

2-AMINOTHIOPHENE.

HETEROCYCLIZATION OF BENZYLTHIONITRILES(1)

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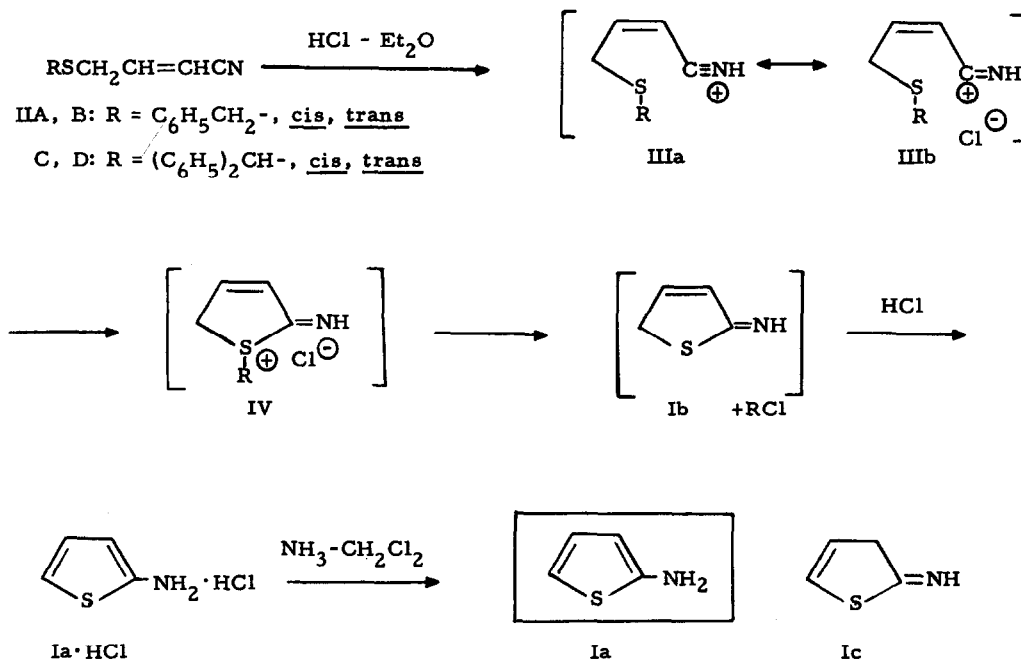
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We wish to report a concinnous heterocyclization procedure, which has led to the isolation and characterization of the previously evasive 2-aminothiophene (Ia). It is surprising that a definitive synthesis of such a fundamental heterocycle had not long since been a matter of record, and hence the current development assumes importance.

Past efforts to prepare 2-aminothiophene (Ia) have involved the obvious reduction of 2-nitrothiophene (3). However, diminutive yields (8-10%) have been the rule, and the free base isolated has been described as "unstable" with poor analytical and limited physical data being reported to the extent that reasonable doubt had to be held as to the nature of the product (4). From our recent work on 2-aminobenzo[b]thiophene (5), the concept of an aluminum bromide-catalyzed ring closure of an appropriate benzylthionitrile (IIA) seemed relevant. However, hydrolysis of the complex (5) would introduce the same suspected limitation of aqueous conditions common to the neutralization of salts of Ia, encountered in the reduction experiments. Thus, the logical modification of hydrogen chloride in an anhydrous ether solution of IIA was adopted. As hydrogen chloride was introduced, a crystalline precipitate formed promptly, and 2-aminothiophene hydrochloride (Ia·HCl) was in fact in hand (54% yield).

SCHEME I



The hydrochloride proved to be actually quite stable; the nmr integration gave the expected 1:1 proton ratio for the thiophene nucleus-ammonium structure (Ia·HCl);

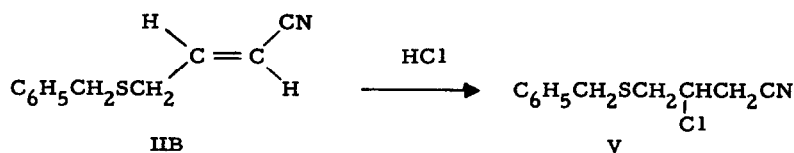
$\delta_{\text{CF}_3\text{CO}_2\text{H}}$ 4.68 (s, -NH₃⁺), 7.23-7.95 ppm (cm, thiophene ring) (6). Further,

Ia·HCl gave on appropriate treatment the known acetyl (7) and benzoyl (3a) derivatives of Ia.

Free 2-aminothiophene (Ia) (8) was obtained by treating Ia·HCl with anhydrous ammonia in methylene chloride; Ia could not be distilled and was unstable even at room temperature. However, by operating at dry ice bath temperatures under nitrogen, we

crystallized Ia in 54% yield from hexane-methylene chloride: mp 12-13°; ν ^{neat} _{max} 3420, 3360 cm^{-1} (m, $-\text{NH}_2$); δ ^{CDCl_3} 3.78 (m, $-\text{NH}_2$), 6.06-6.66 ppm (cm, thiophene ring), ratio 2:3. Accordingly, the amino tautomer Ia (5) and not the imino forms (Ib, Ic) characterize the structure of I in agreement with an earlier report (9). Although unstable as noted, if the substance were stored under nitrogen below its melting point, decomposition was slow.

The course of the reaction, as indicated in Scheme I, is substantiated by structural requirements. If a benzhydryl group (IIC) is substituted for the benzyl group, the reaction occurs with greater facility to give a significantly improved yield (82%). This is perhaps explained by the concept that the benzhydryl group is superior to a benzyl substituent as an $\text{S}_{\text{N}}1$ leaving group (10). The concerted character of the reaction is borne out by its stereochemical requirement. The trans isomers (IIB, D), of course, do not heterocyclize as do the cis isomers (IIA, C). And in the case of the trans-4-benzylthiocrotononitrile (IIB), it was clear that the benzyl group is not removed in the reaction, as 4-benzylthio-3-chlorobutyronitrile (V) was isolated in 60% yield.



This novel heterocyclization appears to be a process of general practicability. Thus, both 2-aminobenzo[b]thiophene hydrochloride, previously obtained in 80% yield (5) and 2,3-dihydro-3,3-dimethyl-2-iminobenzo[b]thiophene hydrochloride, reported earlier in 86% yield (1), were obtained in quantitative yields by this method.

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REFERENCES

- (1) For Paper V on Tautomerism see G. W. Stacy and T. E. Wollner, J. Org. Chem., 32, IN PRESS (1967).
- (2) Dow Research Assistant, Summer 1966; NSF Summer Fellow 1967.
- (3) (a) W. Steinkopf, Ann., 403, 17 (1913). (b) O. Stadler, Ber., 18, 1490 (1885). (c) C. von Seemann and C. C. Lucas, Can. J. Research, 19, 291 (1941).
- (4). (a) The hydrochloride salt has been cited in one instance, but again scant details are given, O. Stadler, Ber., 18, 2316 (1885). For prior chemical investigations reported for 2-aminothiophene, the stannous chloride double salt isolated from the reduction of 2-nitrothiophene has been employed, (b) F. F. Blicke in R. C. Elderfield, "Heterocyclic Compounds," Vol I, John Wiley and Sons, Inc., New York, 1950, p 228. (c) N. I. Putokhin and V. I. Yakovlev, Dokl. Akad. Nauk SSSR, 98, 89 (1954); Chem. Abstr., 49, 12431 (1955).
- (5) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, J. Org. Chem., 30, 4074 (1965).
- (6) All substances reported have been characterized by microanalytical and spectroscopic evidence.
- (7) M. P. Chabrier, B. Tchoubar, and S. Le Tellier-Dupre, Bull. Soc. Chim. France, 332 (1946).
- (8) The enclosure about formula Ia denotes the stable tautomer of the various possibilities under discussion.
- (9) S. Gronowitz and R. A. Hoffman, Arkiv Kemi, 15, 499 (1960). This report required the current validation because of the uncertain integrity of 2-aminothiophene (Ia) up to this present date.
- (10) J. D. Roberts and M. C. Caserio, "Modern Organic Chemistry," W. A. Benjamin, Inc., New York, 1967, p 632.