Tetrahedron Letters,Vol.25,No.43,pp 4979-4982,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

REACTION OF NUCLEOPHILES WITH ELECTRON ACCEPTORS BY S_N2 OR SINGLE ELECTRON TRANSFER (S.E.T.) MECHANISMS: THIOLATES AND 2-HALOMETHYL-5-NITROFURANS.

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Summary: Thiolates react with 2-halomethyl-5-nitrofurans to yield 5-nitrofurfuryl sulphides by a $S_N2(C)$ mechanism, and disulphides and 2-methyl-5-nitrofuran by a $S_N2(X)$ mechanism.

In the last few years there have been numerous reports[1] of the difficulty in distinguishing between S_N2 and single electron transfer (S.E.T.) mechanisms in nucleophilic substitutions. Thiolates have been reported to react with various halo-nitro substrates (2-halo-2-nitropropanes[2], halo-nitromethanes[3], *p*-nitrobenzyl halides[4], and 2-halomethyl-5-nitrofurans[5]) to yield the corresponding sulphides or disulphides by $S_{RN}1$, S_N2 and equivalent redox mechanisms.

(E1)

Prousek, in his important pioneering work[5c] on the reactions between thiolates and 2-halomethyl-5-nitrofurans (E1) has proposed the $S_{RN}1$ mechanism for sulphide formation (E2-E5) and a redox mechanism involving hydrogen (H·) abstraction by the 5-nitrofurfuryl radical from methoxide (E2,E3,E6) or dimerisation (E7). We report our mechanistic studies of the above reactions.

$$O_2NFurCH_2X + RS^- \longrightarrow [O_2NFurCH_2X]^{\ddagger} + RS\cdot \quad (E2)$$

$$[O_2NFurCH_2X]^{\ddagger} \longrightarrow O_2NFurCH_2\cdot + X^- \quad (E3)$$

$$O_2NFurCH_2\cdot + RS^- \longrightarrow [O_2NFurCH_2SR]^{\ddagger} \quad (E4)$$

$$[O_2NFurCH_2SR]^{\ddagger} + O_2NFurCH_2X \longrightarrow O_2NFurCH_2SR + [O_2NFurCH_2X]^{\ddagger} \quad (E5)$$

$$O_2NFurCH_2\cdot + CH_3O^- \longrightarrow O_2NFurCH_3 + [CH_2O]^{\ddagger} \quad (E6)$$

$$2\ O_2NFurCH_2\cdot \longrightarrow O_2NFurCH_2CH_2FurNO_2 \qquad 2RS\cdot \longrightarrow RSSR \quad (E7)$$

Substitution reactions: The results are shown in the table. 2-Bromomethyl-5-nitrofuran was reacted with several thiolates, and phenylsulphinate, to yield only the corresponding substituted products. Similarly, 2-iodomethyl-5-nitrofuran reacted with phenylsulphinate, 2-pyrimidylthiolate (in DMF and DMSO) and *p*-nitrophenythiolate (in DMF) to yield substitution on carbon. Five of these reactions (as shown in the table) were tested for the $S_{RN}1$ mechanism by well established diagnostic techniques.[4a] The absence of light, an oxygen atmosphere, or the addition of 20 molar% of *p*-dinitrobenzene (*p*-DNB, a strong electron acceptor) or di-*t*-butylnitroxide (DTBN, a radical scavenger) all showed no inhibition of substituted product.

Our results indicate that a non-chain mechanism is operative for the substitution on carbon. We propose that a S_N2 on carbon [$S_N2(C)$] mechanism is the best explanation, which concurs with the mechanistic proposals of Russell and Pecoraro[4b] for the reaction between thiolates and *p*-nitrobenzyl halides to yield *p*-nitrobenzyl sulphides. However, thiolates are strong electron-donors and the nitrofurans are strong electron-acceptors and therefore the

$O_2NFurCH_2X + RS^- \longrightarrow O_2NFurCH_2SR + RSSR + O_2NFurCH_3 + (O_2NFurCH_2)_2 + X^-$

X	R	Conditions[a]	$O_2NFurCH_2SR$[b]	RSSR[b]	$O_2NFurCH_3$[b]	$(O_2NFurCH_2)_2$[b]
Br	2-pyrimidyl	MeOH, 10 min[c]; DMF, 10 min	92,83%	0,0%	0,0%	0,0%
Br	*p*-chlorophenyl	MeOH, 10 min[c]	85	0,0	0,0	0,0
Br	Benzyl	MeOH, 10 min	84	0,0	0,0	0,0
Br	phenyl	MeOH, 10 min	74	0,0	0,0	0,0
Br	($PhSO_2^-$)	MeOH, 4h[c]	53[d] [15][e]	0,0	0,0	0,0
I	($PhSO_2^-$)	DMF, 30 min[c]; MeOH, 5h	79[d], 34[d] [17][e]	0,0	0,0	0,0
I	2-pyrimidyl	MeOH, 10 min;	0	43	36	0
		+dark; + O_2	0,0	47,55	41,38	trace, trace
		+20 & 100 molar % *p*-DNB	0,0	65,61	46,51	4,2
		+20 & 100 molar % DTBN	0,0	54,55	43,53	0,0
		+100 molar% norbornadiene	0	55	53	0
		i-PrOH, 45 min; CH_3OD, 10min	25,35	30,30	10,7[f]	20,18
		t-BuOH, 45 min: THF, 45min	65,65	5,13	trace, 0	20,0
		acetone, 45 min	44	34	5	0
		DMF, 10 min[c]; DMSO, 10 min	60,53	0,0	0,0	0,0
I	phenyl	MeOH, 20 min; CH_3OD, 20 min	2,18	84,79	56,25[f]	0,4
		i-PrOH, 20min; *t*-BuOH, 20min	4,3	78,64	20,23	2,14
		THF, 20min; acetone, 20 min	4,2	76,81	2,13	2,5
		DMF, 5min; DMSO, 5 min	29,17	65,67	30,32	0,4
I	*p*-nitrophenyl	MeOH, 10 min; DMF, 10 min	0,36	53,2	47, trace	2,0
I	*L*-cysteine	MeOH:H_2O(85:15), 30 min	0	88	40	0
SPh	phenyl	DMF, 10 min; MeOH, 10 min	61[e], 73[e]	0,0	0,0	0,0
2-pyrimidylthiyl	2-pyrimidyl	MeOH, 10 min	78[e]	0	0	0

(a) Reactions were carried out under an atmosphere of N_2 with hν catalysis (2 x 150W Tungsten 'white light' lamps) with a molar ratio of $O_2NFurCH_2X:RS^-$ of 1:1 for X = Br and 1:2 for X = I (b) % yields based on $O_2NFurCH_2X$ (for X = I, a stoichiometry of 1:2 was assumed). (c) No inhibition with, the absence of hν, O_2, and 20 molar % of *p*-DNB or DTBN. (d) $O_2NFurCH_2SO_2Ph$. (e) Unreacted $O_2NFurCH_2X$. (f) $O_2NFurCH_2D$.

non-chain $S_{ET}2$ mechanism proposed by Russell[16] cannot be excluded (E8). Catalytic amounts of strong electron acceptors and radical scavengers will not inhibit a non-chain reaction, but equimolar amounts should, unless the intermediate radicals and radical-anions remain tightly held in a solvent cage.

$$O_2NFurCH_2X + RS^- \longrightarrow [(O_2NFurCH_2X)^{\cdot-}\ RS\cdot] \longrightarrow [O_2NFurCH_2\cdot\ X^-\ RS\cdot] \longrightarrow O_2NFurCH_2SR + X^- \quad \text{(E8)}$$

Redox reactions: The reaction of 2-iodomethyl-5-nitrofuran with thiolates exhibited a competition between substitution and redox which was surprisingly sensitive to changes in solvent and the nature of the thiolate. The results are shown in the table. We propose that the redox reaction proceeds by a $S_N2(X)$ mechanism (i.e. S_N2 on the X-substituent) to yield the anion of 2-methyl-5-nitrofuran and the corresponding sulphenyl iodide (E9). The anion is protonated by the solvent (E10) or by 2-iodomethyl-5-nitrofuran or reacts with the latter compound to yield the dimer (E11). The sulphenyl iodide reacts rapidly with a second equivalent of thiolate to yield disulphide (E9). The 5-nitrofurfuryl sulphide is unreactive to further thiolate which rules out a $S_N2(C)$, followed by a S_N2 on sulphur, mechanism (E12).

$$O_2NFurCH_2I + RS^- \longrightarrow O_2NFurCH_2^- + RSI \xrightarrow{RS^-} RSSR + I^- \quad \text{(E9)}$$

$$O_2NFurCH_2^- + MeOH \longrightarrow O_2NFurCH_3 + MeO^- \quad \text{(E10)}$$

$$O_2NFurCH_2^- + O_2NFurCH_2I \longrightarrow O_2NFurCH_2CH_2FurNO_2 + I^- \quad \text{(E11)}$$

$O_2NFurCH_2SR + RS^- \not\longrightarrow O_2NFurCH_2^- + RSSR$ (E12)

The S.E.T. mechanisms proposed in E2-E7 are unlikely[1b,2c] because they require the intermediate free-radical ($O_2NFurCH_2\cdot$) to react by two different routes (E4, or E6 and E7) under the same reaction conditions; *e.g.* 2-pyrimidylthiolate in MeOH reacts with 2-bromomethyl-5-nitrofuran to yield the corresponding sulphide, and with 2-iodomethyl-5-nitrofuran to yield disulphide and 2-methyl-5-nitrofuran. The nature of the substituent should not affect the reaction of the radical ($O_2NFurCH_2\cdot$) and thiolate.

$O_2NFurCH_2^- + CH_3OD/CH_3O^- \longrightarrow O_2NFurCH_2D + CH_3O^-$ (E13)

$O_2NFurCH_2\cdot + CH_3OD/CH_3O^- \longrightarrow O_2NFurCH_3 + (CH_2O)^{\pm}/or\ \cdot CH_2OD$ (E14)

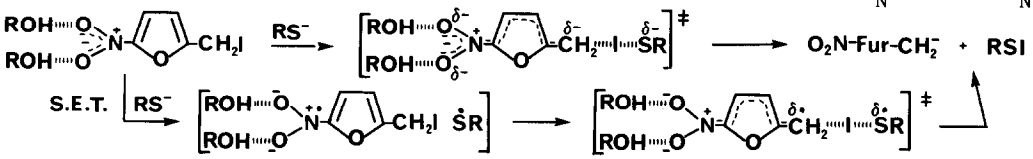
To further elucidate the nature of the intermediate, phenylthiolate was reacted with 2-iodomethyl-5-nitrofuran in CH_3OD/CH_3O^-. The anion would be expected to deuteriate[7] (E13) and the free-radical to abstract hydrogen (H·) from CH_3OD or CH_3O^- (E14).[7] 2-Methyl-5-nitrofuran was isolated in 25% yield with 75% mono-deuteriation and 1% di-deuteriation. We suggest that the 24% of non-deuteriated product does not arise from hydrogen abstraction but from protonation by 2-iodomethyl-5-nitrofuran, which would also explain the formation of 2-methyl-5-nitrofuran in some of the reactions in non-protic solvents. Dimer formation (E11) predominated over protonation (E10) at high concentration or in solvents less acidic than MeOH (*e.g.* *t*-BuOH, *i*-PrOH, CH_3OD).

Further evidence against the S.E.T. redox mechanism was provided by the lack of inhibition of the reaction between 2-pyrimidylthiolate and 2-iodomethyl-5-nitrofuran in MeOH by the absence of light, by an oxygen atmosphere, or by catalytic or equimolar amounts of *p*-DNB and DTBN. Likewise, norbornadiene did not trap any thiyl radicals.[2c] Also, if 2-methyl-5-nitrofuran was formed by hydrogen (H·) abstraction from the solvent, the abstraction should be favoured in different solvents in the order : THF>>*i*-PrOH>>MeOH.[8] The reverse order was observed with both 2-pyrimidyl-and phenyl-thiolate (*i.e.* the order expected for protonation).

$O_2NFurCH_2^- + Me_2CO \longrightarrow O_2NFurCH_2C(OH)Me_2 \xrightarrow{-H_2O} O_2NFurCH{=}CMe_2$ (E15)

In the reaction between 2-pyrimidylthiolate and 2-iodomethyl-5-nitrofuran in acetone, 5% of the olefin formed by reaction of the intermediate anion with acetone (E15) was isolated, giving yet further support for an anion intermediate. Evidence for the sulphenyl iodide intermediate was obtained by trapping[3] it as the thiolsulphonate ($RS\text{-}SO_2Ph$) with phenylsulphinate (5 molar equivalents) in the reaction between 2-pyrimidylthiolate and 2-iodomethyl-5-nitrofuran in MeOH, in 2% yield (5% crude).

The effect of solvent on the reaction between thiolates and 2-iodomethyl-5-nitrofuran is remarkable, *e.g.* the reaction with 2-pyrimidylthiolate in MeOH gives complete redox whereas the reaction in dipolar aprotic solvents gives only substitution. We propose that the solvent effects are explained by solvation of the nitro-group of 2-iodomethyl-5-nitrofuran by protic solvents thereby lowering the electron-density on iodine which favours $S_N2(X)$ over $S_N2(C)$ (E16).



(E16)

(E17)

Bromide is much less easily positively polarised than iodide which explains the lack of

$S_N2(X)$ in the reactions of 2-bromomethyl-5-nitrofuran. Thiolate is largely unaffected by solvation (ref. 2a and refs. therein), thereby providing a unique system in which the solvation of the nucleophile can be largely ignored, allowing observation of the effects of solvation of the electrophile which are normally obscured by the much greater effects of nucleophile solvation in the reaction. Kamlet-Taft solvation parameters[9] (MeOH = 0.990; *i*-PrOH = 0.687; *t*-BuOH = 0.436; acetone, THF, DMSO, & DMF = 0) provide an excellent guide to the strength of solvation observed, *i.e.* MeOH > *i*-PrOH > CH_3OD > *t*-BuOH > acetone, THF, DMSO, DMF. Of interest is the solvating ability of CH_3OD which appears to be slightly weaker than *i*-PrOH and much weaker than CH_3OH (which can be explained by a secondary isotope effect[9]).

A non-chain S.E.T. mechanism (E17), as suggested for the reaction of 2-halo-2-nitropropanes with thiolates,[2a] cannot be excluded. The effects of solvation and the nature of the furfuryl substituent should be similar for both S.E.T. and $S_N2(X)$ mechanisms, and if the radical intermediates are held in a solvent cage they will not be trapped. However, the significant difference in results between the more nucleophilic and more polarisable ("softer") phenylthiolate and cysteine anion, and the less nucleophilic and less polarisable ("harder') 2-pyrimidylthiolate and *p*-nitrophenylthiolate support the $S_N2(X)$ mechanism. The more polarisable thiolate prefers to attack the more polarisable electrophilic iodine centre rather than the less polarisable carbon centre. Comparison of the results in each solvent shows a strong preference for $S_N2(X)$ over $S_N2(C)$ for phenylthiolate relative to 2-pyrimidylthiolate.

The difference in reactivity for the S.E.T. mechanism would have to depend on the intermediate thiyl radical [*i.e.* a reactive thiyl will react rapidly (E17) while a less reactive thiyl will allow dissociation to yield sulphide (E8). Evidence[10] for the reactivity of these thiyls suggests that electron-withdrawing substituents slightly increase reactivity, *i.e.* the opposite required to explain the S.E.T. proposals.

We conclude that our evidence suggests that the most likely mechanisms for the reaction of 2-halomethyl-5-nitrofurans with thiolates is $S_N2(X)$ to yield disulphide and reduced furan products, and $S_N2(C)$ to yield 5-nitrofurfuryl sulphides. We suggest that our mechanistic conclusions also apply to the reactions reported with thiolates and *p*-nitrobenzylhalides.[4c]

We thank the S.E.R.C. for a studentship (C.D.B.).

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(Received in UK 26 July 1984)