Regiospecific C-α Deuteration of Alkyl Ketones; A New Efficient Indirect Procedure

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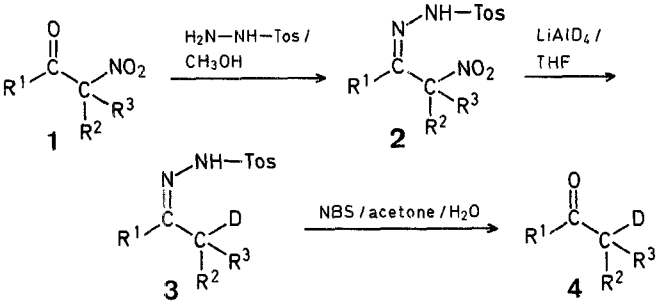
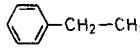
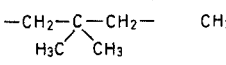
We recently reported[1] that treatment of α-nitroketone tosylhydrazones with lithium aluminum hydride in tetrahydrofuran at 0–10 °C leads to replacement of the nitro group by hydrogen. Based on these findings, we developed a new and efficient indirect method for the synthesis of α-deuterated ketones. Our method consists of the conversion of α-nitroketones (**1**) into their tosylhydrazones (**2**) and treatment of compounds **2** with lithium aluminum deuteride in tetrahydrofuran at 0–10 °C to give the α-deuterioketone tosylhydrazones (**3**) in good yield; of the known methods[2] for regenerating carbonyl compounds from their tosylhydrazones, the *N*-bromosuccinimide procedure[3] was found to be mild enough not to affect the environment of C-α via enolization. The tosylhydrazones **3** could thus be cleaved to the α-deuterioketones **4** without loss of deuterium. According to the mass spectra, the final products are the at least 98% isotopically pure monodeuterated ketones **4**. The ^{1}H-N.M.R. spectra of ketones **4** were in good agreement with the assigned structures.



	R^1	R^2	R^3
a		CH_3	H
b		CH_3	H
c		CH_3	H
d	n-C_3H_7	CH_3	CH_3
e			CH_3

The main features of our indirect route to α-deuterated ketones (**4**) are:

- α-Nitroketones (**1**) are easily available. General methods for their synthesis are: treatment of alkenes with dinitrogen tetroxide[4], nitration of enol acetates[5], addition of nitronates to aldehydes[6] (Henry reaction) followed by oxidation of the isolated nitroalcohols[7,8], as well as acylation reactions of nitroalkanes[9,10].

Table 1. α-Nitroketone Tosylhydrazones (**2**) prepared

2	Yield[a] [%]	m.p.[b] [°C]	Molecular Formula[c]	I.R. (KBr)[d] ν [cm^{-1}]			^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[e] δ [ppm]
				NH	SO_2	NO_2	
a	88	129–130°	$C_{16}H_{17}N_3O_4S$ (347.3)	3203	1345, 1170	1545	1.21 (d, 3H, J=6 Hz); 2.45 (s, 3H); 5.42 (q, 1H, J=6 Hz); 7.88–7.0 (m, 9H)
b	90	104–105°	$C_{18}H_{21}N_3O_4S$ (375.4)	3200	1345, 1160	1552	1.55 (d, 2H, J=7 Hz); 2.42 (s, 3H); 2.8–2.5 (m, 4H); 4.90 (q, 1H, J=7 Hz); 7.8–6.9 (m, 9H)
c	81	126–127°	$C_{16}H_{23}N_3O_4S$ (353.4)	3200	1345, 1170	1552	1.62 (d, 3H, J=6 Hz); 0.8–2.8 (m, 11H); 2.42 (s, 3H); 5.24 (q, 1H, J=6 Hz); 7.57 (AA'BB' pattern, 4H, J=8 Hz); 8.52 (bs, 1H)[f]
d	75	102–103°	$C_{14}H_{21}N_3O_4S$ (327.3)	3210	1345, 1165	1545	0.85 (t, 3H, J=6 Hz); 1.1–1.6 (m, 2H); 1.64 (s, 6H); 2.10 (t, 2H, J=6 Hz); 2.42 (s, 3H); 7.57 (AA'BB' pattern, 4H, J=8 Hz)
e	90	130–131°	$C_{15}H_{21}N_3O_4S$ (339.3)	3212	1350, 1170	1542	1.00 (s, 3H); 1.13 (s, 3H); 1.78 (s, 3H); 1.98 (s, 2H); 2.33 (s, 2H); 2.43 (s, 3H); 7.57 (AA'BB' pattern, 4H, J=8 Hz); 7.68 (bs, 1H)[f]

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Microanalyses were performed using C,H,N Analyzer Model 185 of Hewlett-Packard Co. Maximum deviations from the calculated values: C, ±0.13; H, ±0.08; N, ±0.12; O, ±0.13; S, ±0.11.
[d] Recorded on a Perkin-Elmer 297 spectrometer.
[e] Recorded at 90 MHz using a Varian EM 390 spectrometer.
[f] Signal disappears on treatment with D_2O.

Table 2. α-Deuterioketone Tosylhydrazones **(3)** prepared

3	Yield[a] [%]	m.p.[b] [°C]	Molecular Formula[c]	M.S.[d] m/e (M^+)	I.R. (KBr)[e] ν[cm⁻¹] NH	I.R. (KBr)[e] ν[cm⁻¹] SO_2	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[f] δ [ppm]
a	82	110-112°	$C_{16}H_{17}DN_2O_2S$ (303.3)	303	3200	1171, 1345	1.08 (d, 3H, J=7.5 Hz); 2.42 (s, 3H); 2.62 (q, 4H, J=7.5 Hz); 7.1-8.1 (m, 9H)
b	88	120-121°	$C_{18}H_{21}DN_2O_2S$ (331.3)	331	3220	1160, 1345	0.98 (d, 3H, J=7 Hz); 2.16 (q, 1H, J=7 Hz); 2.30-2.90 (m, 7H); 6.85-7.93 (m, 9H)
c	85	129-131°	$C_{16}H_{23}DN_2O_2S$ (309.4)	309	3240	1160, 1345	0.98 (d, 3H, J=7.5 Hz); 1.07-1.9 (m, 11H); 2.15 (q, 1H, J=7.5 Hz); 2.43 (s, 3H); 7.57 (AA'BB' pattern, 4H, J=8 Hz)
d	88	120-121°	$C_{14}H_{21}DN_2O_2S$ (283.3)	283	3210	1163, 1345	0.85 (t, 3H, J=7.5 Hz); 0.98 (s, 6H); 1.2-1.7 (m, 2H); 2.11 (t, 3H, J=7.5 Hz); 2.4 (s, 3H); 7.57 (AA'BB' pattern, 4H, J=8 Hz)
e	87	90-92°	$C_{15}H_{21}DN_2O_2S$ (295.3)	295	3203	1160, 1345	0.58 (s, 3H); 0.74 (s, 3H); 1.15-1.87 (m, 4H); 1.88 (s, 3H); 7.52 (AA'BB' pattern, 4H, J=8 Hz)

[a] Yield of isolated pure product.
[b] *Uncorrected.*
[c] Microanalyses were performed using C,H,N Analyzer Model 185 of Hewlett-Packard Co. Maximum deviations from the calculated values: C, ±0.15; H, ±0.12; N, ±0.09; O, ±0.10; S, ±0.14.
[d] Recorded with a Varian 112 instrument.
[e] Recorded on a Perkin-Elmer 297 spectrometer.
[f] Recorded at 90 MHz using a Varian EM 390 spectrometer.

- α-Nitroketones can be easily converted into the corresponding tosylhydrazones in high yields at room temperature.
- Commercial lithium aluminum deuteride in tetrahydrofuran is used as deuterium source and it is found to react with the tosylhydrazones **2** with high chemoselectivity.
- Tertiary as well as secondary nitro groups in α-nitroketones can be replaced by deuterium in good yields.

Other methods for the synthesis of α-deuterated ketones **(4)** include sodium deuteroxide tratment of ketones in dioxan[11] and by replacement of the nitro group, from α-nitroketones, with tributyltin deuteride in benzene[12]. Although our present method is an indirect one it compares favorably with the known methods in terms of simplicity of performance, regiospecificity, and efficiency.

All starting materials were obtained commercially. Lithium aluminum deuteride is available from Aldrich Chemical Company, Inc. The tosylhydrazones **2a-e** *were prepared by reaction of tosylhydrazine with the corresponding α-nitroketones according to a published procedure*[1].

α-Deuterioketone Tosylhydrazones (3); General Procedure:
A suspension of lithium aluminum deuteride (1.26 g, 30 mmol) in dry tetrahydrofuran (100 ml) is stirred under nitrogen in a 250 ml flask fitted with a septum inlet and cooled to 0 °C. The tosylhydrazone **2a-e** (10 mmol) is dissolved in dry tetrahydrofuran (30 ml) and added dropwise. (*Caution:* hydrogen evolution). The mixture is stirred for 2 h and then treated carefully with cold water (20 ml), acidified with 2 normal sulfuric acid, and extracted with ether (2 × 100 ml). The ether layer is dried with magnesium sulfate, the solvent removed under reduced pressure, and the product recrystallized from methanol/water.

Cleavage of Tosylhydrazones 3 to α-Deuterioketones 4; General Procedure:
The tosylhydrazone **3a-e** (10 mmol) is dissolved in a mixture of acetone (140 ml) and water (40 ml). When dissolution is complete the mixture is cooled to 0 °C (ice/water bath) and *N*-bromosuccinimide (7.12 g, 40 mmol) is added. Stirring is continued for 2 min and the mixture then quenched with saturated sodium hydrogen sulfite solution (10-20 ml). The ice bath is removed and water (70 ml) is added with stirring. The ketone **4** is then extracted with ether (3 × 100 ml). The combined organic extracts are washed with water (50 ml) and 10% sodium carbonate solution (30 ml), dried with magnesium sulfate, and evaporated under reduced pressure to leave the α-deuterioketone **4**.

Table 3. α-Deuterioketones **(4)** prepared

4	Yield[a] [%]	Molecular Formula[b]	M.S.[c] m/e (M^+)	I.R. (KBr)[d] $\nu_{C=O}$ [cm⁻¹]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[e] δ [ppm]
a	67	C_9H_9DO (135.2)	135	1683	1.23 (d, 3H, J=7.5 Hz); 2.8-3.15 (m, 1H); 7.39-8.15 (m, 5H)
b	78	$C_{11}H_{13}DO$ (163.2)	163	1705	1.03 (d, 3H, J=7 Hz); 2.38 (q, 1H, J=7 Hz); 2.58-2.98 (m, 4H); 7.05-7.35 (m, 5H)
c	75	$C_9H_{15}DO$ (141.2)	141	1703	1.01 (d, 3H, J=7.5 Hz); 1.05-2.05 (m, 10H); 2.15-2.55 (m, 2H)
d	72	$C_7H_{13}DO$ (115.2)	115	1702	0.82 (t, 3H, J=7 Hz); 0.98 (s, 6H); 1.3-1.75 (m, 2H); 2.35 (t, 2H, J=7 Hz)
e	76	$C_8H_{13}DO$ (127.2)	127	1733	0.72 (s, 3H); 0.83 (s, 3H); 0.99 (s, 3H); 1.3-2.0 (m, 4H)

[a] Yield of isolated pure product.
[b] Microanalyses were performed using C,H Analyzer Model 185 of Hewlett-Packard Co. Maximum deviations from the calculated values: C, ±0.39; H, ±0.10; O, ±0.09.
[c] Recorded with a Varian 112 instrument.
[d] Recorded on a Perkin-Elmer 297 spectrometer.
[e] Recorded at 90 MHz using a Varian EM 390 spectrometer.

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[1] G. Rosini, R. Ballini, V. Zanotti, *Synthesis* **1983,** 137.
[2] L. Caglioti et al., *Synthesis* **1979,** 207; and references cited therein.
[3] G. Rosini, *J. Org. Chem.* **39,** 3504 (1974). This method has been claimed to be well suitable to check the stereochemical integrity at C-α in tosylhydrazone intermediates: P. K. Freeman, J. R. Balyeat, *J. Org. Chem.* **42,** 3205 (1977).
[4] W. Voskuil, *Dutch Patent* 8275 (1970), Stamicarbon N.V.; *C.A.* **76,** 85458 (1972).
[5] H. Ozbal, W. W. Zajac, *J. Org. Chem.* **46,** 3082 (1981).
[6] L. Henry, *C. R. Acad. Sci.* **120,** 1265 (1895).
[7] E. W. Colvin, D. Seebach, *J. Chem. Soc. Chem. Commun.* **1978,** 689; and references cited therein.
[8] D. Hurd, M. E. Nilson, *J. Org. Chem.* **20,** 927 (1955); and references cited therein.
[9] Y. Hamada, K. Ando, T. Shioiri, *Chem. Pharm. Bull.* **29,** 259 (1981).
[10] D. C. Baker, S. R. Putt, *Synthesis* **1978,** 478.
[11] A. F. Thomas, R. A. Schneider, S. Meinwald, *J. Am. Chem. Soc.,* **89,** 68 (1967).
A. F. Thomas, B. Willham, *Tetrahedron Lett.* **1965,** 1309.
[12] N. Ono, I. Hamamoto, H. Miyake, A. Kagi, *Chem. Lett.* **1982,** 1079.