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SmI_2-Mediated Sequential Radical Cyclization/Anionic Capture of Aryl Iodides on Solid Support

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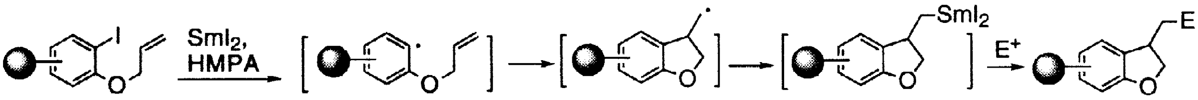
Abstract: Aryl radicals were generated by SmI_2 on solid support, cyclized on to C=C bond, and reduced to their organosamarium anionic species followed by electrophilic capture. However, the capture reaction was substrate-dependant in solution and on solid support. In some examples, results from solid phase reactions were equal or better to the corresponding solution reactions.

Combinatorial chemistry has emerged as a powerful new technology to synthesize large number of compounds for biological evaluation.[1] Apart from many studies toward libraries of small organic molecules, investigations toward more complicated natural product libraries have also emerged.[2] Since many combinatorial libraries are generated on solid support, adapting reactions to resins will increase the applicability of this technique.[3] SmI_2-mediated[4] sequential radical cyclizaton/anionic capture of aryl iodides[5] is a reaction that can form multiple carbon-carbon or carbon-heteroatom bonds in one step without isolation of any intermediates. Furthermore, reactions with reactive intemediates such as radicals, carbenes, nitrenes, etc. are relatively undeveloped in solid phase, and the highly reactive nature of radical intermediates would be of interest to examine on a polymeric support.

We reported[6] recently that SmI_2-mediated aryl radical cyclizations worked efficiently on solid support. Herein, we wish to report that cyclized aryl radicals on solid support can be reduced to their anionic species followed by electrophilic capture (eq 1).



(1)

To study sequential aryl radical cyclization/capture on solid support, a substrate with an additional functional group attachable to solid support is needed. As nothing is known about the influence of ring functional groups on the sequential cyclization/capture, we decided to first investigate the substituent effect in solution. With SmI_2 added to a mixture of the substrate and D_2O, reaction of methyl 4-crotyloxy-3-iodo-5-methoxy benzoate**1** had 32% deuterium incorporation and 17% radical disproportionation product. Reaction of methyl 4-crotyloxy-3-iodo benzoate **2**[7] had 64% deuterium incorporation and 13% radical disproportionation product, and reaction of methyl 4-allyloxy-3-iodophenyl acetate **3** (see scheme 1 for synthesis of **3**) had 55%

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deuterium incorporation. No radical disproportionation was seen for methyl 4-crotyloxy-3-iodophenyl acetate **4**, the crotyloxy analog of **3** (Figure 1). None of the three substrates was as good as the literature example crotyloxy-2-iodo benzene[8] with substrate **3** being relatively the best one. Therefore we decided to study the reaction of **3** on solid support before finding a better substrate.

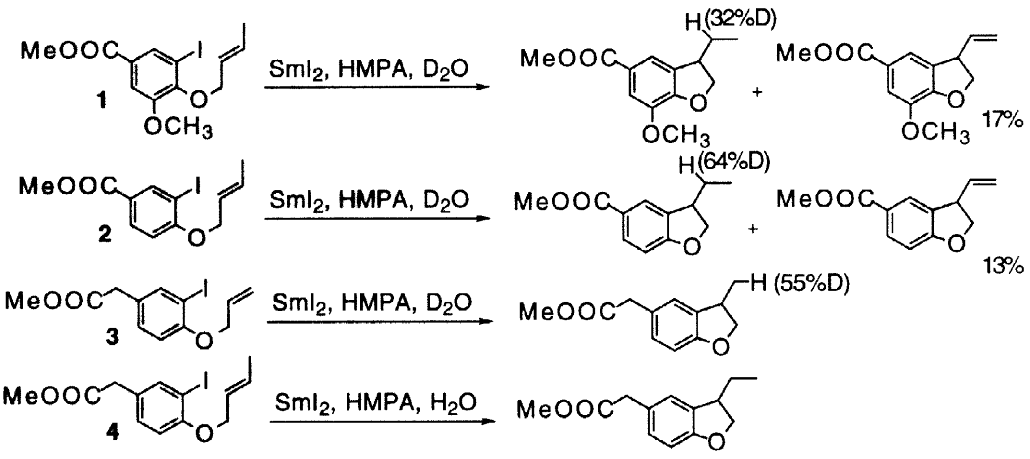


Figure 1. D_2O-quenching experiments of various aryl iodides in solution.

In the literature, the sequential reactions worked best[5a, c] (65-96%) with allyloxy-2-iodo benzene when the electrophiles (both aldehydes and ketones) were added five minutes after the reaction of the substrate and SmI_2. A mixture of the substrate and ketones could also react with SmI_2 (38-81%), but poor yields were obtained with the substrate and aldehydes mixed at the same time.[5b] More detailed capture reactions were performed to find the best timing for addition of electrophiles to substrate **3** and also to compare with reactions on solid support. With SmI_2 added to a mixture of **3** and cyclohexanone, captured product **5** was obtained in 36% yield. With SmI_2 added to a mixture of **3** and 3-pentanone, captured product **6** was obtained in 40%. However, with 3-pentanone added five minutes after the reaction of **3** and SmI_2, only a small amount of **6** (8%) was obtained. This indicated that the reductive species from **3** was generated faster and had a shorter lifetime than allyloxy-2-iodobenzene. With butyraldehyde added immediately after reaction of **3** and SmI_2,[9] **7** was generated in 33% yield as a mixture of 1.7:1 diastereomers (Figure 2). The moderate stereoselectivity was probably a result of the additional ring substituent group.

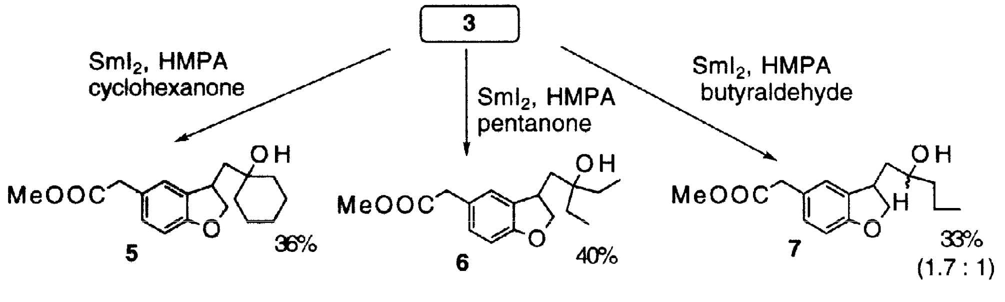
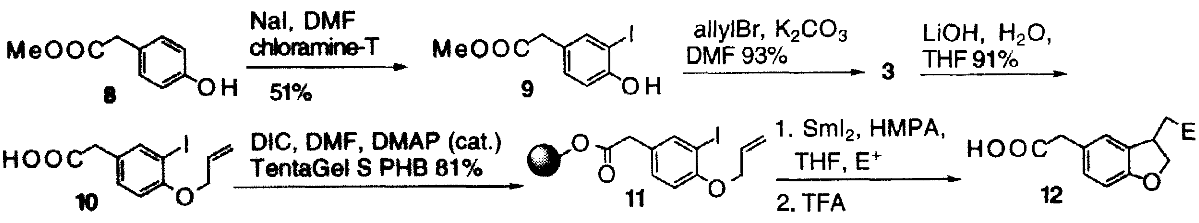


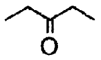
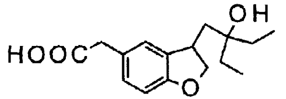
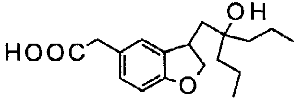
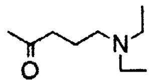
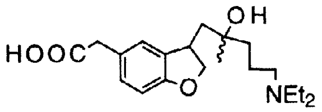
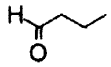
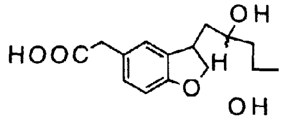
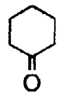
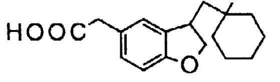
Figure 2. Sequential radical cyclization/anionic capture of **3** in solution.



Scheme 1. Adaptation of sequential radical cyclization/anionic capture to solid support.

Scheme 1 shows the adaption of **3** to solid support. Iodination on methyl 4-hydroxyphenyl acetate **8** generated **9** in 51% yield. Allylation of **9** generated **3** in 93% yield. Hydrolysis of **3** provided acid **10** for solid phase synthesis.

Table I. Products and yields for capture reactions on solid support.

	Electrophile	Product **12**	yield
a			33%[a]
b			20%[a]
c			45%[a, c]
d			5%[b, d]
e			7%[b]

[a] SmI_2 added to the mixture of **11** and electrophile. [b] Electrophile added five minutes after reaction of **11** and SmI_2. [c] 2.2 : 1 diastereomeric ratio. [d] 1.8 : 1 diastereomeric ratio.

Initially, **10** was loaded on Rink resin. Subsequent reaction with SmI_2 added to a mixture of Rink-bound **10** and 3-pentanone gave only the uncaptured cyclized product. This result may be due to the relatively poor swelling property of polystyrene beads or the free amide proton on the Rink linker quenching the reductive anionic species. To avoid these problems, TentaGel S PHB resin[10] was selected as the polymeric support. **10** was loaded on TentaGel via an ester linkage as opposed to an amide linkage. We were encouraged to find that reaction of **11** with 3-pentanone under the same condition as Rink-bound **10** generated captured product **12a** (Table I) in 33% yield.[11] The ^{1}H NMR of the solid-phase reaction product before chromatography showed only the captured and uncaptured cyclized products in a 1:1 ratio, while for the corresponding solution reaction, the ^{1}H NMR obtained before chromatography showed some impurities in addition to the 1:1 product mixture. Consequently, the capture of **11** with other acyclic ketones such as 4-heptanone (see Table I, **12b**) and

5-diethylamino-2-pentanone (see Table I, **12c**) also provided acceptable yields.[12]

Contrary to the solution profiles, with SmI_2 added to a mixture of **11** and cyclohexanone or with butyraldehyde added immediately after reaction of **11** and SmI_2, rapid decoloration of SmI_2 was observed and only **10** was recovered from the reaction. These results indicated that the anionic species was generated more slowly on solid support than in solution and SmI_2 was consumed by reactive electrophiles (cyclic ketones, aldehydes) before it reacted with **11**. To generate the anionic species, **11** and SmI_2 must react for some time before reactive electrophiles were added. With butyraldehyde added one, three, and five minutes after reaction of **11** and SmI_2, the captured product **12d** was observed in small amounts with no large differences in yields.[13] These results indicated that the anionic species was generated gradually on solid support and its concentration was not high enough to obtain a good capture yield. On the other hand, the stability of the anionic species was similar on solid support. With cyclohexanone added after ten minutes of reaction of **11** and SmI_2, no captured product was observed. The stereoselectivity of the capture of butyraldehyde was similar in solution (Figure 2) and solid phase as evidenced by the formation of **12d** in a 1.8:1 diastereomeric mixture.

In conclusion, we have demonstrated SmI_2-mediated sequential radical cyclization/anionic capture on TentaGel S PHB. In some examples, results were equal or better to the corresponding solution reactions. Both solution and solid phase capture reactions are highly substrate-dependent, which may limit its general utility in combinatorial construction.

Acknowledgement. This work was supported by NIH grant number 69674.

References and Notes

1. For reviews, see: (a) *Chem. Rev.* **1997**, *97*, whole issue of No. 2, pp 347-510. (b) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288-2337. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600.
2. Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724-8725.
3. (a) Fruchtel, J. S. and Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17-42. (b) Hermkens, P. H.H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554. (c) Armstrong, R. W.; Combs A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.*, **1996**, *29*, 123-131.
4. For a recent review on SmI_2-mediated reactions, see: Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307-338.
5. For solution studies of SmI_2-mediated sequential radical cyclization/anionic capture of aryl iodides, see: (a) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett*, **1990**, 773-774. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171-6176. (c) Curran, D. P.; Totleben, M; J. *J. Am. Chem. Soc.* **1992**, *114*, 6050-6058.
6. Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678-5679.
7. **2** was synthesized from 3-amino-4-hydroxybenzoic acid as follows: (a) $NaNO_2$, HCl, KI; (b) $TMSCHN_2$, CH_2Cl_2, MeOH; (c) crotyl chloride, K_2CO_3, DMF.
8. Under the same condition, reaction of crotyloxy-2-iodo benzene had 79% deuterium incorporation and no radical disproportionation. This agreed well with the literature (reference 5).
9. SmI_2 addition to a mixture of **3** and butyraldehyde was not performed since butyraldehyde was a more reactive electrophile than ketones and hence it might quench SmI_2 instead of being captured.
10. Wright, P.; Lloyd, D.; Rapp, W.; Andrus, A. *Tetrahedron Lett.* **1993**, *34*, 3373-3376.
11. A typical experimental procedure for reaction of **11** on solid support to capture acyclic ketones is as follows: A flask with resin-bound **11** and stirrer is dried under high vaccuum (3mmHg) at 65°C overnight. HMPA (40 equiv.) and ketone (20 equiv) are added followed by 0.1 M SmI_2 solution in THF (10 equiv., supplied by commercial sources). The resulting mixture is stirred for 2 h at room temperature. The resin is then filtered, washed with methanol, THF, CH_2Cl_2, then satureated $NaHCO_3$, 3% $Na_2S_2O_3$, H_2O, then again the three organic solvents. The resin is cleaved by 20% TFA/CH_2Cl_2 and rinsed by $CHCl_3$ and CH_2Cl_2.
12. All compounds in Table I satisfied spectroscopic characterization (Highres MS, IR, ^{1}H NMR, ^{13}C NMR).
13. The capture of branched aldehydes such as 2,2-dimethyl propionaldehyde on resin was only slightly better than that of butyraldehyde.