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# INTRAMOLECULAR AROMATIC SUBSTITUTION ($S_{RN}1$) REACTIONS, USE OF ENTRAINMENT FOR THE PREPARATION OF BENZOTHIAZOLES

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Summary The process of entrainment (catalytic chain initiation) with the enolate-anion of acetone has been used in intramolecular aromatic $S_{RN}1$ substitution for the preparation of 2-phenyl- and 2-methyl-1,3-benzothiazole in high yield from *o*-iodothiobenzanilide and *o*-iodothioacetanilide

The number of reports[1,2] of aromatic nucleophilic substitutions proceeding by the $S_{RN}1$ mechanism is rapidly increasing A number of these papers[3] refer to the use of $S_{RN}1$ reactions for the preparation of heterocyclic compounds There are however only three reports[4,5,6] of intramolecular $S_{RN}1$ substitutions (Scheme 1)

Scheme 1

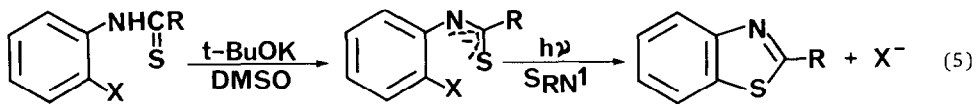
$$X\text{-}Ar\text{-}Y^- + e^- \longrightarrow (X\text{-}Ar\text{-}Y^-)\cdot \qquad \text{Initiation} \quad (1)$$

$$(X\text{-}Ar\text{-}Y^-)\cdot \longrightarrow Ar\text{-}Y^- + X^- \qquad \text{Propagation} \quad (2)$$

$$Ar\text{-}Y^- \longrightarrow (Ar\,Y)\cdot \qquad " \quad (3)$$

$$(Ar\,Y)\cdot + X\text{-}Ar\text{-}Y^- \longrightarrow Ar\,Y + (X\text{-}Ar\text{-}Y^-)\cdot \qquad " \quad (4)$$

This paper reports our application of intramolecular $S_{RN}1$ substitution to the preparation of 1,3-benzothiazoles (Equat 5) Our results are presented in the Table




(5)

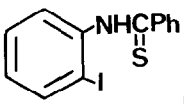
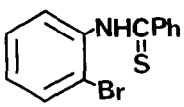
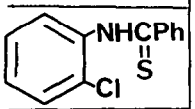
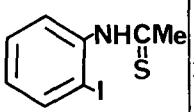
When we attempted to carry out this reaction with various solvents and bases, and with light catalysis, only starting-material was recovered The reaction is apparently not initiated by intermolecular electron-transfer from the thioamide-anion to the aryl-halide Intramolecular electron-transfer would not be predicted to lead to a $S_{RN}1$ chain reaction

We therefore sought a process for catalytic initiation of the chain reaction Although entrainment[7,8] with an anion as the electron-donor had not been previously used in aromatic $S_{RN}1$, we thought that it would be particularly applicable to an intramolecular reaction The intermediate aryl-radical is likely to undergo intramolecular addition (Equat 3) to the thioamide-anion faster than intermolecular addition to the entraining anion We chose the enolate-anion of acetone because its behaviour in aromatic $S_{RN}1$ reactions is well known[2,9]

We used the conditions previously reported for $S_{RN}1$ substitution with the enolate-anion of acetone (8 molar excess, 3½h) and obtained excellent yields of 2-phenyl- and 2-methyl-1,3-benzothiazole from the corresponding *o*-iodoanilides (Equat 5) When lower amounts of the enolate were used the yield dropped, indicating inefficient entrainment

Although successful entrainment is in itself a good criterion for assigning the $S_{RN}1$ mechanism[2,8] we also studied the phenyl reaction in the presence of inhibitors The use of catalytic amounts of strong electron-acceptors (*p*-dinitrobenzene and oxygen) and efficient

Table Preparation of Benzothiazoles from *o*-Iodothioanilides

| *o*-Haloanilide | [a]Conditions | % Benzothiazole | % Starting Material |
|---|---|---|---|
|  | t-BuOK (8 equiv ), 6 h | 0 | 100 |
| | t-BuOK (3 equiv ), 5½h, acetone(0 2 equiv ) | 13 | 42 |
| | t-BuOK (20 equiv ), 3½h, acetone(8 equiv ) | 100 | 0 |
| | $O_2$, dark | 0,0 | 100,100 |
| | 10 molar % *p*-dinitrobenzene or $(t\text{-Bu})_2NO$ | 0,0 | 100,100 |
| | CuI (0 2 equiv ), 5 min r t or 80°, 2h | 100 | 0 |
| | $O_2$ | 100 | 0 |
| | 10 molar % *p*-dinitrobenzene or $(t\text{-Bu})_2NO$ | 100,100 | 0,0 |
|  | t-BuOK (2 5 equiv ), 5½h | 0 | 100 |
| | t-BuOK (20 equiv ), 6h, acetone(8 equiv ) | 22 | 62 |
| | CuBr (0 2 equiv ), 5 min, 80° or 6h, r t | 93,100 | 0,0 |
| | $O_2$, 20 molar % *p*-dinitrobenzene | 98,88 | 0,0 |
| | 30 molar % $(t\text{-Bu})_2NO$ | 100 | 0 |
|  | t-BuOK (3 equiv ), 7h, acetone (0 2 equiv.) | 0 | 98 |
| | t-BuOK (22 equiv ), 5h, acetone(10 equiv ) | 5 | 63 |
| | t-BuOK (22 equiv ), 6½h | 9[b] | 20[b] |
|  | t-BuOK (22 equiv ), 4h, acetone (8 equiv ) | 58 | 0 |
| | NaH (20 equiv ), 6½h, acetone (8 equiv ) | 100 | 0 |
| | CuI (0 2 equiv.), 4¾h | 70 | 0 |

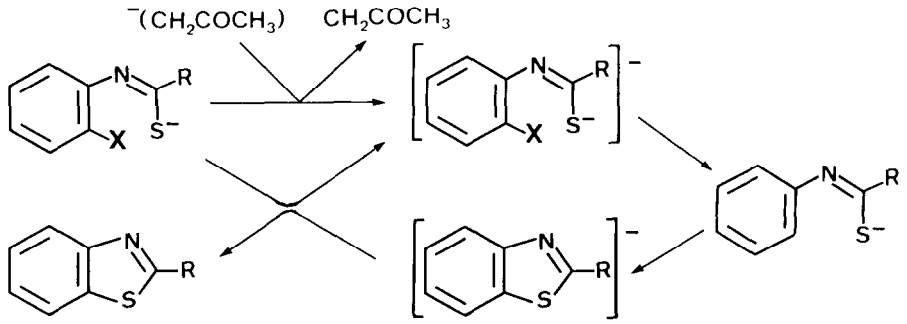
a. Typical Procedures 1) Acetone was added to t-BuOK in DMSO under an atmosphere of nitrogen and dry conditions The haloanilide was added and the irradiation started (12 x 25W at 350nm) 2) CuI or CuBr was added to DMF under an atmosphere of nitrogen and dry conditions This was followed by the addition of t-BuOK and then the haloanilide

b Low yields are due to extensive purification

radical-scavengers (di-tert-butylnitroxide and oxygen) completely inhibited the reaction, with almost quantitative recovery of starting material In the oxygen inhibition traces of a phenol resulting from reaction of the aryl-radical with oxygen and subsequent disproportionation were observed Similarly when the reaction was carried out in the dark, complete inhibition occurred, clearly indicating the requirement for light catalysis Substitution with different halogens in the ortho-position showed I>Br>Cl as the order of nucleofugality (100, 22, and 5% resp ) which is in contrast to the roughly equivalent nucleofugality observed in $S_NAr$ reactions These four experimental methods are established ways[2,8] of assigning the $S_{RN}1$ mechanism We therefore propose that this intramolecular substitution proceeds by the $S_{RN}1$ mechanism as shown in Scheme 2

Benzothiazoles have been prepared[9,10] under similar conditions from the same starting materials via benzyne intermediates If the reaction is proceeding via a benzyne intermediate then the *m*-iodothiobenzanilide should also yield 2-phenyl-1,3-benzothiazole as reported[9,10] When *m*-iodothiobenzanilide was reacted under the same conditions as the ortho-analogue no ring closure was observed after 5h However a quantitative amount of thiobenzanilide was isolated

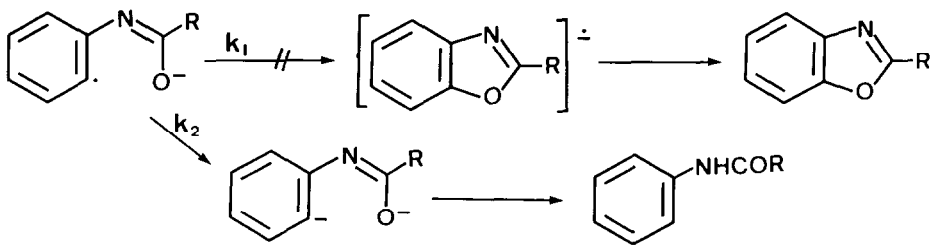
Scheme 2



Interestingly the intermediate aryl-radical does not add to the entraining anion A possible explanation is that electron-donation by the side chain into the ring slows addition by anions The intramolecular addition of the thio-amide anion is fast enough to overcome this effect, but reduction of the aryl-radical is faster than the intermolecular addition of the enolate-anion of acetone Reduction of the aryl-radical instead of addition to anions in slow $S_{RN}1$ reactions has been observed[11] previously

Attempts to prepare 2-phenyl-1,3-benzoxazoles under the same conditions from *o*-iodobenzanilide failed, and a small yield (21%) of benzanilide and unreacted starting material (64%) were isolated A similar result was obtained for the methyl analogue The inability of oxygen centred anions to participate in $S_{RN}1$ reactions has been reported[1,12] Bunnett[1] has suggested that the energy barrier to the intermediate radical-anion is too high to allow reaction (the extra electron in the radical-anion would initially be sited in the high-energy C-O σ* orbital) Therefore, as with the *m*-iodothiobenzanilide reaction, reduction takes place preferentially to substitution (Scheme 3 with $k_1 << k_2$)

Scheme 3



Attempts to initiate the 2-phenyl-1,3-benzothiazole reaction with potassium (20 molar %) in liquid-ammonia gave a low yield of product, but larger amounts of potassium led to intractable products

Copper(I) salts have been reported[6,13,14] to act as useful catalysts in aromatic nucleophilic substitutions The mechanism of these reactions is unknown but it has been suggested[15] that the intermediate is a copper complex More recently[14] $S_{RN}1$ has been proposed as a possible mechanism Reaction of the anions of the *o*-iodothioanilides in DMF with catalytic amounts of CuI at room temperature gave excellent yields of the corresponding benzothiazoles after 5 min We failed to inhibit the phenyl reaction with oxygen, *p*-dinitrobenzene, or di-tert-butylnitroxide This lack of inhibition could be explained by the fast rate of reaction, but when repeated on the slower *o*-bromothiobenzanilide and CuBr reaction (5h) still no

inhibition of benzothiazole formation was observed These results indicate that a $S_{RN}1$ mechanism is unlikely, but it is possible that the inhibitors fail to compete in copper(I) catalysed intramolecular substitutions

The corresponding reaction with *o*-iodobenzanilide with 20 molar % of CuI at room temperature gave almost no yield of 2-phenyl-1,3-benzoxazole, but on heating with one equivalent of CuI for 3½h a quantitative yield of the benzoxazole was isolated This much faster substitution by a sulphur-anion relative to the corresponding oxygen-anion has been previously reported[15] Further studies are required to elucidate whether copper(I) catalysed reactions by thianions proceed by the $S_{RN}1$ mechanism.

We conclude that our results show that intramolecular $S_{RN}1$ reactions can be greatly accelerated by the process of entrainment and that it could prove to be an invaluable synthetic aid to the preparation of heterocycles We have shown that sulphur-anions are much better nucleophiles than oxy-anions in $S_{RN}1$ substitutions It is also the first example of thioamide anions participating in the $S_{RN}1$ mechanism The intramolecular $S_{RN}1$ and copper(I) catalysed reactions provide simple high yield syntheses of 1,3-benzothiazoles We gratefully acknowledge the support of The Boots Company and the S E R C for a CASE studentship (P H G S )

References

1. G Galli and J F Bunnett, J Am Chem Soc , 1981, 103, 7140 and refs cited therein
2 J F Bunnett, Acc Chem Res , 1978, 11, 413, J F Wolfe and D R Carver, Org Preps and Procedures Int , 1978, 10, 227
3 R Beugelmans, H Ginsburg, and M Bois-Choussy, J Chem Soc , Perkin Trans 11, 1982, 1149, R R Bard and J F Bunnett, J Org Chem , 1980, 45, 1547
4 M F Semmelhack and T Bargar, J Am Chem Soc , 1980, 102, 7765
5 J F Wolfe, M C Sleevi and R R Goering, J Am Chem Soc , 1980, 102, 3646
6 T Kametani, K Takahashi, M Ihara, and K Fukumoto, J Chem Soc , Perkin Trans 1, 1976, 389
7 N Kornblum, R T Swiger, G W Earl, H W Pinnick, and F W Stuchal, J Am Chem Soc , 1970, 92, 5513
8 M Chanon and M L Tobe, Angew Chem , Int Ed Engl , 1982, 21, 1
9 J F Bunnett, R G Schamehorn and R P Traber, J Org Chem , 1976, 41, 3677
10 J F Bunnett, T Kato, R R Flynn, and J A Shorey, J Org. Chem , 1966, 28, 1, J F Bunnett and B F Hrutfiord, J. Am Chem Soc., 1961, 83, 1691
11 M F Semmelhack and T M Bargar, J Org Chem., 1977, 42, 1481, R Beugelmans and M Bois-Choussy, Synthesis, 1981, 729, C Amatore, J Rinson, J-M Saveant, and A Thiebault, J Am Chem Soc , 1982, 104, 817
12 R A Rossi and A B Pierini, J Org Chem , 1980, 45, 2914
13 R G R Bacon and A Karim, J Chem Soc , Perkin Trans 1, 1973, 272
14 H Suzuki, H Abe and A Osuka, Chem Lett (Japan), 1980, 11, 1363
15 R G R. Bacon and H A O Hill, J Chem Soc , 1964, 1108

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