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AN EFFECTIVE SYNTHESIS OF MEDIUM-RING KETONES

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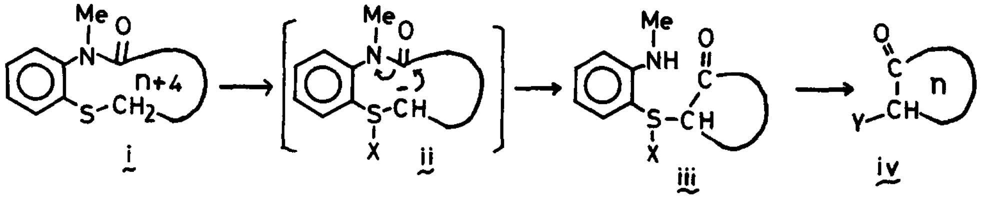
Medium-ring ketones (8-12 membered ketones) were synthesized based on the intramolecular cyclization of large-ring lactam sulfoxides or sulfones.

Construction of medium-ring compounds by ring closure has long been regarded as one of the most difficult processes in organic chemistry and it is only in recent years that interesting reports began to appear[1] although a remarkable progress has been made for a large-ring formation by cyclization.[2] We report here a new and effective method for the formation of 8- to 12-membered ketones starting from the corresponding ω-bromo acids. The outline of the present method was shown in Scheme 1.

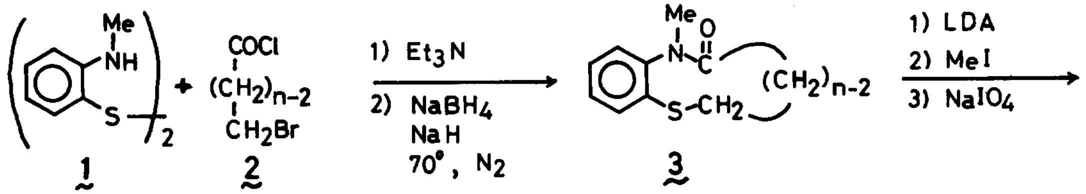
Scheme 1.

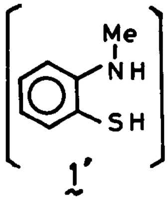


An unfavorable entropy effect inherent to the cyclization of this class of compounds[3] is expected to be minimized when both terminal reaction sites are forced to come closely as is exemplified by an enzymatic reaction. The simplest way to achieve this is to link both sites with suitable chain. We adopted *o*-methylaminothiophenol as this chain and ω-bromo acids as a counterpart which is to be converted to the medium-ring ketone later. When 8-membered ketone is for example intended to prepare, formation of 12-membered lactam sulfide corresponding to i is initially required. This may be done without difficulty since large-ring sulfides are known to be prepared in high yield.[4] Base-induced intramolecular cyclization of ii is presumed to proceed through a less energetic 6-membered transition state affording iii, an amino group being extruded concomitantly. Reductive desulfurization of iii for example should produce the desired medium-ring ketones iv (Y=H).

After extensive model experiments[5] using open chain analogue of i, the

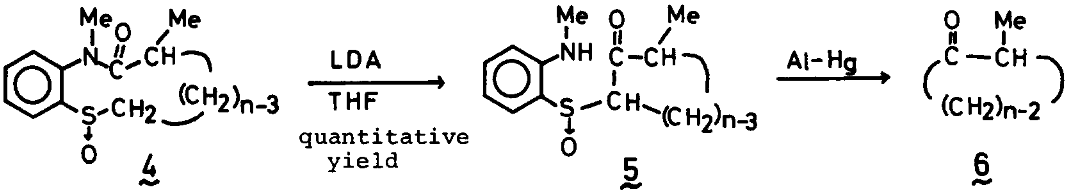
Scheme 2.





a. n= 8
b. n= 9
c. n=10
d. n=11
e. n=12

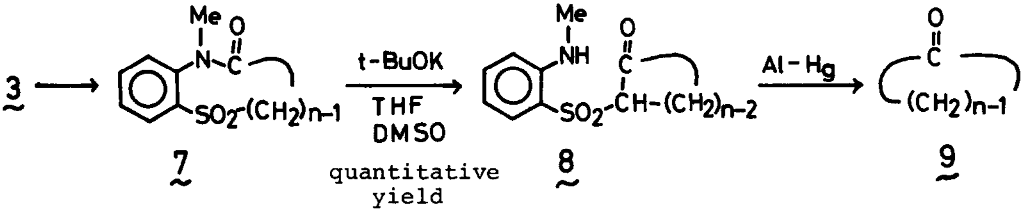
	Yield	mp	IR (CCl_4)
a.	75.0 %	94-5°	1660 cm^{-1}
b.	61.5	102-4°	1665
c.	86.0	82-5°	1667
d.	84.4	87-8°	1667
e.	71.9	oil	1660



	Yield	mp
a.	97.8 %	107-8°
b.	93.5	104-6°
c.	89.0	144-5°
d.	82.3	117-8°
e.	92.6	106-7°

	IR (CCl_4)
a.	3300, 1698 cm^{-1}
b.	3320, 1698
c.	3320, 1695
d.	3300, 1697
e.	3310, 1707

	Yield*1	mp*2
a.	65.5 %	135-7°
b.	63.5	120-2°
c.	74.1	99-101°
d.	97.2	121-3°
e.	69.1	171-5°



	Yield	mp
a.	86.2 %	124-7°
b.	94.8	139-140°
c.	91.6	83-4°
d.	92.0	143-4°
e.	95.5	112-3°

	IR (CCl_4, cm^{-1})
a.	3400, 1740, 1710-1700
b.	3400, 1740, 1710
c.	3400, 1740, 1710
d.	3400, 1710
e.	3400, 1710

	Yield*3	mp*2
a.	70.0 %	171-2°
b.	78.2	138-9°
c.	65.3	158-9°
d.	83.9	146-8°
e.	81.2	145-6°

*1. Overall yields from the lactam sulfoxides 4 (as 2,4-DNP).

*2. Melting points of 2,4-DNP.

*3. Overall yields from the lactam sulfones 7 (as 2,4-DNP).

syntheses of 8- to 12-membered ketones **9** and its α-methyl derivatives **6** were achieved in satisfactory yields as shown in Scheme 2. For example, the 11-membered α-methyl ketone **6d** was synthesized as follows: Treatment of o-methylaminothiophenol (**1'**)[6] with the ω-bromo acid chloride **2d** followed by the slow addition (20 hr) of the resulting amide to t-BuOK in t-BuOH using a mechanical syringe gave the 15-membered lactam sulfide **3d**[7] (mp 87-8°, IR(CCl_4); 1667 cm^{-1}), but the yield was rather unsatisfactory (54 %). One of the reason for this was found to be the ready transformation of **1'** into the disulfide **1** during the reaction. This difficulty was readily overcome by the finding that the sulfur-sulfur bond involved in diphenyl disulfide could be cleaved reductively under mild conditions. Thus, using now the stable, crystalline disulfide **1**[6](mp 64-5°) in place of **1'**, the diamide disulfide was prepared. Slow addition (20 hr) of the diamide disulfide thus prepared into a mixture of $NaBH_4$ and NaH in isopropanol (70°, N_2) brought about reductive cleavage of the sulfur-sulfur bond and concomitant intramolecular coupling of the resulting mercaptan with the terminal bromide to give **3d** in 84.4 % overall yield from **1**. It is noteworthy that the formation of the dimer or polymers of the sulfide was not detected in this procedure.[8]

An attempted intramolecular cyclization of the lactam sulfide **3d** by treatment with lithium diisopropylamide (LDA) in THF led to the recovery of the starting material.[9] On the other hand, LDA treatment (-78° to 0°, THF) of the corresponding lactam sulfoxide (mp 118-120°) obtained by $NaIO_4$ oxidation of **3d** gave a mixture of the 11-membered keto sulfoxide (IR (CCl_4); 3320, 1710-1700 cm^{-1}) and the starting sulfoxide, which without purification was subjected to a reductive desulfurization with aluminum-amalgam to afford cycloundecanone (**9d**) in 19.5 % yield (as 2,4-DNP, mp 146-8°). The poor efficiency of the cyclization may be attributable to a predominant proton abstraction from the methylene group α to the lactam carbonyl rather than from the methylene group α to the sulfoxide group. In order to diminish this unfavorable reaction, the difference in acidity of both active methylenes should be increased. Two approaches for this were taken into account. One is to decrease the acidity of the methylene protons α to the lactam carbonyl by introduction of a substituent such as methyl group and the other is to increase the acidity of the methylene protons α to the sulfur atom by conversion into the corresponding sulfone.

The requisite α-methyl lactam sulfoxide **4d** (mp 117-8°, δ 1.12(3H,d,J=6.5 Hz)) was prepared by methylation of the lactam sulfide **3d** [CH_3I-LDA (1.1 equiv.)] followed by $NaIO_4$ oxidation. Intramolecular cyclization of the sulfoxide **4d** proceeded smoothly by treatment with LDA (3.2 equiv., -78° to 0°) to afford the keto sulfoxide **5d** (IR(CCl_4); 3300, 1697 cm^{-1}, δ 0.32(3H,d,J=7 Hz)) in quantitative yield as expected. Reductive desulfurization of **5d** with aluminum-amalgam in THF-H_2O (9:1) gave 2-methylcycloundecanone (6d) in 97.2 % yield (as 2,4-DNP, mp 121-3°) from **4d**.

Then, the lactam sulfone 7d (mp 143-4°) obtained by oxidation of 3d with mCPBA was subjected to cyclization using *t*-BuOK (3 equiv.), a much weaker base than LDA, in THF-DMSO (2:1) hoping in this case a preferential proton abstraction from the sulfone side. The reaction proceeded quite smoothly at room temperature affording 8d (IR(CCl_4); 3400, 1710 cm^{-1}, δ 4.43(1H,dd,*J*=4.2, 9.0 Hz)) in 92 % yield. Desulfurization with aluminum-amalgam afforded the desired cycloundecanone (9d) in 83.9 % overall yield from 7d (as 2,4-DNP).

In the same way, medium-membered ketones 9a,b,c,e and the α-methyl analogues 6a,b,c,e were obtained in satisfactory yields. The data were shown in Scheme 2.

Thus, we have succeeded in the new and effective syntheses of 8- to 12-membered ketones based on the intramolecular cyclization of large-membered lactam sulfoxides or sulfones. The application of the present method to the synthesis of biologically active natural compounds having a medium-membered ring is now in progress.

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5. Details will be published in the near future.
6. A.I. Kiprianov and Z.N. Pazenko, *Zhur. Obschei. Khim.*, 19, 1523 (1949). cf. *Chem. Abstr.*, 44, 3487g (1950).
7. Satisfactory elemental analytical data were obtained for all new compounds.
8. The sulfides 3a,b,c,d,e were all proved to be a monomer by the molecular weight measurements.
9. The failure was not unexpected from the results of model experiments.[5]

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