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A GENERAL SYNTHESIS OF 4-ALKYL/ARYL SUBSTITUTED SACCHARINS[1]

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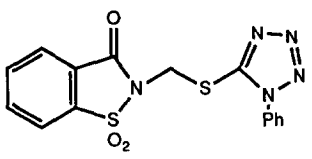
Abstract: A new method for the synthesis of 4-alkyl/aryl substituted saccharins (**2**) has been developed. The key steps include conjugate addition/acylation of cyclohexenone (**3**) and reaction of the resulting β-ketoesters **4** with benzyl mercaptan to give the vinyl sulfides **5** and **6**. The latter were converted to the saccharins (**2**) in high yield.

Human leukocyte elastase (HLE) is a serine proteinase that has been invoked in the etiology of a number of pulmonary disorders such as emphysema[2], acute respiratory distress syndrome and chronic bronchitis[3]. A potential form of therapy is the inhibition of this enzyme in the lungs.[4] Our efforts to design mechanism based inhibitors[5] of HLE, resulted in the identification of compound **1** (K_i = 15 nM) as a lead.[6,7] In order to develop structure-activity relationships based on this structure, 4-alkyl/aryl substituted saccharins (**2**) were needed. A number of methods for the preparation of the saccharin nucleus are available[8] but they are not useful for the



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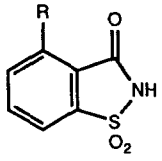

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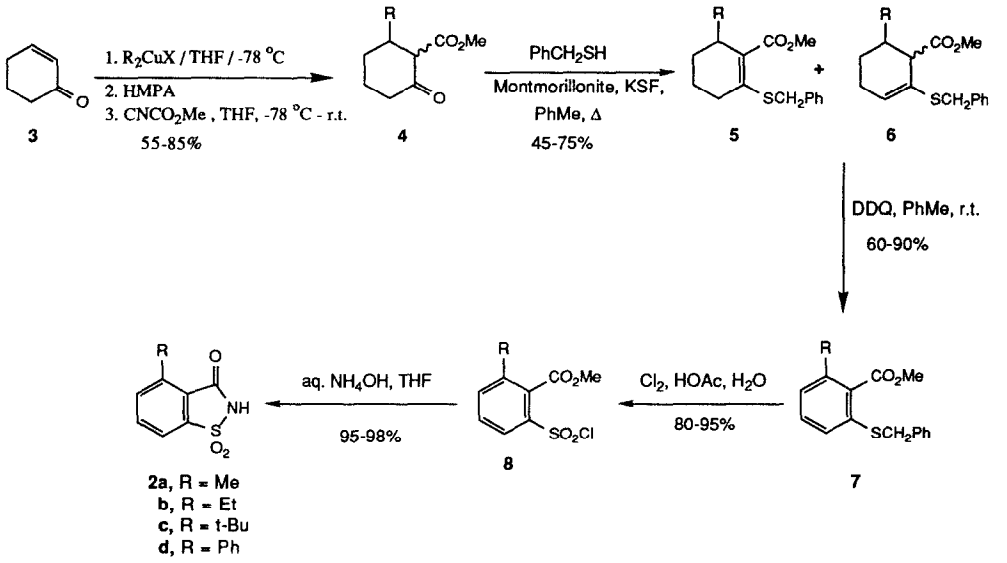
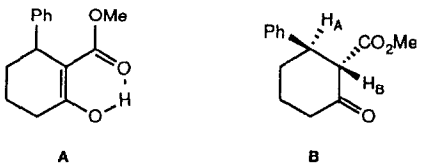
synthesis of 4-alkyl or aryl substituted saccharins. Hence, a short and general synthesis of the title compounds has been developed and is the subject of this paper. The strategy consists of the construction of suitably substituted hydroaromatic compounds **5** and **6** followed by their aromatization to the 1,2,3 trisubstituted benzene derivatives **7**.[9]

The synthetic route is shown in Scheme **I**. Conjugate addition of various organocopper compounds[10] to cyclohex-2-ene-1-one (**3**) followed by trapping[11] of the intermediate enolate with methyl cyanoformate[12] gave the β-ketoesters **4** in good yields. As seen from Table I, this reaction works very well with primary alkyl but only

Scheme 1



fairly with phenyl organocopper reagents. In the case of the t-butyl compound (entry **c**, table **I**), use of the higher order cuprate t-$Bu_2Cu(CN)Li_2$[13] was necessary to obtain good yields of the desired β-ketoester **4d**.The NMR spectra of the β-ketoesters **4** were complicated by the presence of diasteromeric keto and enol forms. An exception was compound **4d** (R = Ph), wherein the chromatographed product was found to exist

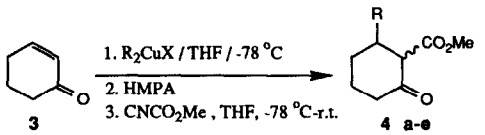


solely in the enol form **A**. However, crystallization of this product (Et_2O/hexanes) led to the isolation of a single diastereomer of **4d** (m.p. 93-95 °C) which now existed exclusively in the keto form **B**. The trans stereochemical assignment for the keto form is confirmed by the observation of a 12.6-Hz coupling between protons H_A and H_B.

Refluxing a mixture of the β-ketoesters **4**, benzyl mercaptan, and an acidic clay montmorrilonite, KSF,[14] in toluene with removal of water furnished, after chromatography on silica gel, the regioisomeric vinyl sulfides **5**

and **6**. The ratio[15] of **5:6** was dependent upon the size of the R group in **4**. Seperation of the regioisomers was unnecessary because DDQ oxidation[16] of the vinyl sulfide mixture provided good yields of the aryl benzyl thioethers **7**. Other reagents which were used to effect this aromatization (S_8, MnO_2, NiO_2, $BaMnO_4$ and Pd on C) gave little or no product. Oxidative debenzylation[17] of **7** with Cl_2 in HOAc / H_2O provided the sulfonyl

Table I



3 4 a-e

entry	R_2CuX	% yield of 4 [i]
a	$Me_2CuMgBr$	76
b	$Et_2CuMgBr$	70
c	$tBu_2Cu(CN)Li$ [ii]	85
d	$Ph_2CuMgBr$ [iii]	55

i. Yields are for distilled (Kugelrohr) or chromatographed material.
ii. Reaction run in Et_2O. See ref. 10 for experimental conditions.
iii. Reaction mixture warmed to 0 °C after the addition of enone and maintained at that temperature for 1 h. It was then cooled to 0 °C before the addition of methyl cyanoformate

chlorides **8** in excellent yields. Treatment of **8** with aqueous ammonium hydroxide in THF afforded the target saccharins (**2**) in near quantitative yield.[18]

In conclusion, a general method for the synthesis of 4-alkyl/aryl substituted saccharins has been developed. The method reported here should also be of general use for the synthesis of polysubstituted benzene derivatives.

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General procedure for the preparation of β-ketoesters **4**: To a suspension of anhydrous CuI (10 mmol) in anhydrous THF (100 mL) was added Me_2S (100 mmol) and the resulting solution was cooled to -78 °C. The Grignard reagent (20 mmol) was added over a period of 15 min. After being stirred at -78 °C for 1 h, a solution of cyclohexenone (10 mmol) in THF (20 mL) was added and stirring continued for another 15 min. To the resulting mixture was added HMPA (5 mL) and after 15 min methyl cyanoformate (30 mmol) in THF (20 mL) and the reaction warmed to room temperature and stirred overnight. The reaction mixture was quenched with 2N HCl (50 mL). The layers were separated and the aqueous phase extracted with Et_2O (1 X 100 mL). The combined organic extracts was washed with saturated NH_4Cl solution (3 X 50 mL), H_2O (2 X 50 mL), brine (1 X 50 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by either Kugelrohr distillation or flash chromatography afforded the desired β-ketoesters **4**.
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15. The ratio of **5:6** was determined from the ^1H NMR of the purified reaction mixture.
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18. All new compounds gave satisfactory NMR (^1H and/or ^{13}C), IR, CIMS and/or elemental analysis data. The melting points for the final saccharins (recrystallized from Et_2O / hexanes) are given below. Compound **2a**: 203-205 °C; **2b**: 183-185 °C; **2c**: 185-187 °C; **2d**: 210-212 °C.