Cyanoethylation of Sulphonamides

By J. S. SHUKLA and R. K. SRIVASTAVA

Abstract

Some substituted sulphonamides have been cyanoethylated and they were subjected to reduction. On hydrolysis with aqueous and alcoholic sodium hydroxide the cyanoethylated sulphonamides gave decyanoethylated products identical to the original sulphonamides.

BRUSON et al.[1]) for the first time prepared the dicyanoethylated product of the type $C_6H_5SO_2N(CH_2CH_2CN)_2$ by condensing acrylonitrile with benzene sulphonamide. The evaluation of biological activity of these compounds showed that all of them possess more or less insecticidal property.

Since, p-chlorodiphenylsulfone exhibits good acaricidal[2]) activity as reported earlier. Hence a large number of substituted sulfones were synthesised[3]), in order to inter relate the insecticidal property with the structure of the different compounds. In the year 1956 MISRA and ASTHANA[4]) reported the preparation of benzyl phenyl sulfones and sulphonamides having general formulae $C_6H_5SO_2CH_2C_6H_4R$ and $RC_6H_4CH_2SO_2NH_2$. Among them p-chlorobenzylphenylsulphone was found to be very effective followed by the O-chlorobenzylphenylsulfone. The cyanoethylation of the sulfonamides was also carried out due to the fact that $-C\equiv N$ group increases the effectiveness of the drug which on testing proved to be very useful.

It seemed worthwhile to aim at synthesising several N-substituted sulfonamides which were cyanoethylated in the usual manner with a view to find out some more potential insecticides. Subsequently these cyanoethylated sulfonamides were reduced and hydrolysed. The purpose of reduction is to obtain amines which are likely to become of pharmacological importance. The reduction was carried out with $LiAlH_4$ according to the method discussed by LAWRENCE et al.[5]). For hydrolysis of cyanoethylated products,

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[1]) BRUSON and RIENER, J. Amer. chem. Soc. **65**, 23 (1943).

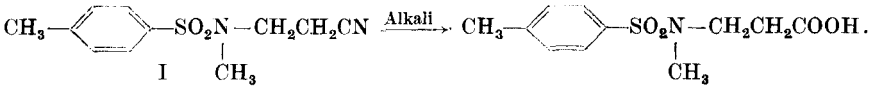
[2]) Chem. Eng. New, **29**, 1983 (1951).

[3]) G. S. MISRA and R. S. ASTHANA, J. prakt. Chem. [4] **3**, 4 (1956).

[4]) G. S. MISRA and R. S. ASTHANA, J. prakt. Chem. [4] **3**, 4 (1956).

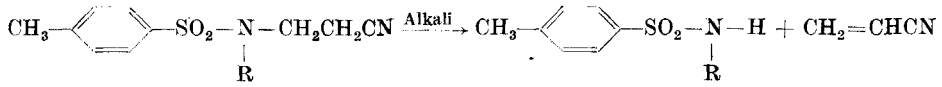
[5]) LOWRENCE, H. AMUNDSEN and Lloyd S. NELSON, J. Amer. chem. Soc. **73**, 242 (1951).

the method[6]) of MISRA and ASTHANA has been followed. According to them, the $-C\equiv N$ group hydrolysed to COOH in alkaline medium without affecting the other positions of the molecule. One example is cited below:



Compound I was hydrolysed i.e. (N-methyl-N-(2-cyanoethyl)-p-toluenosulphonamide) with aqueous caustic soda and alcoholic caustic soda under similar conditions but the results could not be repeated. The products on analysis were found to be identical with the expected known sulphonamide i.e. p-toluene-N-methyl sulphonamide, and not acid as reported by them. Further confirmation was attained by the analysis and I.R. spectra. The I.R. spectra showed typical bands as for disubstituted benzene ring, and alkylated amines.

In substituted cyanoethylated sulphonamides mainly the splitting of acrylonitrile takes place in alkaline medium. Among the products of reaction were observed acrylonitrile and alkyl substituted sulphonamides. Several such substituted-p-toluene sulphonamides were prepared and hydrolysed as given in the following reaction:



(Where R=CH_3, C_2H_5, C_3H_7 and C_4H_9.)

There decyanoethylation at the N-atom takes place in aqueous or alcoholic alkali. This is so because the bond between β-cyanoethyl group and N-alkyl substituted sulphonamide nitrogen is less stronger than other amide N-atom.

Experimental

Substituted sulphonamides and their cyanoethylation products

p-Toluene-N-methyl sulfonamide

It was prepared according to method of REVRDIN[7]), and had m.p. 75°. (Literature gives M.P. 75°C).

N-Methyl-N-(2-Cyanoethyl)-p-toluene sulfonamide

To a stirred solution of p-toluene-N-methylsulfonamide (5 g.) and benzyltrimethyl ammonium hydroxide (0.5 g.) of 40% in dioxane (20 ml.) was added freshly distilled acrylonitrile (2.3 g.) dropwise at 30—35°. The solution was then acidified with dilute hydrochloric acid and poured on ice to yield solid.

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[6]) G. S. MISRA and R. S. ASTHANA, J. prakt. Chem. [4] 4, 270 (1957).

[7]) F. REVRDIN, B. 42, 1523.

The solid obtained was recrystallised from ethanol in colourless needles and melted at 105—106 °C. Yield, 4.8 g. (96% of theory).

$C_{11}H_{14}O_2N_2S_2$ Requires: N, 11.76%, found: N, 11.57%.

P-Toluene-N-ethyl sulfonamide

This sulfonamide was prepared according to method MARCKWALD, DROSTE-HUELSHOFF[8]) and had a m.p. 63—64°. (Literature gives m.p. 63°—64°).

N-Ethyl-N-(2-cyanoethyl)-p-toluene sulfonamide

A mixture of p-toluene-N-ethyl sulfonamide (5 g.), 40% benzyl trimethyl ammonium hydroxide (0.5 g.) and dioxane (20 ml.), was stirred and to this was added freshly distilled acrylonitrile (2.8 g.). At the end of 48 hours, the reaction mixture was acidified with dilute hydrochloric acid and poured on ice to yield a solid which was recrystallised from alcohol, m.p. 55°. Yield, 3.5 g. (70% of theory).

$C_{12}H_{16}O_2N_2S$ Requires: N, 11.11%, found: N 11.2%.

p-Toluene-N-propyl sulfonamide

This sulfonamide was prepared according to method MARCKWALD[9]) and had a m.p. 50—51°. (Literature gives m.p. 52°).

N-Propyl-N-(2-cyanoethyl)-p-toluene sulfonamide

To a well stirred mixture of p-toluene-N-propyl sulfonamide (3 g.), dioxane (15 ml.) and 40% benzyl-trimethyl ammonium hydroxide (0.56 g.) was added to acrylonitrile (1.45 g.) dropwise. The reaction mixture was stirred for 48 hours at room temperature, neutralised with dilute hydrochloric acid and then poured on ice. A white solid separated which was recrystallised from ethanol in colourless crystals, m.p. 73—74 °C. Yield, 2.5 g. (83% of theory).

$C_{13}H_{18}O_2N_2S$ Requires: N, 10.53%, found: N, 10.52%.

p-Toluene N-isopropyl sulfonamide

It was prepared according to the method given by MARCKWALD[10]). The melting point of sulfonamide was founded to be 51 °C. (Literature gives 52 °C).

N-isopropyl-N-(2-cyanoethyl)-p-toluene sulfonamide

Acrylonitrile (1.4 g.) was added to a well stirred mixture of p-toluene-N-isopropyl sulfonamide (2.5 g.), dioxane (10 ml) and 40% benzyl trimethyl ammonium hydroxide (0.4 g.). A white solid was obtained by following the above procedure. It was recrystallised from ethanol in colourless crystals, m.p. 75 °C. Yield, 2 g. (80% of theory).

$C_{13}H_{18}O_2N_2S$ Requires: N, 10.53%, found: N, 10.41%.

P-Toluene-N-butyl sulfonamide

This compound was prepared according to method DEMENY[11]). It melts at 47—48 °C. (Literature gives 48 °C).

[8]) W. MARCKWALD, V. DROSTE-HÜLSHOFF, B. **32**, 560.

[9]) W. MARCKWALD, Ber. dtsch. chem. Ges. **32**, 3508.

[10]) W. MARCKWALD, Ber. dtsch. chem. Ges. **32**, 3508.

[11]) L. DEMENY, Rec. trav. chem. **50**, 51—9 (1931).

N-Butyl-N-(2-cyanoethyl)-p-toluene sulfonamide

To a stirred solution of N-butyl-p-toluene sulfonamide (5 g.), dioxane (20 ml.) and benzyl trimethyl ammonium hydroxide (0.5 g.), was added dropwise acrylonitrile (2.8 g.). The mixture was stirred for 48 hours and the product was neutralised with dilute hydrochloric acid and poured on ice. The semi-solid, which on rubbing with ethanol solidified slowly into a solid mass. This was recrystallised with ethanol, m.p., 69—70 °C. Yield, 4 g. (80% of theory).

$C_{14}H_{20}O_2N_2S$ Requires: N, 10%, found: N, 10.05%.

Reduction of N-alkyl N-(2-cyanoethyl)-p-toluene sulphonamides

(Alkyl = CH_3, C_2H_5, C_3H_7, C_4H_9 etc.).

Method

A solution of N-alkyl N(2-acyanoethyl)-p-toluene sulfonamide (0.02 mole) in dry ether (20 mole) was slowly added to a suspension of $LiAlH_4$ (0.02 mole) in dry ether (50 ml.), and placed in a conical flask, provided with a magnetic stirrer and a dropping funnel. The reaction mixture was refluxed for 2—3 hours. The excess of $LiAlH_4$ was decomposed with ethyl acetate (10 ml.) and the $LiAlH_4$ complex was decomposed by means of water (25 ml.). The etherial layer was separated, washed with water, dried over Na_2SO_4 and the solvent was

Table 1

Alkylsubstituted-aminopropylsulphonamides

Reduction product	M.P.	% of yield	Molecular formula	Percentage of Nitrogen	
				Required	Found
1. N-Methyl-N-(3-amino-propyl) p-toluene sulfon-amide	96—97 °C	79.5	$C_{11}H_{18}N_2SO_2$	11.57	11.52
2. N-Ethyl-N-(3-amino-propyl) p-toluene sulfon-amide	60 °C	75	$C_{12}H_{20}N_2SO_2$	10.93	10.85
3. N-Propyl-N-(3-amino-propyl) p-toluene sulfon-amide	80—81 °C	80	$C_{13}H_{22}N_2SO_2$	10.37	10.27
4. N-isopropyl-N-(3-amino-propyl) p-toluene sulfon-amide sulfonamide-HCl	168—169 °C	78	$C_{13}H_{22}N_2SO_2HCl$	9.14	9.15
5. N-Butyl-N-(3-amino-propyl)-p-toluene sulfon-amide-HCl	142 °C	63.5	$C_{14}H_{24}N_2SO_2HCl$	8.74	8.83

distilled off. The residual mass crystallised from ethanol into colourless crystals with good yield. Analytical data for various N-alkyl-N-(3-aminopropyl)-p-toluene sulphonamide used are summarised in the table 1.

Hydrolysis of N-methyl-N-(2-cyanoethyl)-p-toluene sulphonamide

N-methyl-N (2-cyanoethyl) p-toluene sulfonamide (7 g.), was refluxed with a solution of sodium hydroxide (4 g.) in water (30 ml.) for twenty hours on a sand bath. The reaction mixture was cooled, acidified and extracted with ether. The ethereal layer was thoroughly washed with water, dried and the ether distilled off. The solid mass recrystallised from ethanol which melted at 74—75 °C.

$C_8H_{11}O_2NS$ Requires: N 7.57%, C 51.89%, H 5.95%; found: N 7.3%, C 52.79%, H 6.21%.

In the same way other cyanoethylated sulfonamides were hydrolysed. The results are summarised in table 2.

The above prepared nitriles were also hydrolysed with 20% alcoholic sodium hydroxide for twenty hours. Results are summarised in table 3.

Table 2
Cyanoethylated Sulphonamides

Cyanoethylated sulfonamides	Time in hours	% NaOH	Hydrolysed product	M.P.	Molecular Formula	% of Nitrogen	
						Required	Found
N-Methyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	15	N-methyl-p-toluene sulfonamide	74—75 °C	$C_8H_{11}SO_2N$	7.57	7.30
N-Ethyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	15	N-Ethyl-p-toluene sulfonamide	64 °C	$C_9H_{13}SO_2N$	7.04	7.14
N-Propyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	15	N-Propyl-p-toluene sulfonamide	52 °C	$C_{10}H_{15}SO_2N$	6.57	6.76
Iso Propyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	15	iso-Propyl-p-toluene sulfonamide	51—52 °C	$C_{10}H_{15}SO_2N$	6.57	6.76
N-Butyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	15	N-Butyl-p-toluene sulfonamide	48—49 °C	$C_{11}H_{17}SO_2N$	6.17	6.24

Table 3
Cyanoethylated Sulphonamides

Cyanoethylated sulfonamides	Time in hours	% of alcoholic caustic soda	Hydrolysed product	M.P.	Molecular Formula	% of Nitrogen	
						Required	Found
N-Methyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	20	N-methyl-p-toluene sulfonamide	74–75 °C	$C_8H_{11}SO_2N$	7.57	7.30
N-Ethyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	20	N-Ethyl-p-toluene sulfonamide	63–64 °C	$C_9H_{13}SO_2N$	7.04	7.14
N-Propyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	20	N-Propyl-p-toluene sulfonamide	51–52 °C	$C_{10}H_{15}SO_2N$	6.57	6.76
Iso-propyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	20	p-Toluene isopropyl sulfonamide	50–52 °C	$C_{10}H_{15}SO_2N$	6.57	6.76
N-Butyl-N-(2-cyanoethyl) p-toluene sulfonamide	20	20	p-toluene-N-Butyl sulfonamide		$C_{11}H_{17}SO_2N$	6.17	6.24

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Lucknow (India), Department of Chemistry, Lucknow University.

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