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AN IMPROVED METHOD FOR THE SYNTHESES OF β-SUBSTITUTED CYCLOHEXENONES

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Abstract: An improved method for the preparation of β-substituted cyclohexenones is reported. Conditions were defined to effectuate the key desulfonylation-deketalization step in a mild manner. Several cyclohexenones bearing acid and/or base sensitive β-substituents were prepared by the modified method in moderate to good yields.

The β-substituted cyclohexenones are a class of compounds with great synthetic importance. Synthetic methods developed for these compounds are, in general, based on suitably functionalized cyclohexenones via either normal dipole process or dipole reversed process(umpolung)[1].

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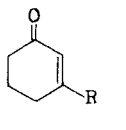
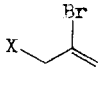
In connection with other on going projects, we needed to prepare compound **1a** in an efficient manner. Most present methods involving conditions not compatible with function groups existing in starting material are inapplicable to the synthesis of **1a** as shown in the following section. Thus, synthesis of **1a** by normal dipole process was first tried.An attempt on addition of the nucleophilic side chain **3a**[2] to 3-bromo-2-cyclohexenone(**2**) failed, whereas, more reactive organometallic reagents(RLi,R_2CuLi,RMgX,RZnX) derived from 2,3-dibromopropene(**3b**) seem to be uncontrolled due to HBr elimination tendency[3]. By umpolung approach, reaction of the lithiated **4** with 2,3-dibromopropene(**3b**) was also unsuccessful as reported in the literature in a similar situation[4a].By a similar approach, the substitution reaction of lithiated sulfone derivative **5** with **3b** gave desired 5**a** in quantitative yield, however, the following desulfonynation reaction under reported conditions(5% HCl-THF, 30-65°C)[4b] completely failed. We wish to report herein a significant modification of the method based on benzenesulfonyl stabilized α-anion leading to an efficient and convenient syn-



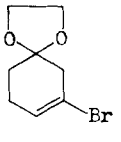
1a. R = 

2. R = Br



3a. X = TMS

3b. X = Br



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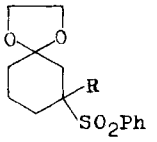
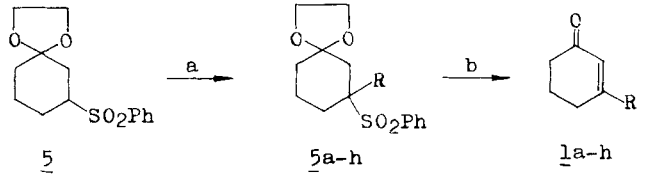


5. R = H

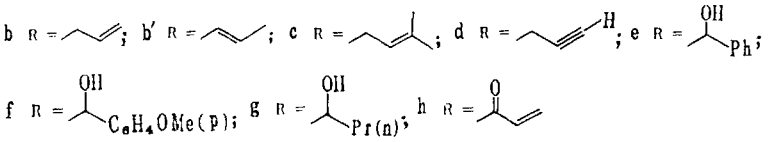
5a. R = 

thesis of **1a**, which seems applicable to the synthesis of other functionalized β-substituted cyclohexenones(Scheme).

Scheme



5 5a-h 1a-h



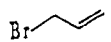
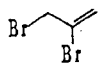
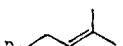
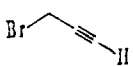
Reagent:(a).LDA or n-BuLi(1.1-3.0 eqs),THF,-78 °C,1-2.5hrs, Electrophiles.(b).TsOH(cat.),$CHCl_3$-acetone(5:1), 40 °C,10 hrs or 25 °C,48 hrs.

3-Benzenesulfonyl-1,1-ethylene dioxycyclohexane(5) was prepared by known method[5] in two steps in an overall yield of 95%. Treatment of 5 with LDA or n-BuLi (1.1 equiv.) at -78 °C and reaction of the resultant anion with 2,3-dibromopropene(**3b**) gave **5a** in 96% yield. The key desulfonylation-deketalization steps are accomplished by using p-toluenesulfonic acid as catalyst. Thus,treatment of the sulfone **5a** with p-toluene-sulfonic acid(5% mol.equiv.) in a mixed solvent system(chloroform-acetone, 5:1) at 40°C(10 hrs) or at

25°C(48hrs) gave,in one step, the desired compound **1a**[6] in a yield of 83%.

Extension of this modified method to the syntheses of other functionalized β-substituted cyclohexenones were also studied. Three types of electrophile were examined and the results were shown in the Table. Both functionalization and desulfonylation steps merit some comments. The reaction of the carbanion of **5** proceeded very well with allylic and propargyl bromide as well as aromatic aldehydes, with aliphatic aldehydes and Michael acceptor, small portion of starting material was recovered in combination with the desired products. However, due to steric hindrance and /or polymerization side reaction, this reaction didn't work at all with ketones, 2-butenyl acid methyl ester and acrylonitrile. The desulfonylation-deketalization steps, on the other hand, gave complex mixture in the cases of **5d** and **5g**(entry 4 and entry 7). In the case of β-allyl-β-sulfonylketal **5b**, although the one-step desulfonylation-deketalization proceeded normally to give **1b** as indicated by ^{1}H-NMR spectrum data[6], but this product is very unstable and it isomerizes almost quantitatively to its more stable fully conjugated form **1b'**(entry 2) upon chromatography purification on silica gel. Interestingly, the overall result of these reactions constituted a mild and convenient method for the synthesis of compound **1b'**, which presented greater synthetic values. This method would be applicable to the synthesis of (±)-terrein[7], a mould metabolite.

Table

Ent	Elctrophiles	Reaction Conditions LDA equiv./Time(h)	Yields of Step a(%) (Compound Number)	mp(°C)	Yield of Step b(%) (Compound Number)
1		1.1 / 1.0	98(5b)	89	65(1b')[a]
2		1.1 / 1 0	96(5a)		83(1a)
3		1.1 / 1.0	100(5c)	114	51(1c)
4		1.1 / 1.0	93(5d)	116	0(1d)
5	PhCHO	3.0 /2.0	87(5e)	75-76	65(1e)
6	p-MeOC$_6$H$_4$CHO	3 0 / 2.5	93(5f)	120	77(1f)
7	n-PrCHO	3.0 / 2.0	82(5g)	112	Trace(1g)
8		1.1 / 1.0	78(5h)[b]	oil	80(1h)

a. 1b quickly isomerized to 1b', b. 1,4-addition product

In conclusion, starting from stable and readily available 2-hexenone synthon **5**, this two-step procedure constitutes both as a complementary method and an alternative route to β-substituted cyclohexenones, especially in the cases where β-substituents bear acid and/or base sensitive function groups.

Experimental:

Typical experimental procedure for synthesis of **1a**

To a solution of 32.9 mmol of lithium diisopropylamine in 135 ml of THF at -78°C under N_2 was added 8.42g (29.9 mmol) of **2** in 25ml of THF over 5 min. The reaction mixture was stirred at -78°C for 20 min. 2,3-dibromopropene(3.1ml, 44.6 mmol) was then added and stirring continued for 1h. The reaction mixture was quenched at this temperature with a saturated solution of aqueous NH_4Cl(2ml/mmol).The resulting mixture was extracted with three 200-ml portions of CH_2Cl_2 and the combined organic layer was dried ($MgSO_4$) and concentrated. Short silica gel column filtration of the crude product(Petroleum ether(60-90°C)-EtOAc(3:1) as eluent) afforded 11.7g of **5a** (96%) as white needles. ^{1}H-NMR ($CDCl_3$, 60MHZ): 1.45-2.00(m, 8H, $4CH_2$), 3.32(d,J=1.7 Hz,1H,CH_2CBr), 3.36 (d,J=2.0Hz, 1H, CH_2CBr), 3.90(s, 4H, OCH_2CH_2O), 5.70, 6.03 (2d, J=1.7 Hz, 2H, $=CH_2$), 7.48-7.97(m, $5H_{arom}$); MS(m/z): 401, 403$[M+1]^+$(1.4,1.1), 321$[M-Br]^+$ (5.7), 259, 261$[M-SO_2Ph]^+$ (100, 87.5), 215, 217$[M-SO_2Ph-OC_2H_4]^+$(82.3, 77.4), 179(44.5), 99$[C_5H_7O_2]^+$(63.7). Anal. Calcd. for $C_{17}H_{21}BrO_4S$: C 50.88; H, 5.27; Found: C 50.56, H 4.92.

To 6.60g (16.5 mmol) of alkylated ketal sulfone **5a** dissolved in 50 ml of chloroform was added 10 ml of acetone and 160 mg (0.83 mmol) of para-toluenesulfonic acid monohydrate, the mixture was stirred at 40°C for 10hs. or at 25°C for 48hs. After neutralization with a 10% of aqueous $NaHCO_3$ solution, H_2O(30ml) was added,and the combined organic phase was dried and concentrated. SiO_2 column flash chromatography[petroleum ether (60-90°C): EtOAc (3:1) as eluent] of the crude product afforded 2.96g of **1a**(83%) as pale yellow oil.IR(film): 1670, 1630, 1620, 1425, 1345, 1250,1185,1140,885cm^{-1}; ^{1}H-NMR(CCl_4-60MHz): 1.72-2.40(m, 6H, $3CH_2$),3.25(s, 2H,CH_2CBr), 5.49(s,1H, $=CH_2$), 5.65(s,1H, $=CH_2$),5.78(s, 1H, CHCO); MS(m/z): 216,214 (M^+)(34.3,34.2), 188, 186(35.2, 37.0), 160, 158(15.1, 15.6), 135(62.5),107(100), 91(49.8), 79(100), 77(100), Anal. Calcd. for $C_9H_{11}BrO$: C 50.26; H 5.15. Found: C 49.87; H 5.06.

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6. ^{1}H-NMR of **1b**: 1.89 (dd, J=2.3 and 3.4 Hz, 3H), 2.03(m, 2H), 2.41(m, 4H), 5.86(s, 1H), 6.20(m, 2H)ppm. ^{1}HNMR of **1b** : 1.59-2.16(m,6H), 3.89(s,2H), 5.01(m,1H), 5.0(s,1H), 5.85(s,1H) ppm.

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