Formation of α-Mono- and αα'-Di-methyl or -Phenyl Derivatives of Tosylhydrazones through an *in situ* Sequence by Treatment with Lithium Dimethyl- or Diphenyl-cuprate

By **Sandro Cacchi**,* Cattedra di Chimica Organica, via Castro Laurenziano 9, 00161 Roma, Italy
  Marcello Felici, Istituto di Chimica Organica e Farmaceutica, Universita' di Camerino, Camerino, Italy
  Goffredo Rosini, Istituto di Chimica Organica e Industriale, Universita' di Bologna, Bologna, Italy

The reaction of a tosylhydrazone with tri-*N*-methylanilinium perbromide in 1 : 1 or 1 : 2 ratio, followed by *in situ* treatment with lithium dimethyl- or diphenyl-cuprate, gives α-mono-methyl or -phenyl or αα'-di-methyl or -phenyl derivatives. The generality, limitations, and usefulness of this process are discussed.

DURING studies of the reactivity of derivatives of tosylhydrazine,[1] we found that tosylazo-alkenes, obtained through basic treatment of tosylhydrazones containing a leaving group on the α-carbon atom,[2] were versatile compounds,[3] inclined to undergo 1,4-addition reactions in the presence of appropriate nucleophiles.[4] This behaviour suggested the possibility of using these compounds as intermediates in the synthesis of α-alkyl or α-aryl ketones, through conjugate addition[5] of lithium organocuprates.

However, tosylazo-alkenes are sensitive materials, not always easy to isolate and purify, and difficult to preserve. We hoped to overcome this disadvantage by deriving the tosylazo-alkene from the corresponding α-halogeno tosylhydrazone *in situ*, in the presence of an excess of lithium organocuprate.

While our investigations were in an advanced stage, an article describing the α-monoarylation of tosylhydrazones starting from the isolated α-halogeno-tosylhydrazones and a lithium organocuprate through an elimination–addition mechanism was published.[6] However, α-halogeno-tosylhydrazones are not always stable nor are they easily purifiable. Their tendency to dehydrohalogenation makes them undesirable intermediates in many cases. Furthermore, their synthesis from α-halogeno-ketones may be difficult.†

We report here the synthesis of α-methyl or phenyl (Table 1) and αα'-di-methyl or -phenyl (Table 2) tosylhydrazones through an *in situ* sequence from the readily obtainable and easily purifiable tosylhydrazones (Scheme 1). Ketones can be regenerated from the methylated or phenylated tosylhydrazones, generally in high yields,
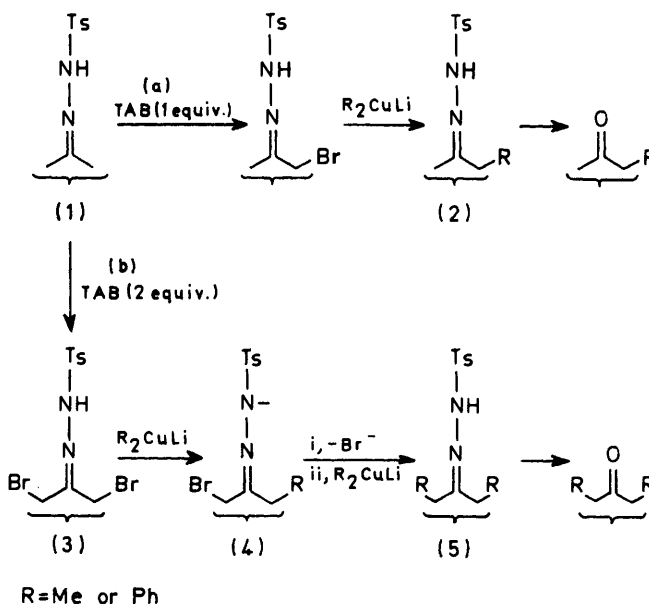
by treatment with *N*-bromosuccinimide[8] or sodium hypochlorite.[9]

The monofunctionalization reaction [Scheme 1(a)]

R=Me or Ph

SCHEME 1

was carried out by slowly adding tri-*N*-methylanilinium perbromide (TAB) to the tosylhydrazone[10] and dropping the mixture thus obtained into a solution containing an excess of lithium organocuprate.

---

† Substitution and/or elimination reactions may take place in a way similar to that observed in the reactions of α-halogeno-ketones with ammonia or primary or secondary amines.[7] The production of 2-bromo-3,3,5,5-tetramethylcyclohexanone tosylhydrazone from the corresponding α-bromo-ketone is very slow; competitive dehydrohalogenation of the α-bromo-tosylhydrazone and decomposition of the corresponding tosylazo-alkene take place, lowering the yield and making the α-bromo-tosylhydrazone very difficult to purify (unpublished results).

[1] L. Caglioti, *Tetrahedron*, 1966, **22**, 487; S. Cacchi, L. Caglioti, and G. Paolucci, *Bull. Chem. Soc. Japan*, 1974, **47**, 2332; G. Rosini, G. Baccolini, and S. Cacchi, *Synthesis*, 1975, 45; F. Angelucci, S. Cacchi, L. Caglioti, and G. Rosini, *Chimica e Industria*, 1970, **52**, 262; S. Cacchi, L. Caglioti, and G. Paolucci, *Chem. and Ind.*, 1972, 213.

[2] L. Caglioti, P. Grasselli, F. Morlacchi, and G. Rosini, *Chem. and Ind.*, 1968, 25; A. Dondoni, G. Rosini, G. Mossa, and L. Caglioti, *J. Chem. Soc. (B)*, 1968, 1404.

[3] G. Rosini and S. Cacchi, *J. Org. Chem.*, 1972, **37**, 1856; G. Rosini and R. Ranza, *ibid.*, 1971, **36**, 1915; L. Caglioti, F. Gasparrini, G. Paolucci, G. Rosini, and P. Masi, *ibid.*, 1973, **38**, 920; P. De Maria, F. Gasparrini, L. Caglioti, and M. Ghedini, *J.C.S. Perkin II*, 1973, 1922; W. Barbieri, L. Bernardi, P. Masi, L. Caglioti, and G. Rosini, *Tetrahedron Letters*, 1970, 1343.

[4] L. Caglioti, A. Dondoni, and G. Rosini, *Chimica e Industria*, 1968, 122; S. Brodka and H. Simon, *Annalen*, 1971, **745**, 193; L. Bernardi, P. Masi, and G. Rosini, *Ann. Chim. (Italy)*, 1973, **63**, 601.

[5] G. H. Posner, *Org. Reactions*, 1972, **19**, 1; H. O. House, *Accounts Chem. Res.*, 1976, **9**, 59; J. F. Normant, *Synthesis*, 1972, 63.

[6] C. E. Sachs and P. L. Fuchs, *J. Amer. Chem. Soc.*, 1975, **97**, 7372.

[7] B. Tchoubar, *Bull. Soc. chim. France*, 1955, 1363; N. H. Cromwell and P. H. Hess, *J. Amer. Chem. Soc.*, 1961, **83**, 1237.

[8] G. Rosini, *J. Org. Chem.*, 1974, **39**, 3504.

[9] Tse-Lok Ho and Chin Ming Wong, *J. Org. Chem.*, 1974, **39**, 3453.

[10] G. Rosini and G. Baccolini, *J. Org. Chem.*, 1974, **39**, 826.

The generality of application and the limitations of this method depend essentially on the course of the bromination step, since the replacement of the bromine in the α-bromotosylhydrazone with an alkyl or an aryl group proceeds in high yield.[6,*]

yield (Scheme 2) through lithium-dimethylcuprate-catalysed isomerization of the intermediate azo-ene (7). The proton affinity of lithium organocuprates is known,[11]

TABLE 1

Mono-methylation (or -phenylation) of tosylhydrazones

Starting material (1) X = N·NHTs	M.p. (°C)	R₂CuLi R =	Mono-methyl or phenyl derivative (2)ᵃ X = N·NHTs	Yield ᵇ (%)	M.p. (°C)	δ[(CD₃)₂SO] ᶜ
a: (1-tetralone tosylhydrazone)	173—175	Me	(2-methyl derivative)	65—69	139—141	1.06 (3 H, d, J 7 Hz, CH·CH₃)
b: PhCH₂—C(=X)—Ph	135—137	Me	Ph—CH(Me)—C(=X)—Ph	64—68	138—140	1.29 (3 H, d, J 7 Hz, CH·CH₃)
c: (chroman-4-one 2-Ph)	174—176	Me	(3-Me, 2-Ph derivative)	54—58	127—129	1.23 (3 H, d, J 7 Hz, CH·CH₃)
d: (2-methylcyclohexanone)	124—126	Me	(2,6-dimethyl derivative)	55—60	121—123	Identical with that of authentic specimen
e: Ph—C(=X)—CH₃	146—148	Ph	Ph—C(=X)—CH₂Ph	35—40	135—137	Identical with that of authentic specimen
f: PhCH₂—C(=X)—CH₂Ph	175—177	Me	Ph—CH(Me)—C(=X)—CH₂Ph	68—72	116—118	1.28 (3 H, d, J 7 Hz, CH·CH₃)

ᵃ All compounds showed i.r. (KBr) bands at ca. 3 200, 1 360, and 1 170 cm⁻¹ and gave satisfactory elemental analyses [C ±0.32%; H ±0.33%; N ±0.35%; available as Supplementary Publication No. SUP 22014 (3 pp.) †]. ᵇ Based on the products isolated, from the tosylhydrazones. ᶜ All compounds showed a characteristic AA′BB′ system (4 H, J 8 Hz, aromatic protons of the tosyl group) at δ ca. 7.6 [partly masked by signals of other aromatic protons in (2a, b, c, e, and f)] and a singlet (3 H, ArCH₃) at δ ca. 2.4.

† For details of Supplementary Publications see Notice to Authors No. 7, J.C.S. Perkin I, 1976, Index issue.

Loss of selectivity in the monobromination of a tosyl-hydrazone may cause formation of a mixture. Sequential treatment of cyclohexanone tosylhydrazone with TAB and Me₂CuLi gave a mixture of the starting tosyl-hydrazone (35.5%), the 2-methyl tosylhydrazone (10%), and the 2,6-dimethyl tosylhydrazone (21%) (formed via the 2,6-dibromo-tosylhydrazone).

Steric crowding near the reaction site may suppress the conjugate addition of the intermediate azo-alkene and favour alternative reaction pathways. Thus the reaction of 2,6-dimethylcyclohexanone tosylhydrazone (6) under the above conditions (TAB, Me₂CuLi) gave 2,6-di-methylcyclohex-2-enone tosylhydrazone (8) in 54%

as is the base-catalysed isomerization of a tosylazo-alkene to an αβ-unsaturated tosylhydrazone.[12]
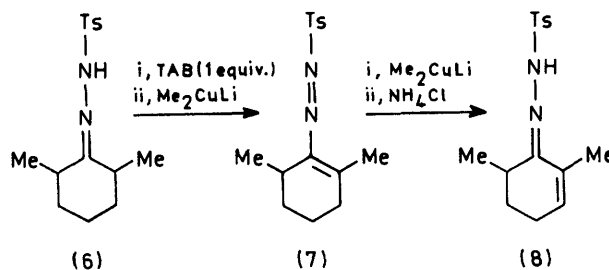
SCHEME 2

In most cases analysed, however, the in situ bromina-

* We find that 2-bromocyclohexanone tosylhydrazone reacts with lithium dimethylcuprate to give the 2-methyl derivative in 70% yield.

[11] H. O. House, J. Org. Chem., 1975, 40, 1461; J. E. Dubois, P. Fournier, and C. Lion, Tetrahedron Letters, 1975, 4263.
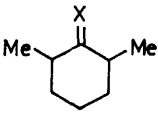[12] A. Dondoni, G. Rosini, G. Mossa, and L. Caglioti, J. Chem. Soc. (B), 1968, 1404.

tion–dehydrobromination–conjugate addition * sequence led to satisfactory results; reduction reactions as observed in the direct reaction of the α-bromo-ketones with lithium dialkyl- and diaryl-cuprates [13],† were not encountered. Yields from ketones are comparable with or better than those obtainable by the more difficult sequence ketone ⟶ α-halogeno ketone ⟶ α-tosylhydrazone ⟶ α-substituted tosylhydrazone.

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. I.r. spectra were recorded with a Perkin-Elmer 337 grating spectrophotometer. N.m.r. spectra were measured with a Varian T60 spectrometer (Me_4Si internal standard). Analytical t.l.c. was carried out on pre-coated plates of Silica Gel F_{254} (0.25 mm) (Merck). High pressure liquid chromatography (h.p.l.c.) analyses were performed with a Waters

TABLE 2

Di-methylation (or -phenylation) of tosylhydrazones

Starting material (1) X = N·HNTs	M.p. (°C)	R_2CuLi R =	Dimethyl or diphenyl derivative (5) [a] X = N·NHTs	Yield [b] (%)	M.p. (°C)	$\delta[(CD_3)_2SO]$ [c]
f : $PhCH_2-\overset{\overset{X}{\|\|}}{C}-CH_2Ph$		Me	$Ph-\underset{\underset{Me}{\|}}{CH}-\overset{\overset{X}{\|\|}}{C}-\underset{\underset{Me}{\|}}{CH}-Ph$	84—88	143—145	1.5—0.86 (6 H, m, 2 CH·CH_3)
g : (cyclohexanone tosylhydrazone)	158—160	Me	(2,6-dimethyl derivative)	55—60	121—123	Identical with that of authentic specimen
h : $Pr-\overset{\overset{X}{\|\|}}{C}-Pr$	78—79	Me	$Et-\underset{\underset{Me}{\|}}{CH}-\overset{\overset{X}{\|\|}}{C}-\underset{\underset{Me}{\|}}{CH}-Et$	80—85	80—82	1.76—0.43 (16 H, m, aliphatic)
h : $Pr-\overset{\overset{X}{\|\|}}{C}-Pr$		Ph	$Et-\underset{\underset{Ph}{\|}}{CH}-\overset{\overset{X}{\|\|}}{C}-\underset{\underset{Ph}{\|}}{CH}-Et$	50—55	99—101	3.68 (1 H, m, benzylic), 3.18 (1 H, m, benzylic), 7.43—6.66 (12 H, m, aromatic) [d]
i : $Et-\overset{\overset{X}{\|\|}}{C}-Et$	101—103	Ph	$Me-\underset{\underset{Ph}{\|}}{CH}-\overset{\overset{X}{\|\|}}{C}-\underset{\underset{Ph}{\|}}{CH}-Me$	53—58	143—145	7.66—6.83 (12 H, m, aromatic)

[a] All compounds showed i.r. (KBr) bands at ca. 3 200, 1 360, and 1 160 cm^{-1} and gave satisfactory elemental analysis [C ±0.32%; H ±0.35%; N ±0.36%; available in the Supplementary Publication (see footnote a, Table 1)]. [b] Based on the products isolated, from tosylhydrazones. [c] All compounds showed a characteristic AA'BB' system (4 H, J 8 Hz, aromatic protons of tosyl group) at δ ca. 7.6 [partly masked by signals of other aromatic protons in (5f), (5h) phenylation reaction, and (5i)] and at δ ca. 2.46 (3 H, s, ArCH_3). [d] In $CDCl_3$.

A number of tosylhydrazones (Table 2) were converted by a double amount of TAB into the corresponding dimethyl or diphenyl derivatives in good yields [Scheme 1(b)].‡

The differences in behaviour between the αα'-dibromo-hydrazones (3) and αα'-dibromo-ketones are noteworthy; sequential treatment of the latter compounds with lithium dialkylcuprates and an electrophilic species yields mono- or di-alkyl derivatives (depending on the nature of the electrophile), through an intermediate cyclopropanone.[16]

* The monomethyl derivative was obtained even with 1,3-diphenylpropanone N-methyl-N-tosylhydrazone as starting material, probably by a direct substitution reaction.[13] The very low yield of alkylated product (19%) and the relatively high acidity of the sulphonamidic proton [14] seem to favour the elimination–addition mechanism when a tosylhydrazone is the starting material.

† The tosylhydrazone recovered (0—20%) is that left unchanged in the bromination step, as may be seen by analysis of the bromination reaction mixture.

Associates 202 Liquid Chromatograph on a column pre-packed with LiChrosorb Si60 (7 μm) (Merck). The products (2a—f) and (5f—i) were purified on silica gel (Merck, 230—400 mesh) columns, with cyclohexane–ethyl acetate as eluant, or by recrystallization.

The solvents (tetrahydrofuran or diethyl ether) were purified by standard methods. Copper(I) iodide was continuously extracted with tetrahydrofuran (Soxhlet; 12 h) and dried in vacuo at room temperature. Alkyl-lithium

‡ The negatively charged intermediate (4) is like that on the conjugate addition of organocuprates to αβ-unsaturated carbonyl compounds with a leaving group on the β-carbon atom.[15]

[13] J. E. Dubois and C. Lion, Tetrahedron, 1975, 31, 1227; G. H. Posner, Org. Reactions, 1975, 22, 253.

[14] J. W. Powell and M. C. Whiting, Tetrahedron, 1959, 7, 305.

[15] C. P. Casey, D. F. Martin, and R. A. Boggs, Tetrahedron Letters, 1973, 2071; G. H. Posner and D. J. Brunelle, J.C.S. Chem. Comm., 1973, 907; S. Cacchi, A. Caputo, and D. Misiti, Indian J. Chem., 1974, 12, 3.

[16] G. H. Posner and J. J. Sterling, J. Amer. Chem. Soc., 1973, 95, 3076; C. Lion and J. E. Dubois, Tetrahedron, 1975, 31, 1223.

reagents (Fluka), stored at 0 °C and titrated by a double titration procedure,[17] were used directly as supplied.

The starting tosylhydrazones were all obtained (75—90% yield) by reactions of the commercially available ketones with tosylhydrazine in an equimolecular amount in refluxing methanol. All tosylhydrazones (1a—i) gave i.r. and n.m.r. spectra and analytical data (C $\pm$ 0.35%, H $\pm$ 0.39%, N = $\pm$ 0.37%) in agreement with the proposed structures.

The procedures for the monomethylation of compound (1f) and the diphenylation of compound (1i) are typical.

Monomethylation of 1,3-*Diphenylpropanone Tosylhydrazone* (1f).—To a solution of the hydrazone (1f) (1.00 g, 2.64 mmol) in anhydrous tetrahydrofuran (40 ml), TAB (0.992 g, 2.64 mmol) was added.[10] The mixture was quickly filtered to remove trimethylanilinium salt and slowly dropped into a stirred solution containing an excess (15.9 mmol) of lithium dimethylcuprate * [from copper(I) iodide (15.9 mmol) and 1.62M-methyl-lithium (19.6 ml) in diethyl ether] at a temperature not exceeding 0 °C † and under argon. After 10 min the solution was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue (0.91 g) was chromatographed on silica gel [eluant 70 : 30 cyclohexane–ethyl acetate] to give 0.74 g of pure 1,3-diphenylbutan-2-one tosylhydrazone (2f) (0.74 g).

*Diphenylation of Pentan-*3-*one Tosylhydrazone* (1i).—The reaction of compound (1i) (1.00 g, 4.20 mmol) with TAB (3.16 g, 8.4 mmol) and lithium diphenylcuprate † (29.4 mmol) and work-up were carried out as above. Recrystal-

lization of the residue from methylene chloride–n-hexane gave pure 2,4-diphenylpentan-3-one tosylhydrazone (5i) (0.95 g).

Reaction of 1,3-*Diphenylpropanone* N-*Methyl*-N-*tosylhydrazone with Lithium Dimethylcuprate.*—Sequential treatment of 1,3-diphenylpropanone N-methyl-N-tosylhydrazone ‡ (0.50 g, 1.27 mmol) with TAB (0.477 g, 1.27 mmol) and lithium dimethylcuprate (7.6 mmol), and work-up as above followed by chromatographic separation gave pure *methyl derivative* (0.085 g, 19%) (Found: C, 70.65; H, 6.3; N, 6.6. $C_{24}H_{26}N_2O_2S$ requires C, 70.9; H, 6.45; N, 6.9%), $\nu_{max.}$ (KBr) 1 320 and 1 160 cm^{-1}, δ (CDCl$_3$) 2.67 (3 H, s, ArCH_3), 2.43 (3 H, s, NCH_3), and 1.33 (3 H, d, J 7 Hz, CH·CH_3). The other products were not studied.

Reaction of 2,6-*Dimethylcyclohexanone Tosylhydrazone* (6) *with Lithium Dimethylcuprate.*—The reaction of the hydrazone (6) (1 g, 3.40 mmol) with TAB (1.28 g, 3.40 mmol) and lithium dimethylcuprate (20.4 mmol) was carried out as before. Chromatographic separation gave 2,6-*dimethylcyclohex-*2-*enone tosylhydrazone* (8) (0.532 g), m.p. 126—128°; $\nu_{max.}$ (KBr) 3 200, 1 320, and 1 160 cm^{-1}; δ [(CD$_3$)$_2$SO] 10.3br (1 H, s, NH), 7.6 (4 H, q, AA'BB', J_{AB} 8 Hz, aromatic), 6.05br (1 H, s, vinylic), 2.37 (3 H, s, ArCH_3), 1.7br (2 H, s, partly overlapped with ring proton signals, =C·CH_3), and 0.93 (3 H, d, J 7 Hz, CH·CH_3).

---

* When the reaction is carried out with lithium diphenyl cuprate, the crude reaction mixture may be washed with n-hexane (to remove biphenyl) before chromatography.

† The brominated mixtures were generally added at −12 to −5 °C. Experiments carried out at −78 to −60 °C gave virtually the same product composition.

‡ Synthesized by N-methylation of the corresponding tosyl-hydrazone by phase-transfer catalysis.[18]

[17] G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, 1971, **93**, 1379.

[18] S. Cacchi, F. La Torre, and D. Misiti, *Synthesis*, in the press.