α-Tosyloxyketones: Convenient [4+3] Cycloaddition Precursors

Scott T. Handy,* Maurice Okello

Department of Chemistry, State University of New York at Binghamton, Vestal Parkway East, Binghamton, NY 13902-6000
Fax +1(607)7774478; E-mail: shandy@binghamton.edu

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Abstract: A concise, simple two-step method for the preparation of [4+3] cycloadducts from ketones using Koser's reagent and trifluoroethanol–triethylamine has been developed. This sequence affords yields similar to those obtained using the α-halo and α-mesyloxyketones, but with the advantages of simplicity in preparation and stability of the intermediates.

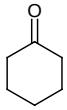
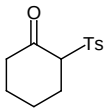
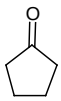
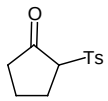
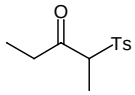
Key words: cycloaddition, ketones, cations, sonication, sulfonyl

The [4+3] cycloaddition of dienes with allylic cations has a long and versatile synthetic history.[1] Of the numerous sources of the cation for this reaction (allylic halides, allylic alcohols, haloenamines, haloketones), those which undergo base-induced solvolysis are the most heavily employed. In particular, α-haloketones have been used to great advantage in a variety of synthetic efforts. Nevertheless, they suffer from two significant limitations: difficulty in preparation and limited stability. Thus, direct chlorination or bromination of ketones typically results in significant amounts of over halogenation. The usual solution to this situation is halogenation of a preformed enolate or enolate equivalent (silyl enol ether), although even then over-halogenation can still occur.[2]

A less common alternative that avoids the complications encountered with halogenation is to employ α-mesyloxyketones.[3] These substrates are prepared from the corresponding α-hydroxy ketone. As such, over-mesylation is not an issue. But, since the starting hydroxyketones are rarely commercially available, this method of oxyallyl cation generation typically requires a minimum of two steps. Even after preparing the α-mesyloxyketone, their stability is sufficiently limited to preclude purification by either distillation or chromatography. As a result, they generally are prepared and then used directly in the [4+3] reaction. This can lead to diminished yields and increased side-products depending upon the efficiency of the mesylation step.

A noteworthy absence from this list of potential oxyallyl-cation precursors is α-tosyloxyketones.[4] One would expect that they should maintain similar reactivity to the mesylates, but with improved stability. More importantly, they can be prepared directly from the parent ketones, as seen in Table 1. Using a method reported by Tuncay, treatment of ketones with Koser's reagent in acetonitrile with sonication affords the desired α-tosyloxy ketones in generally good yields.[5] The resulting products can be readily isolated either by chromatography or, more conveniently, by trituration with hexanes to remove the iodobenzene by-product.[6,7] In our hands, these α-tosyloxyketones were stable for several days at room temperature and for several weeks in the refrigerator. As such, they offer benefits over existing oxyallyl cation precursors.

Table 1 Preparation of α-Tosyloxyketones

Entry	Ketone	Product	Yield[a]
1			89%
2			82%
3			94%

[a] Yields of product isolated by trituration.

Despite the ease of preparation, the question remained as to how they would compare to other [4+3] precursors. In the event, α-tosyloxyketone **1** (X = OTs) was treated with furan under Föhlisch conditions to afford the anticipated [4+3] cycloadduct in 60% yield after 4 hours.[8] A comparison of this result with that reported for other oxyallyl cation precursors is seen in Table 2. From this data, it can be seen that the tosyloxyketone not only works in the [4+3] reaction, but does so with similar rates and yields as the chloro and bromo precursors.

Based on this encouraging result, the scope and limitations of this reaction were explored. As seen in Table 3, tosyloxyketones derived from cyclohexanone, cyclopentanone, and 3-pentanone all afforded good yields of the [4+3] cycloadducts with furan under the trifluoroethanol–triethylamine conditions.[10,11] An attempt using a solution of lithium perchlorate in diethyl ether as the solvent (entry 2) showed no particular advantage, although this solvent has been used to advantage in previous reports.[12] All of these reactions were performed with tosyloxyketones that had been purified by chromatography. Similar results

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1437-2096,E;2002,0,03,0489,0491,ftx,en;S07901ST.pdf.

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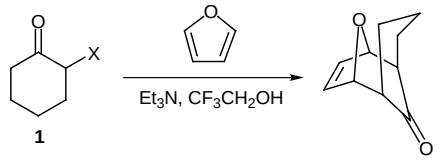
Table 2 [4+3] Reactions with Cyclohexanones



1

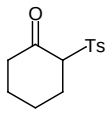
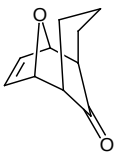
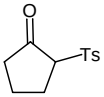
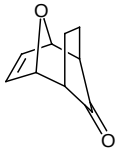
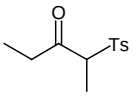
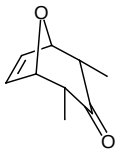
Entry	X	Time	Yield[a]
1	Ts	4 h	60%
2[b]	Br	3 d	84%
3[c]	Cl	3 d	70%

[a] Isolated yield.
[b] Data from ref.[8]
[c] Data from ref.[9]

were obtained with tosyloxyketones that were isolated by simple trituration of the crude product from the reaction with Koser's salt. As a result, both steps could be carried out with only a single chromatographic purification after the [4+3] reaction.

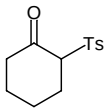
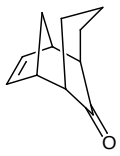
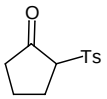
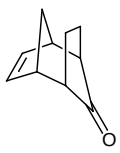
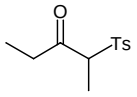
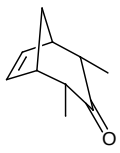
Attempts using cyclopentadiene as the diene also afforded good results (Table 4).[11] These reactions were more rapid, being complete in under 60 minutes at 0 °C. Unfortunately, attempts to extend these reaction conditions to less reactive dienes such as cyclohexadiene or *trans*-piperylene

Table 3 [4+3] Reactions with Furan[a]

Entry	Ketone	Product	Yield[b]
1			60% (33%)
2			(35)[c]
3			70% (30%)
4			57% (47%)[d]

[a] Reactions performed 0.5 M in a 1:1 v/v mixture of furan and trifluoroethanol with 1.8 equiv of triethylamine.
[b] Isolated Yield. Yields in parentheses are overall yields for the 2 steps with isolation of the α-tosyloxyketone by trituration with hexanes.
[c] Reaction performed 0.5 M in a 1:1 v/v mixture of furan and 1 M $LiClO_4$–Et_2O with 1.8 equiv of triethylamine.
[d] 21:1 mixture of the α,α-dimethyl and the β,β-dimethyl isomers by ^{1}H NMR.

Table 4 [4+3] Reactions with Cyclopentadiene[a]

Entry	Ketone	Product	Yield[b]
1			51%[c]
2			59%[d]
3			70%[e]

[a] Reactions performed 0.5 M in a 1:1 v/v mixture of furan and trifluoroethanol with 1.8 equiv of triethylamine.
[b] Isolated yield over the two steps.
[c] 12:1 ratio of endo:exo isomers by ^{1}H NMR.
[d] 5:1 ratio of endo:exo isomers by ^{1}H NMR.
[e] 2.5:1 ratio of α,α-dimethyl:β,β-dimethyl isomers by ^{1}H NMR.

afforded very modest results which is in keeping with general observations for the [4+3] cycloaddition of α-halo ketones.[1] As such, the tosyloxy systems offer the advantages of enhanced stability and simplicity of preparation, but do not appear to afford any reactivity advantages.

In conclusion, we have developed a new method for the preparation of [4+3] cycloadducts in only two steps starting from simple, readily available ketones. The overall yields have not been highly optimized, but are still competitive with other methods currently available. In particular, taking advantage of the ease with which the sonication conditions can be employed, this modification of standard oxyallyl cation precursors should find considerable utility in organic synthesis.

Acknowledgement

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References

(1) For general reviews of [4+3] reactions, see: (a) Rigby, J. H.; Pigge, F. C. *Organic Reactions*, Vol. 51; John Wiley & Sons, Inc.: New York, **1997**, 351–478. (b) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217. (c) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.
(2) For a discussion of various methods for the halogenation of ketones, see: House, H. O. *Modern Synthetic Reactions*, 2nd Ed.; W. J. Benjamin Inc.: Menlo Park, CA, **1972**, 459–478.
(3) This alternative has been most extensively explored by Föhlisch and co-workers. For examples, see: Föhlisch, B.;

Herrscher, I. *Chem Ber.* **1986**, *119*, 524; and further papers from this group.

(4) One similar variation that has been reported is the use of β-keto trifluoromethanesulfones. This option has been used in a number of intramolecular cycloadditions reported by the Harmata and co-workers. For examples, see: Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

(5) (a) Tuncay, A.; Dustman, J. A.; Fisher, G.; Tuncay, C. I.; Suslick, K. S. *Tetrahedron Lett.* **1992**, *33*, 7647. (b) For a review of the use and preparation of α-tosyloxy and mesyloxy ketones, see: Moriarty, R. M.; Prakash, O. *Organic Reactions*, Vol. 54; John Wiley & Sons, Inc.: New York, **1999**, 273–418.

(6) We have noted that chromatographic purification of the tosyloxyketones is generally unnecessary. Trituration with hexanes is sufficient to remove virtually all of the iodobenzene by-product and afford the products as white, crystalline solids with melting points identical to those reported in the literature. Further, in our studies using a standard sonication cleaning bath, the yield of the reaction is very dependent upon the location in the bath (and thus, the strength of the sonication). Optimization in terms of the location of the flask may be necessary to reproduce the yields reported here and in ref.[5]

(7) **Representative Procedure**: To 0.650 g (1.67 mmol) of [hydroxy(tosyloxy)iodo]benzene in a dry round-bottom flask under argon were added 2 mL of cyclohexanone and 15 mL of acetonitrile. The flask was placed in an ultrasound cleaning bath filled with warm (55 °C) water to a depth of 2 inches. The reaction mixture was sonicated for 15 minutes, during which time the suspension cleared to a yellowish-brown solution. After removal of the volatiles in vacuo, the residue was dissolved in methylene chloride (15 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 5 mL). The organic layer was dried with magnesium sulfate and concentrated in vacuo. The residue was then triturated with minimal hexane (2 mL) at ice-bath temperatures to afford 0.375 g (89%) of a pale yellow solid.

(8) For the first report of these now-standard conditions, see: Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 137.

(9) Jin, S.; Choi, J.-R.; Oh, J.; Lee, D.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 10914.

(10) **Representative Procedure**: To 0.1928 g (0.7194 mmol) of 2-tosyloxycyclohexanone in 0.72 mL of furan was added 0.72 mL of 2,2,-trifluoroethanol at 0 °C under argon. The mixture was stirred and 187 μL (1.35 mmol) of triethylamine was added slowly and the reaction was allowed to warm to room temperature. After 4 hours, TLC indicated complete consumption of starting material. The reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (5 × 5 mL). The combined organics were washed with saturated aqueous $NaHCO_3$, dried with magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by chromatography (elution with 1:4 ethyl acetate–hexanes) to afford 70.8 mg (60%) of the cycloadduct as a pale yellow solid.

(11) All compounds exhibited spectroscopic data consistent with that reported in the literature.

(12) For the first report using these conditions, see: Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976.