Novel Solution- and Solid-Phase Chemistry of α-Sulfonated Ketones Applicable to Combinatorial Chemistry

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In our continuing search for enabling technologies for cascade and combinatorial synthesis, we identified the α-sulfonated ketone[1] as a rather unexplored chemical entity with considerable potential in organic synthesis. Particularly enticing was the prospect of loading an organic substrate onto a solid support through a leaving group linker.[2] By tapping into the rich chemistry of the related α-halo ketones[3] and by developing chemistry exclusive to α-sulfonated ketones,[4] we envisaged a unique strategy wherein the essence of new diversity could be introduced at the cleavage step (**I** → **II**, Figure 1). Of utmost importance was the development of a new and efficient synthesis of these systems from readily available materials. In this work we report the realization of such a scenario utilizing a novel one-pot synthesis of α-sulfonated ketones from olefins, both in solution and on solid phase, and leading to a fast-track entry into a wide ranging variety of structural types.

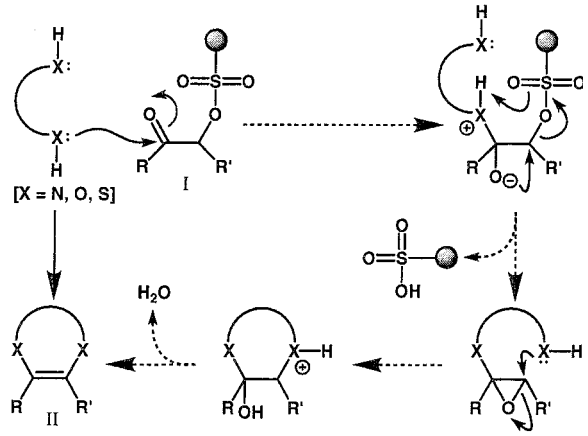
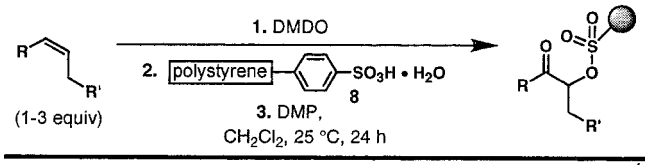
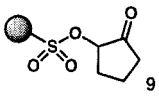
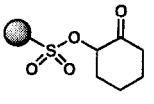
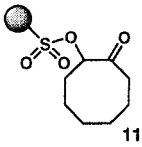
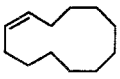
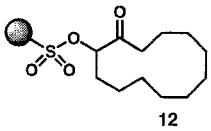
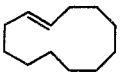
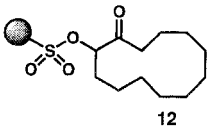
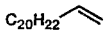
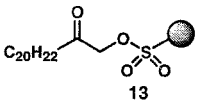
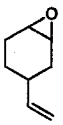
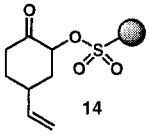


Figure 1. Mechanistic rationale for the "heterocycle-release" strategy.

After considerable experimentation we found that by treating cyclooctene oxide [Scheme 1, derived from cyclooctene **1** by DMDO-mediated[5] (for abbreviations of reagents, see Scheme footnotes) epoxidation in the same pot] with *p*-TsOH in CH_2Cl_2 at room temperature, gradual conversion to the α-hydroxy tosylate was observed. Addition of DMP[6] led cleanly to the α-tosyloxy ketone **2** in 65% isolated yield after flash chromatography (silica, hexane:Et_2O (2:1)). This protocol was considerably simplified and

Table 1. Loading of α-Sulfonated Ketones onto Polystyrene Sulfonic Acid Resin **8** from Olefins/Epoxides in One Pot[a]



Entry	Olefin/Epoxide	Product[a]	Loading(%)[b]
1		 **9**	98
2		 **10**	91
3		 **11**	88
4		 **12**	95
5		 **12**	95
6		 **13**	89
7		 **14**	93[c]

[a] Reagents and conditions: olefin (2.5 equiv), DMDO (4.0 equiv, ∼0.1 M solution in acetone), CH_2Cl_2, 1 h, 25 °C; then resin **8** (1.0 equiv, based on ∼1.0 mmol/g loading), 4 h, 25 °C; then $NaHCO_3$ (6.0 equiv), DMP (2.0 equiv), 25 °C, 12 h. [b] Based on yield of α-hydroxyketone obtained after treatment with K_2CO_3/H_2O/THF (see Scheme 2 for conditions, resin loading ∼1.0 mmol/g) and observed mass gain. [c] 2:1 mixture of regioisomers obtained after basic cleavage.

(1) Previous syntheses of α-sulfonated ketones: (a) via SO_3-mediated nitrosation of olefins: Zefirov, N. S.; Zyk, N. V.; Lapin, Y. A.; Nesterov, E. E.; Ugrak, B. I. *J. Org. Chem.* **1995**, *60*, 6771. (b) From ketones using hypervalent iodine reagents: Tuncay, A.; Dustman, J. A.; Fisher, G.; Tuncay, C. I.; Suslick, K. S. *Tetrahedron Lett.* **1992**, *33*, 7647; Lodaya, J. S.; Koser, G. F. *J. Org. Chem.* **1988**, *53*, 210. (c) From enol ethers using hypervalent iodine reagents: Moriarty, R. M.; Epa, W. R.; Penmasta, R.; Awasthi, A. K. *Tetrahedron Lett.* **1989**, *30*, 667. (d) From enol esters, enol ethers, and enamines using arylsulfonyl peroxides: Hoffman, R. V.; Carr, S. C.; Jankowski, B. C. *J. Org. Chem.* **1985**, *50*, 5148.

(2) For related sulfonate linkers, see: Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998; Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B. *Tetrahedron Lett.* **1998**, 975; Baxter E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, 979. For a recent extensive review on linking and cleavage technology in solid-phase organic synthesis, see: Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. See also: Bräse, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899.

(3) Verhe, R.; De Kimpe, N. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: London, 1983; p 813.

(4) (a) Photochemical reactions of α-tosyloxy and α-methanesulfonyloxy ketones: Charlton, J. L.; Lai, H. K.; Lypka, G. N., *Can. J. Chem.* **1980**, *58*, 458. (b) Addition of methoxide and amines to α-nosyloxy ketones: Hoffman, R. V.; Jankowski, B. C.; Carr, C. S.; Duesler, E. N. *J. Org. Chem.* **1986**, *51*, 130.

(5) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(6) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

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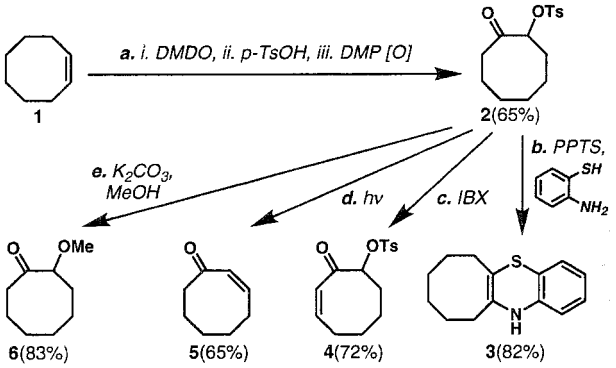
Scheme 1. One-Pot Entry to α-Tosyloxy Ketones from Olefins[a]



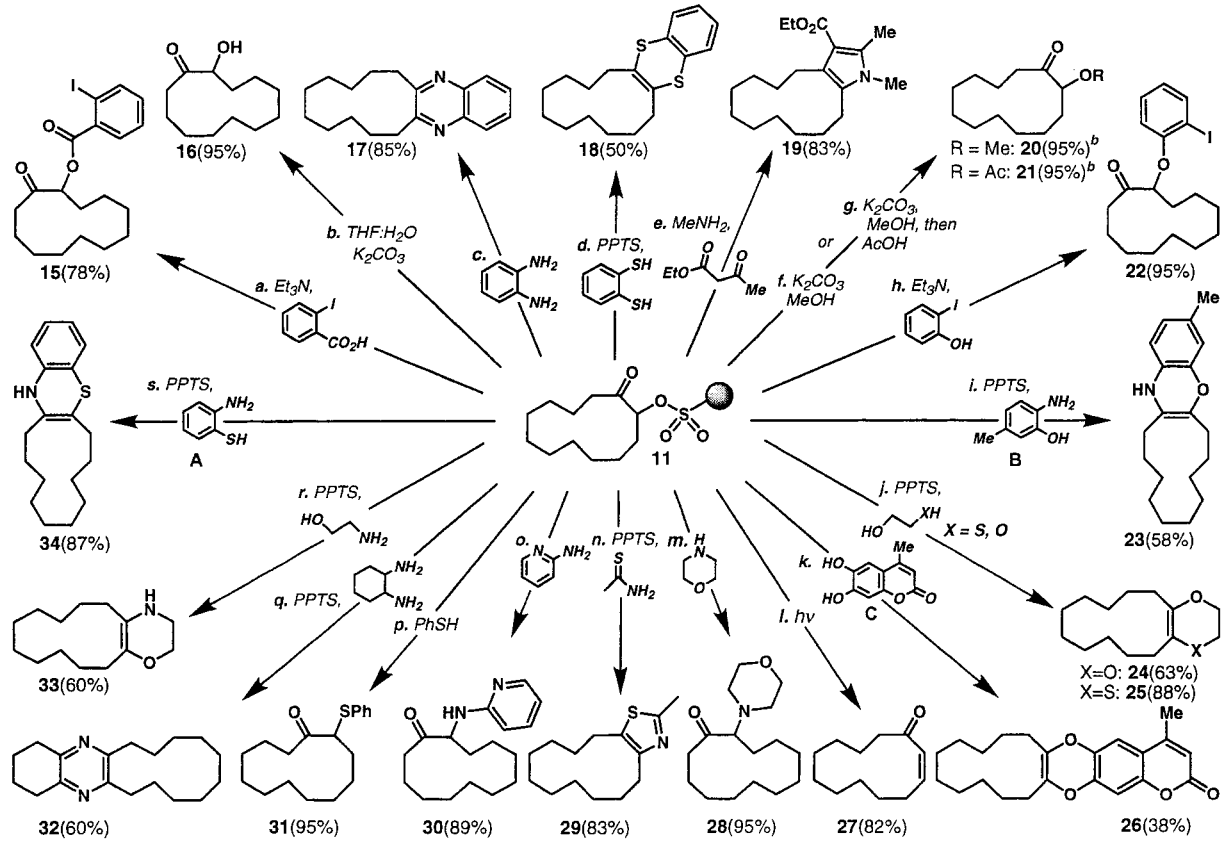
[a] Reagents and conditions: (a) DMDO (1.3 equiv, ∼0.1 M solution in acetone), CH_2Cl_2, 1 h, 25 °C; then *p*-TsOH (5.0 equiv), 12 h, 25 °C, then $NaHCO_3$ (6.0 equiv), DMP (2.0 equiv), 25 °C, 65%; (b) 2-aminothiophenol (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 82%; (c) IBX (2.0 equiv every 5 h), *p*-TsOH (cat.), DMSO:fluorobenzene (10:1), 85 °C, 15 h, 63%; (d) benzene (0.05 M), hanovia (450 W, medium pressure Hg lamp), 8 h, 65%; (e) K_2CO_3 (5.0 equiv), MeOH, 25 °C, 1 h, 83%, DMDO = dimethyldioxirane, *p*-TsOH = *p*-toluenesulfonic acid, DMP = Dess−Martin periodinane, PPTS = pyridinium *p*-toluenesulfonate, IBX = *o*-iodoxybenzoic acid, DMSO = dimethyl sulfoxide.

generalized (Table 1) by synthesizing the immobilized variant of *p*-TsOH[7] (**8**) and using it to load a series of olefinic substrates as α-sulfonated ketones via the one-pot procedure described above and summarized in Scheme 1 and Table 1. *Cis*- and *trans*-olefins (entry 5) are loaded onto the solid support with equal efficiency. The α-sulfonated ketones are remarkably stable chemical entities, both in solution and on solid phase.

Having at our disposal a variety of α-sulfonated ketones, we proceeded to utilize an array of new and classical chemical reactions to implement the unique functionalizing-cleavage stratagem alluded to above (Figure 1). In this regard the carbonyl group which stabilizes the sulfonate moiety adjacent to it was also expected to activate it upon being attacked by a nucleophile.[8]

As depicted in Schemes 1 and 2, we found that α-sulfonated ketones could be dismantled in solution or excised from the solid support, with concurrent formation of a variety of novel molecular frameworks. Thus, treatment of **2** with methanolic K_2CO_3 led to the isolation of α-methoxy-ketone **6** in 83% isolated yield (Scheme 1) while release of **20** occurred with similar efficiency from solid-bound **11** (81%, Scheme 2).[9] Photolytic cleavage of **2** led to the α,β-unsaturated ketone **5** in 65% isolated yield (Scheme 1) and photorelease of **27** occurred in 82% isolated yield from **11** (Scheme 2).[10] Application of our recently disclosed protocol[11] for oxidation adjacent to the carbonyl group furnished unsaturated ketone **4** in 72% isolated yield (Scheme 1). We were delighted

Scheme 2. Twenty Functionalizing-Cleavage Options for Use with the α-Sulfonated Ketone Resin **11**[a]



[a] Reagents and conditions: (a) 2-iodobenzoic acid (10 equiv), Et_3N (5.0 equiv), toluene, reflux (Dean−Stark), 16 h, 78%; (b) K_2CO_3 (1.0 equiv), THF/H_2O (1:1), reflux, 30 min, 95%; (c) 1,2-diaminobenzene (10 equiv), PPTS (cat.), toluene, reflux (Dean−Stark), 16 h, 85%; (d) 1,2-benzenedithiol (10 equiv), PPTS (cat.), benzene, reflux, 16 h, 50% **18** + ∼50% of endocyclic olefin (*cis*/*trans* mixture); (e) ethylacetoacetate (10 equiv), methylamine (10 equiv, 40% solution in H_2O), toluene, 60 °C, 24 h, 83%; (f) for **20**: K_2CO_3 (5.0 equiv), MeOH, 25 °C, 8 h, 95%; (g) for **21**: same as for **20**, then AcOH, 25 °C, 5 h, 95%; (h) 2-iodophenol (10 equiv), Et_3N (5.0 equiv), toluene, 90 °C, 8 h, 95%; (i) 2-amino-5-methylphenol (**B**) (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 58%; (j) for **24**: ethylene glycol/benzene (1:1), PPTS (cat.), 90 °C, 12 h, 63%; for **25**: 2-mercaptoethanol (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 16 h, 88%; (k) 4-methylesculetin (**C**) (10 equiv), PPTS (cat.), benzene/DMSO (10:1), 85 °C, 24 h, 38%; (l) benzene, hanovia (450 W, medium pressure, Hg lamp), 45 °C, 6 h, 82%; (m) morpholine (5.0 equiv), CH_2Cl_2, 25 °C, 12 h, 95%; (n) thioacetamide (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 36 h, 83%; (o) 2-aminopyridine (5.0 equiv), benzene, reflux, 16 h, 89%; (p) thiophenol (5.0 equiv), benzene, reflux, 12 h, 95%; (q) 1,2-diamino cyclohexane (10 equiv, *cis*/*trans*), PPTS (cat.) benzene, reflux (Dean−Stark), 24 h, 60%; (r) ethanolamine (10 equiv), PPTS (cat.), benzene, reflux (Dean-Stark), 36 h, 60%; (s) 2-aminothiophenol (**A**) (10 equiv), PPTS (cat.), benzene, reflux (Dean−Stark), 24 h, 87%. [b] Formed via the labile, but detectable, methoxy-epoxide intermediate, see Supporting Information.

to observe efficient conversion of **2** to the novel heterocycle **3** simply upon condensation with 2-aminothiophenol (**A**) (benzene, Dean−Stark trap, reflux, cat. PPTS, 82% isolated yield, Scheme 1). Heterocycle **34** cleanly departed from the solid support (87% yield) following treatment of **11** with **A** under similar conditions (Scheme 2).

This "heterocycle-release" strategy (see Figure 1) was tested repeatedly and delivered a range of ubiquitous[13] heterocyclic systems (Scheme 2). Thus, derivatives of both the dioxane (**24**, **26**) and morpholine (**33**) ring systems were released from the resin simply by heating with ethylene glycol, 4-methylesculetin (**C**), or 1-amino-2-hydroxy ethylene in benzene, respectively. The fused thiazole **29** was constructed by heating **11** with excess thioacetamide, while treatment with 1,2-dithiobenzene or 2-mercaptoethanol led to the thianthrene derivative **18** and the 1,4-oxathiene **25**, respectively.[12a] Pyrazines **17** and **32** were fabricated simply by reaction with 1,2-diamino benzene and 1,2-diamino cyclohexane (*cis*/*trans* mixture), respectively. Access to the phenoxazine derivative **23** from **11** was accomplished using 2-amino-5-methylphenol (**B**). Treatment of **11** with ethyl acetoacetate and methylamine furnished the tetrasubstituted pyrrole **19** in 85% yield.[12b] To the best of our knowledge,[14] the direct synthesis of heterocycles such as **17**, **18**, **23**, **24**, **32**−**34** from α-halo or sulfonated ketones is unprecedented.[15] Using a polymer-bound isocyanate (Aldrich) or liquid−liquid extraction, excess reagents can be easily removed, thus potentially facilitating high-throughput applications of this method.

Finally, a range of nucleophiles were employed to elicit useful functionalizing-cleavage events resulting in a variety of α-substituted ketones (Scheme 2). Thus, upon treatment of conjugate **11** with mild aqueous base (catalytic K_2CO_3, THF:H_2O (2:1)), cleavage ensued to furnish the α-hydroxy ketone (**16**). Formation of α-amino ketones **28** and **30** was accomplished using morpholine and 2-aminopyridine, respectively.[4b] Phenols, carboxylic acids, and thiols were also found to be viable nucleophiles in this reaction. Thus products **22**, **15**, and **31** were obtained upon treatment of resin **11** with 2-iodophenol, 2-iodobenzoic acid, and thiophenol, respectively.

In conclusion, we have explored the chemistry of the α-sulfonated ketone moiety and proven its versatility in the construction of molecular diversity including novel heterocycles. The reactions reported herein perform equally well in solution and on solid support. The solid-phase version, in particular, provides both a novel linking forum for ketones and a new concept for extensive and wide ranging diversity introduction via cleavage from the resin (heterocycle-release), enabling combinatorial chemistry and key building-block construction. Carbon nucleophiles also enter these reactions (unpublished results).

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Supporting Information Available: Full characterization for new compounds and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002768P

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(8) This hypothesis is supported by the observations reported in ref 4b and the isolation of an epoxide intermediate en route to compounds **20** and **21** (Scheme 2, see Supporting Information for spectral data).

(9) These compounds (**6**, **20**, **21**) arise from the corresponding labile methoxy epoxides. See Supporting Information for spectral data. See also ref 4b for related studies.

(10) For a discussion of the mechanism of this reaction and its use on a steroidal substrate, see: Iwasaki, S.; Schaffner, K. *Helv. Chim. Acta* **1968**, *51*, 557.

(11) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

(12) (a) Thiazoles from α-halo ketones: Schwarz, G. *Organic Syntheses*; Wiley & Sons; New York, 1955; Collect. Vol. III, p 332. (b) Pyrroles from α-halo ketones: Roomi, M. W.; MacDonald, S. F. *Can. J. Chem.* **1970**, *48*, 1689.

(13) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.

(14) Literature search using SciFinder Scholar; see also: Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman & Hall: New York, 1995.

(15) According to a recent SciFinder Scholar search, benzothiazines, phenoxazines, pyrazines, and derivatives thereof are valuable small-molecule leads for a plethora of uses including antifungal, antiinflammatory, antitumor, anti-HIV, antimicrobial, CNS disorders, and potassium channel openers.