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UNUSUALLY VERSATILE VILSMEIER-HAACK REAGENTS

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The adducts of dimethylformamide (DMF) with acyl halides $[(CH_3)_2N\text{-}CHX]^+y^-$ (1) are the key reagents in the Vilsmeier-Haack reaction (2). While phosphorus oxychloride has been the halide mainly used, there have also been reported reactions using other phosphoryl halides, thionyl chloride, phosgene and aryl sulphonyl chlorides. We now report the first use in such reactions of sulphamyl halide-DMF systems and record three different kinds of reactions with these.

The first of these reactions was the normal Vilsmeier-Haack substitution exemplified by the reaction of dimethyl sulphamyl chloride with primary aromatic amines in DMF solution when the corresponding formamidine hydrochloride was obtained, thus

$$(CH_3)_2N\text{-}SO_2Cl.(CH_3)_2N\underset{\underset{O}{\|}}{C}\text{-}H \;+\; XNH_2 \longrightarrow H\text{-}\underset{\underset{N\text{-}X}{\|}}{C}\text{-}N(CH_3)_2.\ HCl \qquad (1)$$

I, X = Ar, II, X = NHAr

Table I summarises the data obtained in this reaction together with that from the corresponding reaction with substituted arylhydrazines (where the products were the corresponding hydrazidines (II),) and the table also includes the results of some cognate reactions. In our work we made products of types I and II, by reaction (1) and confirmed their identities by their synthesis in one or both of two other ways as well, namely from the corresponding reactions with either toluene-sulphonyl chloride-DMF adducts (3) or from dimethylaminoformacetal (4). A typical example of one of our runs is as follows.

To a mixture of 0.025 moles of dimethylsulphamyl chloride in 0.26 moles of DMF was added 0.025 moles of m-chloroaniline. The resulting

Table I Formamidine and Hydrazidine Syntheses

Run	Halide System + DMF	Amine	Formamidine Structure	Yield	m.p.
1.	$(CH_3)_2NSO_2Cl$	$m\text{-}NO_2C_6H_4NH_2$	I, Ar = $C_6H_4NO_2(m)$	84	248-250°
2.	TsCl			60	248-250°
3.	$(CH_3)_2NSO_2Cl$	$C_6H_2NH_2,NO_2,Cl_2$[1]	I, Ar = $C_6H_2Cl_2NO_2(2,6,4)$	38	260-261°
4.	TsCl			65	260-261°
5.	TsCl	$m\text{-}ClC_6H_4NH_2$	I, Ar = $C_6H_4Cl(m)$	55	232°
6.	$(CH_3)_2NSO_2Cl$	$p\text{-}NO_2C_6H_4NHNH_2$	II, Ar = $C_6H_4NO_2(p)$	81	169-170°[2]
7.	$HCN(CH_3)_2(OCH_3)_2$			80	169-170°[2]
8.	$(CH_3)_2NSO_2Cl$	$2,4\text{-}(NO_2)_2C_6H_3NHNH_2$	II, Ar = $C_6H_3(NO_2)_2(2,4)$	71	234°
9.	$(C_4H_8NO)^3\text{-}SO_2Cl$			78	234°
10.	TsCl	$2,4\text{-}(NO_2)_2C_6H_3NHNH_2$	II, Ar = $C_6H_3(NO_2)_2(2,4)$	71.5	246°[2]
11.	$HCN(CH_3)_2(OCH_3)_2$			84	246°[2]

Table II Sulphamide and Sulphonic Acid Formation

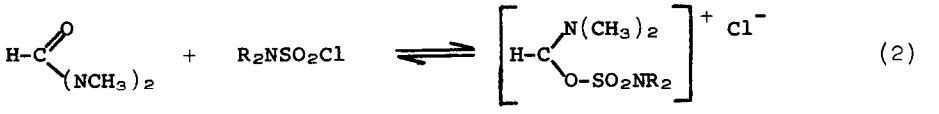
Run	Aromatic Component	Halide + DMF	Reaction Temp.	Products	Yield	m.p.
1.	$C_6H_5N(CH_3)_2$	$(C_4H_8NO)^3\text{-}SO_2Cl$	0°	$(C_4H_8NO)_2{}^3\text{-}SO_2$	24	141°
				$(C_4H_8NO)^3\text{-}SO_2N(CH_3)_2$	38	42°
2.	$C_6H_5N(CH_3)_2$	$(C_4H_8NO)^3\text{-}SO_2Cl$	75°	$(C_4H_8NO)_2{}^3\text{-}SO_2$	14	141°
				$(CH_3)_2NC_6H_4SO_3H$	68	-
				$(CH_3)_2NC_6H_4SO_2(C_4H_8NO)^3$	0.9	202°
3.	$C_6H_5OCH_3$	$(CH_3)_2NSO_2Cl$	0°	$(CH_3)_2NSO_2N(CH_3)_2$	39	77°
4.	$C_6H_5N(C_2H_5)_2$	$(CH_3)_2NSO_2Cl$	0°	$(CH_3)_2NSO_2N(CH_3)_2$	67	77°[4]
			75°	$(C_2H_5)_2NC_6H_4SO_3H$	77	292°

[1] 2,6-dichloro-4-nitroaniline. [2] Free base. [3] C_4H_8NO represents morpholinyl. [4] m.p. of Na salt.

solution was heated at 75° for one hour. On standing overnight at room temperature, N,N-dimethyl-N'-(m-chlorophenyl)formamidine hydrochloride m.p. 230-233° separated out in 68% yield. An additional 23% of product was obtained on work-up of the filtrate. Recrystallisation from ethanol gave the pure product m.p. 233°.

We next attempted to extend these sulphamyl halide-DMF reactions to substitution in aromatic nuclei. Thus, repeat of one of the standard procedures (5) in this type of reaction, namely treatment of dimethylaniline with $POCl_3$.DMF (at 0°C) followed by basification and steam-distillation of the reaction mixture yielded p-dimethylaminobenzaldehyde in 56% yield(reported (5) 50%). On the other hand, under identical conditions, treatment of dimethylaniline with $(CH_3)_2NSO_2Cl$.DMF resulted in the formation of tetramethylsulphamide in 71% yield. Control of the reaction temperature was critical because the dimethyl sulphamyl chloride-DMF plus dimethylaniline reaction mixture when maintained at 75°for 1 hour yielded p-dimethylaminobenzene sulphonic acid in 80% yield. In cognate experiments, tetramethyl sulphamide did not sulphonate dimethylaniline nor did dimethyl sulphamyl chloride yield tetramethyl sulphamide on treatment with triethylamine or pyridine in DMF at 0°C.

We can formulate the three modes of behaviour of these sulphamyl halide-DMF complexes as follows :



(2)

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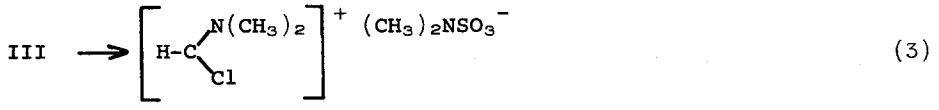

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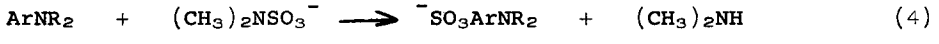

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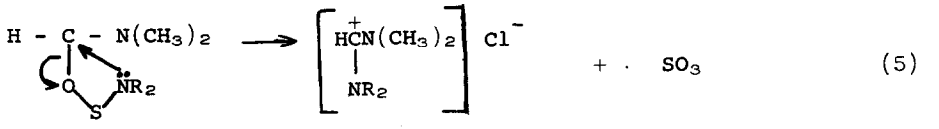

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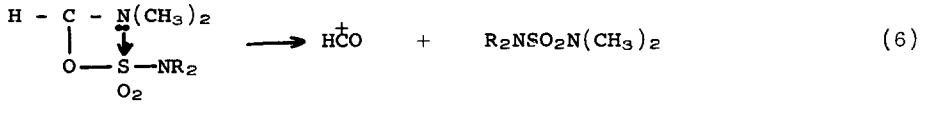

(6)

The sulphonation reactions we have detected thus can arise either via the counter anion, dimethylsulphamate (reaction 4) or from SO_3 (as in 5). The generation of SO_3 by the reaction of primary sulphamyl halides with amides has been reported very recently by Lohaus (6).

The formation of sulphamides of type $R_2NSO_2N(CH_3)_2$ can arise in the way suggested (reaction 6) or perhaps first by decomposition of the DMF to dimethylamine which then reacts with the sulphamyl halide. Interestingly, when a solution of DMF and dimethylsulphamyl chloride was refluxed for 4 hours no substituted sulphamide was obtained (contrast the reaction of DMF with aroyl halides (7). We have demonstrated elsewhere (8) that sulphamides of the type $R_2NSO_2NR_2$ can arise from R_2NSO_2Cl in the absence of any DMF.

We have found that when DMF is excluded from the aromatic reactions substitution of a different type takes place as shown in reaction (7).

$$C_6H_5NMe_2 + Me_2NSO_2Cl \longrightarrow Me_2NC_6H_4SO_2NMe_2 + Me_2NC_6H_4SO_2C_6H_4NMe_2 \quad (7)$$

Thus, when 0.019 moles of dimethylsulphamyl chloride and 0.047 moles of dimethylaniline were heated at 120° for 4 hours and kept at room temperature for a further 24 hours N,N-dimethyl-p-dimethylaminobenzene sulphonamide and bis-(4-dimethylaminophenyl) sulphone were obtained in 33% and 6% yields respectively.

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