A Facile Regioselective Decomposition of Tosylhydrazones: An Application towards the Synthesis of α-Lipoic Acid

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Abstract: A facile regioselective decomposition of tosylhydrazones using NaOH as a base in refluxing isopropyl alcohol is described. This finding has been successfully applied towards the synthesis of (±)-α-lipoic acid (**1**).

Key words: tosylhydrazones, regioselectivity, olefins, α-lipoic acid

The decomposition of tosylhydrazones to olefins has become a popular tool in organic synthesis for conversion of ketones into olefins.[1] The Shapiro reaction[2] permits the convenient conversion of a ketone into a less substituted olefin almost always exclusively, however, it requires strong bases such as alkyl lithium reagents. The Bamford–Stevens[3] reaction employs very high temperature for decomposition of tosylhydrazones in the presence of base to give olefins. Both olefins and ketones are fundamental building blocks in synthetic organic chemistry; both may be readily and easily transformed into an array of diverse functionality. There are few reports in which tosylhydrazones of cyclic ketones containing sulfur are thermally decomposed at very high temperatures in presence of base whereas photolytic decomposition has resulted in the formation of olefins in poor yields.[4–6] However, in these cases regioselectivity in the formation of olefins observed is moderate to poor.

During our approach towards the synthesis of α-lipoic acid (**1**), it has been found that tosylhydrazones **2a–e** on treatment with NaOH in isopropyl alcohol at reflux temperature resulted in the regioselective decomposition of the tosylhydrazones to furnish more substituted olefins

3a–e along with minor amounts of less substituted olefins **4a–e** with the regioselectivity of ca. 9:1 (Scheme 1).

The tosylhydrazones **2a–e** were prepared starting from methyl thioglycolate as shown in Scheme 2. Methyl thioglycolate **5** on acetonoide protection[7] gave 88% of diester **6**, which was then subjected to Dieckmann condensation[8] to give cyclic β-ketoester **7** in 86% yield. A singlet at $\delta = 12.60$ ppm in the ^{1}H NMR spectrum of **7** revealed that it existed in the enolic form. After a few trials, conditions for the C-alkylation of β-ketoester **7** were developed with different alkylating agents RX using K_2CO_3 as a base in the presence of phase transfer catalyst.[9] The C-alkylated products **8a–e** were subjected to decarboxylation using Krapcho's protocol[10] to furnish ketones **9a–e** in a wide range of yields. The ketones **9a–e** were converted into their corresponding tosylhydrazones **2a–e** by treatment with tosylhydrazine in methanol at room temperature (Table 1).[11]

The different tosylhydrazones prepared as above, were treated with NaOH in refluxing isopropyl alcohol and the results are summarized in Table 2. It was observed that the tosylhydrazones were decomposed to olefins with the
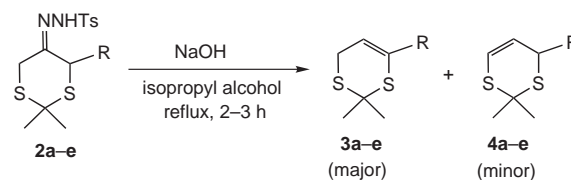
Scheme 1
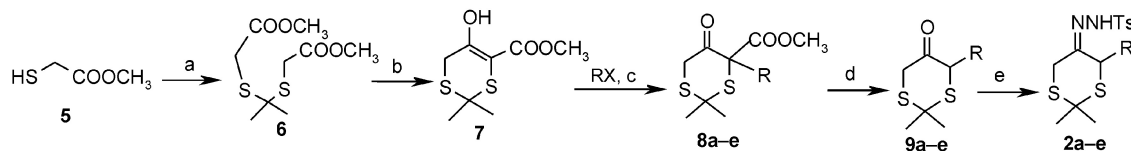
RX = *n*-BuBr, *n*-BnBr, Br-(CH₂)₄-COOMe, allyl bromide, ethyl iodide

Scheme 2 *Reagents and conditions:* a) acetone, BF₃·Et₂O (cat.), 0 °C to r.t., 6 h, 88%; b) NaH, THF, 60 °C, 3 h, 86%; c) K₂CO₃, Bu₄NHSO₄, THF, r.t., 5–24 h; d) DMSO, NaCl, H₂O, 135–140 °C, 5–8 h; e) TsNHNH₂, MeOH, r.t., 2–3 h.

Table 1 Formation of Products **8a–e**, **9a–e** and **2a–e**
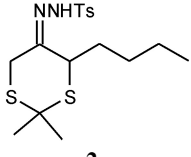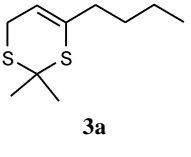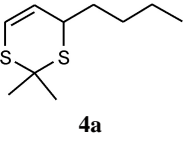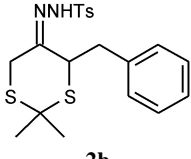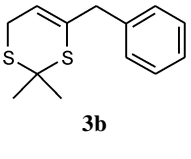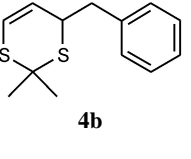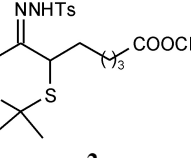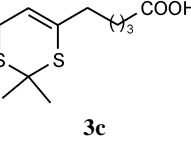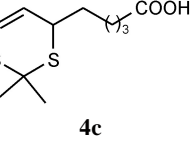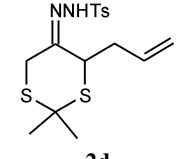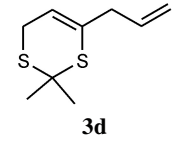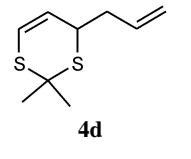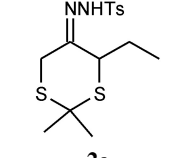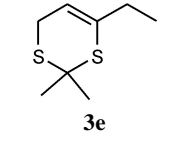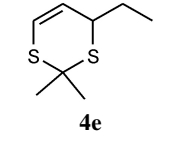
R	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
n-Butyl	**8a**	71	**9a**	90	**2a**	92
Benzyl	**8b**	62	**9b**	49	**2b**	94
-(CH$_2$)$_4$-COOCH$_3$	**8c**	70	**9c**	81	**2c**	87
Allyl	**8d**	88	**9d**	48	**2d**	83
Ethyl	**8e**	84	**9e**	69	**2e**	82

regioselectivity of around 9:1 in moderate to high yields. The regioselectivity was determined by the ratio of integrations of olefinic protons in the ^{1}H NMR spectra.

This procedure was then utilized to synthesize α-lipoic acid (**1**), a naturally occurring highly biologically active as well as pharmaceutically and industrially highly important molecule.[12] After the isolation of α-lipoic acid in 1951, its valuable biological activity and pharmocological importance soon triggered off a burst of efforts towards its synthesis.[13–15]

Although the biological activity of α-lipoic acid is confined to the naturally occurring *R*-isomer,[16] the racemic form is equally important in medicine in view of the fact that the presence of *S*-isomer has no detrimental effect on its therapeutic value.[17] α-Lipoic acid has the ability to control diabetes.[18] α-Lipoic acid and its derivatives show inhibitory effects against HIV replication,[19] act as antitumor agents,[20] are used in skin lotions, ointments and creams as skin-whitening cosmetics[21] as well as in hair tonics to control dandruff and stimulate hair growth.[22]

Table 2 Decomposition of Tosylhydrazones **2a–e** to Olefins Using NaOH as a Base[26]
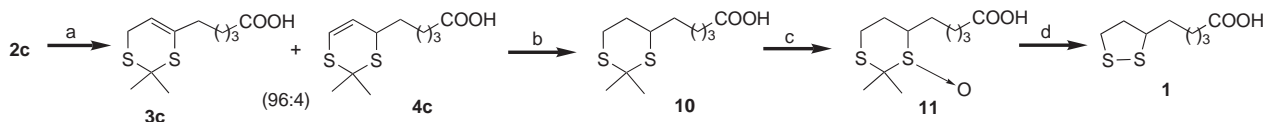
| Entry	Tosylhydrazones 2	Products 3	4	Isolated yield (%) (**3:4**)
1	**2a**	**3a**	**4a**	88 (87:13)
2	**2b**	**3b**	**4b**	80 (93:7)
3[27]	**2c**	**3c**	**4c**	84 (96:4)
4	**2d**	**3d**	**4d**	53 (86:14)
5	**2e**	**3e**	**4e**	71 (89:11)

Scheme 3 *Reagents and conditions*: a) NaOH, *i*-PrOH, reflux, 2–3 h, 84%; b) Et$_3$SiH (1 equiv), TFA, 0 °C to r.t., 2 h, 73%; c) NaIO$_4$, MeOH, 0 °C, 2 h, 68%; d) aq HCl (1:1), benzene, 50 °C, 7 h, 69%.

After several unsuccessful attempts towards the deoxygenation of ketone **9c**[25] using different literature methods, we turned our attention towards the reduction of mixture of olefins (**3c** and **4c**, ratio 96:4) by using a more suitable protocol for hydrogenation of sulfur containing heterocycles, i.e. ionic hydrogenation.[23]

Accordingly, the mixture of olefins (**3c** and **4c**) on treatment with 1 equivalent of triethylsilane in trifluoroacetic acid at 0 °C to room temperature for two hours resulted in the formation the desired dithiane acid **10** in 73% yield. The dithiane acid **10** was then oxidized to monosulfoxide **11** by treatment with an aqueous solution of NaIO$_4$ in methanol at 0 °C for two hours.[24]

Examination of the ^{1}H NMR and ^{13}C NMR spectra of the sulfoxide revealed that the sulfoxide was formed by the oxidation of sulfur attached to more substituted carbon giving the product **11**, which was unexpected due to steric reasons. To confirm this observed regioselectivity of sulfoxide formation, the same sulfoxide **11'** was prepared by a known literature method (Scheme 4).[24]
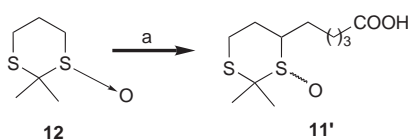
Scheme 4 *Reagents and conditions*: a) bromovaleric acid, LDA–TMEDA, THF, –78 °C, 5 h, 38%.

Comparison of the ^{1}H NMR and ^{13}C NMR spectra of sulfoxide **11'** prepared by the literature method indicated that it was a mixture of two isomers, and it was found that the sulfoxide **11** was identical with one of the isomers present in the compound **11'**. Finally, sulfoxide **11** was converted into lipoic acid by treatment with aqueous HCl (1:1) in benzene at 50 °C for seven hours (Scheme 3).[24]

In conclusion, an efficient protocol has been developed for the decomposition of tosylhydrazones of cyclic ketones containing sulfur atoms with a regioselectivity of around 9:1 to give more substituted olefins as the major products, using NaOH as a base. This is a complementary method to the Shapiro reaction which leads to less substituted olefins as major products in the presence of strong base. Moreover, this protocol has been successfully applied for a simple and practical synthesis of α-lipoic acid.

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(25) **Data for Selected Compounds.** (a) Methyl 4-(4-
methoxycarbonyl-butyl)-2,2-dimethyl-5-oxo-(1,3)-
dithiane-4-carboxylate (**8c**): molecular formula:
$C_{14}H_{22}O_5S_2$; yield 70%; viscous liquid. IR ($CHCl_3$): 3021,
2953, 2925, 1748, 1713, 1439, 1160, 765 cm^{-1}. ^1H NMR
(200 MHz, $CDCl_3$ + CCl_4): δ = 3.76 (d, *J* = 18.6 Hz, 1 H),
3.75 (s, 3 H), 3.60 (s, 3 H), 3.30 (d, *J* = 18.6 Hz, 1 H), 2.24
(t, *J* = 7.3 Hz, 2 H), 1.64–1.85 (m, 5 H), 1.72 (s, 3 H), 1.64
(s, 3 H), 1.17–1.27 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$ +
CCl_4): δ = 197.1 (s), 173.5 (s), 170.0 (s), 61.7 (s), 53.1 (q),
51.4 (q), 50.6 (s), 36.6 (t), 33.6 (t), 32.7 (q), 32.6 (t), 32.2 (q),
25.0 (t), 24.2 (t). MS (EI): *m/z* (%) = 334 (26), 303 (6), 270
(15), 260 (10), 237 (2), 228 (18), 212 (14), 197 (27), 180
(36), 169 (23), 159 (27), 155 (39), 141 (32), 127 (81), 123
(68), 115 (100), 99 (94), 87 (51), 73 (76), 59 (25). HRMS
(ESI$^+$ mode): *m/z* calcd for $C_{14}H_{22}O_5NaS_2$ [M + Na]$^+$:
357.0806; found: 357.0811. (b) Methyl 5-[2,2-dimethyl-5-
oxo-(1,3)-dithian-4-yl]pentanoate (**9c**): molecular formula:
$C_{12}H_{20}O_3S_2$; yield 81%; viscous liquid. IR ($CHCl_3$):
3020, 1732, 1711, 772, 744 cm^{-1}. ^1H NMR (200 MHz,
$CDCl_3$ + CCl_4): δ = 3.98 (dd, *J* = 6.8, 5.9 Hz, 1 H), 3.64 (s,
3 H), 3.63 (d, *J* = 16.6 Hz, 1 H), 3.25 (d, *J* = 16.6 Hz, 1 H),
2.29 (t, *J* = 7.3 Hz, 2 H), 1.76–1.92 (m, 1 H), 1.84 (s, 3 H),
1.56–1.71 (m, 2 H), 1.66 (s, 3 H), 1.34–1.49 (m, 3 H). ^{13}C
NMR (125 MHz, $CDCl_3$ + CCl_4): δ = 204.0 (s), 173.6 (s),
51.4 (q), 50.4 (s), 47.1 (d), 37.1 (t), 33.7 (t), 32.8 (q), 31.9
(q), 27.2 (t), 26.6 (t), 24.7 (t). MS (EI): *m/z* (%) = 276 (57),
262 (3), 243 (13), 225 (6), 211 (8), 202 (11), 179 (8), 170
(100), 153 (24), 142 (28), 127 (36), 111 (16), 93 (21), 73
(68), 56 (11). HRMS (ESI$^+$ mode): *m/z* calcd for
$C_{12}H_{20}O_3NaS_2$ [M + Na]$^+$: 299.0752; found: 299.0742.
(c) 5-[5-(*p*-Toluenesulfonyl)hydrazono-2,2-dimethyl-(1,3)-
dithian-4-yl]pentanoic acid methyl ester (**2c**): molecular
formula: $C_{19}H_{28}O_4N_2S_3$; yield 87%; white solid, mp 120 °C.

IR ($CHCl_3$): 3020, 2400, 1731, 757 cm^{-1}. ^1H NMR (200
MHz, $CDCl_3$ + CCl_4): δ = 8.53 (s, 1 H), 7.58 (d, *J* = 8.3 Hz,
2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 3.74 (dd, *J* = 7.8, 6.4 Hz, 1
H), 3.61 (s, 3 H), 3.56 (d, *J* = 15.6 Hz, 1 H), 3.21 (d, *J* = 15.6
Hz, 1 H), 2.37 (s, 3 H), 2.19 (t, *J* = 7.8 Hz, 2 H), 1.76–1.84
(m, 1 H), 1.68 (s, 3 H), 1.46 (s, 3 H), 1.20–1.61 (m, 5 H).
^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 173.6 (s), 155.7 (s),
143.9 (s), 135.4 (s), 129.3 (d), 128.1 (d), 51.2 (q), 49.7 (s),
45.1 (d), 33.6 (t), 32.2 (q), 31.0 (q), 28.9 (t), 26.1 (t), 25.6 (t),
24.4 (t), 21.3 (q). MS (ESI, solvent: MeCN + H_2O +
CH_3COONH_4): *m/z* = 445.04 [M + 1]. HRMS (ESI$^+$ mode):
m/z calcd for $C_{19}H_{29}N_2O_4S_3$ [M + H]$^+$: 445.1289; found:
445.1271.

(26) **General Procedure for Decomposition of Tosylhydra-
zones to Olefins.**
A mixture of tosylhydrazone (1 mmol) and NaOH (2 mmol)
in *i*-PrOH (10 mL) was refluxed for 2–3 h. The reaction was
monitored by TLC, and after the completion of the reaction,
i-PrOH was removed under vacuum and the residue was
extracted with Et_2O. The ether layer was dried over anhyd
Na_2SO_4 and filtered. Then Et_2O was removed under vacuum
and the residue was purified by column chromatography.

(27) **Typical Procedure for Entry 3 in Table 2 (3c and 4c).** The
mixture of tosylhydrazone **2c** (200 mg, 0.450 mmol) and
NaOH (40 mg, 2 mmol) in *i*-PrOH (10 mL) was refluxed for
2–3 h. The reaction was monitored by TLC and after the
completion of the reaction, *i*-PrOH was removed under
vacuum and H_2O was added to the reaction mixture. Then
aqueous layer was washed with Et_2O and then acidified with
dilute HCl. Finally, the aqueous layer was extracted with
Et_2O (3 × 15 mL). The ether layer was dried over anhyd
Na_2SO_4, filtered and Et_2O was removed under vacuum. The
residue was purified by column chromatography to give 93
mg (84%) of pure product (**3c** and **4c**).
Data for 5-(2,2-dimethyl-6*H*-[1,3]dithiin-4-yl)pentanoic
acid(**3c**): molecular formula: $C_{11}H_{18}O_2S_2$; yield 84%;
viscous liquid. IR ($CHCl_3$): 2985, 1709, 1216, 1167 cm^{-1}. ^1H
NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 10.06 (br s, 1 H), 5.75
(t, *J* = 4.4 Hz, 1 H), 3.44 (d, *J* = 4.4 Hz, 2 H), 2.34 (t, *J* = 7.3
Hz, 2 H), 2.20 (t, *J* = 6.4 Hz, 2 H), 1.67 (s, 6 H), 1.42–1.74
(m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 179.2 (s),
136.5 (s), 111.4 (d), 47.3 (s), 38.2 (t), 33.8 (t), 31.0 (q), 28.3
(t), 26.4 (t), 23.7 (t). MS (ESI, solvent: MeCN + H_2O +
CH_3COONH_4): *m/z* = 263.05 [M + NH_3], 245.05 [M – 1].