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Direct α-Oxytosylation of Carbonyl Compounds: One-Pot Synthesis of Heterocycles

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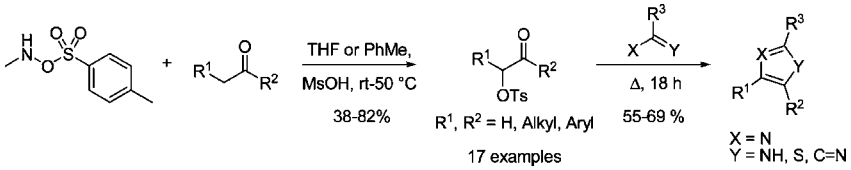
ABSTRACT



***N*-Methyl-*O*-tosylhydroxylamine is an effective reagent for the direct α-oxytosylation of carbonyl compounds. The reactions proceed smoothly at room temperature in the presence of both moisture and air and functional group tolerance in the substrate is good. With nonsymmetrical substrates regioselectivity for primary over secondary centers is observed and complete regiospecificity for primary over tertiary centers is obtained. Addition of a bis-heteronucleophile directly to the crude reaction mixture in a one-pot process leads to the corresponding heterocyclic product.**

Hydroxylamines have a rich and distinguished chemistry,[1] the inherent weakness of the N−O bond frequently being used to provide a thermodynamic driving force for their associated transformations.[2] This has allowed for established transformations such as the Lossen[3] and Beckmann[4] rearrangements, as well as the development of effective electrophilic aminating[5] and oxygenating[6] agents revealing their synthetic versatility. It has also been effectively exploited in a variety of [3,3]-sigmatropic rearrangement processes providing access to a broad range of densely functionalized materials.[7]

We have recently reported the *N*-alkyl-*O*-acyl reagents **1** to be effective for the one-pot α-oxyacylation of carbonyl compounds,[8] the key bond-forming process involving [3,3]-sigmatropic rearrangement of the enamine intermediate **4**, driven by cleavage of the weak N−O bond and formation of a stronger C−O bond (Figure 1). We were intrigued to discover if an analogous reagent could be developed for the transfer of an oxysulfonyl group, providing synthetically

(1) For recent advances in hydroxylamine chemistry see: Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967−993.

(2) The N−O bond strength in hydroxylamine has been calculated to be 63 kcal mol^{-1}: Wiberg, K. B. *J. Phys. Chem.* **1992**, *96*, 5800−5803.

(3) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed.* **1974**, *13*, 376−385.

(4) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420.

(5) For recent progress in the area see: (a) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219−224. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364−366. (c) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799−1801. (d) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680−5681.

(6) For examples see: Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919−934.

(7) For some typical examples see: (a) Reis, L. V.; Lobo, A. M.; Prabhakar, S.; Duarte, M. P. *Eur. J. Org. Chem.* **2003**, *1*, 190−208. (b) Clark, A. J.; Al-Faiyz, Y. S. S.; Patel, D.; Broadhurst, M. J. *Tetrahedron Lett.* **2001**, *42*, 2007−2009. (c) Clark, A. J.; Al-Faiyz, Y. S. S.; Broadhurst, M. J.; Patel, D.; Peacock, J. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1117−1127. (d) Lantos, I.; Zhang, W.-Y. *Tetrahedron Lett.* **1994**, *35*, 5977−5980. (e) Reis, L. V.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1994**, *35*, 2747−2750. (f) Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070−2076. (g) House, H. O.; Richey, F. A. *J. Org. Chem.* **1969**, *34*, 1430−1439.

(8) (a) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729−5732. (b) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Commun.* **2005**, 1478−1479. (c) Hall, A.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Porzig, R.; Taylor, P. H.; Yau, S. C.; Tomkinson, N. C. O. *Synlett* **2006**, 3435−3438. (d) Hall, A.; Huguet, E. P.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Yau, S. C.; Tomkinson, N. C. O. *Synlett* **2007**, 293−297.

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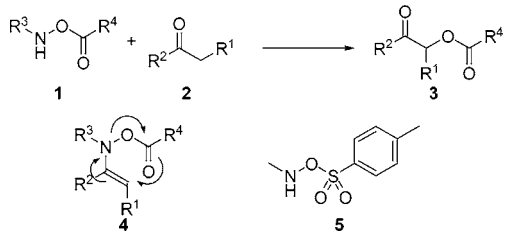


Figure 1. α-Functionalization of carbonyl compounds.

important α-oxytosyl carbonyl compounds (such as **11**).[9] Herein, we report on an effective method for the direct α-oxytosylation of a wide variety of carbonyl compounds using *N*-methyl-*O*-tosylhydroxylamine **5**, which complements and augments the Koser reagent,[10,11] and demonstrate its versatility in the one-pot preparation of a series of heterocycles.

The target oxysulfonylation reagent **5** has been prepared previously as a crystalline solid in three steps from *N*-methylhydroxylamine hydrochloride in 72% overall yield.[12] In our hands the reaction sequence worked well (66%) and could be performed without the need for chromatography on a large scale (see the Supporting Information for full details).

In contrast to our proposed transformation the related *N*-methyl-*O*-(4-nitrobenzene)sulfonylhydroxylamine **7** has been shown to have a different reactivity profile by Hoffman and co-workers.[13] Addition of **7** to cyclohexanone **6** gave the corresponding lactam **9** (73%) via the aminol intermediate

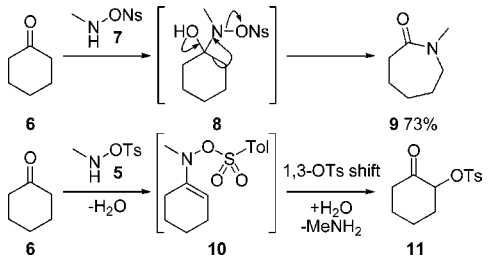


Figure 2. Reaction of cyclohexanone with **5** and **7**.

8 (Figure 2).[14] However, we were delighted to discover that reaction between **5** and cyclohexanone **6** revealed that an alternative reaction pathway was adopted, which gave the desired product **11** (Table 1).

Table 1. Reaction of **5** with Cyclohexanone[a]

entry	acid	solvent	% yield of **11**[b]
1	none	THF	12
2	HCl	THF	0
3	TFA	THF	43
4	MsOH	THF	72
5	BzOH	THF	17
6	MsOH	DMSO	0
7	MsOH	H_2O	0
8	MsOH	CH_2Cl_2	65
9	MsOH	EtOAc	63
10	MsOH	PhMe	57

[a] All reactions were performed at room temperature at 0.5 M concentration for 24 h. [b] Isolated yield.

In the absence of acid the reaction was sluggish proceeding in just 12% yield after 24 h (entry 1). Addition of a co-acid to the reaction medium greatly accelerated the process (entries 3−5) with methanesulfonic acid (entry 4) emerging as the most efficient candidate. Examination of a variety of solvents (entries 6−10) showed that apart from highly polar reaction media the transformation worked well in a broad spectrum of solvents any of which we found could be adopted.

Having established effective reaction conditions for the transformation we went on to examine the scope and limitations of the protocol (Table 2). Under the aqueous acidic reaction conditions hydrolytically unstable functionalities remain in tact (entries 1−3). Additionally, substrates that have been reported to be unreactive to Koser's reagent (cycloheptanone)[10] also give the α-oxytosylated product upon reaction with **5** in the presence of methanesulfonic acid (entry 5). In contrast to our observations with the α-oxybenzoylation reagents **1**,[8] the oxytosylation reagent **5** was also effective for the α-functionalization of primary centers which greatly adds to the general applicability of the reagent (entry 6). Examination of a series of nonsymmetrical substrates also revealed an important trend in reactivity (entries 9−12). Functionalization takes place exclusively at the primary position when distinguishing primary and tertiary centers (entry 9). Primary center functionalization is also favored when discriminating primary and secondary centers, where sterics appear to play an important role (entries 10−12). With the more hindered 4-methylpentan-2-one a 4.2:1 selectivity for the primary center was obtained (entry 10), for unbranched linear ketones this selectivity droped to 2.6:1 in favor of primary functionalization (entries 11 and 12). Comparison of these results to those observed with the Koser

(9) For examples of the synthetic versatility of this functionality see: (a) Nicolaou, K. C.; Montagnon, T.; Ulven, T.; Baran, P. S.; Zhong, Y.-L.; Sarabia, F. *J. Am. Chem. Soc.* **2002**, *124*, 5718−5728. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2000**, *122*, 10246−10248.

(10) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487−2489.

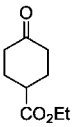
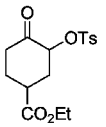
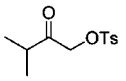
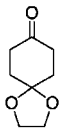
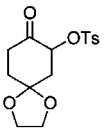
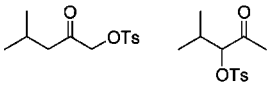
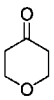
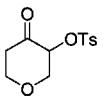
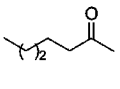
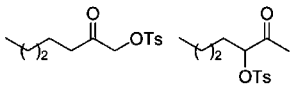
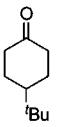
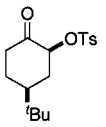
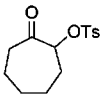
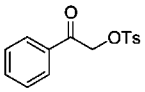
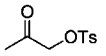
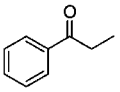
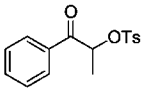
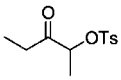
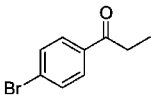
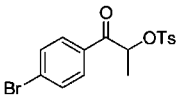
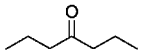
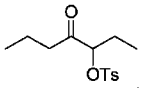
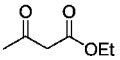
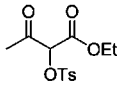
(11) For alternative preparations and reaction conditions involving this reagent see: (a) Yusubov, M. S.; Wirth, T. *Org. Lett.* **2005**, *7*, 519−521. (b) Nabana, T.; Togo, H. *J. Org. Chem.* **2002**, *67*, 4362−4365. (c) Abe, S.; Sakuratani, K.; Togo, H. *J. Org. Chem.* **2001**, *66*, 6174−6177. (d) Tuncay, A.; Dustman, J. A.; Fisher, G.; Tuncay, C. I. *Tetrahedron Lett.* **1992**, *33*, 7647−7650.

(12) Tamura, Y.; Ikeda, H.; Morita, I.; Tsubouchi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1982**, *30*, 1221−1224.

(13) For an excellent review on this work see: Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109−1135.

(14) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1989**, *30*, 4207−4210.

Table 2. Scope of Transformation

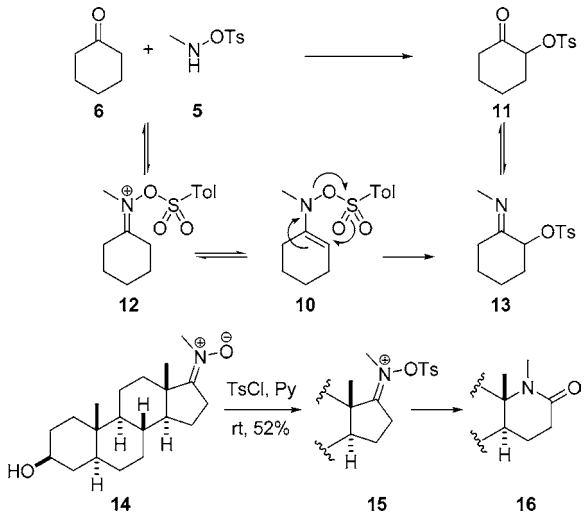
entry	reactant	product	% yield	entry	reactant	product	% yield
1[a]			70	9[c]			59
2[a]			62	10[c]		 4.2 : 1	82
3[a]			61	11[c]		 2.6 : 1	47
4[a]			38	12[c]		 2.6 : 1	60
5[a]			70	13[b]			52
6[b]			62	14[b]			48
7[b]			75	15[b]			46
8[b]			68	16[a]			73

[a] Reaction performed at room temperature in THF. [b] Reaction performed at 40 °C in a 1:1 mixture of THF/PhMe. [c] Reaction performed in THF at 40 °C.

reagent shows a distinct advantage where selectivities of 1:1.57 have been reported for the reaction of butanone.[10] Acetophenone, propiophenone, and β-ketoesters were also effective substrates for the transformation (entries 13−16).

Mechanistically we believe that these reactions are proceeding in a similar fashion to that described previously.[8] Condensation of the reagents provides the iminium ion **12**, which converts to the enamine **10**. Subsequent [1,3]-shift of the oxytosyl group[15] followed by hydrolysis of the resulting imine **13** leads to the observed reaction product **11**. Interestingly, a similar intermediate iminium ion has been invoked previously by Barton[16] and utilized by Jeffs[17] in a Beckmann-type rearrangement of nitrones. Thus, treatment of the nitrone **14** with tosylchloride in pyridine gave the *O*-sulfonylated intermediate **15**, which then underwent rearrangement, under the basic reaction conditions, to give the corresponding amide **16** (Scheme 1). This Beckmann-type rearrangement has also been reported in the preparation of β-lactams via stabilized carbinolamine intermediates.[18] Therefore, under acidic condi-

Scheme 1



(15) This type of group transfer has been proposed by Hoffman, in the reaction of sulfonyl peroxides with enamines: Hoffman, R. V.; Jankowski, B. C.; Carr, C. S.; Duesler, E. N. *J. Org. Chem.* **1986**, *51*, 130−135.

(16) (a) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764−1767. (b) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *Chem. Commun.* **1971**, 945−946.

(17) Jeffs, P. W.; Molina, G. *Chem. Commun*. **1973**, 3−4.

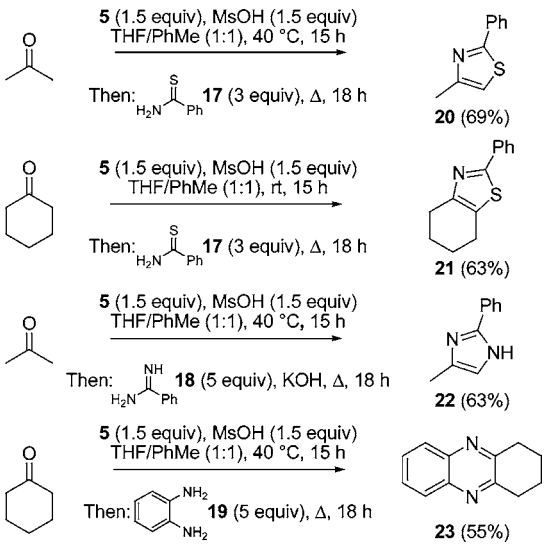
tions an alternative mechanistic pathway is available for iminium ion intermediates of the type **12**.

Finally, we went on to investigate whether the α-oxytosyl carbonyl compounds could be used directly in a one-pot synthesis of heterocycles. The importance of the α-oxytosyl functional group in synthesis was recently demonstrated by Nicolaou and co-workers, who showed the reaction of α-oxysulfonylketones (derived from the addition of sulfonic acids to alkenes) with a series of nitrogen-, sulfur-, oxygen-, and carbon-based nucleophiles allowed for the introduction of an array of functionality including a wide variety of biologically significant heterocycles.[9]

The byproducts from the reaction of **5** with a carbonyl compound are methylamine and methanesulfonic acid, which we did not consider would hinder the formation of heterocycles from the α-oxytosyl precursors. Therefore, we added benzothioamide **17** directly to the crude mixture from the reaction between acetone and **5** and heated the resulting solution at reflux for 18 h. Pleasingly, this led to the desired thiazole **20** in an excellent 69% overall yield (Scheme 2). In a similar manner, the reaction of acetone with **5** followed by benzamidine hydrochloride **18** gave the imidazole **22** (63%) and reaction of cyclohexanone with **5** followed by the addition of benzene-1,2-diamine **19** gave **23** (55%), suggesting the overall transformation should be of broad utility in the one-pot preparation of heterocyclic compounds from ketones.

In summary, we have described the reactivity of *N*-methyl-*O*-tosylhydroxylamine **5**, which provides a new platform for the direct α-oxytosylation of carbonyl compounds. The reaction is tolerant of a range of functional groups and is effective for a broad scope of substrate. The transformation is particularly easy to perform and is tolerant of the presence of both moisture and air, greatly adding to the practical utility of the work. The reagent complements the reactivity of Koser's reagent and is effective for the reaction of less-enolizable substrates such as cycloheptanone broadening the scope of substrates for this class of transformation. It can also be used in a one-pot method for the direct formation of heterocyclic products from carbonyl compounds by the addition of a bis-nucleophile to the reaction mixture and heating to promote a cyclo-condensation process. The reagent adds to a growing family of easy-to-prepare hydroxylamine reagents of broad synthetic utility.[8] We are currently developing an asymmetric variant of this reagent and will report on our findings shortly.

Scheme 2



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Supporting Information Available: Analytical data and experimental details for the preparation of reagent **5**, the α-functionalized products (Tables 1 and 2), and the heterocycles **20**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701774Y

(18) Wasserman, H. H.; Glazer, E. A.; Hearn, M. J. *Tetrahedron Lett.* **1973**, *14*, 4855−4858.