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AN EFFICIENT NEW METHOD FOR THE DESULFONYLATION OF β-KETO PHENYLSULFONES

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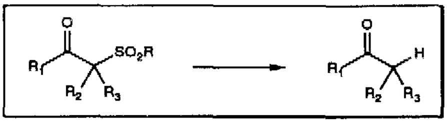
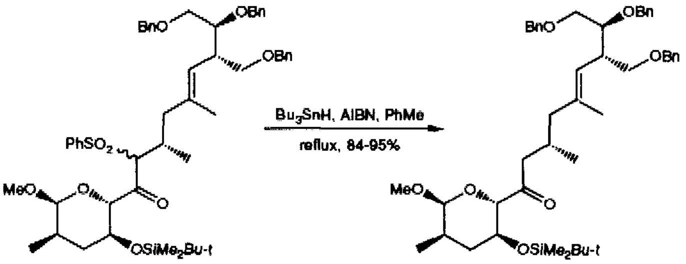
Summary: β-Keto phenylsulfones can be readily desulfonylated with excess tri-*n*-butylstannane and AIBN, when heated at reflux in toluene, to provide the corresponding ketones in good-to-excellent yields. The reaction proceeds under neutral conditions and is compatible with a wide variety of functionalities.

The reduction of β-keto sulfones to the corresponding ketones (eq. 1) frequently proves to be problematic when attempted on complex, multifunctional molecules. During the course of recent synthetic work on the immunosuppressant FK-506,[1] we found that the conventional method of Al(Hg) was ineffective for desulfonylation of β-keto phenylsulfone **1**.[2]



(1)

We then explored the feasibility of a new, radical-initiated cleavage employing tri-*n*-butylstannane and AIBN, whereupon the desired ketone **2** was obtained in 84-95% yield (eq. 2). This initial observation prompted us to explore further the potential of the new protocol with other β-keto phenylsulfones (Table 1); we report here that the method constitutes a very effective means of carrying out this important transformation.



(1)	(**2**)

(2)

Initially we attempted the reduction with four equivalents of tributylstannane in toluene at reflux in the presence of a *catalytic amount* of azobisisobutyronitrile (AIBN, 0.1 equiv); the reaction was very slow and did not proceed to completion. *However, when larger amounts of AIBN (up to a total of 2.0 equiv) were added portionwise every 2-5 min, reduction was generally complete within 15-40 min.* These results may reflect a short radical chain length. Use of triphenylstannane allowed the reaction time to be reduced even further, but an excess of initiator was still required. As indicated in Table 1, a wide variety of ketones ranging from simple methyl ketones to benzylic ketones can be prepared via this procedure.

Table 1

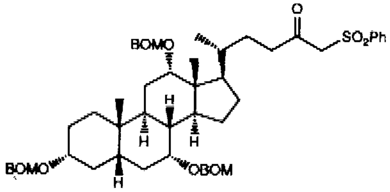
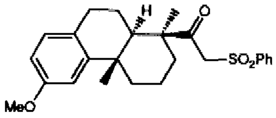
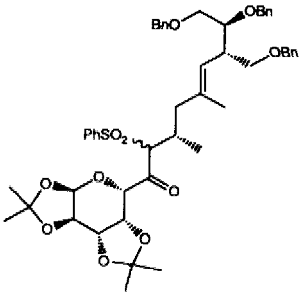
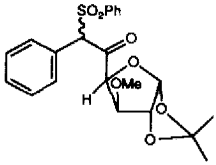
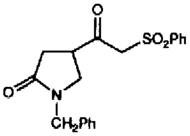
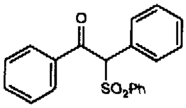
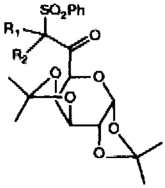
Entry	β-Keto Sulfone[8]	Reaction Time (min)	Yield of Ketone (%)[8]	Reactant,[a] Solvent
1		30	83	Bu_3SnH, PhMe
2		30	96	Bu_3SnH, PhMe
3		40	68	Bu_3SnH, PhMe
4		15	83	Bu_3SnH, PhMe
5		40	89	Bu_3SnH, PhMe[b]
6		40 5	16 43	Bu_3SnH, PhMe Ph_3SnH, PhMe

Table 1 Cont.

Entry	β-Keto Sulfone[8]	Reaction Time (min)	Yield of Ketone (%)[8]	Reactant,[a] Solvent
				
7	$R_1 = R_2 = H$	20	80	Bu_3SnH, PhMe
		10	79	Ph_3SnH, PhMe
8	$R_1 = H, R_2 = Me$	30	86	Bu_3SnH, PhMe
		25	78	Bu_3SnH, PhH
		5	91	Ph_3SnH, PhMe
9	$R_1 = R_2 = Me$	20	66	Bu_3SnH, PhMe
		5	91	Ph_3SnH, PhMe

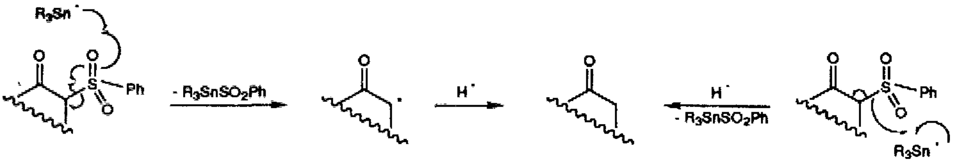
a) All reactions were conducted at reflux in the presence of 4 equiv of stannane.
AIBN was added in 0.25-equiv portions every 2-5 min.
b) This reaction required 6 equiv of Bu_3SnH.

However, the method does not appear to work well with substrates possessing a phenyl ring attached to the carbonyl of the β-keto phenylsulfone unit (Entry 6).

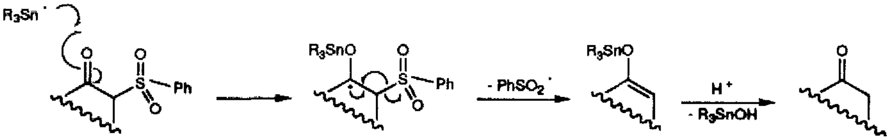
A distinct advantage of this method vis-á-vis many existing procedures is that desulfonylation can be achieved under essentially *neutral conditions*, a particularly valuable characteristic for substrates that are labile toward acid or base (e.g., **1**→**2**, entries 3-5, 7-9). Desulfonylations with Na(Hg) amalgam have been effected in the presence of disodium hydrogen phosphate buffer to prevent competing β-elimination.[3] Unfortunately, this tactic cannot be employed in reductions conducted with $Li/EtNH_2$,[4] Li/NH_3 or Ca/NH_3.[3] The latter reagents also suffer the disadvantage of their incompatibility with acetamido and benzyl protecting groups. Two other widely exploited desulfonylation methods involve zinc metal[5,6] and chromous ion;[6] these procedures employ acidic media for prolonged periods, often at elevated temperatures, and thus are applicable only to molecules containing a very limited range of functionality. In contrast, the reductive cleavage of β-keto sulfones with trialkyl- or triphenylstannanes circumvents most of these problems. The present approach also permits selective desulfonylation in systems containing an alkoxy group α to the carbonyl, whereas zinc metal[5] and samarium diiodide[7] effectively reduce both of these moieties. Interestingly, we have observed that unactivated alkyl phenylsulfones are completely inert to tin hydride reduction; thus, the selective desulfonylation of a β-keto phenylsulfonyl group in the presence of an alkyl sulfone should be feasible.

Finally, it should be emphasized that the present method is amenable to both small- and large-scale work. For example, we have performed the reduction of **1** to **2** (eq. 2) on scales ranging from 150 mg to 21 g. Generally, the product ketones can be efficiently separated from the tin by-products by simple gradient-elution flash chromatography. A typical experimental procedure is given for entry 4 (Table 1): a stirred solution of the β-keto sulfone[8] (0.99 g, 2.29 mmol) and tri-*n*-butylstannane (2.5 mL, ca. 4 equiv) in 25 mL of dry toluene was brought to reflux under an argon atmosphere. AIBN (250 mg, 1.52 mmol) was added, followed after 5 min by the addition of a further 160 mg (0.97 mmol) of AIBN. Heating was continued for 10 min further, whereupon TLC (EtOAc/hexanes, 2:1) revealed that all of the starting material had been converted to a single faster-moving, UV active product. Removal of solvent *in vacuo* and flash chromatography, eluting initially with hexane/EtOAc (13:1) to remove the tin by-products and then with hexane/EtOAc (8:1), gave 595 mg of the pure ketone (83% yield).[8]

Although further study will be required to elucidate the reaction mechanism, two possible reaction pathways (eq. 3) involve attack by the tin radical at either the oxygen[9] or sulfur atom[10] of the sulfonyl group to give a stabilized α-keto radical,



(3)



(4)

which would abstract hydrogen from the alkylstannane.[11] Alternatively, attack by the tin radical on the carbonyl oxygen would furnish a ketyl radical (eq. 4); the latter could then afford the tin-enolate via elimination of the phenylsulfonyl radical. A further possibility involves single electron transfer from the tin radical to the keto group, again leading to enolate formation. However, all our efforts to intercept the putative tin enolate have thus far been unsuccessful.[12]

In summary, this new desulfonylation protocol shows considerable promise, and should greatly expand the synthetic utility of β-keto sulfones. We are currently continuing our work in this area to delineate fully the scope of the reaction.

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