A NOVEL SYNTHESIS OF PYRROLES BY THE REACTIONS OF TRIS(ALKYLTHIO)CYCLOPROPENIUM SALT WITH AMINES[1]

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Abstract - "One pot" synthesis of 2,3-bis(alkylthio)pyrroles in 45∿80% yields under mild conditions was achieved by the reactions of tris(tert-butylthio)cyclopropenium salt (1) with secondary amines in the presence of t-BuOK in DMF. Although the reaction of 1 with primary amine such as methylamine gave only the ring opening product, the use of primary amines having structure of XCH_2NH_2 (X=CN, COOMe, Ph) resulted in the formation of the pyrroles bearing the substituent at the α-position in 44∿71% yields.

Owing to its unique electronic structure,[2] the tris(alkylthio)cyclopropenium ion[3] undergoes a wide range of reactions including substitution,[4] ring opening,[4] and one-electron oxidation[5] reactions. We have recently reported that the reaction of tris(tert-butylthio)cyclopropenium perchlorate (1) with hexamethylphosphorus triamide resulted in the formation of N-methyl-2,3-bis(tert-buthylthio)pyrrole (2a).[1] This finding led us to explore a new "one-pot" synthesis of pyrroles from 1 and amines under mild reaction conditions.

We now wish to report the successful synthesis of pyrroles by the ring expansion reaction of 1. The procedure is described for the reaction of 1 with dimethylamine. To a solution of 1 (1 mmol) in dry DMF, dimethylamine (1 mmol) was added at 0°C under nitrogen, followed by t-BuOK (3 equiv) in dry DMF. The reaction mixture was stirred at room temperature for an additional 30 min, poured into acidic aqueous solution, and taken up in petroleum ether. The solvent was evaporated off, the residual oil was chromatographed on silica gel, and final purification by distillation gave 2a[6] in 80% yield: bp 111-112°C/5 mmHg; nmr (CCl_4) δ 1.22 (9H, s, t-butyl), 1.23 (9H, s, t-butyl), 3.73 (3H, s, N-methyl),

6.34 (1H, d,J=3.9 Hz, pyrrole C-3), 6.80 (1H, d, J=3.9 Hz, pyrrole C-4); MS 257 (M^+). Similar treatment of 1 with dialkylamines ($R^1NHCH_2R^2$) yielded the corresponding bis(alkylthio)pyrroles 2b~d, a previously unknown pyrrole derivatives, in good yields. The pyrrolizine (2c) and indolizine (2d) derivatives are able to be synthesized. The yields and spectral data are summarized in Table I.

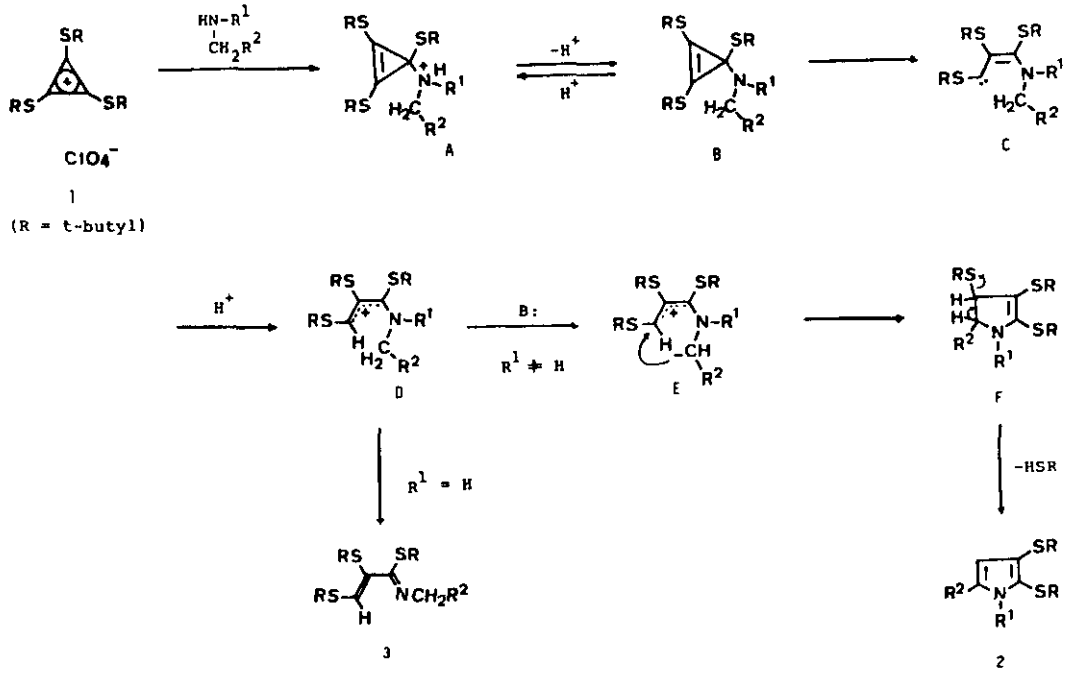
Table I 2,3-Bis(tert-butylthio)pyrroles (2) from Tris(tert-butylthio)-cyclopropenium Salt and Amines

Product 2			mp (bp)	nmr (CCl_4)	Mass	Yield[a]
	R^1	R^2	(°C)	δ(ppm)	(m/e, M^+)	(%)
2a	CH_3	H	(111-112 /5mmHg)	1.22(s, 9H), 1.23(s, 9H), 3.73(s, 3H), 6.34(d, 1H), 6.80(d, 1H)	257	80
2b	C_2H_5	CH_3	86	1.16(t, 3H), 1.22(s, 18H), 2.26(s, 3H), 4.13(q, 2H), 6.08(s, 1H)	285	70
2c	$-(CH_2)_3-$		41	1.24(s, 18H), 2.40(p, 2H), 2.88(t, 2H), 4.00(t, 2H), 6.02(s, 1H)	283	59
2d	$-(CH_2)_4-$		70	1.22(s, 18H), 1.84(m, 4H), 2.75(t, 2H), 3.99(t, 2H), 6.03(s, 1H)	297	45
2e	H	$COOCH_3$	136	1.23(s, 9H), 1.28(s, 9H), 3.87(s, 3H), 6.92(d, 1H), 9.75(broad s, 1H)	301	44
2f	H	CN	134	1.23(s, 9H), 1.30(s, 9H), 6.90(d, 1H), 9.83(broad s, 1H)	268	40
2g	H	Ph	143	1.25(s, 9H), 1.33(s, 9H), 6.93(d, 1H), 7.42(m, 5H), 8.40(broad s, 1H)	319	71

a) Yield of isolated product.

Scheme I outlines a possible pathway for the ring expansion reaction of 1. Reversible generation of B from the initially formed ammonium salt A leads to a facile ring-opening to give C. Protonation[7] of C would afford D followed by generation of E. Subsequent intramolecular ring closure would give the five-membered intermediate F and result in the formation of 2 by thiol elimination.

SCHEME I



When the reaction was carried out in the presence of other bases (NaH, n-BuLi, or excess dialkylamine) in a suitable solvent (DMF, DMSO, ether, or methylene chloride), the pyrroles were also obtained, but in lower yields. Pyrroles (2a~d) were easily desulfurized by treating with Raney nickel(W-7)in ethanol for 2-2.5h. Results are shown in Table II. Thus biologically active[8] 2,3-dihydro-1H-pyrrolizine (2'c) and 5,6,7,8-tetrahydroindolizine (2'd) are very conveniently prepared by combining both the "one-pot" pyrrole synthesis and the desulfurization. In contrast to the reaction of 1 with secondary amines, no pyrrole formation was observed with primary alkylamines under similar conditions. For example, treatment of 1 with methylamine in the presence of t-BuOK in DMF at room temperature and workup as above led to the ring opening product 3 (R^2=H in Scheme I) in 82%

Table II Desulfurization of 2,3-Bis(tert-butylthio)pyrroles (2)

Product (2')[a]	Time	Temp.	Solv.	bp (°C)	Yield[b] (%)
2'a	2 h	r.t.	EtOH	——[c]	82
2'b	2 h	r.t.	EtOH	155-157/760 mmHg	86
2'c	2.5 h	r.t.	EtOH	66-70/12 mmHg	88
2'd	2.5 h	r.t.	EtOH	86-98/14 mmHg	82

a) All the pyrroles (2'a-d) were fully characterized by nmr spectra.

b) Yields after chromatography on silica gel by using methylene chloride-hexane (1:3) as eluent.

c) 2'a was identical with an authentic sample by GLC.

yield; mp 52-54°C; nmr (CCl_4); δ 1.35 (9H, s, t-butyl), 1.40 (9H, s, t-butyl), 1.46 (9H, s, t-butyl), 3.27 (3H, s, N-methyl), 7.07 (1H, s, olefinic). When R^1 is hydrogen, simple deprotonation of D to 3 prevents formation of type E intermediates required for cyclization. However, the use of primary amines (R^1=H, R^2=CN, CO_2Me, and Ph) provides a successful synthesis of the N-unsubstituted pyrroles (2e~g) in reasonable yields as seen in Table I. This N-unsubstituted pyrrole (e.g., 2f) should be useful for porphyrin synthesis. Although synthetic reactions of pyrroles are well documented in the literature,[9] the new methodology described here is considered to be superior to the previously reported pyrrole syntheses, unique as the pyrrole ring synthesis from the cyclopropenium salt and useful as the general bis(alkylthio)pyrrole synthesis, because none of the known reactions lead to preferential bis(alkylthio)-substitution at the 2- and 3-positions. Work is in progress to investigate a full scope of the parent pyrrole synthesis and the applicability of the ring expansion of 1 to other heterocycle synthesis.

References

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6. All compounds gave satisfactory analyses.

7. The nucleophilic lone pair of electrons in C does not abstract a proton intramolecularly. This was confirmed by the reaction of 1 with dimethylamine-d_6, in which no distribution of deuterium was observed at the β-position of the product 2 in the nmr spectrum.

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