HETEROCYCLES FROM CHLOROSULFONYL ISOCYANATE I. REACTION WITH 2-AMINOAZINES

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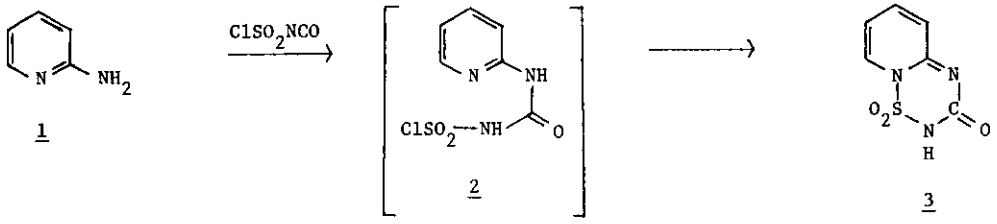
Abstract - The reaction of chlorosulfonyl isocyanate (CSI) with 2-aminopyridine affords thiatriazine 3. The reaction of this heterocycle with water, morpholine as well as alkylating agents is the subject of this publication.

Although the chemistry of chlorosulfonyl isocyanate (CSI) has received considerable attention in recent years[1], its potential as a 1,3-dielectrophile in cyclizations has been studied only to a limited extent[2]. A possible reason for this is the very potent electrophilic nature of CSI which makes many condensations difficult to control. In this and the following publication, we would like to demonstrate some successful cyclizations of CSI with 1,3 dinitrogen nucleophiles. The reaction of CSI with 2-aminopyridine and 2-aminopyrazine and some chemistry of the ensuing 1,2,4,6-thiatriazene-1,1-dioxide system[2,3] are presented below[4].

2-Aminopyridine reacts vigorously with CSI in acetonitrile at 0° producing the intermediate 2 which cyclizes on the addition of a tertiary base to afford a 50% yield of 3, mp 247°d; IR (nujol) 1680, 1620 cm^{-1}, UV (CH_3OH) λ max (ε) 302 nm (6600), 235 nm (12,000); m/e 199 (M^+), 121 ($M^+-C_5H_4N$), 107 ($M^+-C_5H_4N_2$).

2-Aminopyrazine (4) reacted similarly producing a 50% yield of 5, mp 183° d; UV (MeOH) max λ (ε) 323 nm (2500), 231 nm (4000); m/e 200 (M^+), 158 (M^+-NCO), 121 (M^+-SO_2NH).



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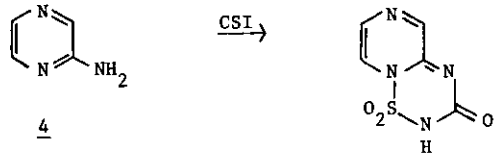
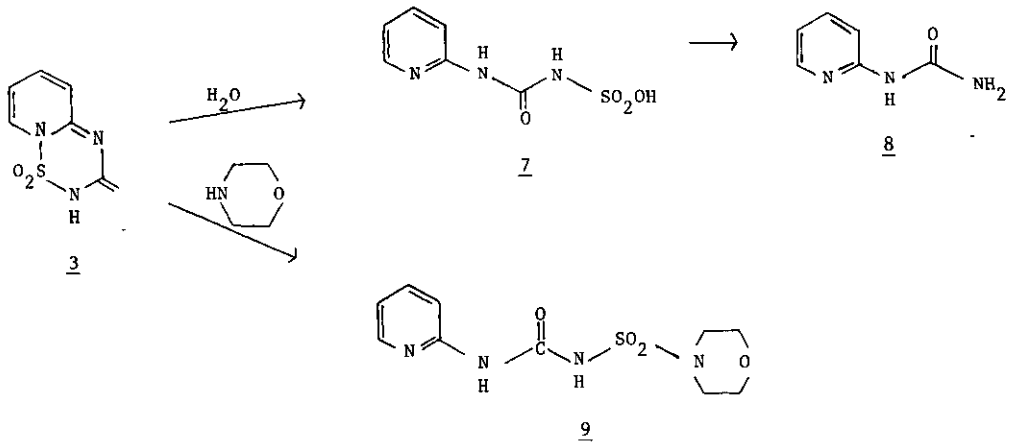


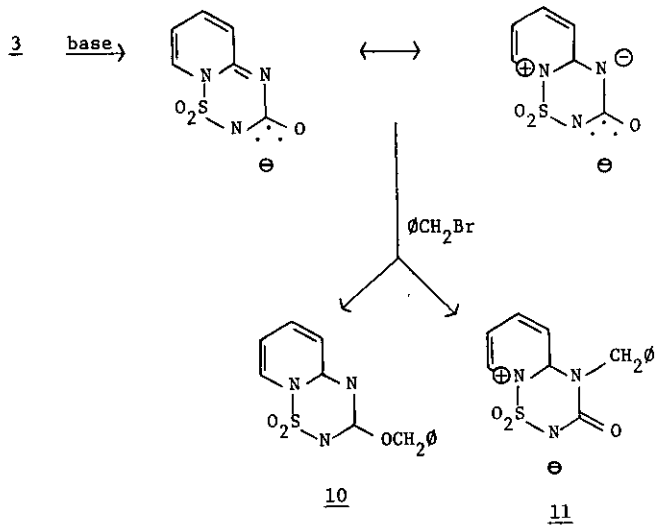
4 5

In a typical experiment one equivalent of CSI was slowly added to a solution of the 2-aminoazine in acetonitrile at 0°. After 30 minutes aging an equivalent of ethyl diisopropylamine was added, the mixture was stirred 16 hours at 20° and the product removed by filtration.

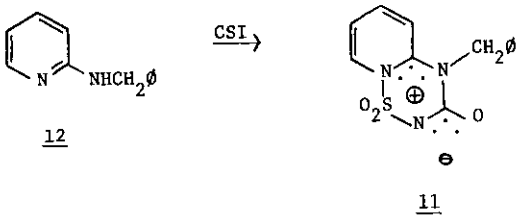
The thiatriazenes 3 and 5 are acidic and exhibit both electrophilic and nucleophilic properties. Compound 3, for example, is readily soluble in dilute aqueous sodium bicarbonate forming a sodium salt which is slowly hydrolyzed to the urea 8 via 7. The electrophilic nature of the sulfonyl group in 3 is also demonstrated in its reaction with morpholine to produce a 70% yield of 9, mp 146-148°; IR ($CHCl_3$) 1700 cm^{-1}; m/e 286 (M^+), 200 ($M^+-C_4H_8NO$), 137 ($M^+-C_4H_7NO_3S$), 120 ($C_6H_4N_2O$).

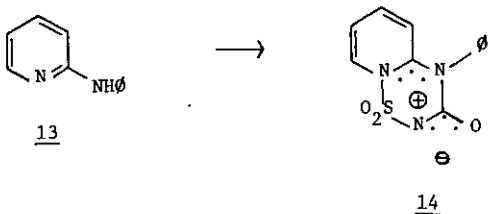


Under anhydrous conditions, the salts of 3 are stable and can be readily alkylated. Thus the reaction of 3 with benzyl bromide in acetonitrile in the presence of ethyl diisopropylamine gave equal amounts of the two alkylation products: 10, mp 124-125°, IR ($CHCl_3$) 1630 cm^{-1}; ^{13}C NMR (CD_3CN) 71.7 ppm ($\phi\underline{CH_2}O$); UV (CH_3CN) λ_{max} (ε), 332 nm (9700), 257 nm (9000); m/e 289 (M^+), 119 ($C_6H_3N_2O$) and 11, mp 165-170°; IR (nujol) 1660 and 1620 cm^{-1}; ^{13}C NMR (CD_3CN) 49.1 ppm ($\phi\underline{CH_2}N$); UV (CH_3CN) λ_{max} (ε) 312 nm (9100); m/e 289 (M^+), 183 (M^+-SO_2NCO, exact mass 183.0924, calcd. for $C_{12}H_{11}N_2$, 183.0922).

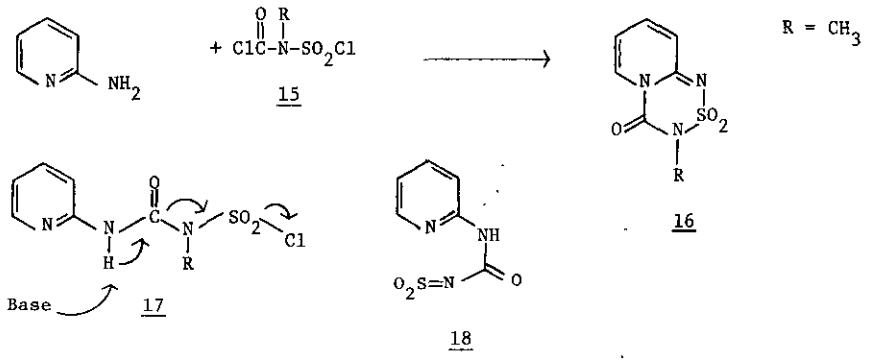


An unequivocal structure proof for 11 was its preparation from benzylaminopyridine (12) and CSI in acetonitrile in 60% yield. Another analog of 11 was provided by the conversion of 13 into 14 in 52% yield, mp 209-212°, IR (nujol) 1690, 1620 cm^{-1}, UV (CH_3CN) λ_{max} (ε) 311 nm (7800), 237 nm (7800), m/e 275 (M^+), 169 (M^+-SO_2NCO).





In a recent publication[5], the reaction of 2-alkyl-2-chlorosulfonyl carbamoyl chloride (15) with 2-aminopyridine was reported to afford 16 in 20% yield. The likely reason for the opposite orientation of this reagent as compared to CSI is, the facile decomposition of the normal adduct 17 in base as shown.



The analogus product from CSI, 17 (R=H or 2) would more likely eliminate HCl to give 18, which is a possible intermediate in the cyclization process.

The conclusion of this paper is that CSI is a valuable reagent for the introduction of the C-N-S substructure into heterocycles.

†Deceased August 12, 1978.

REFERENCES

1. For recent review see: J. K. Rasmussen and A. Hassner, Chem. Rev., 1976, 76, 389.
2. a) H. W. Roesky and H. Zamankhan, Chem. Ber., 1976, 109, 2107.
   b) R. Appel, H. Uhlenhaut and M. Montenark, Z. Naturforsch, 1974, B-29, 799.
   c) J. K. Rasmussen and A. Hassner, J. Org. Chem., 1973, 38, 2114.
3. Z. Arnold and B. Fiszer, Rocz. Chem., 1975, 285.
4. With the exception of 3 and 5 which could not be crystallized all new products gave acceptable microanalyses (C, H, N, S). Only diagnostic spectral data are given.
5. D. Bartholomew and I. T. Kay, J. Chem. Research, 1977, 5, 238.

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