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A NEW SYNTHESIS OF CYCLOPENTANONES BY THE RING EXPANSION OF 1-ACYL-1-[p-TOLYL(OR METHYL)THIO]CYCLOBUTANES

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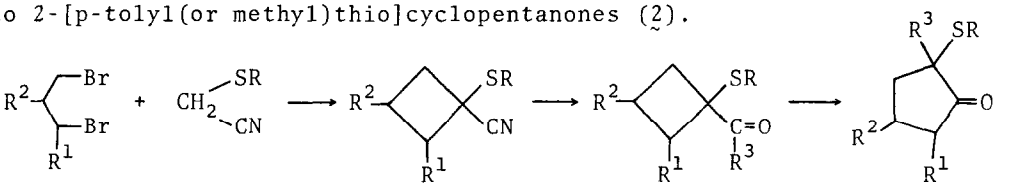
Abstract: A new ring expansion of 1-acyl-1-[p-tolyl(or methyl)thio]cyclobutanes to give 2-[p-tolyl(or methyl)thio]cyclopentanones and its application to the synthesis of 2-, 2,4-, or 2,5-substituted cyclopentanones were studied.

Establishment of a new and efficient method to make cyclopentanones or cyclopentenones is one of the central problems in synthetic organic chemistry.[2] Although numerous methods have been developed for this purpose, little was studied for the route which involves the expansion of four-membered ring to five-membered ring.[3,4] In this letter, we wish to report a new method for the synthesis of 2-, 2,4-, or 2,5-substituted cyclopentanones, of which the key step is an acid-catalyzed conversion of 1-acyl-1-[p-tolyl(or methyl)thio]cyclobutanes (1) to 2-[p-tolyl(or methyl)thio]cyclopentanones (2).



3 4 5 1 2

Preparation of 1-acyl-1-[p-tolyl(or methyl)thio]cyclobutanes (1) can be readily achieved by one-step cyclization of 1,3-dibromoalkanes (3) with [p-tolyl(or methyl)thio]acetonitriles (4), followed by the transformation of the resulting 1-cyano-1-[p-tolyl(or methyl)thio]cyclobutanes (5) to 1. For this cyclization, two kinds of methods were employed. Method A: In the presence of potassium hydride (2 mol-equiv to 4), 3 and 4 were allowed to react in tetrahydrofuran (THF) at 0 °C to room temperature. Method B: Two mol-equiv of the lithiated 4, which was generated by the action of lithium diethylamide, was allowed to react with 3 in THF at -5 °C to room temperature. The results are summarized in Table 1. The characteristic nature of this cyclization is to afford four-membered compounds 5 in high yields, without using dilution method.[5]

The transformation of 5 to 1, where R^1 was alkyl or aryl, could be performed

Table 1. Synthesis of 5

3	4	Method[b]	Yield
$R^1 = R^2 = H$	R = Tol[a]	A	82%
$R^1 = H$, $R^2 = PhCH_2$	R = Me	B	98%
$R^1 = Me$, $R^2 = H$	R = Tol	B	91%

[a] Tol = p-$CH_3C_6H_4$ [b] see Text.

Table 2. Conversion of 5 to 1 by the Grignard Reaction

5	R^3MgX	Yield of 1
$R^1 = R^2 = H$, R = Tol	MeMgI	80%
$R^1 = R^2 = H$, R = Tol	EtMgBr	60%
$R^1 = R^2 = H$, R = Tol	n-BuMgI	59%
$R^1 = R^2 = H$, R = Tol	PhMgI	88%
$R^1 = Me$, $R^2 = H$, R = Tol	MeMgI	92%
$R^1 = H$, $R^2 = PhCH_2$, R = Me	n-BuMgI	73%

by the reaction of Grignard reagents (R^3MgX) with 5 in toluene, followed by hydrolysis. Yields of 1 obtained by this Grignard reaction are shown in Table 2 1-Formyl-1-(p-tolylthio)cyclobutane (1b) was afforded in 65% yield by the reduction of 5 ($R^1 = R^2 = H$, R = Tol) with diisobutylaluminum hydride in toluene.

When 1-propanoyl-1-(p-tolylthio)cyclobutane (1a, $R^1 = R^2 = H$, $R^3 = Et$, R = Tol) was treated with $AlCl_3$ (1 mol-equiv to 1a) in toluene at room temperature for 30 min, 2-ethyl-2-(p-tolylthio)cyclopentanone (2a)[6] was produced in 89% yield. For this reaction, $AlBr_3$ and $FeCl_3$ are also effective, but $BF_3 \cdot Et_2O$ and protonic acids such as sulfuric acid and perchloric acid did not work. Hexane and dichloromethane were good solvent besides toluene. Yields of this conversion under various conditions are summarized in Table 3. The formation of 2a is well accounted for by the mechanism which involves coordination of $AlCl_3$ to carbonyl oxygen, followed by the ring expansion to form sulfur-stabilized carbonium ion, and migration of ethyl group to the carbonium ion center with concomitant regeneration of carbonyl function.

Table 3. Yields of the Conversion of 1a to 2a

Catalyst	Solvent	Time	Yield
$AlCl_3$	toluene	30 min	89%
	hexane	6 h	88%
	CH_2Cl_2	10 min	93%
$AlBr_3$	toluene	10 min	53%
	hexane	30 min	86%
$FeCl_3$	toluene	30 min	67%

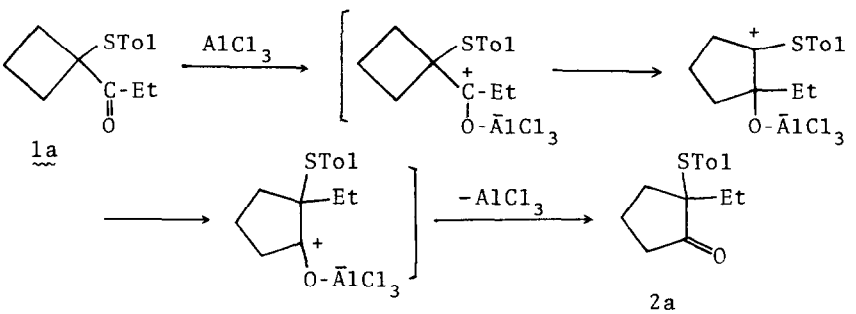


Table 4. Yields of the Conversion of 1 to 2[a]

1	AlX_3	Solvent	Time	Yield of 2
1a: $R^1=R^2=H$, $R^3=Et$, R = Tol	$AlCl_3$	toluene	30 min	89%
1b: $R^1=R^2=R^3=H$, R = Tol	$AlCl_3$	toluene	10 min	90%
1c: $R^1=R^2=H$, $R^3=Me$, R = Tol	$AlBr_3$	hexane	1 h	60%
1d: $R^1=R^2=H$, $R^3=n$-Bu, R = Tol	$AlBr_3$	hexane	30 min	86%
1e: $R^1=R^2=H$, $R^3=n$-Bu, R = Me	$AlCl_3$	toluene	20 min	55%
1f: $R^1=H$, $R^2=PhCH_2$, $R^3=n$-Bu, R = Me	$AlCl_3$	toluene	30 min	59%
1g: $R^1=R^3=Me$, $R^2=H$, R = Tol	$AlBr_3$	hexane	10 min	68%

[a]The reactions were carried out at room temperature.

Various 1-acyl-1-[p-tolyl(or methyl)thio]cyclobutanes (1) were subjected to this ring expansion reaction, and the results are summarized in Table 4.[7] As seen in this Table, 2f ($R^1=H$, $R^2=PhCH_2$, $R^3=n$-Bu, R = Me), a synthetic precursor of a 2,4-disubstituted cyclopentanone, could be obtained from 1f.

In case of the ring expansion of 1 having R^1 other than hydrogen atom, there are two possible reaction paths: One involves migration of bond "a" to the cationic center, leading to a cyclopentanone having R^1 at 5-position (Path A) and another involves migration of bond "b" to the cationic center, leading to a cyclopentanone having R^1 at 3-position (Path B), as shown in Figure 1.

When 1-acetyl-2-methyl-1-(p-tolylthio)cyclobutane (1g, $R^1=R^3=Me$, $R^2=H$, R = Tol) was treated with $AlBr_3$ (1 mol-equiv) in hexane for 10 min at room temperature, 2,5-dimethyl-2-(p-tolylthio)cyclopentanone (2g, $R^1=R^3=Me$, $R^2=H$, R = Tol) was obtained in 68% yield[8,9] and formation of 2,3-dimethyl-2-(p-tolylthio)cyclopentanone was not observed. Thus, the ring expansion of 1g appeared to take place passing through only Path A to give 2g.

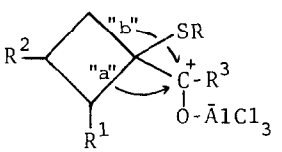
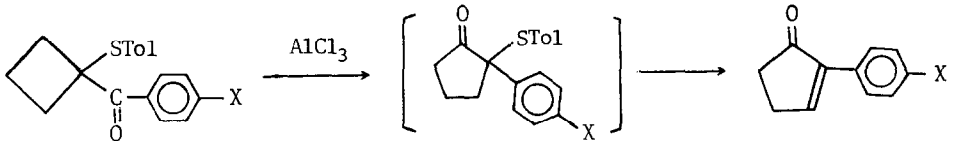


Figure 1.

Meanwhile, when 1-benzoyl-1-(p-tolylthio)cyclobutane (6, X = H) was treated with 2 mol-equiv of $AlCl_3$ in chlorobenzene for 2 h at room temperature, 2-phenyl-2-cyclopentenone (8, X = H) was produced in 84% yield through the intermediary formation of 2-phenyl-2-(p-tolylthio)cyclopentanone (7, X = H) followed by elimination of p-toluenethiol.[10]

This reaction was applied to the synthesis of 2-[p-(3-hydroxypropyl)phenyl]-2-cyclopentenone [8, $X=HO(CH_2)_3$], of which the corresponding carboxylic ester, 2-[p-(2-methoxycarbonylethyl)phenyl]-2-cyclopentenone [8, $X=MeOOC(CH_2)_2$] was proposed as a key-intermediate for the synthesis of 4,5,6,7-tetranor-3-8-inter-p-phenylene-11-deoxyprostaglandin, a new prostaglandin-analogue.[11] Thus, the reaction of a Grignard reagent derived from p-(3-benzyloxypropyl)bromobenzene



6 7 8

with 1-cyano-1-(p-tolylthio)cyclobutane (5, $R^1 = R^2 = H$, R = Tol) in THF afforded 1-[p-(3-benzyloxypropyl)benzoyl]-1-(p-tolylthio)cyclobutane [6, X = $PhCH_2O(CH_2)_3$] in 86% yield. The treatment of 6 [X = $PhCH_2O(CH_2)_3$] with $AlCl_3$ (4 mol-equiv) in chlorobenzene for 4 h at room temperatrue gave 8 [X = $HO(CH_2)_3$] in 90% yield, with concurrent cleavage of the protective benzyl group.[12]

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4. For bicyclic or tricyclic system, see R. L. Cargill, T. E. Jackson, N. P. Peet, and D. M. Pond, *Acc. Chem. Res.*, 7, 106 (1974).
5. The similar one-step cyclization of 1,ω-dibromo- or 1,ω-bis(p-toluenesulfonyloxy)alkanes with methyl methylthiomethyl sulfoxide was reported: K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 1975, 2767.
6. 2a: an oil; IR (film) 1732 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7 Hz), 1.16–2.98 (6H, m), 1.51 (2H, q, J = 7 Hz), 2.30 (3H, s), 7.06 (2H, d, J = 8 Hz), 7.25 (2H, d, J = 8 Hz). Found: C, 71.46; H, 7.64; S, 13.73%. Calcd for $C_{14}H_{18}OS$: C, 71.51; H, 7.74; S, 13.68%.
7. The compounds 2b, 2c, 2d, 2e, 2f, and 2g, listed in Table 4, showed acceptable IR and NMR spectra and gave satisfactory elemental analyses. Furthermore, desulfurization of 2c with Raney Ni in ethanol gave 2-methylcyclopentanone.
8. Both 1g and 2g were mixtures of two geometric isomers.
9. The structure of 2g was identified by a comparison of its IR and NMR spectra with those of the authentic specimen which was synthesized by the reaction of 2,5-dimethylcyclopentanone with p-tolyl p-toluenethiosulfonate in the presence of lithium diethylamide in THF. Further, desulfurization of 2g with Raney Ni in ethanol afforded 2,5-dimethylcyclopentanone.
10. Treatment of 6 (X = H) with $AlCl_3$ (1.6 mol-equiv) in chlorobenzene for 50 min at room temperature afforded 7 (X = H) in 64% yield and 8 (X = H) in 26% yield, respectively. Treatment of 7 (X = H) with $AlCl_3$ (2.0 mol-equiv) in chlorobenzene for 2 h at room temperature gave 8 (X = H) in 84% yield.
11. A. J. Birch, P. Dahler, A. S. Narula, and C. R. Stephenson, *Tetrahedron Lett.*, 1980, 3817.
12. 8 [X = $HO(CH_2)_3$]: pale yellow crystals; mp 101–103 °C (from hexane-diethyl ether-ethyl acetate); IR (KBr) 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.62–3.10 (9H, m), 3.61 (2H, t, J = 6 Hz), 7.16 (2H, d, J = 8 Hz), 7.55 (2H, d, J = 8 Hz), 7.73 (1H, t, J = 2 Hz). Found: C, 77.47; H, 7.66%. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46%.

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