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Rates of the Ring Opening of Some Bicyclic 3-Thienyllithium Derivatives

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The rates of ring opening of some cycloalkane [*b*]-annellated thienyllithium derivatives have been determined. The cyclopenta[*b*] system appeared to be several thousand times more reactive than the cyclohepta[*b*] and cycloocta[*b*] systems. The rate difference is explained by a considerable ring strain in the five-membered case.

We recently reported that the ring opening of bicyclic 3-thienyllithium derivatives gave, after *S*-alkylation, cyclic acetylenic vinlyl sulfides.[1] Even though a variety of cycloalkyl-annellated 3-thienyllithium derivatives ring-opened easily, some others showed great resistance towards this reaction. This made us investigate, a little more in detail, how the rate of ring opening was affected by the size of the annellated rings.

RESULTS AND DISCUSSION

Compounds *1a-f* (Scheme 1) were all treated with phenyllithium in ether at +2 °C in a thermostated reaction vessel. For comparison the ring-opening rate of the fully substituted lithium derivative of *1g* was determined, since it possesses no ring strain due to annellation. The reaction mixtures were quenched with dimethyl sulfate at different intervals and the methylated products were analyzed with GLC/MS. The mass spectra of the two types of reaction products *4* and *5* were consistently and sufficiently different to permit correlation of GLC peak and structure. In all cases the ring-opened products *5* had longer retention times than *4*. The molecular ion peak was quite abundant (57–100 %) in the mass spectra of all reaction products except for *4e* (13%) and *4f* (19 %). However, the M−1 ion fragment was weak in the spectra of the ring-opened products *5*, while the methylated thiophenes, except for *4e* and *4f* had more abundant M−1 ions than *5*. Compounds *4e* and *4f* had instead a predominant M−15 fragment. Additional structural evidence was obtained from ^{13}C NMR data. Thus, all compounds *5* had their acetylenic carbon resonances at 75.8–81.2 ppm and 90.6–92.4 ppm, in agreement with our previously reported data[1]. Moreover, compound *5b* was synthesized by another route[1] and its structure was therefore rigorously determined. This fact, together with the spectral data, certainly provides good evidence for the proposed structures of compounds *4* and *5*. The *S*-benzyl and *S*-acetic acid derivates of the ring-opened products have previously been fully characterized.[1]

In Table 1 the rate constants and half-lives are shown, measured as the time necessary for the 3-methylthiophene derivatives *4* to decrease to 50 % of the amount of *5* (quenching with Me_2SO_4). This approximation was justified since the only products were the ring-opened substances, together with 10–15 % of the corresponding hydrolyzed 3-thienyllithium derivatives. It is impossible to judge whether these originate from the thienyllithium *2* or the lithium thiolate *3* and were not considered further. The halogen–metal exchange was shown to be complete within less than 10 s at +2 °C, and we assume that the

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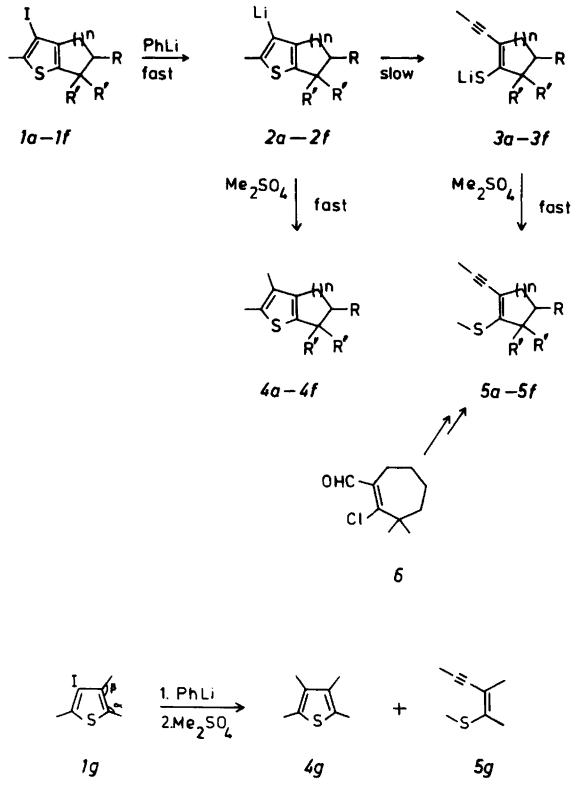


Scheme 1. *a*, n=1, R=CH_3, R′=H; *b*, n=2, R=R′=H; *c*, n=3, R=R′=H; *d*, n=4, R=R′=H; *e*, n=2, R=H, R′=CH_3; *f*, n=3, R=H, R′=CH_3.

quenching with DMS does not significantly influence the ratio of *2* and *3*, *i.e.* that the half-lives of the 3-thienyllithium derivatives *2* are reflected by the time at which the ratio of *4*:*5* is 1:1.

Table 1. Kinetic data for the ring opening of *2a–f* at +2 °C. 2,3,5-Trimethyl-4-thienyllithium is included for comparison.

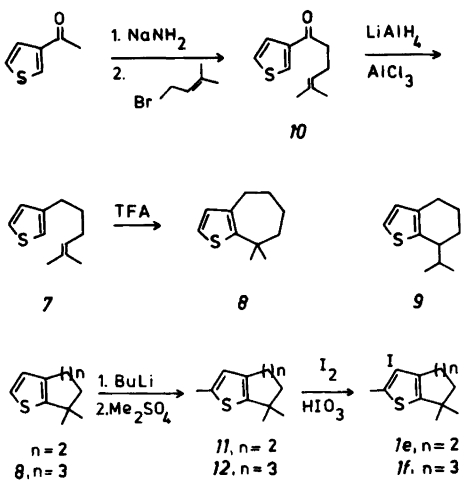
Substance	$t_{½}$ (min)	k 10^3 (min^{-1})
2a	<0.08	>8.10^3
2b	35	20
2c	510	1.4
2d	138	5.0
2e	3120	0.22
2f	–[a]	–[a]
2,3,5-trimethyl-4-thienyllithium	198	3.5

[a] Ring opening could not be observed.

The ring-opening of some non-annellated 3-thienyllithium derivatives has been shown to obey first-order kinetics,[2] and there is no reason to believe that the annellation should change this matter. The rate constants were thus calculated accordingly ($\ln 2/t_{½}=k$).

As expected, the five-membered derivative *2a* had the highest rate of reaction, which we believe is due to a considerable ring strain. Compounds *2b–2d* and 2,3,5-trimethyl-4-thienyllithium were more similar, although the differences are significant. It is possible that *2b* has a higher ring strain than *2c* and *2d*, which would explain part of the 15-fold increase in rate as compared to *2c*.

An indication of the ring strain in the tetrahydrobenzo[b]thiophene system could be sensed by its synthesis. Cyclization of *7* to give *8* could conceivably give *9* as a by-product (Scheme 2), as was the case with the corresponding benzene compounds, which gave the cycloheptane and



Scheme 2.

cyclohexane systems in a 1:2 ratio.[3] The absence of *9* in the crude product could indicate that the ring strain in *9* is not negligible. Inspection of molecular models gives an additional explanation for the difference in ring-opening rate between *2b* and *2c*. It appeared that the hydrogens of the α-thenylic position 7 in *2b* (and even more those of 6 in *2a*) are in a staggered position in relation to the sulfur atom, while in *2c* and *2d* they are almost eclipsed in the reasonable low-energy conformations.[4] Thus, the α-thenylic hydrogens in *2c* and *2d* would impose more steric hindrance than those in *2a* and *2b* when the negative charge on the sulfur increases as the ring opening proceeds, resulting in an increase of the radius of the sulfur. Thus, ring strain and steric hindrance from the α-thenylic hydrogens seem to operate in the same direction.

The effect of a *gem*-dimethyl functionality at the α-thenylic position demonstrates the steric hindrance more clearly, which is shown in the cases of *2e* and *2f*. While there is a 100-fold decrease in reaction rate on going from *2b* to *2e*,*2f* did not ring-open at all. This parallels the case previously reported, in which a *t*-butyl group decreased the ring-opening rate by a factor of 82 as compared to a methyl group in a similar situation.[2] Not even at room temperature after 24 h could any ring-opening products be observed. A 100-fold decrease in rate would have given 5–10 % ring-opening product after this time. From a synthetic view point, the resistance of *2f* to give *5f* is not serious, since it can almost certainly be obtained *via* the β-chlorovinyl aldehyde *6*, as outlined previously.[1]

The relatively slow ring opening of the trimethylthiophene system (as compared to 2,5-dimethyl-3-thienyllithium, $t_{1/2}$=4.5 min at +2 °C)[2] could be due to an increasing strain resulting from the approach of the 4- and 5-methyl groups owing to the decrease of the outer angles of thiophene (α and β) from 128 and 125° to approximately 120°.These values represent the "normal" thiophene sp^2-hybridized carbon angles and do not refer to experimentally determined values for these specific cases.

Explanations for why the 3-lithium derivatives of the 5-membered heterocyclic aromatics ring-open at all have never been discussed. The 3-thienyllithium derivatives seem to be less "aromatic" than expected and the following suggestion may account for this. Several aromatic lithium derivatives have been shown to exist as aggregates of dimeric or tetrameric nature with the anionic carbon coordinating up to three different lithium atoms.[5] This would imply that this carbon must rehybridize its orbitals to some extent as compared to the parent or halogen-substituted derivative in order to distribute its electrons to the lithium atoms. It is conceivable that the resonance energy of the aromatic system is reduced in this way. Thus, the ring-opening process would be more like the β-elimination of an aliphatic system.

EXPERIMENTAL

GLC analyses were performed on a Perkin-Elmer 900 gas chromatograph, GLC/MS analyses were performed on a Finnegan 4021 mass spectrometer. NMR spectra were recorded with a Jeol MH 100 or a Varian XL 200 NMR spectrometer. All reactions with organometallic reagents were performed in ether freshly distilled over sodium wire under a nitrogen atmosphere. The iodothiophenes *1a–1d* were prepared as previously described.[1] The syntheses of *1e* and *1f* are described below. 3-Iodo-2,4,5-trimethylthiophene *1g* was prepared according to Ref. 6.

RATE DETERMINATION

A 1.5-fold excess of phenyllithium was added to 0.1 g samples of the iodothiophenes *1a–1g*[1]

and 4-iodo-2,3,5-trimethylthiophene[6] in 1 ml of dry ether at +2 °C under a nitrogen atmosphere. The temperature was controlled with a cryostat and kept within ±0.5 °C. After appropriate times, a large excess of freshly distilled dimethyl sulfate was added with a syringe. After 30 min the mixture was treated with aqueous ammonium hydroxide and the ethereal layer analyzed by GLC/MS.

The ratio of *4* and *5* was taken as the degree of ring opening, although in all cases 10–15 % of dehalogenated starting material was present. In some cases small amounts of dimethylated compounds were found, probably originating from metallation of the propargylic position of *3*, followed by methylation by dimethyl sulfate. The dimethylated compounds were structure determined from their mass spectra. Similar compounds have been isolated and characterized previously.[6] The amount of these dimethylated products was added to that of compounds *5* in order to estimate the half-lives of *2*. The ring-opened products were isolated (preparative TLC, hexane) and characterized by ^{13}C NMR spectroscopy. The thioenol ethers had satisfactory analytical data (±0.4 % for C and H).

1-(3'-Thienyl)-5-methyl-4-hexen-1-one 10. To a suspension of 3.4 g (0.086 mol) of sodium amide in 25 ml of dry ether under a nitrogen atmosphere, 10.8 g (0.086 mol) of 3-acetylthiophene in 50 ml of dry ether was added. The mixture was refluxed for 3 h, whereupon 12.8 g (0.086 mol) of prenyl bromide in 50 ml of dry ether was added. Reflux was continued for another 3 h. Aqueous work-up and distillation afforded 7.0 g (42 %) of the title compound, b.p. 116–121 °C (1.3 mm). IR(film): 1675 cm^{-1} (C=O). NMR ($CDCl_3$): δ 1.62 (bs, 3H, Z-CH_3), 1.67 (d, 3H, J=1.2 Hz, E-CH_3), 2.38 (q, 2 H, 3-CH_2), 2.89 (m, 2 H, 2-CH_2), 5.15 (m, 1 H, 4-H), 7.28 (q, 1 H, J =3.0 Hz, 5.2 Hz, 5'-H), 7.53 (q, 1 H, J=1.3 Hz, 5.2 Hz, 4'-H), 8.02 (q, 1 H, J=1.3 Hz, 3.0 Hz, 2'-H). Anal. $C_{11}H_{14}OS$: C,H.

2-Methyl-6-(3'-thienyl)-2-hexene 7. Compound *10* (13.6 g, 0.070 mol) was reduced with $LiAlH_4$/$AlCl_3$ according to Brown and White.[7] The crude product was distilled: yield 8.0 g (63 %), b.p. 109–113 °C (8 mm). NMR ($CDCl_3$): δ 1.58 (bs, 3 H, Z-CH_3), 1.69 (d, 3 H, J=1.2 Hz, E-CH_3), 1.6–1.8 (m, 2 H, 5-CH_2), 2.00 (q, 2 H, 4-CH_2), 2.62 (t, 2 H, J=8 Hz, 6-CH_2), 5.14 (m, 1 H, 3-H), 6.90 (m, 2 H, 2'-H and 4'-H), 7.19 (q, 1 H, J=3.0 Hz, 4.8 Hz, 5'-H). Anal. $C_{11}H_{16}S$: C,H.

8,8-Dimethyl-4,5,6,7-tetrahydro-8H-cyclohepta-[b]thiophene 8. Compound 7 (7.5 g, 0.042 mol) was dissolved in 50 ml of dry, methylene chloride, and 18 ml of trifluoroacetic acid in 150 ml of dry methylene chloride was added at room temperature during 30 min.[8] The mixture was stirred for 24 h. After aqueous work-up the crude product was flash chromatographed on silica gel using light petroleum (40:60) as eluent. Distillation gave 4.6 g (62 %) of the title compound, b.p. 110–115 °C (9 mm). NMR ($CDCl_3$): δ 1.35 (s, 6 H, 2 CH_3), 1.4–2.0 (m, 6 H, aliphatic), 2.6–2.9 (m, 2 H, thenylic), 6.66 (d, 1 H, J=5.3 Hz, 3-H), 6.85 (d, 1 H, J=5.3 Hz, 2-H). Anal. $C_{11}H_{16}S$: C,H.

4,5,6,7-Tetrahydro-2,7,7-trimethylbenzo[b]-thiophene 11. 7,7-Dimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene[8] (4.4 g, 0.028 mol) was dissolved in 30 ml of dry ether under a nitrogen atmosphere and 28 ml (0.042 mol) of 1.5 M butyllithium was added. The mixture was refluxed for 1 h and then cooled to −70 °C. Dimethyl sulfate (5.3 g, 0.042 mol) dissolved in 25 ml of dry ether was added dropwise. After 2 h, the cooling bath was removed and after 1 h at room temperature the reaction mixture was poured into aqueous ammonium hydroxide and worked up. Distillation gave 3.4 g (68 %) of the title compound, b.p. 110–112 °C (12 mm). NMR ($CDCl_3$): δ 1.28 (s, 6 H, 2 CH_3), 1.4–1.9 (m, 4 H, aliphatic), 2.3–2.7 (m, 2 H, thenylic), 2.38 (d, 3 H, J=1.2 Hz, CH_3), 6.33 (m, 1 H, 3-H). Anal. $C_{11}H_{16}S$: C,H.

4,5,6,7-Tetrahydro-2,8,8-trimethyl-8H-cyclohepta[b]thiophene 12 was prepared in the same way as *11*, starting from 2.5 g (0.014 mol) of *8*. Yield: 1.5 g (56 %), b.p. 128–131 °C (11 mm). NMR ($CDCl_3$): δ 1.32 (s, 6 H, 2 CH_3), 1.5–2.0 (m, 6H, aliphatic), 2.33 (d, 3 H, J=1.2 Hz, CH_3), 2.5–2.8 (m, 2 H, thenylic), 6.35 (m, 1 H, 3-H). Anal. $C_{12}H_{18}S$: C,H.

General procedure for the iodination of 11 *and* 12. The methylthiophenes *11* and *12* were iodinated by the iodine-iodic acid method.[9]

3-Iodo-4,5,6,7-tetrahydro-2,7,7-trimethyl-benzo[b]thiophene 1e. Yield: 2.2 g (62 %) from 2.1 g (0.012 mol) of *11*. B.p. 113–116 °C (1.5 mm), m.p. 52–53 °C (ethanol). NMR ($CDCl_3$): δ 1.27 (s, 6 H, 2 CH_3), 1.5–1.9 (m, 4 H, aliphatic), 2.3–2.6 (m, 2 H, thenylic), 2.37 (s, 3 H, CH_3). Anal. $C_{11}H_{15}IS$: C,H.

3-Iodo-4,5,6,7-tetrahydro-2,8,8-trimethyl-8H-cyclohepta[b]thiophene 1f. Yield: 1.4 g (71 %) from 1.2 g (6.2 mmol) of *12*. M.p. 43–44 °C (ethanol). NMR ($CDCl_3$): δ 1.30 (s, 6H, 2 CH_3), 1.5–2.1 (m, 6 H, aliphatic), 2.34 (s, 3 H, CH_3), 2.7–2.9 (m, 2 H, thenylic), Anal. $C_{12}H_{17}IS$: C,H.

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