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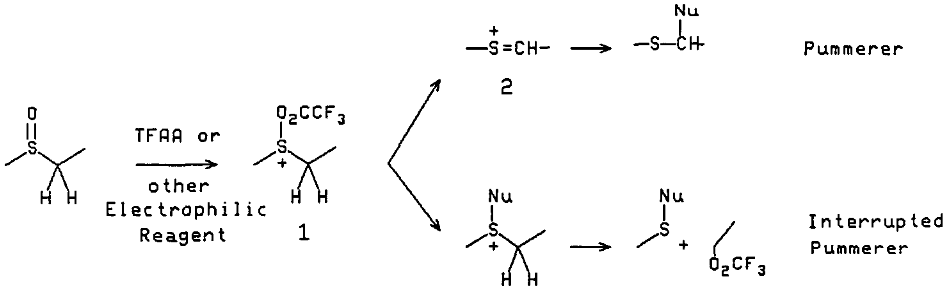
AN INTERRUPTED PUMMERER REACTION INDUCED BY VILSMEIER REAGENT ($POCl_3$/DMF)[1]

Dallas K. Bates*, Burnell A. Sell, and Joseph A. Picard
Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, MI
49931 USA

Abstract: In a one pot sequence, treatment of N-(2-ethylsulfinylphenyl)pyrrole (3a) with $POCl_3$/DMF (Vilsmeier reagent) produces 1- and 3- pyrrolo[2,1-b]benzothiazole carbaldehydes (5 and 6) in 73% and 9% yields, respectively.

The Pummerer reaction normally proceeds from sulfoxide to product via an activated sulfoxide (1) and a sulfenium ion (2) which reacts with a nucleophile at carbon. In the interrupted Pummerer reaction, the tricoordinate sulfur intermediate (1) undergoes reaction with the nucleophile **at sulfur** leading to unexpected products under Pummerer reaction conditions.

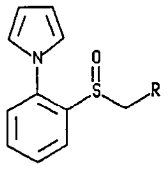


We recently reported an interrupted Pummerer reaction that provides a very simple and convenient procedure for preparation of pyrrolo[2,1-b]benzothiazole (4) by treatment of N-(2-ethylsulfinylphenyl)pyrrole (3a) with trifluoroacetic acid/ trifluoroacetic anhydride at 0°C [2]. While investigating the chemistry of this ring system we needed a sample of 1-pyrrolo[2,1-b]benzothiazole carbaldehyde (5).

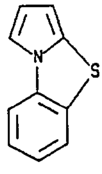
Simple pyrroles readily undergo Vilsmeier-Haack formylation with $POCl_3$/DMF [3]; similar treatment of 4 gave the desired 5 in 62% yield (after chromatography, not optimized) along with the 3-carbaldehyde 6.

In considering ways to improve the overall yield of 5 from 3, it occurred to us that the Vilsmeier-Haack reagent itself might be capable of inducing Pummerer or related rearrangements. These reactions are initiated by reagents which share the ability to convert a sulfoxide oxygen into a leaving group. We therefore hoped that electrophilic reagents such as imminium species 7 or 8 formed in the V-H process would similarly react at the sulfoxide oxygen of 3 in a reaction paralleling that of more traditional reagents used in Pummerer-type reactions [4-6].

To our immense satisfaction, compound 3a when treated with 2 equivalents of POCl$_3$ in DMF gave the interrupted Pummerer product 5 in 73% yield (after chromatography) along with the 3-isomer (6, 9%) [7]. Although the exact nature of the electrophilic species is not known, this is the first example of a Pummerer-type rearrangement catalyzed by V-H reagent or any other imminium species.



3 a R=CH$_3$
b R=CN



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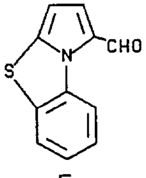
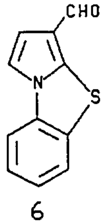
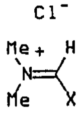


5



6



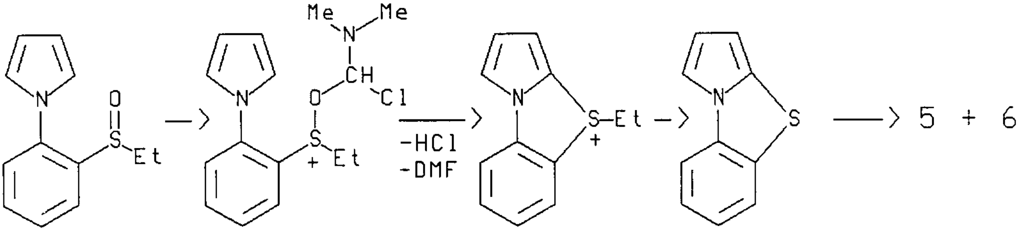
7 X=OPOCl$_2$
8 X=Cl

Structures 5 and 6 were assigned to the products based on spectral data [for 5 [8]: mp 132-132.5 $^{\circ}$C (from hexanes); IR (KBr): 1650 cm^{-1} (vinylogous formamide); NMR (CDCl$_3$, 200 MHz): 6.45 (1H, d, J=4.35 Hz, H-3), 7.25-7.50 (3H, m [including a d, J=4.35 Hz centered at 7.33],H-2, H-6, H-7), 7.62 (1H, ddd, J=7.85, 1.43, 0.52 Hz, H-5), 9.31 (1H, dd, J=8.26, 0.70 Hz, H-8), 9.47 (1H, s, CHO); ^{13}C NMR (CDCl$_3$): 102.3, 118.0, 118.3, 123.0, 125.0, 126.1, 128.9, 130.8, 131.7, 140.9, 175.2; MS [m/z (rel intensity)]: 201(100, M$^+$), 200(75), 172(57), 145(22), 128(15), 69(69) and for 6 [8]: mp 133.5-134 $^{\circ}$C (from hexanes); IR (KBr); 1645 cm^{-1} ; NMR (CDCl$_3$, 200 MHz: 6.99 (1H, d, J=3.21 Hz, H-2), 7.22-7.54 (3H, m [including a d, J=3.21 Hz centered at 7.45]), H-1, H-6, H-7), 7.69 (1H, d, J=7.60 Hz, H-5), 7.76 (1H, d, J=7.50 Hz, H-8), 9.86 (1H, s, CHO); MS [m/z (rel intensity): 201(89, M$^+$), 200(100), 172(24), 145(12), 128(20), 69(22)]. These data clearly establish the pyrrolo[2,1-b]benzothiazole ring system which would be expected from interrupted Pummerer rearrangement of 3.

There are no reports in the literature of electrophilic reactions of pyrrolo[2,1-b]benzothiazoles. By analogy to reactivity patterns of simple pyrroles in which an electron donating substituent on C-2 directs incoming electrophiles to C-3 and C-5 [3], one would expect the sulfur atom of 4 to direct incoming electrophiles to C-1 and C-3. This is the case; the position of the aldehyde group on C-1 in the major product 5 is confirmed by the large downfield shift of the C-8 ring hydrogen as a result of shielding by the proximate carbonyl at C-1. In both 5 and 6, H-2 is located adjacent to the aldehyde carbonyl; these hydrogens exhibit chemical shifts of 7.33 and 6.99 ppm, respectively, shifted from 6.52 ppm in the parent ring system. The coupling constant J$_{1,2}$ (3.21 Hz) in 6 is smaller than that for J$_{2,3}$ (4.35 Hz) in 5, a trend also observed in simple pyrroles.

Under reaction conditions that convert 3a into 5/6 the corresponding cyanomethyl sulfoxide 3b gave a 40% yield of a 1:1 mixture of 5 and 4-cyanopyrrolo[2,1-c]benzothiazole 11, the normal Pummerer rearrangement product from 3b [9]. Compound 11 is not formylated under the reaction conditions because the pyrrolo[2,1-b]benzothiazole system 4 is much more reactive in electrophilic reactions than pyrrolo[2,1-c]benzothiazines, *ie.* 11, due to the activating effect of direct attachment of the sulfur atom to the pyrrole ring in 4.

The mechanism we postulate for benzothiazole formation reaction is shown below and is similar to that proposed for the interrupted Pummerer reaction of **3** induced by trifluroacetic anhydride [2]. The greater propensity of **3b** to undergo normal Pummerer rearrangement is due, at least in part, to the presence of the electron withdrawing cyano group. This substituent, having an acidifying influence on the *alpha*-hydrogen, would aid elimination from the activated sulfoxide (9) to form the sulfenium ion, *ie* **2**, leading down the path to normal products. Compound **3a** and other sulfoxides with simple alkyl side chains undergo elimination to sulfenium ions at a much slower rate, if at all, under the reaction conditions. Consequently the activated sulfoxide has an opportunity to undergo nucleophilic attack at sulfur leading to a sulfonium salt (10)[10] (of course the pyrrole ring sees this reaction as aromatic electrophilic substitution [11]). Under the reaction conditions nucleophilic displacement of the side chain from **10** produces the parent heterocycle (4). Once formed, **4** undergoes standard V-H formylation to the observed products.

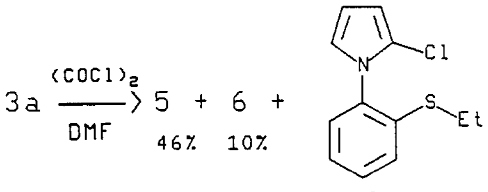


3a 9 10 4

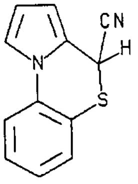
That the reaction is catalyzed by Vilsmeier-Haack reagent and not $POCl_3$ is evidenced by the fact that treatment of **3a** with $POCl_3$ alone in toluene gave only deoxygenation to the corresponding sulfide (88%) [12].

Compound **3b** is the first example we have observed to produce both normal and abnormal products in the same reaction. The reaction solvent (DMF vs toluene or trifluoroacetic acid) and the nature of the leaving group (DMF vs CF_3COO^-) are different from other cases we have studied and their relative influence in determining the course of the reaction is unknown. From a synthetic standpoint however the message is clear: simple alkyl side-chains in the sulfoxide enhance the likelihood of interrupted Pummerer products.

Oxalyl choride has been substituted for phosphorus oxychloride in formylation reactions [13]. When 1a was treated with oxalyl chloride in DMF in addition to **5** (46%) and **6** (10%) another product identified as 12 (32%) [8] [data: oil(darkened on standing]; bp 105 ^oC (bath temperature)/ 0.4 torr; IR (neat): 2980, 2940, 1660, 1490, 1430, 1410, 1320, 1255, 1070, 760, 730, 710 cm^{-1}; NMR ($CDCl_3$, 60 MHz): 1.25 (3H, t, J=7



12 (32%)



11

Hz), 2.85 (2H, q, J= 7 Hz), 6.30-6.55 (2H, m), 6.90 (1H, dt, J= 12, 2 Hz), 7.20-7.70 (4H, m); MS [m/z(rel intensity)]: 239/237(4,11, M$^+$), 210/208(8,23), 202(33), 174(78), 173(100)] was isolated [14]. Subsequently in large scale preparations of **5** we have observed traces of **12** from the reaction of **3a** with POCl$_3$/DMF.

The following experimental procedure is illustrative:
To stirred DMF (3.0 mL) at 0 ^{o}C was added phosphorus oxychloride (0.56 g, 3.66 mmol). A solution of 3a (0.4 g, 1.83 mmol) in DMF (12 mL) was added dropwise to the complex at 0 ^{o}C over 15 min. After an additional 15 min, the ice bath was removed and the mixture stirred at room temperature for 1 h followed by an additional 1 h at 70 ^{o}C. The reaction mixture was then poured into 100 mL of water and the pH adjusted to pH 8 by addition of 4 M sodium acetate (about 125 mL). The precipitate which formed on stirring this mixture overnight was identified as pure **5**. The aqueous filtrate was extracted with benzene (2x 100mL) and the combined extract chromatographed on alumina to give **6** and additional **5**.

References and Notes

1. Paper 3 in the series "Intramolecular Capture of Pummerer Rearrangement Intermediates." For Part 2 see reference 2.

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3. R.A. Jones, G.P. Bean, The Chemistry of Pyrroles, Academic Press, New York, New York, 1977, pp 152-155.

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5. Sulfonyl chlorides: R.E. Boyle, **J. Org. Chem., 1966.** *31*, 3880-3882; E.H.A.-Neizer, S.K. Ray, R.A. Shaw, B.C. Smith, **J. Chem. Soc., 1965**, 6250-6252.

6. DCC: Displacement of dicyclohexyl urea from the DMSO/DCC adduct by a primary alcohol in the Moffatt oxidation is an example of interrupted Pummerer rearrangement. However DCC has not been examined as a general reagent for Pummerer and related rearrangements. *cf.* K.E. Pfitzner and J.G. Moffatt, **J. Am. Chem. Soc., 1965**, *87*, 5661-5670; P.M. Pojer and S.J. Angyal, **Austr. J. Chem., 1978**, *31*, 1031-1040.

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8. Satisfactory combustion analyses (Spang Microanalytical Laboratory, Eagle Harbor, MI) were obtained for all new compounds.

9. D.K. Bates, R.T. Winters, B.A. Sell, **J. Heterocyl. Chem., 1986**, *23*, 695-699.

10. For a review of nucleophilic attack at tricoordinate sulfur see J.G. Tillet, **Chem. Rev., 1976**, *76(6)*, 747-772.

11. In a mechanistically related reaction dimethyl sulfide/ NCS adduct reacts with pyrroles to give 2-dimethylsulfoniumpyrrole chlorides which thermally decompose to 2-methylthiopyrroles (and methyl chloride): F.Franco, R. Greenhouse, and J. M. Muchowski, **J. Org. Chem., 1982**, *47*, 1682-1688.

12. Although POCl$_3$ has not been previously reported to induce Pummerer or related reactions, cyclic phosphochloridates (formed from POCl$_3$ and diols) convert DMSO into chloromethyl methyl sulfide: R. Roetz, O.J. Sweeting, **Tetrahedron Lett., 1963**, 529-532.

13. G.H. Barrett, H.J. Anderson, C.E. Loader, **Can. J. Chem., 1980**, *58*, 409-411.

14. The corresponding brominated product is isolated (30 %) when **3a** is treated with BBr$_3$.S(CH$_3$)$_2$ in CH$_2$Cl$_2$ (unpublished results of Joseph A. Picard). BBr$_3$ has previously been used as a reagent for sulfoxide deoxygenation: Y. Guindon, J.G. Atkinson, H.E. Morton, **J. Org. Chem., 1984**, *49*, 4538-4540.

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