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Solid-Phase Approach to Tetrahydroquinolones Using a Sulfur Linker Cleaved by SmI_2

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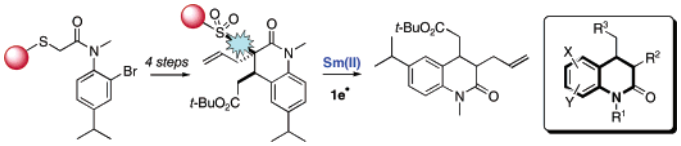
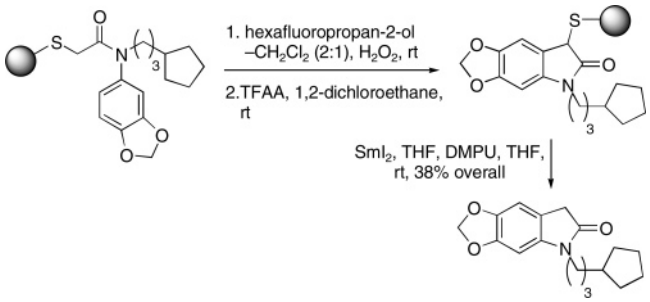
ABSTRACT



A sulfur α-heteroatom-substituted carbonyl (HASC) linker has been utilized in a solid-phase approach to tetrahydroquinolones. The route illustrates the compatibility of the linker system with palladium-catalyzed transformations and its utility for library synthesis. The linker is cleaved by electron transfer from samarium(II) iodide.

Solid-phase synthesis remains a powerful tool for synthetic organic chemists. The development of versatile linker designs is important for continued advancements in the area.[1] We have previously described a new traceless linker strategy for solid-phase organic synthesis where the link to resin is cleaved using samarium(II) iodide (SmI_2).[2] We refer to this family of linkers as HASC (α-heteroatom-substituted carbonyl) linkers. We originally focused on an ether-based HASC linker[3] but have begun to explore the considerable potential of sulfur-based HASC linkers. For example, α-sulfanyl *N*-aryl acetamides, attached to resin via the sulfur atom, undergo efficient Pummerer cyclization upon activation of the sulfur link, to give oxindoles. Heterocyclic products can then be cleaved from the support in a traceless manner using SmI_2 (Scheme 1).[4]

Scheme 1



In our approach, the linking sulfur atom operates in a multifunctional sense, mediating C−C bond formation during

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(1) For recent 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) McAllister, L. A.; McCormick, R. A.; Procter, D. J. *Tetrahedron* **2005**, *61*, 11527.

(2) For reviews on the use of samarium(II) iodide in organic synthesis, see: (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. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: New York, 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.

(3) (a) McKerlie, F.; Procter, D. J.; Wynne, G. *Chem. Commun.* **2002**, 584. (b) McKerlie, F.; Rudkin, I. M.; Wynne, G.; Procter, D. J. *Org. Biomol. Chem.* **2005**, *3*, 2805.

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and after heterocycle formation, in addition to its fundamental role as a link to the support.[4]

In this letter, we further explore the potential of our linker system in an approach to tetrahydroquinolones.

The tetrahydroquinolone framework can be found in many natural and nonnatural biologically active compounds and is therefore an attractive scaffold for synthesis (Figure 1).[5]

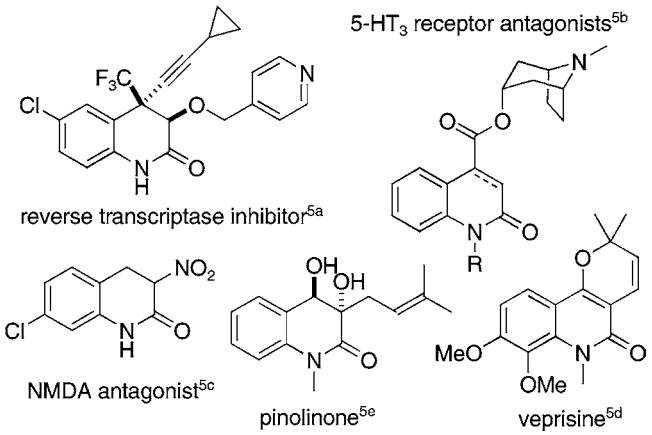
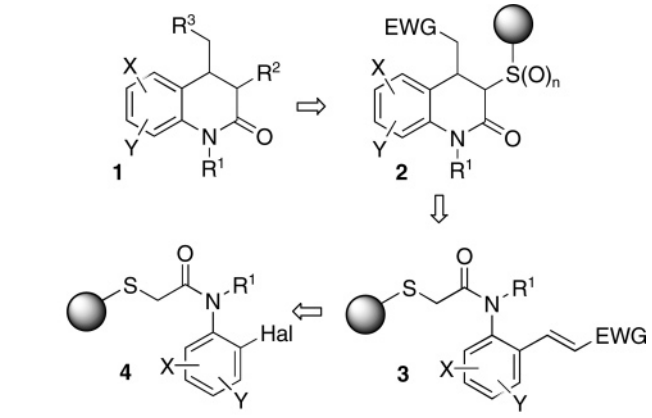


Figure 1. Tetrahydroquinolone framework.

Our proposed, solid-phase approach to tetrahydroquinolones **1** is outlined in Scheme 2. Heck reactions of immobilized

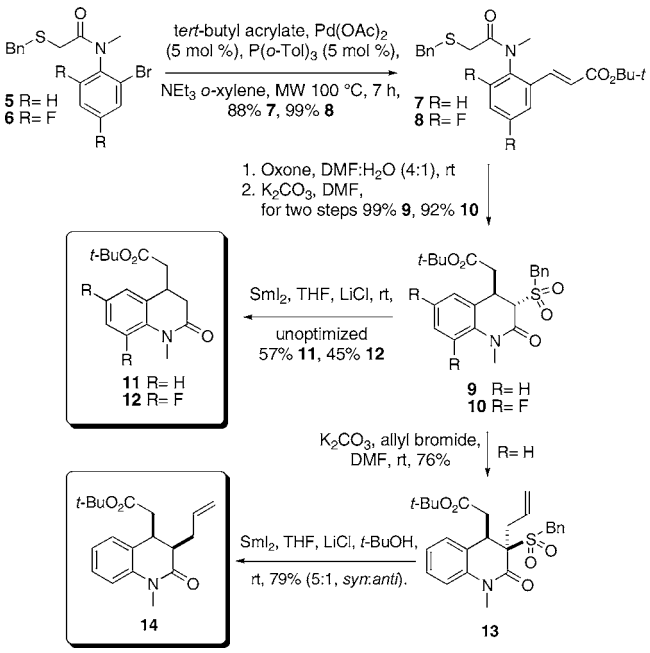
Scheme 2



aryl halides **4** with electron-deficient alkenes should allow access to key intermediates **3**. Base-mediated cyclization will then furnish the tetrahydroquinolone core **2** which can be modified before cleavage from the support.

We began our studies by evaluating the route using a solution-phase model system. α-Sulfanyl amides **5** and **6** were prepared in which the benzyl sulfanyl group mimics a benzylic sulfur resin. Although few Heck reactions of *N*-α-halophenylamides and carbamates have been reported,[6] both **5** and **6** underwent efficient Heck coupling in *o*-xylene with *tert*-butyl acrylate under microwave conditions. Oxidation of **7** and **8** to the corresponding sulfones and treatment with K_2CO_3 gave the *anti*-tetrahydroquinolones **9** and **10** in good yield. The relative stereochemistry of **9** and **10** was confirmed by X-ray crystallography.[7] The cleavage reaction was next investigated in the model system. We have previously shown that cleavage of the linker can be carried out at both the sulfide and sulfone oxidation levels.[4] Treatment of **9** and **10** with SmI_2 using LiCl as a promotor[8] gave the expected products in moderate, unoptimized yields. Further modification of **9** was readily achieved by alkylation to give **13**, the relative stereochemistry of which was confirmed by X-ray crystallography.[7] Cleavage using SmI_2/LiCl gave **14** as a ∼1:1 mixture of diastereoisomers. Interestingly, the use of *t*-BuOH as a proton source in the reduction gave *syn*-**14** as the major product (5:1 diastereoisomeric ratio) (Scheme 3).

Scheme 3



The relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallography.[7]

(4) (a) McAllister, L. A.; Brand, S.; de Gentile, R.; Procter, D. J. *Chem. Commun.* **2003**, 2380. (b) McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 452.

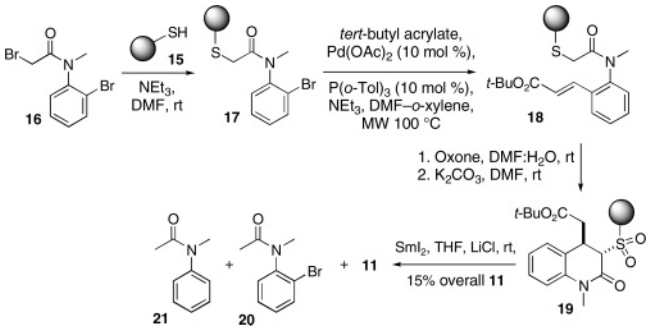
(5) (a) Patel, M.; McHugh, R. J., Jr.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Biorg. Med. Chem. Lett.* **2001**, *11*, 1943. (b) Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. *J. Med. Chem.* **1992**, *35*, 4893. (c) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397. (d) Christopher, E.; Bedir, E.; Dunbar, C.; Khan, I. A.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M. *Helv. Chim. Acta* **2003**, *86*, 2914. (e) Ito, C.; Itoigawa, M.; Otsuka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1344.

(6) For an example, see: Arnold, L. A.; Luo, W.; Guy, R. K. *Org. Lett.* **2004**, *6*, 3005.

(7) See Supporting Information for X-ray structures and CCDC numbers.

Satisfied that our approach was feasible, we moved on to the solid phase. Benzyl thiol resin **15**[9] was prepared, and the loading was determined to be approximately 0.54 mmol g^{-1}.[4] An early reaction sequence on the solid phase is shown in Scheme 4.

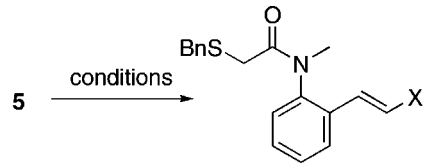
Scheme 4

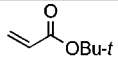
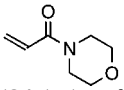


Immobilization of α-bromoamide **16** gave amide **17**. A microwave-assisted Heck reaction with *tert*-butyl acrylate was unsatisfactory using *o*-xylene because of poor swelling of the resin and gave low conversion as indicated by FTIR. The use of a DMF/*o*-xylene solvent mixture in the Heck reaction appeared to solve this issue and gave **18**. Cyclization then gave supported tetrahydroquinolone **19**. As expected, treatment of **19** with SmI_2/LiCl gave **11**, although in a disappointing overall yield of 15% (for five steps). The isolation of amide byproducts **20** and **21** indicated that the Heck reaction was not proceeding efficiently on the solid phase.[10] A more detailed solution-phase study on the pivotal Heck reaction was therefore carried out to provide improved conditions for use on the solid phase (Table 1). Although *o*-xylene was an excellent solvent for the Heck reaction, in solution it was clearly unsuitable for use on the solid phase.[11] The use of a combination of DMF and *o*-xylene (3:7) gave lower conversion (entry 3). In neat DMF, a more suitable solvent for solid-phase reactions, conversion was acceptable particularly after a retreatment (entries 4 and 5).

The improved Heck coupling conditions were applied in the solid-phase sequence with the additional modification that *m*-CPBA was used for oxidation to the sulfone.[12]

Table 1. Optimizing the Heck Reaction



entry		conditions[a]	hours	yield[b]
1		*o*-xylene, thermal	48	39%
2	"	*o*-xylene, microwave	7	88%
3	"	DMF–*o*-xylene (3:7), microwave	10 x 2	75%
4	"	DMF, MW 100 °C	10 x 2	90%
5		DMF, MW 100 °C	10 x 2	76%

[a] $Pd(OAc)_2$ (5 mol %) and $P(o\text{-Tol})_3$ (5 mol %) NEt_3. [b] Isolated yields.

Pleasingly, employing these conditions gave **11** in an improved 27% overall yield after purification (Figure 2). We have utilized the approach to prepare a collection of tetrahydroquinolones using α-bromoamide starting materials **16** and **22**−**25**. Additional diversity was introduced by the Heck reaction with a different olefin and by alkylation of an intermediate sulfone.

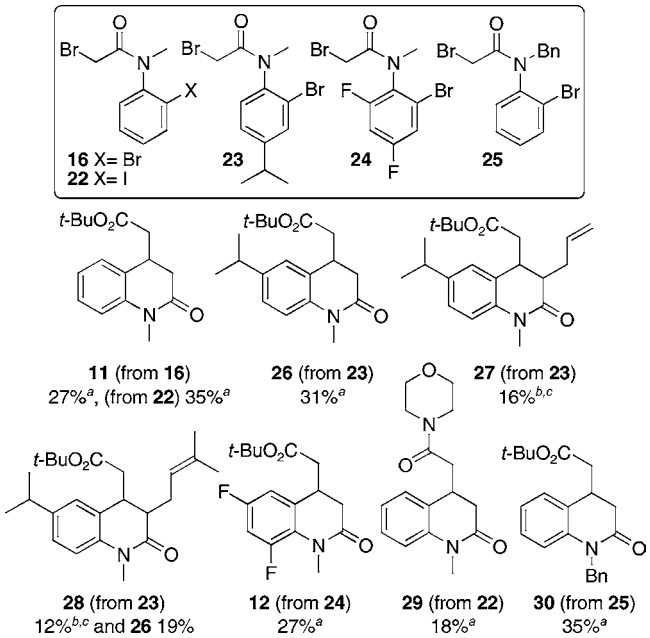


Figure 2. Starting materials and tetrahydroquinolone products.

The expected products were obtained in satisfactory overall yields for five and six steps on the solid phase. Aryl iodide **22** gave improved yields due to more efficient Heck

(8) (a) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 8157. (b) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2000**, *122*, 7718. (c) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295.

(9) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809.

(10) The debrominated product **21** most likely results from SmI_2 reduction during the cleavage step, although it is possible that reduction of the aryl bromide occurs under the conditions of the Heck reaction.

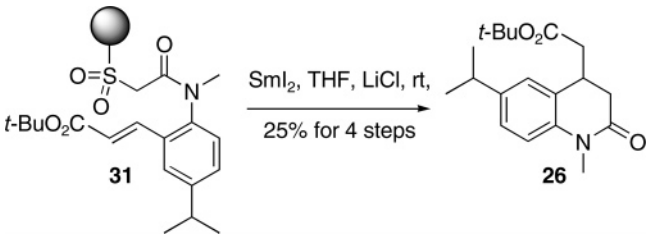
(11) The use of JandaGel, a support more suitable for use with nonpolar solvents such as *o*-xylene, also gave **11** in low yield.

(12) The use of oxone for the oxidation caused problems with inorganic byproducts contaminating the resin after washing. Solution-phase oxidation of sulfide **7** with *m*-CPBA gave the corresponding sulfone in 71% yield (*m*-CPBA, K_2CO_3, CH_2Cl_2, 2 h, room temperature). Longer reaction times led to some epoxidation of the electron-deficient alkene.

reactions. Alkylations of intermediate sulfones proved to be more difficult than solution models had predicted, and more forcing conditions were necessary (50 °C, KI). Products **27** and **28** were obtained with little diastereoselectivity possibly because of residual moisture in the resin acting as an alternative proton source to the added *t*-BuOH (Figure 2).

Finally, we have investigated the feasibility of a cyclative cleavage strategy using the HASC linker. Pleasingly, treatment of sulfone **31** with SmI_2 resulted in cleavage of the sulfur linkage and cyclization to give **26** in moderate overall yield (Scheme 5).[13]

Scheme 5



In summary, we have developed a solid-phase approach to tetrahydroquinolones using a HASC sulfur linker cleaved using SmI_2. The route involves a Heck reaction and a Michael cyclization as the key steps. Our studies illustrate the compatibility of sulfur HASC linkers with palladium-catalyzed transformations and also provide a further illustration of the multifunctional roles possible using sulfur linkers.

Acknowledgment. We thank the EPSRC and Pfizer for an Industrial CASE award (K.L.T.), AstraZeneca and Pfizer for additional untied funding which was used to support undergraduate project students (T.M.B. and S.I.), Dr. D. Apperley at the EPSRC Solid State NMR facility for MAS NMR, and Prof. M. Helliwell (Manchester) and Dr N. Feeder (Pfizer) for X-ray crystallographic studies.

Supporting Information Available: Experimental procedures and data for all new compounds, ^{1}H and ^{13}C NMR and ^{13}C MAS NMR and IR spectra, and X-ray structures and crystallographic data for **9**, **10**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The cyclization may be either a radical or an anionic process.