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A NEW RING EXPANSION APPROACH TO 3-FORMYL-2-CYCLOHEPTEN-1-ONES

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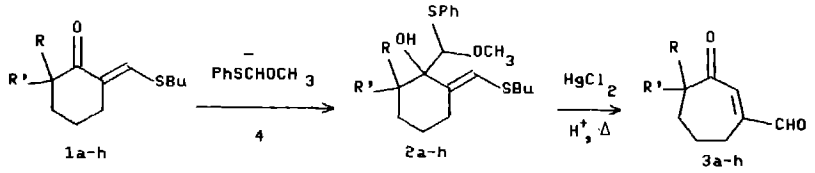
Summary. Reaction of non-enolizable 2-n-butylthiomethylene cyclohexanones with methoxy-(phenylthio)methyllithium, followed by hydrolysis of the diastereomeric mixture of resulting alcohols, provides a new and efficient ring enlargement reaction for the synthesis of the previously unreported 3-formyl-2-cyclohepten-1-ones.

Carbocyclic ring expansion reactions have attracted considerable attention among synthetic organic chemists[1]. However, and in spite of the large number of approaches appeared in the literature, versatile procedures towards the synthesis of medium-size rings are still needed, in particular those leading to rings with specific functionality[2]. In this paper, we describe, in a two-step process, an efficient and new ring enlargement of *gem*-disubstituted cyclohexanones to the previously undescribed in the literature 3-formyl-2-cyclohepten-1-ones, *via* the corresponding 2-n-butylthiomethylene derivatives.

In the course of our work directed to the total synthesis of (±)-muzigadial[3], we observed the unexpected formation of keto aldehyde 3h in the Hg^{2+}-assisted hydrolysis of adduct 2h, obtained by reaction of the corresponding decalone with methoxy(phenylthio)methyllithium 4. The reagent was initially developed by Trost and coworkers[4] in a new ring expansion approach to α-methylene δ-lactones, and later applied to a variety of one-carbon homologation reactions[5]. The above result encouraged us to study the scope of application of this reaction in other cyclic ketones and we found that the ring expansion efficiently proceeds with non-enolizable cyclohexanones and decalones activated in α position by the n-butylthiomethylene group. While the use of this moiety as protective group of cyclic ketones is well documented in the literature, to our knowledge, its application as a driving force in a ring expansion approach for the synthesis of medium-size rings is unprecedented. The process involves initial introduction of the n-butylthiomethylene group[6] followed by reaction with methoxy(phenylthio)methyllithium 4. The resulting diastereomeric mixture of alcohols 2 undergo the ring expansion when treated with $HgCl_2$ and HCl at 80-90ºC, to yield keto aldehydes 3, as shown in Scheme 1.

As a representative example compound 3g was prepared as follows. In a three-neck round-bottomed flask was placed, under A, 0.15 g (1.03 mmole) of methoxy(phenylthio)methane in 3 ml of anh. THF. The solution was cooled to -35ºC and then 1.23 ml of a 0.84M BuLi in hexane

(1.03 mmole) was slowly added and the mixture stirred for 1 h. After cooling to -78ºC a solution of 220 mg (0.83 mmole) of ketone 1g[6] in 1.5 ml of anh. THF was added dropwise. The reaction mixture was stirred for 2 h, quenched with NH_4Cl sat. soln. and repeatedly extracted with ether. Usual work-up furnished an oily residue which was chromatographed on silica gel eluting with hexane:ether (100:1.5) to yield 202 mg (58%) of the α-epimer **2g** and 132 mg (38%) of the β-epimer **2g**[7]. Hydrolysis of the diastereomeric mixture of alcohols **2g** (171 mg, 0.405 mmole) in 20 ml of CH_3CN in the presence of 441 mg (1.623 mmole) of $HgCl_2$ and 6 ml of 1N HCl at 80ºC for 2 h, afforded 57 mg (73%) of keto aldehyde **3g** after purification on silica gel eluting with hexane:ether (100:5)[7].

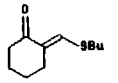
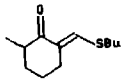
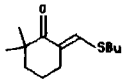
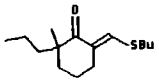
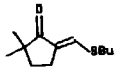
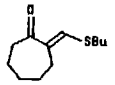
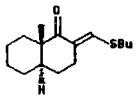
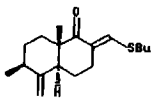


Scheme 1

As shown in the Table, whereas the yields of the diastereomeric alcohols **2** are excellent in all cases, the ring expansion process to **3** occurs efficiently only with activated non-enolizable cyclohexanones or decalones. 6-Unsubstituted ketones such as cyclohexanone **1a** (entry 1) and cycloheptanone **1f** (entry 6) gave mixtures of compounds, whereas 6-monosubstituted ketones such as 6-methylcyclohexanone **1b** (entry 2) afforded the expected keto aldehyde **3b** in a better but not synthetically useful yield. 5,5-Dimethylcyclopentanone **1e** was also a poor substrate for the expansion but 6,6-dimethylcyclohexanone **1c**, 6-methyl-6-n-propylcyclohexanone **1d** and decalones **1g** and **1h** efficiently expanded to the corresponding keto aldehydes in fair to good yields (entries 3, 4, 7 and 8)[8]. It must be noted that the presence of the n-butylthiomethylene group in α-position to the carbonyl is essential for the expansion, since the corresponding adducts of cyclohexanone and 1-decalone with **4** did not undergo any rearrangement under our standard conditions[9]. On the other hand, the same adduct was recovered unchanged when treated with 2 equivalents of sec-butyllithium, in an analogous way to that described by Cohen[10] for the ring enlargement of non-activated ketones with bis(phenylthio)methyllithium. In this case, the higher stabilization of the anion by the phenylthio group in comparison with the methoxy group may account for this result.

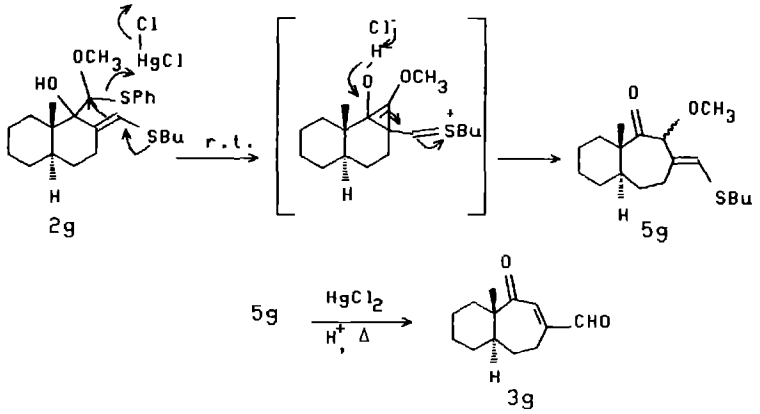
In order to postulate a plausible mechanism for the expansion reaction, the diastereomeric mixture of alcohols **2g** was subjected to selective hydrolysis conditions. Thus, treatment of **2g** with $HgCl_2$/HCl/acetone for 2h at room temperature or $HgCl_2$/HgO/CH_3CN:H_2O (4:1) for 15h at 90ºC afforded, in either case, the intermediate 7-member ring n-butylthiomethylene ketone **5g** as a mixture of isomers[11]. Further hydrolysis of this ketone with concomitant dehydromethoxylation needed stronger conditions ($HgCl_2$/CH_3CN/1N HCl for 2h at 80ºC), to yield the expected keto aldehyde **3g** in 70-75% overall yield from **2g**. These results point out to a mechanism wherein a presumably anchimeric assistance of the n-butylthiomethylene group could compensate the positive charge induced by the $HgCl_2$-promoted cleavage of the C-S bond. The resulting intermediate of carbocationic character might then

Table

Entry	Ketone		Adduct (%)[a]	Keto aldehyde (%)[a]
1		1a	2a (94)[b]	3a (6)
2		1b	2b (99)[b]	3b (27)
3		1c	2c (96)	3c (56)
4		1d	2d (88)	3d (58)
5		1e	2e (69)	3e (5)
6		1f	2f (91)[c]	3f (<10)[d]
7		1g	2g (96)	3g (73)
8		1h	2h (96)	3h (89)

[a]Isolated yield unless stated otherwise.
[b]Crude yield. The compound could not be purified due to partial decomposition to the rearrangement product, α-phenylthio aldehyde[12].
[c]Crude product partially contaminated with the rearrangement product, α-phenylthio aldehyde, as detected by ^{1}H NMR (δ=9.56 ppm).
[d]The expected keto aldehyde 3f contained (ca. 30%) of the intermediate methoxy compound 5f (see below).

undergo ring expansion to the methoxy ketone 5g, as shown in Scheme 2. Therefore, the n-butylthiomethylene group appears to activate the cleavage of the C-SPh group, favoring consequently the occurrence of the ring expansion process.



Scheme 2

In summary, the ring expansion approach described herein, although restricted to α,α'-dialkylsubstituted cyclohexanones, is an efficient, two-step method for the synthesis of the previously unreported 3-formyl-2-cyclohept-en-1-ones[13], a class of compounds which otherwise might not be easy to prepare.

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5. J. Otera, *Synthesis* 1988, 95 and references cited therein.
6. R.E. Ireland and J.A. Marshall, *J. Org. Chem.* 27, 16 (1962).
7. α-**2g**: IR ν 3450, 3060, 1595, 1580, 1435, 1375, 1100, 975, 690 cm^{-1}. ^1H NMR: δ 7.55-7.2 (m, 5H, C_6H_5), 6.01 (ds, 1H, =CH), 5.1 (s, 1H, $CHOCH_3$), 3.3 (s, OCH_3), 2.9 (s, 1H, OH), 2.71 (t, 2H, J=6.5 Hz, CH_2S), 2.65-2.2 (m, 2H, $CH_2C=C$), 1.9-1.1 (c, 15H), 0.93 (t, 3H, J=6.5 Hz, CH_3), 0.91 (s, 3H, CCH_3). ß-**2g**: IR ν 3550, 3050, 1625, 1580, 1470, 1440, 1100, 910, 690 cm^{-1}. ^1H NMR δ 7.7-7.15 (m, 5H, C_6H_5), 6.12 (ds, 1H, =CH), 5.14 (s, 1H, $CHOCH_3$), 3.35 (s, 3H, OCH_3), 3.10 (s, OH), 2.85-2.5 (c, 4H, CH_2S and $CH_2C=C$), 1.9-1.1 (c, 15H), 0.94 (c, 3H, CH_2CH_3), 0.84 (s, 3H, CCH_3). ^{13}C NMR δ 136.6, 135.3, 133.3, 133.3, 128.6, 128.6, 127.3, 120.3, 95.4, 82.6, 65.7, 57.3, 44.9, 41.1, 33.4, 32.5, 29.3, 28.5, 28.2, 26.2, 22.0, 21.6, 13. **3g**: IR ν 1700, 1680, 1450, 1375, 1075 cm^{-1}. ^1H NMR δ 9.6 (s, 1H, CHO), 6.6 (s, 1H, CHCO), 2.9-2.1 (c, 2H, $CH_2C=C$), 1.9-1.25 (c, 11H, $5CH_2$ and CH), 1.2 (s, 3H, CH_3). ^{13}C NMR δ 210.5, 194.1, 145.5, 145.0, 49.9, 41.8, 35.3, 30.2, 29.0, 26.3, 23.8, 21.0, 15.0. MS m/z (%) 206 (M^+, 94), 178 (44), 177 (37), 164 (33), 163 (84), 149 (40), 147 (30), 138 (39), (100), 109 (84), 96 (32), 95 (39), 79 (30), 6 (32), 67 (64), 55 (34), 41 (49). HRMS: exact mass for $C_{13}H_{18}O_2$: calcd., 206.130680; found, 206.131606.
8. All new compounds exhibited satisfactory IR, ^1H NMR, ^{13}C NMR, MS and HRMS data consistent with the proposed structures.
9. This finding has also been noted: B.M. Trost and G.K. Mikhail, *J. Am. Chem. Soc.* 109, 4124 (1987).
10. W.D. Abraham, M. Bhupatty and T. Cohen, *Tetrahedron Lett.* 28, 2203 (1987).
11. **5g**: IR ν 1700, 1610, 1460, 1450, 1100, 1050, 905 cm^{-1}. ^1H NMR δ 6.19 (s, 1H, =CHSBu), 4.7 (s, 1H, $CHOCH_3$), 3.35 (s, 3H, OCH_3), 2.1-1.8 (c, 2H, $CH_2C=C$), 1.9-1.1 (b, 15H, $7CH_2$ and CH), 1.1 (s, 3H, CH_3C), 0.87 (t, 3H J=7 Hz, CH_3). ^{13}C NMR δ 211.2, 131.2, 124.7, 88.2, 85.5, 56.9, 41.2, 36.6, 33.5, 32.4, 31.4, 31.1, 29.9, 26.1, 21.6, 20.6, 14.5, 13.5. MS m/z (%): 310 (M^+, 40), 282 (27), 225 (23), 221 (9), 194 (15), 193 (100), 162 (12), 161 (92), 159 (11), 147 (9), 143 (10), 133 (8), 123 (8), 85 (7), 41 (13). HRMS exact mass for $C_{18}H_{30}O_2S$: calcd., 310.196652; found, 310.197376.
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