a fluorous-tagged intermediate, such as **1**, with SmI_2, releases **2** in high yield.[3f,g] The cleavage of the linker proceeds by electron transfer to form a radical intermediate that is then reduced to a Sm(III)−enolate before protonation to give products such as **2**.

In this Letter, we describe our attempts to construct cyclic motifs by exploiting the intermediates or products formed upon removal of the fluorous tag. We envisaged that a portfolio of cleavage−cyclization processes would allow us to build product scaffolds in a traceless[6] fashion while introducing diversity during the removal of the tag (see Scheme 1).

We wished to investigate the formation of heterocyclic rings in cleavage−cyclization reactions using SmI_2. An additional aim was to improve our understanding of the reactivity of samarium enolates.

We began by studying the formation of heterocycles using a carbon−carbon bond-forming process triggered by the removal of the tag. Fluorous-tagged oxindoles **3** and **4** were modified conveniently by alkylation with divinylsulfone and DBU to give adducts **5** and **6** in high yield after purification by fluorous solid-phase extraction (FSPE)[7] (Scheme 3). We

Scheme 3



envisaged that treatment of **5** and **6** with SmI_2 would result in cleavage of the tag and addition of the resultant reactive intermediate to the electron-deficient alkene,[8] thus generating a quaternary center where the tag had been located. Pleasingly, treatment with SmI_2 gave unusual spirocyclic sulfones **7** and **8** in 62% and 40% yields, respectively (Scheme 3). The structure of **8** was confirmed by X-ray crystallography.[9] As expected, the reduction of **5** in the presence of a proton source (MeOH) resulted in protonation of the Sm−enolate intermediate and the isolation of **9** in 72%. When the reaction of **5** with SmI_2 was carried out at higher concentrations (35 vs 10 mM), **10** was isolated as a byproduct (12%) in addition to **7** (40%). Sulfide **10** arises from removal of the fluorous tag and its reintroduction via Sm(III) thiolate addition to the vinylsulfone group (Scheme 3).

(4) For a discussion of fluorous tagging, see: (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. For recent reviews, see: (b) Curran, D. P. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Ed.; Wiley-VCH: Weinheim, 2004. (c) Zhang, W. *Tetrahedron* **2003**, *59*, 4475. (d) Zhang, W. *Chem. Rev.* **2004**, *104*, 2531.

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(6) Comely, A. C.; Gibson, (née Thomas), S. E. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1012.

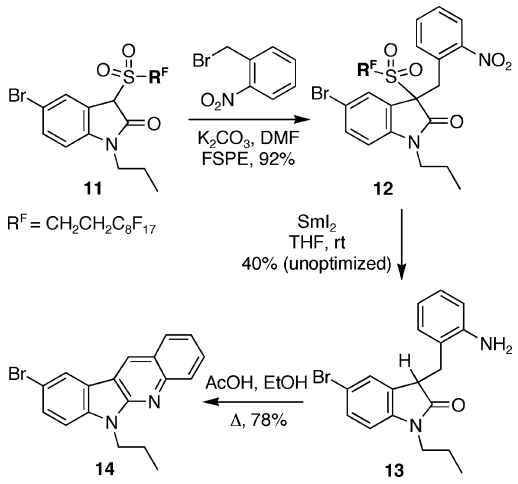
(7) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069. See also ref 4.

(8) Spirocyclic sulfones **7** and **8** could form by a radical or anionic pathway.

(9) See Supporting Information for X-ray crystallographic data and CCDC number.

We have also investigated a cleavage−cyclization process that constructs a heterocyclic ring through the formation of carbon−heteroatom bonds. Alkylation of fluorous-tagged oxindole **11** with 2-nitrobenzyl bromide gave **12** in 92% yield after FSPE. Treatment of **12** with SmI_2 results in sequential removal of the fluorous tag and reduction of the aryl nitro group[10] to give **13** in moderate overall yield. Acid−mediated cyclization[11] then gave indoloquinoline **14** (Scheme 4). The

Scheme 4



overall sequence corresponds to removal of the fluorous tag and construction of a pyridine ring. The indoloquinoline framework is found in natural products[12] and compounds displaying significant biological activity. For example, substituted indoloquinolines show cytoxicity and are DNA topoisomerase II inhibitors.[13]

Interestingly, interrupting the SmI_2 reduction of **12** allowed two intermediates to be isolated, giving an insight into the mechanism of the sequential reduction: azaspirocycle **15** and tertiary alcohol **16** were obtained in a 1:1 ratio and in 70% yield (Figure 1). Both intermediates are reduced by SmI_2 to

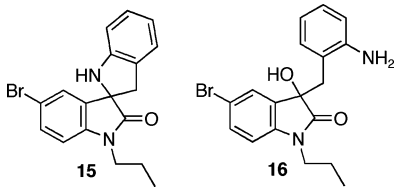
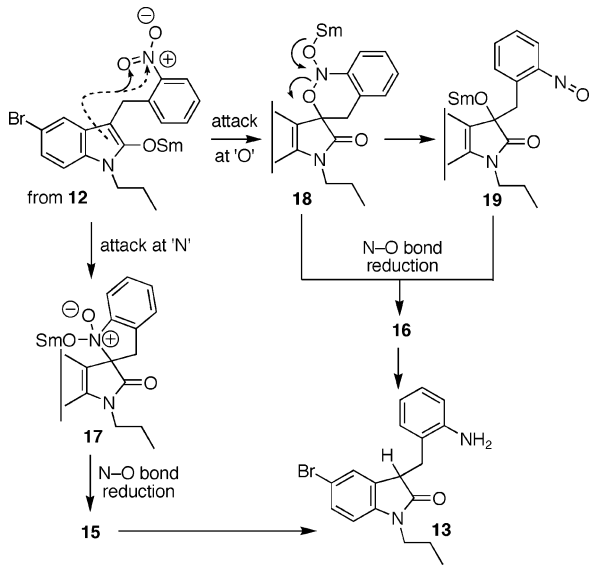


Figure 1. Intermediates in the reduction of **12**.

give **13**.[14] Azaspirocycles related to **15** display antifungal and antibacterial activity.[15]

Azaspirocycle **15** appears to arise from attack of the Sm(III)−enolate intermediate at the nitrogen of the nitro group[16] or a nitroso intermediate formed by the reduction of the nitro group, followed by N−O bond reduction.[17] We believe tertiary alcohol **16** is formed by attack of the Sm(III)−enolate intermediate at the oxygen of the nitro group[18] followed by N−O bond reduction of an intermediate heterocycle **18** or of a nitroso intermediate **19**, formed by elimination of a samarium alkoxide from **18** (Scheme 5).

Scheme 5



Alcohol **16** is also isolated when the reaction mixture is thoroughly degassed, suggesting that enolate oxidation is not responsible for its formation. Additional support for the proposed origin of **16** was gained by alkylation of **11** with *p*-nitrobenzyl bromide and treatment of the adduct with SmI_2. No product analogous to **16** was obtained, suggesting that an intramolecular reaction of a samarium enolate with the nitro group is responsible for product formation. To our knowledge, this is the first report of a samarium enolate addition to a nitro group.

To illustrate the potential of tag cleavage−cyclization processes using the linker, a small library synthesis was

(10) Brady, E. D.; Clark, D. L.; Keogh, D. W.; Scott, B. L.; Watkin, J. G. *J. Am. Chem. Soc.* **2002**, *124*, 7007 and references therein.

(11) Ho, T.-L.; Jou, D.-G. *Helv. Chim. Acta* **2002**, *85*, 3823.

(12) For example, see: Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703.

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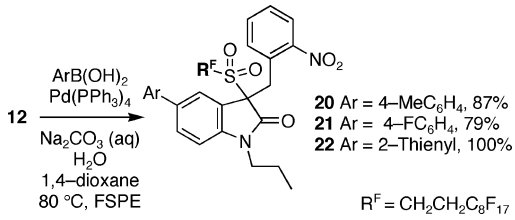
(16) (a) Preston, P. N.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627. (b) Dean, F. M.; Patampongse, C.; Podimuang, V. *J. Chem. Soc., Perkin Trans 1* **1974**, 583.

(17) For examples, see: (a) Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2485. (b) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265.

(18) For an example of the addition of an organometallic to the oxygen of an aryl nitro group, see: Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991**, 657. For the addition of an enolate to the oxygen of an aryl nitro group, see: Stolz, D.; Kazmaier, U.; Pick, R. *Synthesis* **2006**, 3341.

carried out using such an approach. Fluorous-tagged oxindole **12** underwent efficient Suzuki−Miyaura coupling[19] with three boronic acids to give products **20**−**22** in 79−100% yield after rapid purification using FSPE (Scheme 6).

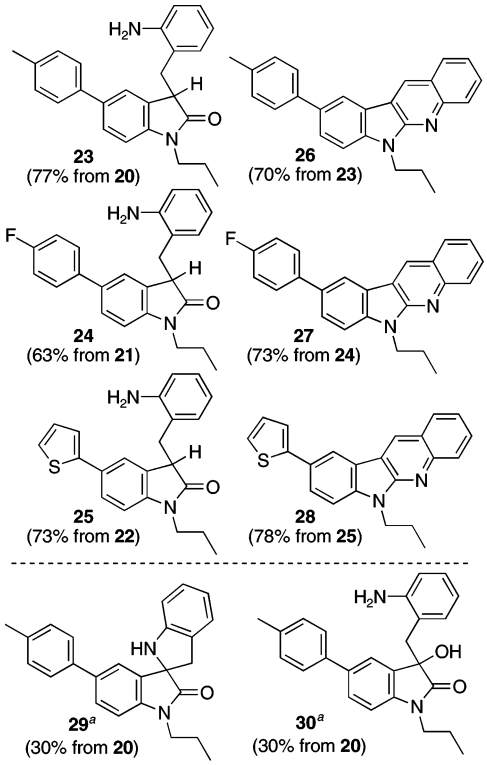
Scheme 6



Treatment of **20**−**22** with SmI_2 resulted in removal of the fluorous tag and reduction of the nitro group to give the expected aniline products **23**−**25** that could then be converted to pyridines **26**−**28** (Figure 2). We have used our improved understanding of the mechanism of the sequential reduction to introduce additional diversity during the removal of the fluorous tag from oxindole **20** by varying the reaction time with SmI_2. As described above, treatment of **20** with SmI_2 for 48 h gave aniline **23** that could be converted to **26**. However, treatment of **20** with SmI_2 for only 3.5 h gave **29** and **30** (60%) that were readily separable. Thus, from one, fluorous-tagged intermediate, using a single strategy, removal of the tag using SmI_2 allows four products with different architectures to be prepared (Figure 2).

In summary, SmI_2 has been used to mediate reaction sequences that remove a fluorous tag and introduce diversity through the formation of heterocyclic rings. These sequential reactions illustrate how a higher synthetic return can be obtained from the unavoidable cleavage step at the end of a phase tag-assisted synthesis using a sulfur linker. Our studies also shed further light on the behavior of samarium enolates.

(19) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.



[a] **29** and **30** were obtained as a 1:1 mixture and were readily separated by chromatography.

Figure 2. Tag cleavage−cyclization in library synthesis.

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Supporting Information Available: Experimental procedures and data for all new compounds and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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