Tetrahedron Letters,Vol.23,No.14,pp 1505-1508,1982 0040-4039/82/141505-04$03.00/0
Printed in Great Britain

AN EFFICIENT ONE-POT SYNTHESIS OF NITRILES FROM ACID CHLORIDES

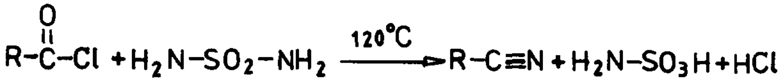
A.Hulkenberg* and J.J. Troost

Duphar B.V. Research Laboratories
P.O. Box 2, 1380 AA Weesp, The Netherlands

Summary: Treatment of aliphatic, aromatic as well as heterocyclic acid chlorides with sulfonamide in sulfolane at 120°C for 3 hours produces the corresponding nitriles in high yields.

In general the conversion of acids or acid chlorides into the corresponding nitriles requires two or more steps. One of the most popular methods consists of converting an acid chloride into the primary amide followed by dehydration[1]. Another generally applicable conversion of an acid into a nitrile makes use of the extreme air and humidity sensitive chlorosulfonyl isocyanate but the intermediate chlorosulfonyl amide needs a separate basic decomposition step[5]. Relatively few one step procedures have been described, all of them require drastic reaction conditions, e.g. the conversion of aromatic acids with urea[2] at 240°C or the reaction of acids with para-toluenesulfonamide[3] or methanesulfonamide[4] and phosphorus pentachloride at 175-210°C. These methods give variable yields and are only satisfactory for the conversion of aromatic acids; whereas aliphatic acids generally give very poor results.

We wish to present a general procedure for the one-pot conversion of acid chlorides into their corresponding nitriles. The method consists of simply warming together the acid chloride with an equivalent of sulfonamide[6] for three hours in sulfolane at 120°C.



$$R-\overset{\overset{O}{\|}}{C}-Cl + H_2N-SO_2-NH_2 \xrightarrow{120^{\circ}C} R-C\equiv N + H_2N-SO_3H + HCl$$

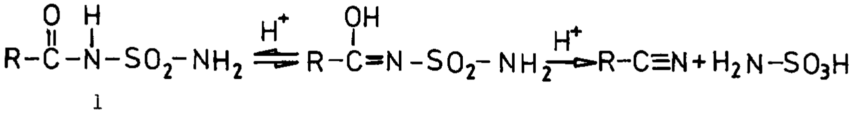
To our knowledge this conversion of an acid chloride into a nitrile mediated by sulfonamide has not previously been described[7]. As can be seen from the results, summarized in the table, the method is successful for a large variety of acid chlorides: aliphatic-, aromatic- with electron withdrawing and electron donating substituents, sterically hindered as well as heterocyclic nitriles are obtained in high yield after a simple work-up procedure. The method can also be used for upscaling.(see table entries 19 and 20)

With the choice of sulfolane there is the advantage of good solubility of all reactants and the possibility of using higher temperatures if needed. Thus it was found that the sterically hindered 2.6-dichlorobenzoyl chloride did not react at all at 120°C but a nearly quantitative conversion into the nitrile took place at 180°C. The yield of 4-nitrobenzonitrile also benefits from higher temperatures (see table entries 8 and 9).

It is also possible to perform the reaction without a solvent (see table entry 1) but good results are not always obtained[8].

Instead of an acid chloride it is also possible to use an acid as starting material. In this case 1.05 equivalent of thionyl chloride is added to the solution of the acid and sulfonamide (see table entries 3, 10 and 14).

Another important feature of sulfolane is the good solubility of hydrogen chloride in this solvent which is necessary for the decomposition of the initially formed acylsulfonamide 1, according to the following reaction pathway.



$$R-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-SO_2-NH_2 \overset{H^+}{\rightleftharpoons} R-\overset{\overset{OH}{|}}{C}=N-SO_2-NH_2 \xrightarrow{H^+} R-C\equiv N + H_2N-SO_3H$$

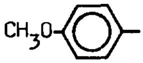
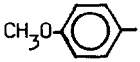
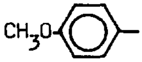
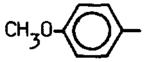
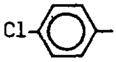
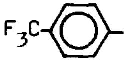
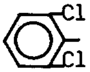
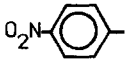
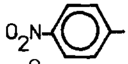
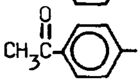
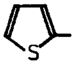
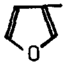
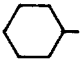
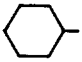
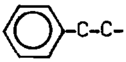
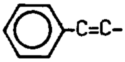
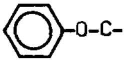
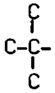
1

Heating the intermediate 1, e.g. 4-methoxybenzoylsulfonamide, alone or in solution at 120°C gives no decomposition into the nitrile whereas only traces of nitrile are observed at 180°C[9]. Addition of para-toluenesulfonic acid accelerates the decomposition of 1 drastically. So 4-methoxybenzoylsulfonamide is quantitatively decomposed into the corresponding benzonitrile by refluxing in toluene with a catalytic amount of para-toluenesulfonic acid. Thus toluene or xylene instead of sulfolane can also be used. Due to the poor solubility of hydrogen chloride in these solvents, however, 0.1 equivalent of para-toluenesulfonic acid has to be added at the start of the reaction, otherwise poor, if any conversion of the intermediate 1 will be observed (see table entries 4 and 18). Omission of the added acid leads to quantitative formation of the intermediate acylsulfonamides[7,7a].

General procedure[10]

0.01 mole of an acid chloride and 0.012 mole of sulfonamide are dissolved in 10 ml of sulfolane and the solution is subsequently warmed for three hours at 120°C. After cooling, the reaction mixture is poured into 75 ml of 1 N sodium hydroxide and extracted three times with ether-cyclohexane (1:1). The organic layer is then washed three times with water in order to remove traces of sulfolane, dried over sodium sulfate and subsequently evaporated; an almost pure product results[11].

Table: RC≡N; Sulfonamide-mediated conversion of acid chlorides into nitriles

nr.	R[12]	T$^{\circ}$C	yield (%)[13]	Remarks
1		120	89	no solvent used
2		120	97	
3		120	95	from RCOOH
4		120	78	toluene as solvent para-toluenesulfonic acid as catalyst
5		120	91	
6		120	93	
7		180	93	no reaction at 120°C
8		120	62	
9		150	78	
10		120	82	from RCOOH[14]
11		120	87	
12		120	81	
13		120	95	
14		120	88	from RCOOH
15		120	80	
16		120	90	
17		120	78	
18	-C-C-C-C-	120	85	toluene as solvent para-toluenesulfonic acid as catalyst
19	 $\mathrm{C{-}\overset{C}{\underset{C}{C}}{-}}$	120	85[15]	
20	Cl-C-C-	120	81[15]	

References and Notes

1. Buehler and Pearson, Survey of organic synthesis, Wiley Interscience N.Y. 951 (1970)

2. J. Lücke, R.E. Winkler, Chimia, 25 94 (1971)

3. C.S. Miller, Organic Synthesis, Collective Vol. 3 646 (1955)

4. E.N. Grivsky, Bull.Soc.Chim.Belges, 80 245 (1971)

5. H. Vorbrüggen, Tetrahedron Letters, 1631 (1968)

6. Sulfonamide is commercially available from Fluka A.G. Switzerland

7. Acylsulfonamides, aliphatic as well as aromatic, which are intermediates in this reaction are well known compounds to be synthesized from sulfonamide and acid chlorides or anhydrides in hydrocarbon solvents.

7a Farbenfabriken Bayer A.G. Germ.Pat. 876, 846 (1953), Chemical Abstracts 48 12172d

8. e.g. 4-chlorobenzoylchoride gives a good melt with sulfonamide at 120°C but hardens again after some time, due to the formation of the 4-chlorobenzoylsulfonamide. Only traces of the nitrile are formed and a considerable amount of the acid chloride remains unchanged.

9. In the presence of electronegative substituents it seems possible to decompose an acylsulfonamide into a nitrile by thermolysis. Only one example is described by N.P. Aktaev c.s., Zhurnal Organicheskoi Khimii, 9 462 (1973)

10. All experiments are performed on a 10 mmole scale at temperatures as indicated in the table.

11. Purity established by quantitative ^{1}H NMR analysis: 90 to >98%

12. All the structures of the isolated nitriles were confirmed by their ^{1}H NMR spectra

13. Yields are not optimized and are not corrected for the purity of the acid chlorides. The acid chlorides used are commercially available or freshly prepared. The yields given are based on isolated yield as evaluated from quantitative ^{1}H NMR data.

14. Under the same conditions 2-carbomethoxybenzoic acid gives phthalimide

15. The nitrile was synthesized on a 0.25 mole scale and distilled directly from the reaction mixture.

(Received in UK 28 January 1982)