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A FACILE PROCEDURE FOR REGIOSELECTIVE 1,2-CARBONYL TRANSPOSITION. ONE-POT CONVERSION OF KETONE TOSYLHYDRAZONES TO ENOL THIOETHERS OF TRANSPOSED KETONES

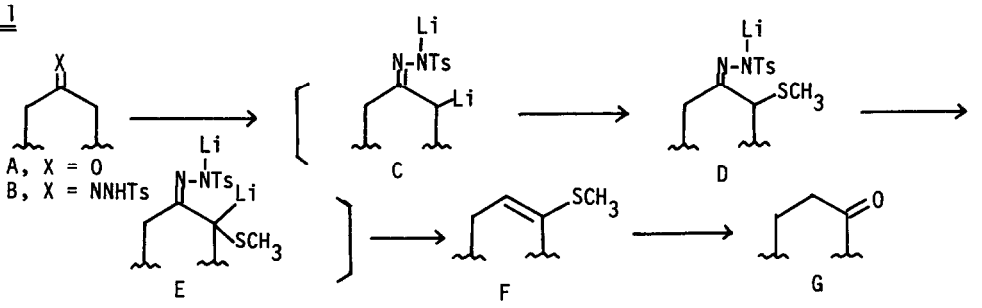
Takeshi Nakai* and Tetsuya Mimura

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

The importance of the carbonyl group in organic synthesis makes the ability to relocate it within a molecule an important and challenging problem.[1] Although a number of methods have become available for effecting 1,2-carbonyl transposition in recent years,[2] these methods suffer from inferior yields, multistep manipulation of intermediates, and lack of the regioselectivity.

We now wish to report a facile method for the regioselective 1,2-carbonyl transposition which is represented by the conversion A⟶G (Scheme 1). The complete transformation is therefore a three-step operation and the key step is the one-pot conversion of tosylhydrazone (B) to the enol thioethers (F) of transposed ketones[3] which relies upon the regioselective sulfenylation of dianion (C) followed by the Shapiro reaction[4-6] of the regenerated dianion (E). The transformation of enol thioethers to ketones has been well established.[7]

Scheme 1



Typically, a ketone tosylhydrazone was treated with 2.1 equiv of a hexane solution of n-butyllithium in tetramethylethylenediamine(TMEDA)-tetrahydrofuran(THF) (1 : 2) in the range of -50° to -30°C under argon producing a deep red solution of dianion C[8] which was then quenched with 1.0 equiv of dimethyl disulfide giving a pale yellow solution of D. After 10 min, addition of n-butyllithium to the solution again produced a deep red solution of dianion E. The solution was allowed to warm to room temperature and stirred for 3 to 24 hr with nitrogen evolution. The resulting solution was quenched with an aqueous ammonium chloride. Work-up in the usual

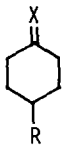
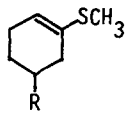
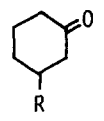
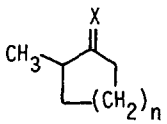
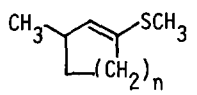
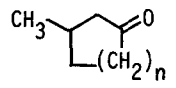
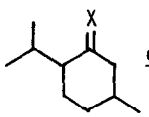
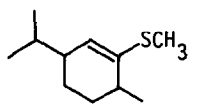
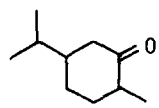
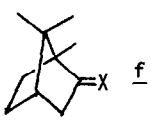
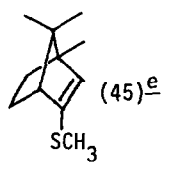
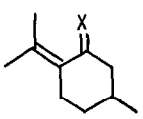
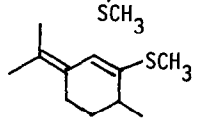
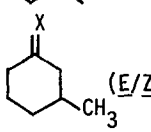
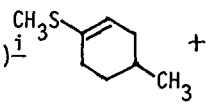
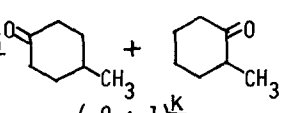
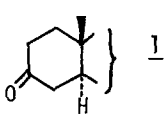
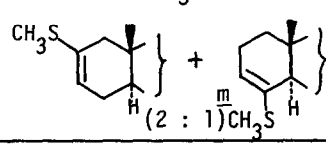
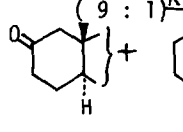
manner followed by TLC gave the enol thioether (F). Hydrolysis to ketone G was performed with 2 equiv of mercuric chloride in hot aqueous acetonitrile.[9] Table I summarizes the examples.

The versatility of our procedure is particularly well demonstrated by conversions of menthone to carvomenthone (entry 5) and of (+)-camphor to (-)-epicamphor (entry 6).[10] The most notable advantages of our approach compared with previous ones[2,6] are the shorter length of the sequence and the regioselectivity. While previous work attacked the carbonyl shift with respect to symmetrical and α-substituted ketones, methods for effecting a regioselective 1,2-shift of the carbonyl group adjacent to two methylenes of unsymmetrical ketones are lacking. In view of syn preference in the formation of the tosylhydrazone dianion in certain cases,[4,5] highly regioselective 1,2-shift might be embodied in our approach by using geometrically pure tosylhydrazones or by controlling the stereochemistry of hydrazone employed.

Thus the role of hydrazone stereochemistry upon the regioselectivity has been evaluated. As seen in entry 7, the use of E-pulegone tosylhydrazone[11] afforded exclusively the syn sulfenylation product, though the yield was low, without detectable contamination with the expected[5a] γ-sulfenylation product. More significantly, substantially regioselective shift in the α,α'-dimethylene systems were accomplished without any attempts to separate the stereoisomers of hydrazones (entries 8 and 9). For instance, an isomeric mixture (E/Z= 1.0 by ^{1}H and ^{13}C NMR[12,13]) of 3-methylcyclohexanone tosylhydrazone was subjected to the above transposition sequence carried out under the standard conditions, ultimately yielding 4- and 2-methylcyclohexanone in the ratio of 9 : 1 (entry 8). The unexpected result strongly indicates that, under these reaction conditions, the course of the sulfenylation of dianions involved is independent, at least partially, of the hydrazone stereochemistry. Although the observed regioselectivity is synthetically useful in limited cases, the exact origin has no straightforward explanation and still awaits detailed studies. Preliminary experiments suggest that the nature of the solvent system might play an important role in governing the course of the sulfenylation.[14] Details of such complex effects of solvents on the regioselectivity will be published elsewhere.

In summary, the one-pot conversion of ketone tosylhydrazones to the enol thioethers which combines the direct sulfenylation of the dianions with the Shapiro reaction provides a short, efficient method for the regioselective 1,2-carbonyl transposition. Further improvement and extensions of the method outlined here are in progress.

Table 1

Entry	Tosylhydrazone[a] (X=NNHTs)	Enol Thioether[b] (%yield)[c]	Ketone[b] (%yield)[c]
1	 R=CH_3	 R=CH_3 (92)	 R=CH_3 (82)
2	R=t-Bu	R=t-Bu (76)	R=t-Bu (73)
3	 n=1	 n=1 (55)	 n=1 (67)
4	n=2	n=2 (92)	n=2 (78)
5	 [d]	 (48)[e]	 (98)
6	 [f]	 (45)[e]	 (84)[g]
7	 [h]	 (26)[e]	
8	 (E/Z=1.0)[i]	 (90)[j]	 (88)[j]
			(9 : 1)[k]
9	 [l]	 (2 : 1)[m]	(30)[j]  (91)[j,n]

[a] Unless otherwise noted, tosylhydrazones were obtained as single isomers (by NMR) and their mp's were in accord with the reported ones. [b] All products exhibited spectral data in accord with the assigned structures or with the reported values. [c] Isolated yields, not optimized. [d] Mp 112.5-114.5°C. [e] For the lower yields, see ref 10. [f] Prepared from (+)-camphor, $[\alpha]_D^{20}$ +41.24° (c=1, benzene); mp 157.5-161.2°. [g] $[\alpha]_D^{20}$ -38.86° (c=1, benzene). [h] Pure E-isomer: mp 145.6-148.5°C (Lit.,[5a] mp 143-145°C). [i] See ref 13. [j] Yield of a mixture of the positional isomers. [k] Determined by VPC (DC 550, 125°C) comparison with an authentic mixture. [l] 5α-Cholestan-3-one tosylhydrazone, mp 162.0-163.5, after repeated recrystallizations (Lit., 168-170°C (E-isomer): J. E. Herz, E. Gonzalez, and B. Mandel, Aust. J. Chem., 23, 857 (1970)). [m] Determined by ^1H NMR. [n] Mp 118.5-119.3°C. Cf. Lit. mp for the 2-keto isomer, 127-128°C.

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References and Notes

1) For a general review on carbonyl transposition, see T. Nakai and T. Mimura, Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem., Jpn.), 35, 964 (1977).

2) For leading recent references of 1,2-carbonyl transpositions, see B. M. Trost, K. Hiroi, and S. Kurozumi, J. Am. Chem. Soc., 97, 438 (1975).

3) To our knowledge, this work represents the first 1,2-carbonyl transposition in which both the requisite oxidation and reduction steps are carried out in a one-pot manner.

4) Review: R. H. Shapiro, Org. React., 23, 405 (1976).

5) (a) W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, J. Am. Chem. Soc., 99, 3414 (1977);(b) A. R. Chamberlin, J. E. Stemke, and F. T. Bond, J. Org. Chem., 43, 147 (1978).

6) Very recently two examples of the utility of the Shapiro reaction for 1,2-carbonyl shifts have appeared: W. E. Fristad, T. R. Bailey, and L. A. Paquette, J. Org. Chem., 43, 1620 (1978); S. Kano, T. Yokomatsu, T. Ono, S. Hibino, and S. Shibuya, J. Chem. Soc., Chem. Commun., 414 (1978).

7) For a recent review, see B.-T. Gröbel and D. Seebach, Synthesis, 357 (1977).

8) Alternatively, the dianion was generated by treatment of a tosylhydrazone with sodium hydride (1.0 equiv) followed by n-butyllithium (1.0 equiv). Although the mixed dianion procedure is operationally more tedious, we found that the mixed dianion (E) decompsed to the vinyl anion substantially faster.

9) E. J. Corey and J. I. Shulman, J. Org. Chem., 35, 777 (1970).

10) In these cases, yields of the enol thioethers seem to be lowered by steric hindrance of the alkyl group(s) on the carbon β to the hydrazone moiety. The incompleteness of the sulfenylation was evidenced the observation that 2-menthene and 2-bornene were isolated in 35-40% as by-products.

11) Separated from an isomeric mixture following the procedure of Dauben and co-workers.[5a]

12) For unequivocal determination of E-Z stereochemistry for tosylhydrazones via ^{13}C NMR spectroscopy, see C. A. Bunnell and P. L. Fuchs, J. Org. Chem., 42, 2614 (1977).

13) Mp 113.8-118.7°C (Lit.,[5b] 108-110°C; E/Z ratio was not specified); E/Z = 1 : 1 based on the 90-MHz ^{1}H and 20-MHz ^{13}C NMR spectroscopy; ^{1}H NMR (benzene, TMS), δ 1.24(d) and 1.13 ppm(d); ^{13}C NMR ($CDCl_3$,TMS), δ 21.67 (3-Me for E), 24.49 (syn-C for E), 33.32 (anti-C for E), 21.44 (3-Me for Z), 26.31 (syn-C for Z), and 32.50 ppm (anti-C for Z).

14) Very recently such complex effects of solvents (and/or bases) on the course of deprotonation in the Shapiro olefin formations have been reported for each of E- and Z-pulegone tosylhydrazone[5a] and an isomeric mixture of 3-methylcyclohexanone tosylhydrazone.[5b]

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