Tetrahedron, 1966, Vol. 22, pp. 487 to 493. Pergamon Press Ltd. Printed in Northern Ireland

THE REDUCTION OF TOSYLHYDRAZONES AND OF ACYL TOSYLHYDRAZIDES[1]

L. CAGLIOTI
Istituto di Chimica, Centro per lo Studio delle Sostanze Naturali del C.N.R.,
Politecnico di Milano-Italia

(*Received* 28 *July* 1965; *in revised form* 5 *September* 1965)

Abstract—The treatment of tosylhydrazones with reducing hydrides constitutes an efficient method for the reduction of a carbonyl to a CH_2 group. The intermediate alkyl-tosylhydrazides formed in this reaction have been isolated. The reduction of acyl-tosylhydrazides with LAH provides a new method for the reduction of a —COOH group to methyl group.

THE derivatives of *tosylhydrazide*[2] can be grouped in two categories: the *tosylhydrazones* (derivatives of aldehydes and ketones: general formula $Ts—NH—N=CR_1R_2$) and the *substituted tosylhydrazides* (acyl, aryl or alkyl-tosylhydrazides: general formula Ts—NH—NH—R).

In recent years the development of the Bamford–Stevens and the McFadjen–Stevens reactions depend on the use of tosylhydrazones and the substituted tosylhydrazides.

The Bamford–Stevens reaction described in 1952 demonstrated that the treatment of the tosylhydrazones with the sodium salt[3] of ethylene glycol in ethylene glycol leads to the formation of nitrogen, *p*-toluenesulphinic acid and olefins.

This reaction was intensively applied, without substantial modifications, until in 1960 two groups, the one Powell and Whiting (England) and the other Friedman and Schechter (U.S.A.) demonstrated[4] that the decomposition of tosylhydrazones with basic agents leads firstly to the formation of a diazo compound although some evidence of this had already been given by Bamford and Stevens.

The diazo compound undergoes: (a) proton transfer from proton donor solvents and cationic decomposition and (b) carbenic decomposition in aprotic solvents.

In both cases, *p*-toluenesulphinic acid and nitrogen are obtained, and in the first case olefins and Wagner-Meerwein rearrangement products, in the second case olefins and insertion products.

$$\mathrm{Ts{—}NH{—}NH{—}R \rightarrow Ts^- + HN{=}NR \rightarrow N_2 + RH}$$

FIG. 1

---

[1] Preliminary works on the argument: [a] L. Caglioti and M. Magi, *Tetrahedron Letters* 1261 (1961); [b] L. Caglioti and M. Magi, *Tetrahedron* **19**, 1127 (1963); [c] L. Caglioti and P. Grasselli, *Chem. & Ind.* 153 (1964); [d] L. Caglioti, *Ric. Sci.* **34**, (I) 41 (1964); [e] L. Caglioti, P. Grasselli and G. Maina. *La Chim. e l'Ind., Milan* **45**, 559 (1963); L. Caglioti, P. Grasselli and A. Selva, *Gazz. Chim. Ital.* **94**, 537 (1964); [f] L. Caglioti and P. Grasselli, *La Chim. e l'Ind., Milan* **46**, 799 (1964); [g] L. Caglioti and P. Grasselli, *Ibid.* **46**, 1492 (1964); [h] L. Caglioti, P. Grasselli and G. Zubiani, *Ibid.* **47**, 62 1965).

[2] Usually this is preferred in the literature to "Tosylhydrazine".

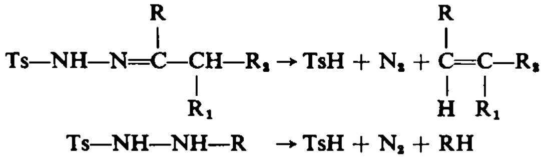
[3] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.* 4735 (1952).

[4] J. Powell and M. C. Whiting, *Tetrahedron* **7**, 305 (1959); **12**, 163 (9961); L. Friedman, H. Shechter, *J. Amer. Chem. Soc.* **81**, 5513 (1959); **82**, 1002 (1960); **83**, 3159 (1961); **87**, 935 (1965); For carbenic decomposition of steroidal tosylhydrazones at relatively low temperature see Ref. 1*e*.

In the reaction of McFadjen–Stevens[5] decomposition of the tosylhydrazides of carboxylic acids with basic agents yields *p*-toluenesulphinic acid, nitrogen and aldehydes. Acyldiimides as intermediate compounds were postulated in this reaction[6] (Fig. 1, R = acyl). This reaction proceeds very well in aprotic solvents.[7]

Alkyl-tosylhydrazides also undergo thermal decomposition, in protic or aprotic solvents, with or without basic catalysis, to N_2, *p*-toluenesulphinic acid and alkanes.[8]

Alkyl-diimides (Fig. 1, R = alkyl) as intermediate compounds were postulated. Accordingly, therefore, the tosylhydrazones decompose to N_2, *p*-toluenesulphinic acid and *olefins* while the alkyl-tosylhydrazides decompose to N_2, *p*-toluenesulphinic acid and *saturated compounds* (Fig. 2).



$$\mathrm{Ts{-}NH{-}N{=}\underset{R_1}{\overset{R}{C}}{-}CH{-}R_2 \rightarrow TsH + N_2 + \underset{H}{\overset{R}{C}}{=}\underset{R_1}{C}{-}R_2}$$

$$\mathrm{Ts{-}NH{-}NH{-}R \rightarrow TsH + N_2 + RH}$$

FIG. 2

In order to find a new method for the reduction of ketonic and aldehydic carbonyls to CH_2, the following hypothesis was postulated. If the double bond >C═N— of a tosylhydrazone could be reduced to >CH—NH then the decomposition of the substituted tosylhydrazide obtained should lead to the formation of a CH_2 group:

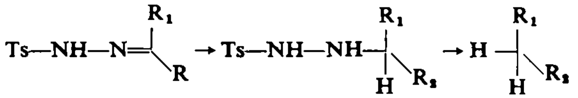


FIG. 3

As both $NaBH_4$ and LAH reduce >C═N— to >CH—NH—, a series of tosylhydrazones were submitted to the action of these two reagents and in both cases, with some differences, the reactions were successful.

In Table 1 the results obtained with LAH[1b] are summarized.

TABLE 1

Tosylhydrazone of	Product	Yield %
5α-Cholestan-3-one	Cholestane	70
Coprostan-3-one	Coprostane	60–70
3β-Acetoxy-5α-cholestan-7-one	3β-Hydroxy-5α-cholestane	65
Hecogenin acetate	Tigogenin	50
Indol-3-aldehyde	Skatole	50
α-Naphthaldehyde	α-Methyl-naphthalene	70

---

[5] J. S. McFadjen and T. S. Stevens, *J. Chem. Soc.* 584 (1936).

[6] M. L. Dhar, E. D. Hughes, C. Ingold, A. M. Mandour, G. A. Maw and L. I. Woolf, *J. Chem. Soc.* 2093 (1948).

[7] L. Friedman, 142nd *Meeting Amer. Chem. Soc.* Sept (1962).

[8] D. J. Cram and J. S. Bradshaw, *J. Amer. Chem. Soc.* **85**, 1108 (1963).

In most cases examined gas was evolved during the reaction and good yields of saturated compounds and *p*-toluenesulphinic acid were obtained.[9]

Generally the saturated products obtained were contaminated by traces of unsaturated compounds.[10] In the case of tosylhydrazones of 17-keto steroids only Δ^{16} androstenes were obtained.[1a]

It is not surprising that a multifunctional compound such as a tosylhydrazone can react with LAH in different ways leading to the formation of different products.[11]

Acylhydrazones are reduced by $NaBH_4$ to acylhydrazines.[12] Under the mild conditions used, side reactions are insignificant. In Table 2, the results obtained with $NaBH_4$ are summarized.[1c]

TABLE 2

Starting material tosylhydrazone of	Solvent: Dioxan product	Methanol yield %	Solvent: Dioxan product	Dioxan yield %
Cyclohexanone	Cyclohexane	70–80	Cyclohexane	70–80
Cholestan-3-one	Cholestane	70–80	Cholestane	70–80
Coprostan-3-one	Coprostane	75–80	Coprostane	65–75
17-β-Acetoxy-5α-androstane-3-one	17-β-Acetoxy-5α-androstane*	70–80	17-β-Acetoxy-5α-androstane*	65–70
3β-Acetoxy-5α-cholestane-7-one	3β-Acetoxy-5α-cholestane*	70–80	3β-Acetoxy-5α-cholestane*	65–75
3β-Acetoxy-5α-androstane-17-one	Starting material†	—	3β-Acetoxy-5α-androstane*	60–70
3β-Acetoxy-5α-pregnane-20-one	Starting material†	—	3β-Acetoxy-5α-pregnane*	60–70
α-Tetralone	Tetraline	30–35	Tetraline	30–35
Stearinaldehyde	Octadecane	60–70		
Lauraldehyde	Dodecane	60–70	Dodecane	55–70

* After acetylation † With saponification of acetoxyl group

Except for aromatic carbonyls the use of this reagent is advantageous as the products obtained are generally pure and the yields high. In many cases the conversion of ketones and aldehydes to saturated hydrocarbons takes place in one step without isolation of the tosylhydrazones.[13] As in other cases, gas is copiously evolved (also in aprotic solvents) and *p*-toluenesulphinic acid may be isolated.

In order to ascertain the course of the reaction, a series of tosylhydrazones were reduced in the cold with $NaBH_4$ in a *proton donor solvent*. In many cases thin layer chromatographic evidence indicated the formation of an intermediate compound.

[9] In many cases, variable amounts of thiolsulphonic ester were isolated. Thiosulphonic ester is reported to be formed from *p*-toluensulphinic acid during handling [cf. Vogel, *Practical Organic Chemistry* (Landmans, III Edition) p. 826].

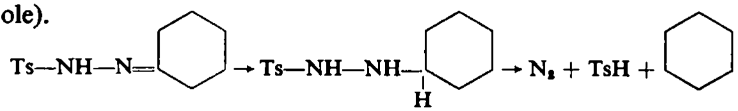
[10] TLC on Kieselgel G-$AgNO_3$ plates according to C. B. Barret, M. S. J. Davies and F. B. Padley, *Chem. & Ind.* 1050 (1962) has been widely applied in these analysis.

[11] The course of the formation of olefinic compounds during the reaction of tosylhydrazones with LAH has been elucidated by Prof. Djerassi *et al.* (private communication): see M. Fischer, Z. Pelah, D. H. Williams and C. Djerassi, *Chem. Ber.* in press.

[12] C. Bracci Torsi and M. Vuat, *Gazz. Chim. Ital.* **91**, 1461 (1961); D. Evans and T. F. Grey, *J. Chem. Soc.* 3006 (1965).

[13] A typical experiment is given: Cholestanone (1 g) is treated in MeOH (50 ml) with tosylhydrazide (1 g). The solution is refluxed for 2 hr, cooled, $NaBH_4$ (1 g) added in small portions, and the solution refluxed again for 4 hr. On cooling cholestane separates from the solution.

Direct chemical proof of the formation of substituted tosylhydrazides as intermediate compounds was obtained[1g] with the tosylhydrazone of cyclohexanone (I). The reduction of I under controlled conditions produces a compound, isolated in satisfactory yields (60–70%) and identical with cyclohexyl-tosylhydrazide (II). The latter (II) on refluxing in MeOH yields cyclohexane (1 mole), N_2 (1 mole) and *p*-toluenesulphinic acid (1 mole).



I II

FIG. 4

In the reduction of tosylhydrazones in *aprotic solvents* evidence has been obtained of the formation of intermediate compounds. The tosylhydrazone of cholestan-3-one (III) when reduced with diborane[14] in the cold, [1f]results in a mixture which produces high yields of cholestane,[15] only after it has been heated under reflux with water[16] or with LiH in toluene.

Similar results, though experimentally less evident, are obtained with LAH. If an ethereal solution of tosylhydrazone (III) is treated in the cold with LAH, the resulting mixture after evaporation of the solvent yields about 5% cholestane. If, however, the mixture is heated under reflux for 4 hr with water, the yield of cholestane is improved to 30%.[1f] The reaction, therefore, proceeds in two stages: reduction to an intermediate compound which is then decomposed.

All efforts to isolate this intermediate compound have been unsuccessful. The reduction intermediate cannot be the hydrazone (IV) of cholestanone since (IV) on treatment with $NaBH_4$ or LAH does not yield cholestane under the conditions under which the tosylhydrazone (III) furnishes cholestane in high yield. It is also noteworthy that $NaBH_4$, B_2H_6 and at least under the conditions reported, LAH do not cleave the sulphonamidic bond. It is possible[25] that the intermediate compound is a tosylhydrazide or an equivalent organometallic compound in which (case of diborane) the $>C{=}N{-}$ of the tosylhydrazone is transformed to $>CH{-}\underset{\substack{| \\ B \\ / \ \backslash}}{N}{-}$.

1:2-Elimination of *p*-toluenesulphinic acid and boron[17] could then lead to a diimide (or equivalent organometallic adduct) and then to nitrogen and the alkane. (Fig. 5).[25]

In the case of LAH, the course of the reaction should be similar and the formation of organometallic complexes is, moreover, very probable.

According to this mechanism, the two hydrogen atoms of the CH_2 formed, originate one from the reducing hydride and the second from the NH of the tosylhydrazone or

---

[14] Diborane is reported to reduce $>C{=}N{-}$ to $>CH{-}NH$, through the intermediate formation of organometallic compounds of the type $CH{-}\underset{\substack{| \\ B \\ / \ \backslash}}{N}{-}$: H. Feuer and B. F. Vincent, *J. Amer. Chem. Soc.* **84**, 3771 (1962).

[15] No gas was evolved during this first step of the reaction (comparison with blank experiment). Over 90% of the theoretical amount of N_2 was found in the mixture.

[16] Heating is necessary in order to obtain cholestane: the treatment of the mixture with water in the cold is not sufficient.

[17] Similar eliminations, with formation of C=C double bond, are not new in organoboron chemistry: L. Caglioti, G. Cainelli, G. Maina and A. Selva, *Gazz. Chim. Ital.* **92**, 309 (1962).

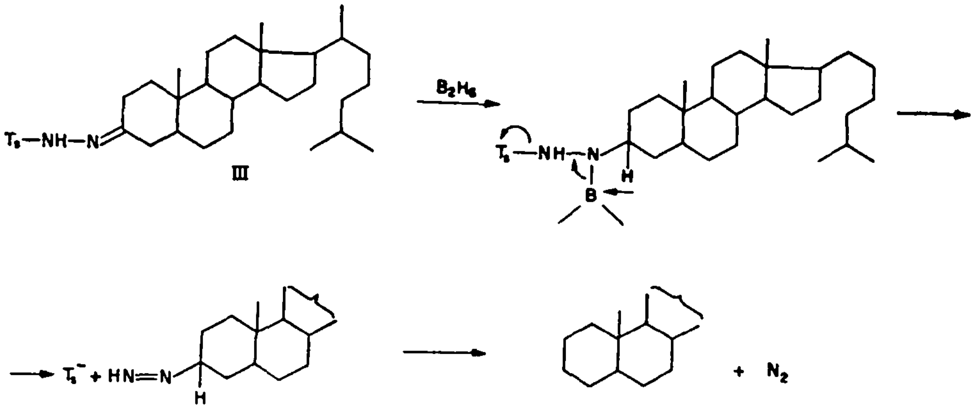
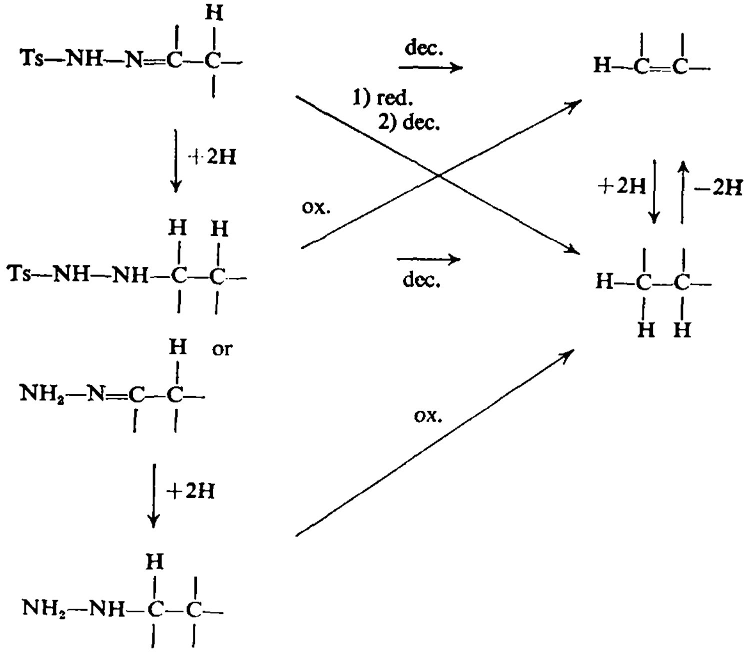


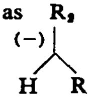
FIG. 5

from the water added during the working up of the reaction mixture. Prof. Djerassi demonstrated that in the case of LAH water is indispensable.[18]

The reduction of tosylhydrazones with reducing hydrides, therefore, provides a new and efficient method for the reduction of a ketonic or aldehydic carbonyl group



---

[18] In June 1965 Prof. Djerassi kindly sent us the manuscript of a work presently in press (M. Fischer, Z. Pelah, D. H. Williams and C. Djerassi *Chem. Ber.* in press) informing us that, with the use of deuterated complex hydrides, independently from our previous results, he demonstrated that anions such as  $\overset{R_2}{\underset{H \quad R_1}{\overset{(-)}{C}}}$ (in some way complexed) are intermediate during the reduction of tosylhydrazones with LAH at 70–80°. The formation of similar compounds, and the observation that, of the two hydrogen atoms of the formed CH_2 only one comes from the reducing hydride, agrees with our views.

to CH_2 under mild conditions. This reaction is part of a scheme interrelating the reactions of oxidation and reduction of hydrazones, tosylhydrazones, hydrazines and tosylhydrazines. In the following scheme these reactions are summarized.[1d]

It is important to realise that a substituted tosylhydrazide is equivalent, from the point of view of its oxidation level,[19] to a hydrazone. Consequently a substituted tosylhydrazide, and also tosylhydrazone, when decomposed with basic agents suffers an internal oxidation-reduction the original sulphonate residue being reduced to the corresponding sulphinate.

As part of this scheme and in order to find a new method to reduce a —COOH group to $—CH_3$ the reduction of acyl-tosylhydrazides was undertaken.

The problem of reducing a —COOH to $—CH_3$ generally requires a series of operations—reduction of the corresponding ester to alcohol, and LAH reduction of the corresponding tosylate or mesylate, or reduction to an aldehyde and subsequent transformation of the aldehydic carbonyl into a $—CH_2$ group.

As the carbonyl of acylhydrazides may be reduced to CH_2 through the action of LAH,[20] a series of acyl-tosylhydrazides were reduced with LAH[21] since if an alkyl-tosylhydrazide were produced then this, after decomposition, should give the desired result.

$$R—CO—NH—NH—Ts \rightarrow [R—CH_2—NH—NH—Ts] \rightarrow TsH + N_2 + R—CH_3$$

FIG. 6

The results obtained[1h] are given in Table 3.

TABLE 3

Starting material tosylhydrazide of	Product	Yield %
Palmitic	Hexadecane	—
Stearic	Octadecane	50–60
3α-Acetoxy-cholanic	3α-Hydroxy-cholane	45–50
α-Naphthoic	α-Methynaphthalene	25
β-Naphthoic	β-Methylnaphthalene	15
α-Naphthylacetic	α-Ethylnaphthalene	35
β-Indolilacetic	β-Ethylindole	15–20

Good results were obtained with aliphatic compounds but in the aromatic series the yields were much lower. In some cases, the corresponding alcohols or aldehydes, and variables amounts of thiosulphonic ethers[9] were isolated as by-products.

Under the conditions adopted,[22] the isolation of the probable intermediate alkyl-tosylhydrazides is impossible since alkyl-tosylhdrazides decompose at the temperature of the reaction.

---

[19] Oxidation levels are used as suggested by R. Robinson *The Structural Relations of Natural Products*, p. 4. Oxford Univ. Press (1955); A. Nickon and A. S. Hill, *J. Amer. Chem. Soc.* **86**, 1152 (1964).

[20] K. Kratzl and K. P. Berger, *Monats.* **89**, 83 (1958).

[21] 1,2,-Diacylhydrazines are not easily reduced by LAH [R. L. Hinmann, *J. Amer. Chem. Soc.* **78**, 2463 (1956)]. Therefore, particular conditions were adopted.

[22] A typical experiment is given: Tosylhydrazide of palmitic acid (1 g) was treated in dry dioxan (40 ml) with LAH (1 g) and the mixture refluxed 24 hr. The excess hydride was destroyed with water and the mixture worked up with ether yielding hexadecane (270 mg).

Work is in progress, in order to find more general and satisfactory conditions for this potentially useful reaction, and also to determine the course of the reaction.

The reduction of tosylhydrazones and acyl-tosylhydrazides apart from an academic interest in that the reactions are related to the oxidation and reduction of hydrazones and hydrazines etc., should possibly provide a solution to particular problems[23] notably for specific deuterium labeling.[24]

Acknowledgement—We wish to thank Prof. A. Quilico for his interest in this work. The present paper summarizes a series of papers published in preliminary form in English and Italian journals. The author is indebted to the valuable assistance given by Drs. P. Grasselli, G. Maina, M. Magi, A. Selva and G. Zubiani.

[23] For an extension of the reduction of the tosylhydrazones to the carbohydrates see A. N. De Belder and H. Weigel, *Chem. & Ind.* 1689 (1964).

[24] H. Budzikiewicz. C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry* Vol. I; pp. 30–31. Holden-Day, San Francisco (1964).

[25] (added in proofs on 25th Nov. 1965) The conversion of the tosylhydrazone of cyclohexanone (I) into cyclohexyl-tosylhydrazide (II) recently achieved in our laboratory through reduction with B_2H_6, or with $NaBH_4$ *in aprotic solvents* in the cold, and successive treatment with acetone and water, confirm our conclusions.