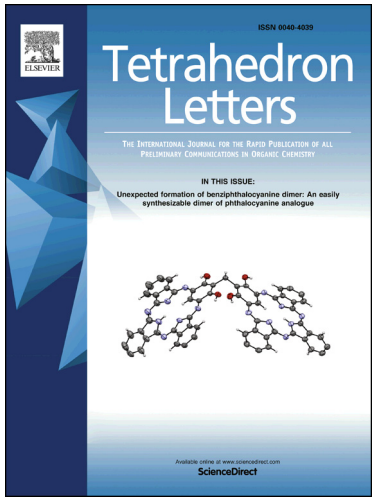



# A mixed anhydride approach to the preparation of sulfinate esters and allylic sulfones: Trimethylacetic *p*-toluenesulfinic anhydride

Eric Jacobsen, Mihir K. Chavda, Kokou M Zikpi, Stephanie L. Waggoner, Daniel J. Passini, Jesse A. Wolfe, Robert Larson, Chelsea Beckley, Christopher G. Hamaker, Shawn R. Hitchcock

PII: S0040-4039(17)30812-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.06.074
Reference: TETL 49066

To appear in: *Tetrahedron Letters*

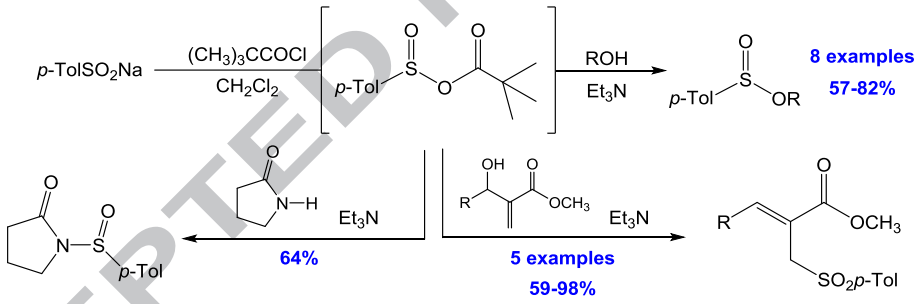
Received Date: 26 May 2017
Revised Date: 11 June 2017
Accepted Date: 23 June 2017

Please cite this article as: Jacobsen, E., Chavda, M.K., Zikpi, K.M., Waggoner, S.L., Passini, D.J., Wolfe, J.A., Larson, R., Beckley, C., Hamaker, C.G., Hitchcock, S.R., A mixed anhydride approach to the preparation of sulfinate esters and allylic sulfones: Trimethylacetic *p*-toluenesulfinic anhydride, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.06.074

# A mixed anhydride approach to the preparation of sulfinate esters and allylic sulfones: Trimethylacetic *p*-toluenesulfinic anhydride

Eric Jacobsen, Mihir K. Chavda, Kokou M Zikpi, Stephanie L. Waggoner, Daniel J. Passini, Jesse A. Wolfe, Robert Larson, Chelsea Beckley, Christopher G. Hamaker, and Shawn R. Hitchcock*

*Department of Chemistry, Illinois State University, Normal, IL 61790-4160*



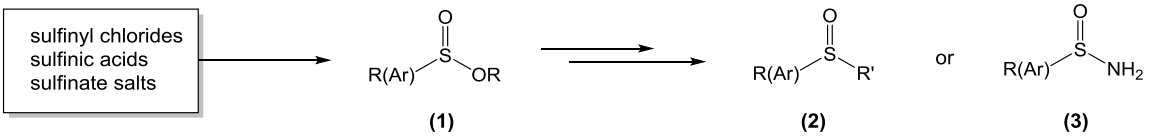

*Abstract:* A reagent combination of toluenesulfinic acid and trimethylacetyl chloride affords a putative trimethylacetic *p*-toluenesulfinic anhydride. This reagent has been used to prepare a series of sulfinate esters from primary and secondary alcohols. In addition, the reagent was used to convert Baylis-Hillman substrates into allylic sulfones. Attempts to use the reagent to convert amines to sulfinamides were unsuccessful. In contrast, the use of 2-pyrrolidinone afforded *N*-*p*-

toluenesulfinyl pyrrolidinone in 64% yield. The use of a chiral 4-benzyl-1,3-oxazolidinone or 4-benzyl-1,3-oxazolidine-2-thione led to the isolation of *S*-*p*-tolyl *p*-toluenethiosulfonate.

*Key words:* Trimethylacetic sulfinic anhydride, sulfinate ester, Baylis-Hillman, allylic sulfones, sulfinamide

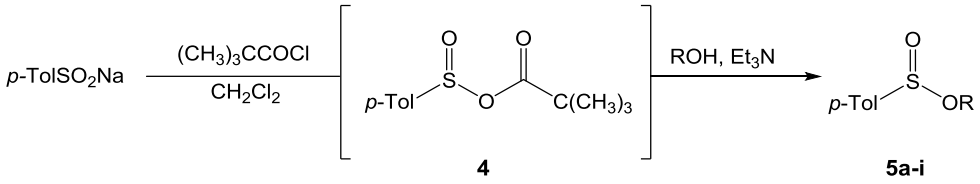
## Introduction

Sulfinate esters **(1)** are versatile synthetic intermediates that have been used in the preparation of chiral sulfoxides[1-3] and sulfinamides (Scheme 1).[4-6] These compounds have also been recently employed as highly selective probes for thiol bioimaging.[7] The synthesis of sulfinate esters has been achieved through a variety of methods including esterification of aryl- and alkylsulfinates in presence of sulfuric acid,[8] treatment of sulfinyl chlorides with alcohols,[9] or DCC coupling of sulfinic acids with alcohols[10a-c], and other methods.[10d,e] A less common method for the preparation of sulfinate esters that has not been explored is that of the reaction of mixed anhydrides of sulfinic acid reacting with alcohols. Kobayashi and coworkers[11] explored the synthesis of mixed anhydrides containing a *p*-toluenesulfinyl moiety, but did not fully explore the possibility of using these compounds as tools for the preparation of sulfinate esters.



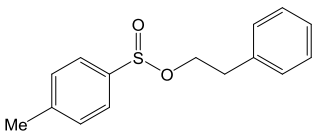
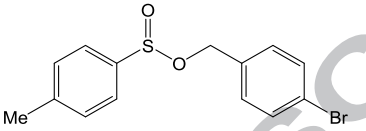
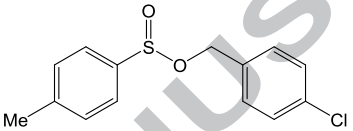
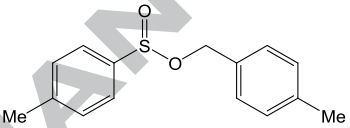
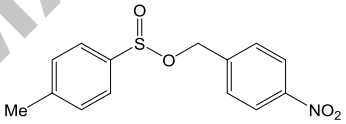
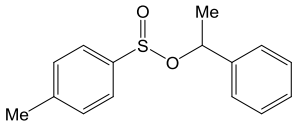
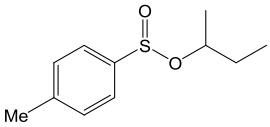
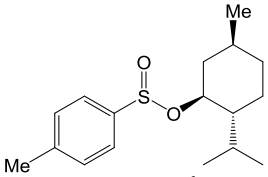

**Scheme 1.** Sulfinate ester synthesis and utility.

In the context of employing an anhydride based methodology, we became interested in determining if such a reagent could be prepared and successfully used in the preparation of sulfinate esters. We opted to pursue the use of the synthesis and application of a mixed anhydride reagent in which the *p*-toluenesulfinyl group would be the favored group for nucleophilic attack. This inspired the use of trimethylacetyl (pivaloyl) group as based on its success in amide bond formation.[12] Thus, the proposed trimethylacetic *p*-toluenesulfinic anhydride reagent was prepared by the addition of trimethylacetyl chloride to a methylene chloride solution of anhydrous sodium *p*-toluenesulfinate (Scheme 2). The solution was initially heterogeneous with the suspended sulfinate salt, but became an opaque, homogeneous solution within an hour. This solution was stirred for a total of 5 hours, and an alcohol substrate was added in addition with triethylamine (scavenger base). The reaction was then stirred for 12-15 hrs and the sulfinate ester product was isolated in 57 to 82% yield (Table 1). The alcohol substrates included primary and secondary alcohols, including L-menthol. In the case of the sterically hindered L-menthol, the compound *S*-*p*-tolyl *p*-toluenethiosulfonate **(6)** also formed as a byproduct (~4%) (Scheme 3). The identity of **6** was confirmed by spectroscopy ($^{1}$H, $^{13}$C NMR, IR) and X-ray crystallography (Figure 1). It is proposed that this material originated from a disproportionation of the anhydride **4** when there is no suitable nucleophile present. Kobayashi and coworkers[11] proposed a pathway for this disproportionation that involves the formation of a variety of species in solution (Scheme 4).



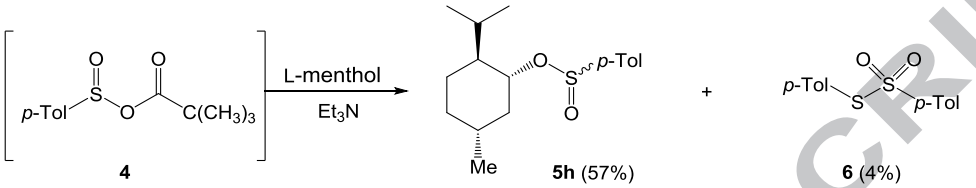
**Scheme 2.** Synthesis and application of the Trimethylacetic *p*-toluenesulfinic anhydride.

**Table 1. Isolated yields for the synthesis of the sulfinate esters.**

| entry | alcohol substrate | | product | yield[a] |
|---|---|---|---|---|
| 1 | $C_6H_5CH_2CH_2OH$ | **5a** |  | 71% |
| 2 | $BrC_6H_4CH_2OH$ | **5b** |  | 73% |
| 3 | $ClC_6H_4CH_2OH$ | **5c** |  | 79% |
| 4 | $MeC_6H_4CH_2OH$ | **5d** |  | 73% |
| 5 | $NO_2C_6H_4CH_2OH$ | **5e** |  | 63% |
| 6 | *rac*-$C_6H_5(CH_3)CHOH$ | **5f** |  | 82% |
| 7 | *sec*-butyl alcohol | **5g** |  | 65% |
| 8 | L-menthol | **5h** |  | 57%[b] |

[a]Isolated chemical yields were determined after flash chromatography. [b]The crude product was obtained as a 66:34 ratio of diastereomers. The purified product was obtained as a 74:26 mixture of diastereomers.

The thiosulfonate **6** has been proposed to originate from the disproportionation that forms *p*-toluenesulfinic anhydride **9** which then undergoes a rearrangement to a labile intermediate thioxosulfonate **9'** that ultimately forms the observed thiosulfonate **6**.




**4** **5h** (57%) **6** (4%)

**Scheme 3.** *S*-*p*-tolyl *p*-toluenethiosulfonate **(6)**

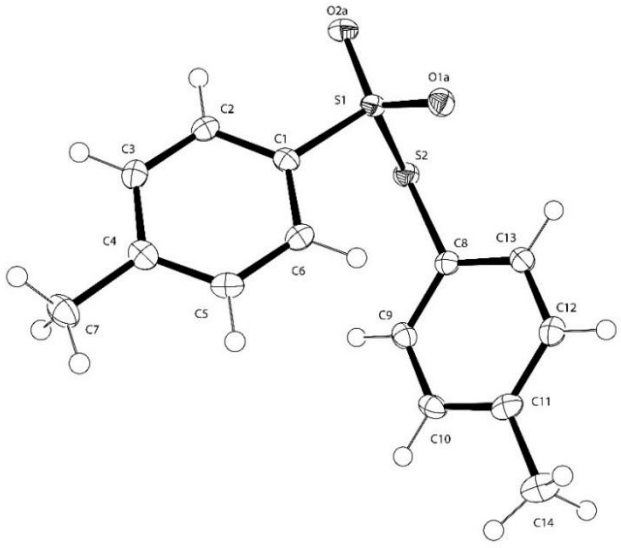
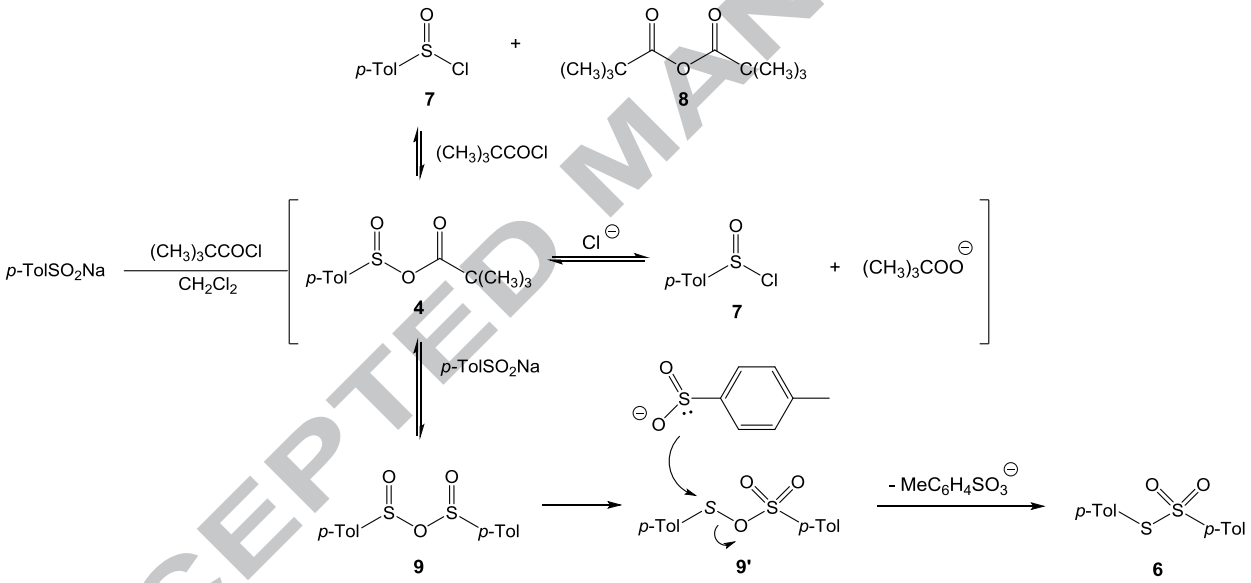



**Figure 1.** *S*-*p*-Toluenesulfinyl *p*-toluenesulfonate formation.

Based on the Kobayashi disproportionation, the sulfinylating agent could be anhydride **4** or the sulfinyl chloride **7**, having been formed *in situ* via the putative anhydride. Regardless of the identity of the agent, there was an interest in applying this reagent combination to the synthesis of allylic sulfones derived from allylic alcohols sourced from the Baylis-Hillman (BH) reaction. In 2009, Tian and coworkers developed an expeditious route to allylic sulfones from Baylis-

Hillman adducts by direct reaction of phenylsulfinyl chloride (PhSOCl) with MBH derived allylic alcohols.[13] In addition to this work, Tian and coworkers also developed a methodology in which MBH derived sulfonamides could be converted into allylic sulfones.[14] More recently, in 2010 and 2011, Yadav and coworkers[15a,b] developed a method for the preparation of these compounds by the use of *p*-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of the ionic liquid 1-*n*-hexyl-3-methyl-imidazolium bisulfuate. Finally, Reddy and coworkers developed a method for the preparation of MBH allylic sulfones by using *p*-toluenesulfonyl cyanide.[16]

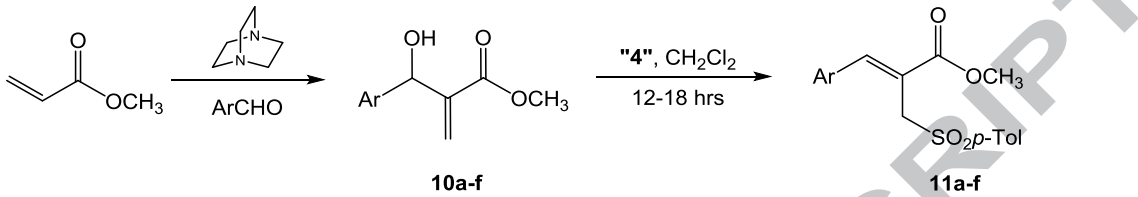



**Scheme 4.** The disproportionation proposed by Kobayashi and coworkers.

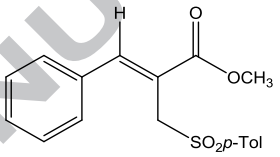
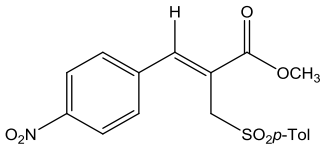
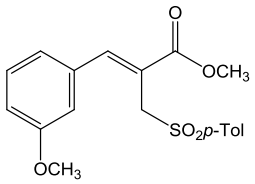
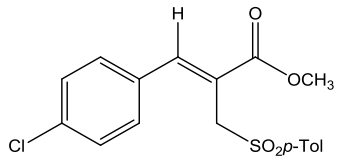
To pursue the alternate methodology of the trimethylacetic *p*-toluenesulfinic anhydride, Baylis-Hillman adducts **10a-e** were prepared using the method of Aggarwal and coworkers (Table 2).[17] These adducts were then reacted with **4** and stirred for 12-15 hrs. This process yielded the targeted allylic sulfones **11a-e** in fair to good yield (59-98%). In all cases, the

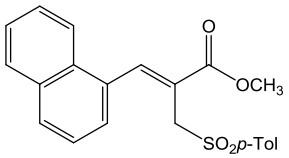
products were primarily obtained as the (*Z*)-diastereomer (*Z*:*E*, ~ 95:5) as determined by $^1$H NMR spectroscopy.

**Table 2.** Preparation of allylic sulfones via the trimethylacetic *p*-toluenesulfinic anhydride.




**10a-f** **11a-f**

| entry | Aldehyde | adduct | yield (%)[a] | Allylic sulfone | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $C_6H_5CHO$ | **10a** | 70 | **11a**  | 74 |
| 2 | *p*-$NO_2C_6H_4CHO$ | **10b** | 62 | **11b**  | 65 |
| 3 | *m*-$CH_3OC_6H_4CHO$ | **10c** | 80 | **11c**  | 88 |
| 4 | *p*-Cl-$C_6H_4CHO$ | **10d** | 34 | **11d**  | 59 |

| | | | | | |
|---|---|---|---|---|---|
| 5 | 1-$C_8H_7CHO$ | **10e** | 31 |  **11e** | 98 |

[a]Isolated chemical yield after purification.

The stereochemistry of the product was confirmed by X-ray crystallography of allylic sulfone **11e** (Figure 2). Mechanistically, it is proposed that the BH adduct undergoes formation of the *p*-toluenesulfinate ester which then rearranges to the sulfone. This argument is proposed based on the work of Tian and coworkers[13] wherein the use of phenylsulfinyl chloride was employed to initially create the sulfinate ester as a transient intermediate in the formation of the sulfone target.

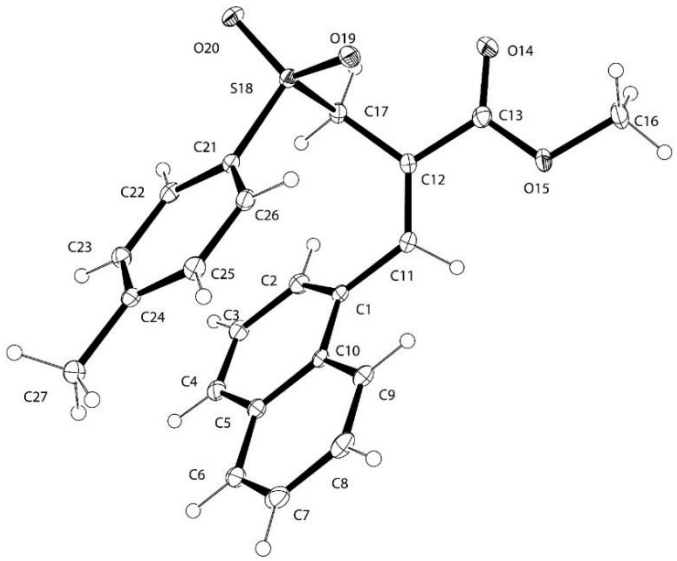
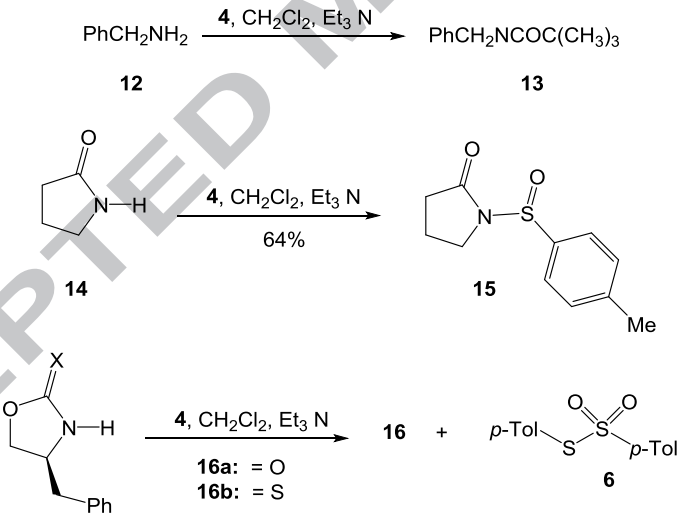



**Figure 2.** X-ray crystal structure for **11e**.

We were gratified to learn that the synthesis of the allylic sulfones was viable. This inspired further study with the trimethylacetic *p*-toluenesulfinic anhydride in reacting with amines. Attempts to employ benzylamine **(12)** in the reaction of the anhydride **4** failed to produce the

expected sulfinamide, but afforded the pivalamide as part of a mixture of products (Scheme 5). This was an interesting observation in connection with the Kobayashi disproportionation (Scheme 3). If a *p*-toluenesulfinyl chloride entity was present in significant amount, the facile formation of the sulfinamide would have been predicted. Reaction of 2-pyrrolidinone with anhydride **4** was successfual and afforded the product in 64% yield. It is proposed that the reduced nucleophilicity of the amide as compared to the benzylamine contributed to the success of the reaction. The success of this reaction prompted the use of oxazolidinone **16a** and oxazolidine-2-thione **16b** in this process. The reaction generated the thiosulfonate **6** and the oxazolidinone and oxazolidine-2-thione unchanged. The failure of the coupling reaction was attributed to the steric hindrance associated with the appendant C4-benzyl substituent structure.




**Scheme 5.** Reaction of anhydride **4** with nitrogen based nucleophiles.

A new reagent mixture based on the reaction of trimethylacetyl chloride and sodium *p*-toluenesulfinate has been investigated. The utility of the method described in this work has been

demonstrated in the synthesis of a series of sulfinate esters derived from primary and secondary alcohols. In addition, the reagent has been used to synthesize allylic sulfones from Baylis-Hillman adducts. Finally, the reagent does not readily react with amines, but does with 2-pyrrolidinone.

---

**Acknowledgements**

The authors wish to thank Tejas Idate for his technical assistance. The authors also thank the Department of Chemistry of Illinois State University for support of this research.

**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at…

**References**

1. Lenstra, D. C.; Vedovato, V.; Ferrer Flegeau, E.; Maydom, J.; Willis, M. C. *Org. Lett.* **2016**, *18*, 2086-2089.
2. (a) Chelouan, A.; Recio, R.; Alcudia, A.; Khiar, N.; Fernandez, I. *Eur. J. Org. Chem.* **2014**, 6935-6944. (b) Khiar, N.; Araujo, C. S.; Alcudia, F.; Fernandez, I. *J. Org. Chem.* **2002**, 67, 345-356. (c) Khiar, N.; Alcudia, F.; Espatero, J.-L.; Rodriguez, L.; Fernandez, I. *J. Am. Chem. Soc.* **2000**, *122*, 7598-7599.
3. Ridley, D. D.; Smal, M. A. J. Chem. Soc., *Chem. Comm.* **1981**, 505-506.
4. Robak, M. T.; Herbarge, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-740.

5. Aggarwal, V. K.; Barbero, N.; McGarrigle, E. M.; Mickle, G.; Navas, R.; Suarez, J. R.; Unthank M. G.; Yar, M. *Tetrahedron Lett.* **2009**, *50*, 3482-3484.

6. (a) Hans, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Su, X; Wilkinson, H. S.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Tetrahedron* **2005**, *61*, 6386-6408. (b) Hans, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 7880-7881. (c) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977-5985.

7. Malwal, S. R.; Labade, A.; Andhalkar, A. S.; Sengupta, K.; Chakrapani, H. *Chem. Comm.* **2014**, *50*, 11533-11535.

8. Tranquilino, A.; Andrade, S. R. C. P.; Da Silva, A. P. M.; Menezes, P. H.; Oliveira, R. A. *Tetrahedron Lett.* **2017**, *58*, 1265-1268.

9. (a) Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646-2650. (b) Evans, J. W.; Fierman M. B.; Miller, S.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134-8135. (c) Peltier, H. M.; Evans, J. W.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 1733-1736. (d) Whitesell, J. K.; Wong, M. S. J. Org. Chem. **1991**, *56*, 4552-4554. (e) Klunder, J.; Sharpless, K. B. *J. Org. Chem.* **1987**, *30*, 91-96. (f) Furukawa, M.; Okawara, T.; Noguchi, Y.; Nishikawa, M. *Synthesis* **1978**, *6*, 441-442. (g) Douglass, I. B. *J. Org. Chem.* **1965**, *30*, 633-635.

10. (a) Hajipour, A. R.; Falahati, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2006**, *47*, 2717-2719. (b) Furukawa, M.; Ohkawara, T.; Noguchi, Y.; Nishikawa, M.; Tomimatsu, M. *Chem. Pharm. Bull.* **1980**, *28*, 134-141. (c) Miyaji, Y.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jap.* **1971**, *44*, 862-863. (d) Li, H.-J.; Wang, R.; Gao, J.; Wang, Y.-Y.; Luo, D.-H.; Wu, Y.-C. *Adv. Synth. Catal.* **2015**, 1393-1397. (e) Harpp, D. N.; Back, T. G. *J. Org. Chem.* **1973**, *38*, 4328-4334.

11. (a) Kobayashi, M.; Terao, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1292-1296. (b) Kobayashi, M.; *Bull. Chem. Soc. Jpn.* **1966**, *39*, 967-970. (c) Kobayashi, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 961-967.

12. (a) Gill, M. A.; Manthorpe, J. M. *Synth. Comm.* **2013**, *43*, 1460-1468. (b) Joullie, M. M.; Lassen, K. M. *ARKIVOC* **2010**, 189-250. (c) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447-2467.

13. Li, H.-H.; Dong, D.-J.; Jin, Y.-H.; Tian, S.-K. *J. Org. Chem.* **2009**, *74*, 9501-9504.

14. Liu, C.-R.; Li, M.-B.; Cheng, D.-J.; Yang, C.-F.; Tian, S.-K. *Org. Lett.* **2009**, *11*, 2543-2545.

15. (a) Yadav, J. S.; Subba Reddy, B. V.; Singh, A. P.; Majumder, N. *Tetrahedron Lett.* **2010**, *51*, 2291-2294. (b) Garima; Srivastava, V. P.; Yadav, L. D. S. *Tetrahedron Lett.* **2011**, *52*, 4622-4626.

16. Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem. Int. Ed.* **2008**, *48*, 172-174.

17. Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692-700.

# Highlights

## "A mixed anhydride approach to the preparation of sulfinate esters and allylic sulfones: Trimethylacetic *p*-Toluenesulfinic anhydride"

Eric Jacobsen, Mihir K. Chavda, Kokou M Zikpi, Stephanie L. Waggoner, Daniel J. Passini, Jesse A. Wolfe, Robert Larson, Chelsea Beckley, Christopher G. Hamaker, and Shawn R. Hitchcock*

---

- A new putative reagent tirmethylacetic *p*-toluenesulfinic anhydride has been prepared
- The reagent has been used to synthesize sulfinate esters
- Sulfones were prepared from Baylis-Hillman derived alcohols
- The reagent has been used to prepare a *N*-*p*-toluenesulfinylamide.