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1-Benzyloxy-3-(*p*-tolylsulfonyl)alkenes as Enal β-Anion Equivalents. Synthesis of 2,3-Disubstituted Furans

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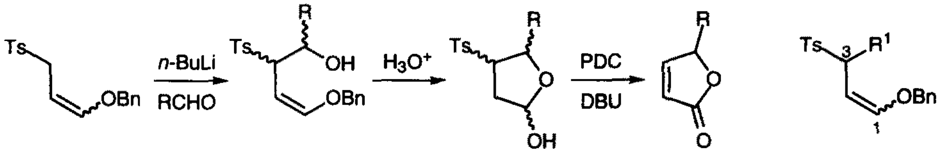
Abstract: An efficient three-step method is described for the synthesis of 2,3-disubstituted furans from (*p*-tolylsulfonyl)alkanes **6** and 2-benzyloxyethanal.

We recently described[1] an efficient procedure for the synthesis of 4-substituted butenolides **4** from 1-benzyloxy-3-(*p*-tolylsulfonyl)propene **1** and aldehydes. The method involves reaction with aldehydes of the lithio-anion of **1**, hydrolysis–cyclization of the adducts **2**, and oxidation of the product lactols **3** followed by base-mediated elimination of the elements of *p*-tolylsulfinic acid from the resulting butanolides (Scheme 1).

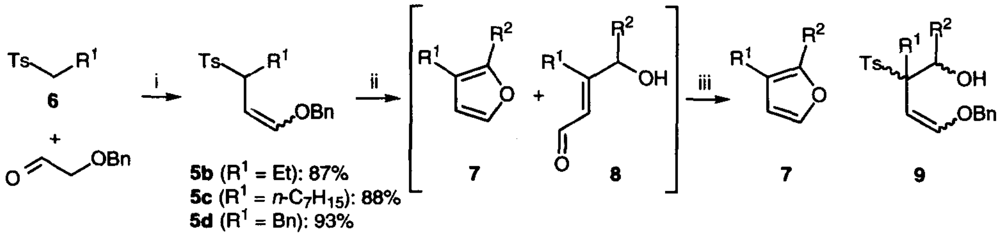


1 **2** **3** **4** **5**

Scheme 1

It occurred to us that the more highly substituted adducts resulting from reaction of the anions derived from 3-substituted analogues **5** with aldehydes would be substantially more protiolytically labile than **2** on account of the greater degree of substitution at C-3. Acid-catalyzed elimination of the elements of water and *p*-tolylsulfinic acid under anhydrous conditions would then give 2,3-disubstituted furans. Such furans are found in a variety of natural products including a wide range of pharmaceutically active compounds, and are useful intermediates in organic synthesis. Whilst methods may be found in the literature for the synthesis of these materials,[2] generally they have disadvantages such as the need for complex starting materials, harsh reaction conditions and low yields. This new methodology helps to overcome these problems.

Initially, sulfones **5** were prepared via alkylation of the parent compound **1**. Treatment of a cold (-78°C) THF solution of **1** with *n*-BuLi followed by addition of 3-bromo-1-propene gave **5a** in 96% yield.[3] Since **1** was derived ultimately from (*p*-tolylsulfonyl)methane,[1] we reasoned that **5** would be accessible from 1-(*p*-tolylsulfonyl)alkanes **6** using a similar sequence of transformations. We have found that **5b–d** *may be prepared in one pot* via treatment of **6**[4] with two equivalents of base followed by phosphorylation, Wadsworth-Emmons reaction of the resulting phosphorus-stabilized carbanions with 2-benzyloxyethanal, and in situ potassium *tert*-butoxide-mediated isomerization[1,5] of the vinylic sulfones so formed. Reaction of lithiated **5** with aldehydes followed by low-temperature stoichiometric proton quench presumably gave the adducts **9**; these were unstable to isolation and eliminated *p*-TolSO$_2$H on work-up to give a 1:1 mixture of the required 2,3-disubstituted furans **7** and *E*-γ-hydroxyenals **8**. Immediate[6] treatment of these crude mixtures with silica gel in dichloromethane followed by chromatography gave furans **7** in excellent overall yields (Table). The method does not work well for furans having either α-branched or unsaturated substituents at the 3-position; in these cases (R^1=*i*-Pr, CH=CH$_2$, Ph) the reactivity of the lithio-anion of **6** and of the intermediate phosphonate is attenuated



Reagents and conditions: (i) LDA (2.2 eq), THF, -78°C; $(EtO)_2P(O)Cl$, -78°C; $BnOCH_2CHO$, THF, -78°C → 20°C, 15 h; *t*-BuOK (2.2 eq), THF; AcOH (2.4 eq), THF; (ii) *n*-BuLi (1.1 eq), THF, -78°C; R^2CHO, THF, -78°C; AcOH (1.1 eq), THF, -78°C; aq $NaHCO_3$, -78°C → 20°C; (iii) SiO_2, CH_2Cl_2, 20°C.

Sulfone **5**	**5a**	**5a**	**5a**	**5a**	**5b**	**5b**	**5c**	**5c**	**5c**	**5d**	**5d**
R^1	C_3H_5	C_3H_5	C_3H_5	C_3H_5	Et	Et	n-C_7H_{15}	n-C_7H_{15}	n-C_7H_{15}	Bn	Bn
R^2	n-C_6H_{13}	$(CH_2)_5OP$[7]	Ph	c-C_6H_{11}	$(CH_2)_5OP$[7]	Ph	n-C_6H_{13}	Ph	c-C_6H_{11}	n-C_6H_{13}	c-C_6H_{11}
Yield of **7** (%)[8]	95	97	96	91	97	95	98	85	86	95	93

Table

to such an extent that the phosphorylation and Wadsworth-Emmons reactions are prohibitively sluggish. We are currently investigating related aldol-type methodology in order to overcome these problems.

Acknowledgements

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References and notes

1. Craig, D.; Etheridge, C. J.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 7445.
2. For examples, see: Pelletier, S. W.; Djarmati, Z; Lajsic, S. D.; Micovic, I .V.; Yang, D. T. C. *Tetrahedron* **1975**, *31*, 1659; Kotake, H.; Inomata, K.; Kinoshita, H.; Aoyama, S.; Sakamoto, Y. *Heterocycles* **1978**, *10*, 105; McCombie, S. W.; Shanhar, B. B.; Ganguly, A. K. *Tetrahedron Lett.* **1987**, *28*, 4123; Kim, S.; Kim, Y. G. *Synlett* **1991**, 869; Ji, J.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 764; Marshall, J. A.; Dubay, W. J. *J. Org. Chem.* **1993**, *58*, 3435 and references cited therein.
3. Iodomethane and 1-iodoheptane also participate effectively in these alkylation reactions: Smith, A. M. Ph.D. thesis, University of London, 1991.
4. 1-(*p*-Tolylsulfonyl)alkanes **6** were prepared by reaction (DMSO, 20°C) of anhydrous sodium *p*-tolylsulfinate with the appropriate 1-iodoalkane, or with the corresponding bromoalkane in the presence of a catalytic amount of lithium iodide.
5. Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 695.
6. Crude reaction mixtures containing **7** and **8** were unstable, rapidly decomposing to give unidentified, highly coloured and apparently polymeric compounds on standing in air.
7. P = *tert*-butyldiphenylsilyl.
8. All yields cited herein are for pure materials isolated by flash chromatography on silica gel. All new compounds gave ^1H nmr, ir and ms data, and elemental combustion analyses in accord with the proposed structures.

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