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4-[(4-Methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone and its Dianion as Versatile Tools in Organic Synthesis

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Abstract: The title compound and the corresponding dianion have been used as convenient precursors for substituted divinyl ketones in both carbo- and heterocyclization reactions in a one-pot three-step sequence leading to substituted carbo- and heterocyclic ring systems and for the construction of the 4-keto-2-alkenoate subunit, a common structural feature of a variety of natural compounds, respectively.

The concept of "tandem reaction" sequence has been widely used for shortening of the synthetic pathway and for relaying of stereochemical control in a multistep approach to complex natural products.[1]

As an extension of our continuous interest in this area, we needed an easy entry to differently substituted divinyl ketones able to participate to a domino reaction sequence initiated by a nitrogen- or carbon-centered nucleophile as a tool for building up six-membered heterocyclic and carbocyclic rings.[2]

In this paper, we wish to describe the preparation and the reactivity of the hitherto unknown 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **1**,[3] which can be considered as a new four-carbon synthon for substituted divinyl ketones.

This compound features a stabilized ylide function useful for the installation of a double bond through a Wittig reaction and a γ-keto sulfone system, functionality stable in neutral or acidic media but susceptible to *p*-toluensulfinic acid elimination under the basic conditions required in the initial event of the synthetic sequence.

The reaction of the ylide **1** with the aldehydes **2a-h** proceeded uneventfully to produce the expected unsaturated ketones **3a-h** in good to optimum yields by heating in some solvents or at room temperature (**3g**) as shown in the following Scheme 1.

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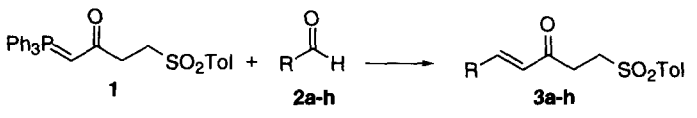
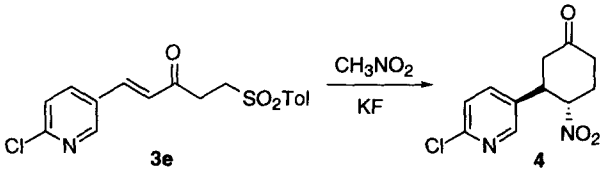
Scheme 1



a: R = Me; **b**: R = Ph
c: R = C_9H_{19}; **d**: R = CH_2-N(Bn)-Boc
e: R =2-Cl-5-pyridyl
f: R =3-pyridyl; **g**: R = CO_2Me
h: R =2,2-dimethyl-1,3-dioxolan-4-yl

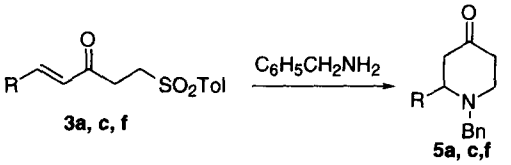
Our goal was the utilization of the derived unsaturated ketones **3a-h** as substrates for the construction of substituted carbo- and heterocyclic compounds. A nice example of the methodology is offered by the preparation of the nitrocyclohexanone **4**, an advanced intermediate already converted by us[4] and others[5] into (±)-epibatidine, an unusual alkaloid which has received a great deal of synthetic attention. Thus, smooth cyclization occurred when **3e** was reacted with nitromethane (1 equiv) at room temperature in THF : H_2O in the presence of potassium fluoride (stronger bases are ineffective causing only polymerization) to give **4** (86%) (Scheme 2).

Scheme 2



On the other hand, the formation of substituted nitrogen containing heterocycles could be easily accomplished simply by using a primary amine as nitrogen centered nucleophile for the available unsatured ketones. Thus, the piperidones **5a**, **c**, **f** are conveniently obtained in good yield by reacting at room temperature the vinyl ketones **3a**, **c**, **f** respectively with benzylamine. (Scheme 3)

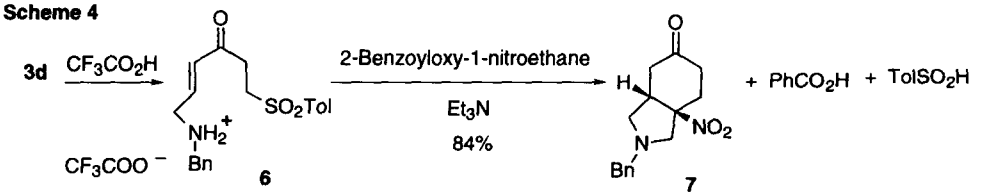
Scheme 3



a: R = Me;
b: R = C_9H_{19};
c: R = 3-pyridyl

Interestingly, the method could be also applied to the construction of polycyclic systems. Thus, when the required substrate **6**, derived from the ketosulfone **3d** by TFA removal of the nitrogen protective group (Boc), was treated with nitroethylene, generated in situ from 2-benzoyloxy-1-nitroethane in the presence of an excess of Et_3N, the bicyclic compound **7** was obtained as the sole product through a sequence of Michael reactions (Scheme 4).

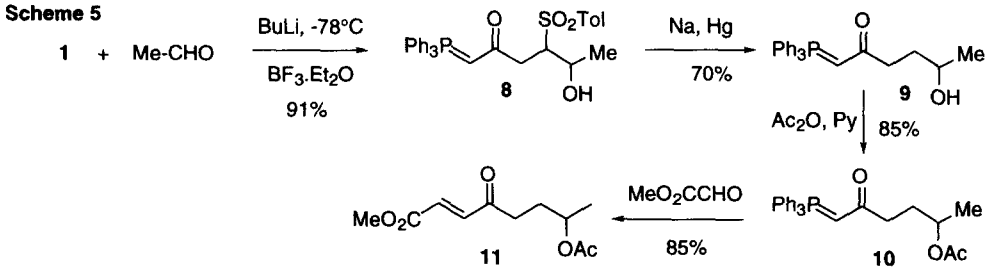
Scheme 4



Moreover, further applications of the building block **1** could arise through the generation of its α-sulfonyl anion, thus creating a dianion able to react with different electrophiles at both terminus of its four carbon atom chain. The straightforward route to methyl (±)-7-acetyloxy-4-oxo-2-octenoate **11**, a known precursor to the macrolide antibiotic pyrenophorin, along the steps outlined in the following Scheme 5, illustrates the utility of this strategy.

Initial attempts to perform the aldol condensation between the anion resulting by treatment of **1** with n-BuLi at -78°C in THF with aliphatic or aromatic aldehydes were unsuccessful, even in the presence of added HMPT (1 equiv). However, increasing the reactivity of the carbonyl partners by addition of boron trifluoride etherate and quenching the reaction mixture with water at -20°C in order to avoid retroaldolization,[6] represented a simple but substantial improvement, allowing the corresponding aldol adducts to be obtained in good yield. Thus, the reaction of **1** with acetaldehyde proceeded smoothly in the presence of boron trifluoride etherate to give the adduct **8**, which was then submitted to reductive cleavage of the *p*-tolylsulfone group (6%Na/Hg, MeOH, 2h) to produce the intermediate **9**, which was converted under standard conditions (Ac_2O/Py, r.t., 3h) into the corresponding acetylated phosphorane derivative **10**. Its Wittig coupling with methyl glyoxylate at room temperature afforded in high yield methyl (±)-7-acetyloxy-4-oxo-2-octenoate **11**, a known precursor to the macrolide antibiotic pyrenophorin, already taken to the natural product.[7]

Scheme 5



In conclusion, we have demonstrated that 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **1** can be considered a convenient precursor of substituted divinyl ketones, which are useful intermediates for the preparation of a wide variety of substituted carbo- or heterocyclic ring systems through a multiply convergent process entailing on a three-step sequence initiated by their reaction with a carbon or nitrogen-centered nucleophile under mild and experimentally simple conditions.

Moreover, a convenient methodology for the preparation of heavily functionalized carbon frameworks emerges from the reaction of the dianion of **1** with two different aldehydes and reductive removal of *p*-tolylsulfone group. As an example, we have developed a general protocol for the synthesis of the 4-keto-2-alkenoate subunit, a key structural element of a family of biologically active compounds, which constitues a very useful alternative to currents methods since the ketone needs not to be protected and the double bond is installed under mild conditions.

Further applications of these functionalized frameworks to the synthesis of biologically active compounds are in progress in our laboratories.

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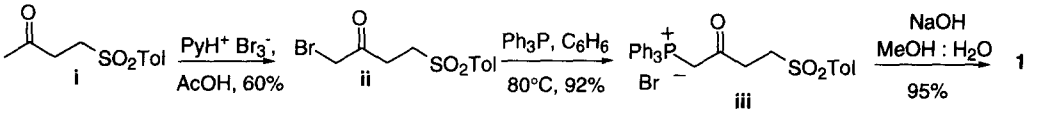
3. The preparation of **1** utilizes the Michael adduct[8] **i** of sodium *p*-toluensulfinate to 2-butenone as the starting material. Its bromination with pyridinium bromide perbromide produces a 3 : 1 mixture of **ii** [(mp 108-110°C; ^{1}H NMR ($CDCl_3$) δ: 2.48 (s, 3H), 3.15 (t, 2H, J=7.2), 3.40 (t, 2H, J=7.2), 3.20 (s, 3H), 7.36 (d, 2H, J=8), 7.79 (d, 2H, J=8); IR (nujol): 1720, 1600, 1450 cm^{-1}] and its regioisomer, which could be easily separated by flash chromatography using ethyl ether : light petroleum 1 : 1 as eluent. The reaction of **ii** with triphenyl phosphine afforded the corresponding phosphonium salt **iii**, which was quantitatively transformed into the phosphorane **1** [mp 163-165°C; ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H), 2.69-2.77 (m, 2H), 3.42-3.50 (m, 2H), 3.72 (d, 1H, J = 24), 7.26-7.80 (m, 19H)], by treatment with sodium hydroxide in methanol and subsequent precipitation with water.



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