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REGIOCHEMICAL CONTROL IN THE 1,2-CARBONYL TRANSPOSITION OF α,α'-DIMETHYLENE SYSTEMS THROUGH REGIOSELECTIVE SULFENYLATION OF TOSYLHYDRAZONE DIANIONS

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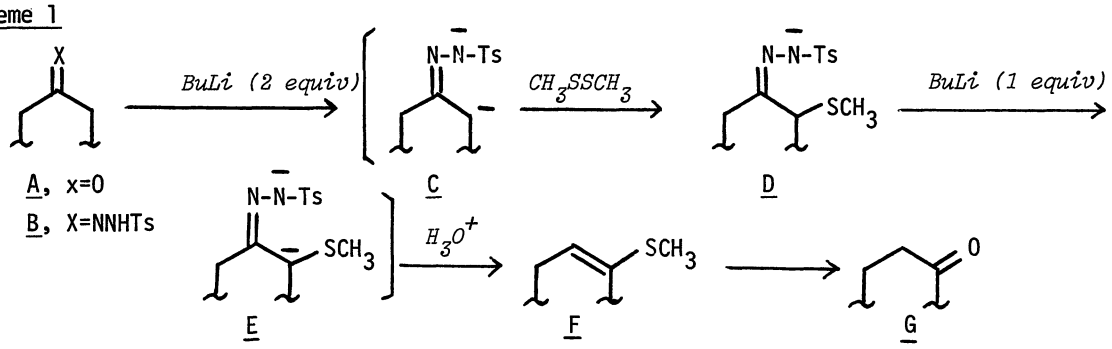
The regiochemical outcomes are described in the 1,2-carbonyl shift of α,α'-dimethylene systems which relies upon the regioselective sulfenylation of tosylhydrazone dianions leading to the enol thioethers of transposed ketones. Notably, a high regiospecificity was obtained with β-methyl- and β,β-dimethylcyclohexanone without any attempts to separate the stereoisomers of the hydrazones.

The ability to transpose the carbonyl group from one carbon to the adjacent one (*i.e.*, 1,2-carbonyl transposition) offers a wide degree of latitude in organic synthesis.[1] Recently a number of synthetic methods have become available for effecting the 1,2-carbonyl shift.[1,2] While most of the previous works have attacked the carbonyl shift with respect to symmetrical and α-substituted ketones in which no problem of regioselectivity arises, methods for regiospecific 1,2-carbonyl transposition of α,α'-dimethylene systems are still lacking.

Recently we have reported the facile synthetic sequence for the 1,2-carbonyl shift depicted in Scheme 1.[3] The key step is the one-pot conversion of tosylhydrazones (B) to the enol thioethers (F) which relies upon the sulfenylation of dianions (C) followed by the Shapiro reaction of the regenerated dianions (E).

Scheme 1



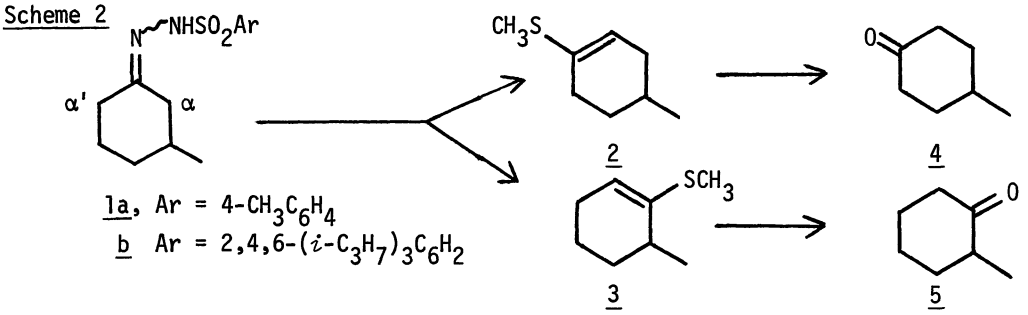
To access further the synthetic utility of this transformation, our attention has now been focused on the regiochemical outcomes in applying this sequence to a variety of α,α'-dimethylene systems which differ in the substitution pattern on the β- and β'-carbon. Herein we wish to report the regiochemical outcomes with respect to unsymmetrical cyclohexanones and to demonstrate that our synthetic procedure can achieve substantially regioselective 1,2-carbonyl shift in limited α,α'-dimethylene cases without any attempts to separate the stereoisomers of tosylhydrazones.

First of all, we should mention that in this transformation the direction of the carbonyl shift should be controlled solely by the regiochemistry of the formation (more strictly, the sulfenylation) of the dianion (C). Although the regiochemistry of the dianion formation has been

extensively studied within the context of the Shapiro olefin synthesis from tosylhydrazones,[4,5] combination of all the foregoing results indicates that the regioselectivity of α *vs.* α' proton abstraction is quite complicated, depending upon the *Z-E* stereochemistry of the tosylhydrazones, the nature of the base/solvent system employed, and combination thereof.

With the previous regiochemical results in mind, we first examined the 1,2-carbonyl shift of 3-methylcyclohexanone which obviously offers the most difficult problem of regioselectivity because the *E/Z* ratio of its tosylhydrazone (1a) is 1 : 1.[6] Thus the isomeric mixture of 1a was converted to the isomeric enol thioethers (2 and 3) using different base/solvent systems, finally yielding mixtures of the respective transposed ketones (4 and 5) (Scheme 2). In view of distinct advantages of 2,4,6-triisopropylbenzenesulfonylhydrazones (trisylhydrazones) over tosylhydrazones recently claimed for the Shapiro olefin synthesis,[5b] we also performed the same sequence on the trisylhydrazone (1b) of which the *E/Z* ratio was found to be also 1 : 1 (by ^{13}C NMR assay).[7,8] Table 1 summarizes the regiochemical outcomes thus obtained.

Scheme 2



1a, Ar = 4-$CH_3C_6H_4$
b Ar = 2,4,6-(i-C_3H_7)$_3C_6H_2$

Of particular interest in Table 1 is the fact that the ratio of 4 : 5 (equal to 2 : 3) varied from 9 : 1 (entry 1) to 3 : 2 (entry 3) with the base/solvent systems employed, giving preferences for the carbonyl shift to the less hindered position (α'). This preference appears to decrease with an increase in the amount of TMEDA added. Another interesting finding is that no increased regioselectivity was observed with the trisylhydrazone (1b) (entries 8 and 9). Consequently, these results suggest that, under these reaction conditions, *the regioselectivity in the sulfenylation of the hydrazone dianion depends largely upon the nature of the base/solvent system rather than the hydrazone stereochemistry.*[9] Although the observed base/solvent dependency on the reaction course has no straightforward explanation at the present time,[10] the pronounced effect of base/solvent system on the regiochemistry should be synthetically utilizable in certain cases.

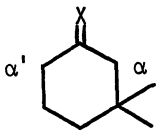
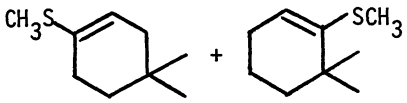
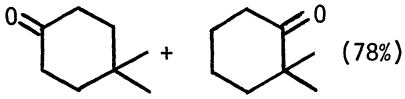
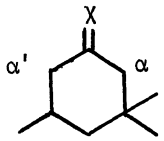
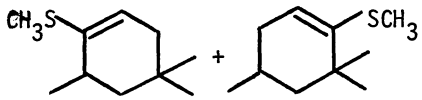
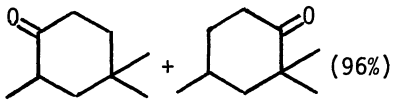
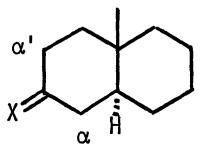
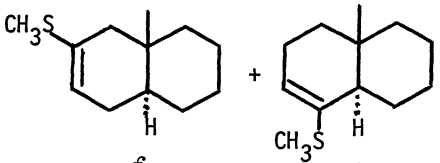
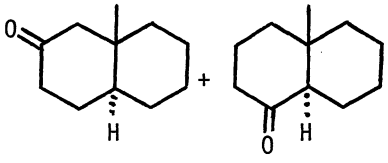
By using the optimum reaction conditions described in entry 1, we further studied the regiochemical outcomes with other cyclohexanone tosylhydrazones which are different from 1a in the substitution pattern on the β-, β'- and/or γ'-carbon (Table 2). The high regiospecificity observed with the β,β-dimethylcyclohexanone system (entry 10) is not surprising in view of the fact that the tosylhydrazone (6) possesses exclusively the *E* geometry (by ^{13}C NMR assay)[11] which can direct the lithiation (and thus the sulfenylation) to the *syn* position presumably through the chelation effect by the hydrazone monoanion.[12, 13] Thus, this result suggests that *the regiospecificity in the 1,2-carbonyl shift can also be controlled by the stereochemistry of tosylhydrazones employed.* However, we also found that the introduction of an additional methyl group on the β'-carbon of 6 decreased the level of regiospecificity (entry 11). This observation is somewhat expected in view of the stereochemistry of the tosylhydrazone (7) (*E/Z*= 1 : 1 based on ^{13}C NMR).[14] Another interesting conclusion made from Table 2 is that the preference for the carbonyl shift to the less hindered position (α') described above was nearly completely lost with β,γ',γ'-trisubstituted case (8) (entry 12) which was found to be a 1 : 1 mixture of the stereoisomers.[15]

Table 1 [a]

Entry	Hydrazone	Base	Solvent (mℓ)[b] THF : TMEDA[e] : Hexane	Enol Thioethers[c] Yield of (2 + 3)(%)	Ketones[d] 4 : 5
1	1a (5 mmol)	BuLi	11 : 10 : 5	93	91 : 9
2			8 : 15 : 6	98	79 : 21
3			0 : 25 : 30	83	64 : 36
4			16 : 15 : 0	94	79 : 21
5			11 : 10 : 0	88 [f]	85 : 15
6			0 : 50 : 0	90	74 : 26
7	1a (2 mmol)	LDA[g]	4 : 4 : 6	76	77 : 23
8	1b (2 mmol)	BuLi	5 : 5 : 2	74	86 : 14
9			0 : 7 : 12	76	63 : 37

[a] Unless otherwise noted, both the conversion of 1 to 2 and 3 and their hydrolysis to 4 and 5 were conducted in the same manner as reported in our previous paper (ref 3). [b] Indicates the solvent system for the sulfenylation step. [c] The NMR spectra (CCl_4,TMS) showed two olefinic peaks (m) at δ 5.29 and 5.34. [d] Determined by VPC comparisons (DC 550, 125°C) with an authentic mixture. [e] N,N,N',N'-Tetramethylethylenediamine [f] Diphenyl disulfide was used as the sulfenylating agent. [g] Lithium diisopropylamide

Table 2 [a]

Entry	Tosylhydrazone[b] (X=NNHTs) [E/Z Ratio]	Enol Thioethers (Total Yield)[c] [Isomeric Ratio]	Ketones[d] (Total Yield)[c] [Isomeric Ratio][e]
10	 6 [E only]	 (97%)	 (78%) [99 : 1]
11	 7 [1 : 1]	 (76%)	 (96%) [80 : 20]
12	 8 [1 : 1]	 (54%)[f] [1.2 : 1.0][g]	 (65%)

[a] The same base/solvent system as that in entry 1 (Table 1) was used. [b] Prepared by the standard method (MeOH, HCl (one drop), reflux). For their mp's and ^{13}C NMR data, see the appropriate note. [c] Isolated yields, not optimized yet. [d] Exhibited spectral (IR and NMR) properties in accord with the assigned structures. [e] Determined by VPC (Deg succinate column). [f] A considerable amount of the unsulfenylated olefin was obtained which was separated by preparative TLC. [g] The ^1H NMR spectrum (CCl_4, TMS) showed two olefinic peaks at δ 5.21 and 5.37.

In summary, the present synthetic sequence allows the substantially regiospecific 1,2-carbonyl transposition of α, α'-dimethylene systems in which the tosylhydrazones possess the single geometry leading to the exclusive *syn* lithiation (sulfenylation) or the stereoisomeric mixtures of the tosylhydrazones exhibit a pronounced base/solvent effect in the dianion formations leading to the great preference for the lithiation (sulfenylation) to the less hindered position. Thus, the present method should find unique applications in synthetic design of natural products. Further improvement and applications of the method outlined here is in progress.

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References and Notes

1) For a general review on carbonyl transpositions, see T. Nakai and T. Mimura, *Yuki Gosei Kagaku Kyokai Shi*, 35, 964 (1977).
2) For representative methods, see B. M. Trost, K. Hiroi, and S. Kurozumi, *J. Am. Chem. Soc.*, 97, 438 (1975); T. Shono, I. Nishiguchi, and M. Nitta, *Chem. Lett.*, 1976, 1319; W. E. Fristad, T. R. Bailey, and L. A. Paquette, *J. Org. Chem.*, 43, 1620 (1978), references cited therein.
3) T. Nakai and T. Mimura, *Tetrahedron Lett.*, 1979, 531.
4) For a review, see 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); (c) K. J. Kolonko and R. H. Shapiro, *ibid.*, 43, 1404 (1978); M. F. Lipton and R. H. Shapiro, *ibid.*, 43, 1409 (1978).
6) For the stereochemical assignments based on ^{1}H and ^{13}C NMR spectra, see ref 3.
7) For unequivocal determinations of the *Z-E* stereochemistry for tosylhydrazones *via* ^{13}C NMR spectroscopy, see C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, 42, 2614 (1977).
8) Mp 128.0-129.5°C; ^{13}C NMR ($CDCl_3$, TMS), δ 21.29 (3-CH_3 for *E*), 24.5 (*syn*-C for *E*), 33.36 (*anti*-C for *E*), 21.76 (3-CH_3 for *Z*), 26.01 (*syn*-C for *Z*), 32.58 (*anti*-C for *Z*).
9) A similar base/solvent effect has been observed in the Shapiro olefin synthesis of related systems.[5a,b] In these cases, the regioselectivity of proton abstraction has been shown to be independent of the hydrazone stereochemistry.
10) However, it is evident that factors dealing with the solvation of the organometallic species and with the state of aggregation of the organometallic complex must be considered.
11) Mp 124.1-128.3°C; ^{13}C NMR ($CDCl_3$, TMS), δ 28.85 (*syn*-C for *E*).
12) A similar *syn* lithiation in the Shapiro olefin synthesis has been established for each of *E*- and *Z*-pulegone tosylhydrazone[5a] and other systems.[5c,d]
13) For different examples of the *syn* lithiation in the dianion formation through the chelation effect of the intermediate nitrogen monoanion, see T. Nakai and K. Mikami, *Chem. Lett.*, 1979, 469; W. G. Kofron and M. K. Yeh, *J. Org. Chem.*, 41, 439 (1976); M. E. Jung, P. A. Blair, and J. A. Lowe, *Tetrahedron Lett.*, 1976, 1439.
14) Mp 122.0-125.5°C; ^{13}C NMR ($CDCl_3$, TMS), δ 28.46 (*syn*-C for *E*), 29.63 (*syn*-C for *Z*).
15) Mp 102.5-105.8°C; ^{13}C NMR ($CDCl_3$, TMS), δ 23.23 (*syn*-C for *E*), 26.36 (*syn*-C for *Z*).

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