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Polymer-bound 4-Benzylsulfonyl-1-triphenylphosphoranylidene-2-butanone as a Tool for the Solid-Phase Synthesis of Substituted Piperidin-4-one Derivatives.

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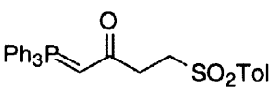
Abstract: An efficient method for the construction of 2-substituted-piperidin-4-one derivatives on solid support has been developed using polymer-bound 4-benzylsulfonyl-1-triphenylphosphoranylidene-2-butanone as a convenient precursor for substituted divinyl ketones in the heterocyclization reaction with amines. The resin was released in a recyclable sulfinate form.

'Keywords: Solid-phase synthesis; Michael reactions; piperidinones.

The introduction of combinatorial techniques as a rapid and convenient tool for drug discovery and lead generation, possibly the most exciting development in medicinal chemistry for several decades, has spurred a renaissance in the area of organic synthesis on polymeric supports.[1]

The development of novel solid-phase synthetic methods is an important aspect of the drug discovery process and a current trend is to perform on solid supports a variety of organic reactions known to occur in homogeneous phase, the strategic advantages including ease workup procedures and product isolation and ready recovery of the polymer resin by a simple filtration.

We have recently described[2] the preparation and the reactivity of 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **1** as a new four-carbon synthon for substituted divinyl ketones able to participate in a domino reaction sequence[3] initiated by a nitrogen- or carbon-centered nucleophile as a tool for building up six-membered heterocyclic and carbocyclic rings.



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The central feature of our strategy was the sequential generation of the two double bonds adjacent to the central carbonyl group by Wittig reaction of the ylide function with a suitable aldehyde and through a base-promoted β-elimination of the sulfone group respectively. Interestingly, there is also the possibility of generating

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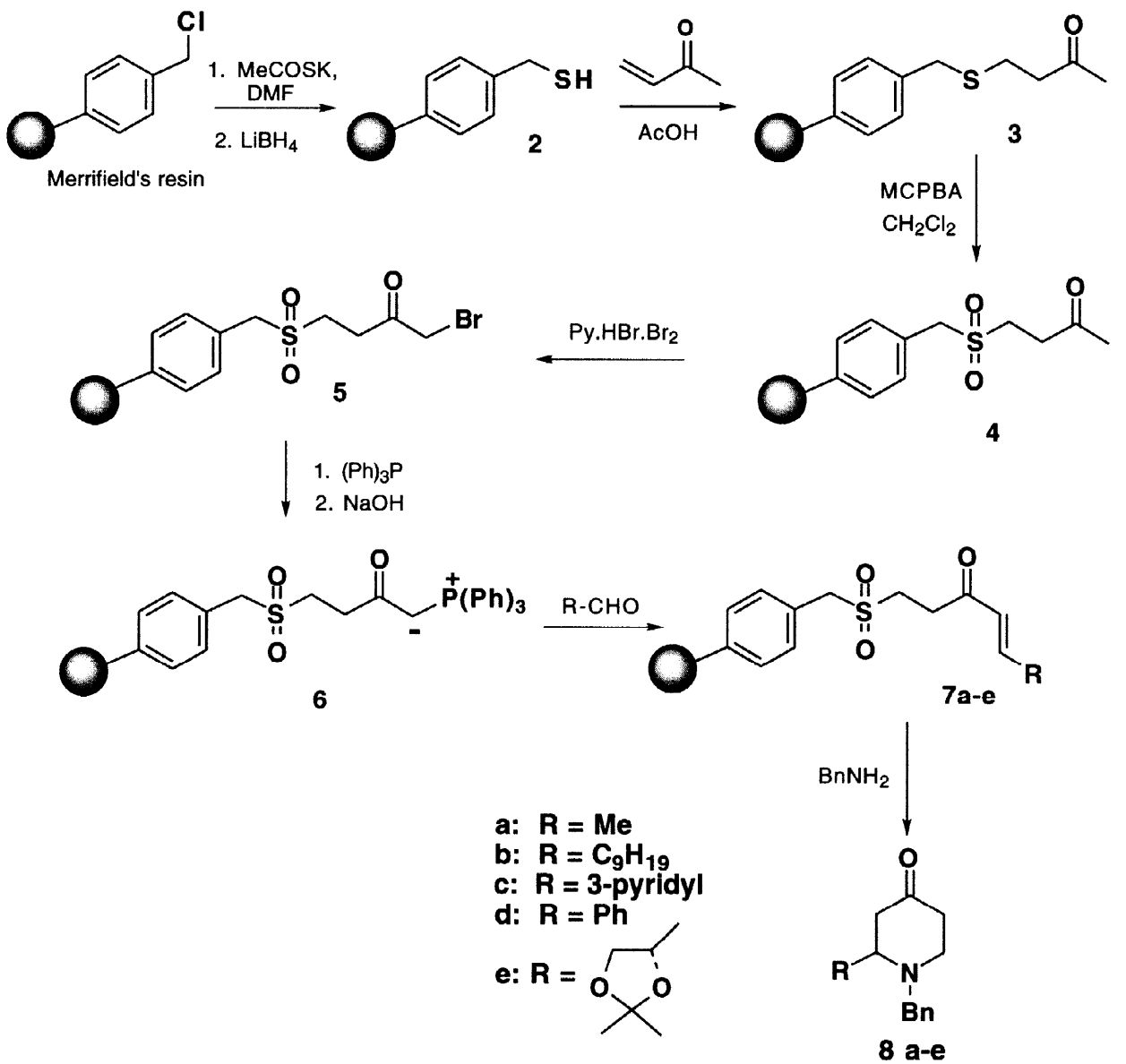
the α-sulfonyl anion, thus creating a dianion able to react with different electrophiles at both termini of its four carbon atom chain.

In the course of our investigations, aimed at developing efficient methodologies for combinatorial synthesis, we were especially intrigued by the prospect of immobilizing the new synthon **1** to a suitable solid support. We expected to be able to combine the advantages of a cascade process (shortening of the synthetic pathway, relaying of stereochemical control in a multistep approach to complex natural products) with those inherent to solid-supported reactions.

In this paper we disclose the preparation of the polymer-supported 4-benzylsulfonyl-1-triphenylphosphoranylidene-2-butanone and describe our preliminary results concerning its reaction with nitrogen centered nucleophiles, as shown in Scheme I.

SCHEME I



The polymer-supported reagent was prepared according to the protocol described by Kobayashi et al.[4] from chloromethyl copoly-(styrene-1%divinylbenzene) resin. Treatment with potassium thioacetate in DMF

followed by reduction of the derived thioester with $LiBH_4$, in ether, at room temperature, led to the formation of the solid-anchored thiol **2** which underwent Michael addition with 3-butenone (3equiv.) and acetic acid (2equiv.) in EtOH for 3h at room temperature. * FTIR spectroscopy showed a strong absorption at 1718 cm^{-1}. Oxidation[5, 6] of the sulfide **3** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 gave the required sulfone derivative **4** anchored to the resin, displaying bands at 1312 and 1144 cm^{-1} in its IR spectra for the sulfone and at 1718 cm^{-1} for the carbonyl group. The bromination step was carried out in AcOH at 60°C by treatment with pyridinium bromide perbromide within 16 hours under agitation by N_2 bubbling producing the bromide **5** which reacted subsequently with excess of triphenylphosphine in toluene at 40°C for 24 hours to afford the corresponding phosphonium salt. The formation of a mixture of brominated regioisomers, as previously observed in solution, cannot be excluded. However, only the primary bromide reacts with triphenylphosphine to produce the corresponding phosphonium salt, the secondary bromide undergoing a Perkov reaction to give the starting material. The required resin-bound stabilized ylide **6** useful for the installation of a double bond through a Wittig reaction was then generated by treatment with sodium hydroxide in methanol. Its reaction with the aldehydes was performed at 80°C in toluene (entries b-d) or at room temperature in $CHCl_3$ (entries a,e) for 12 hours to produce the expected unsaturated ketones **7a-e** in good to optimum yields as indicated by the isolation of triphenylphosphine oxide in the filtrate.

Our initial goal had been the utilization of the resin-bound unsaturated ketones **7a-e** as substrates for the construction of substituted heterocyclic compounds. We easily accomplished this simply by reacting at room temperature the vinyl ketones **7a-e** respectively in THF with excess of benzylamine within 3 days at room temperature. Benzylamine acts both as appropriate nucleophile and base: it undergoes easy 1,4-addition to the existing enone, then induces elimination of the sulfone group followed by 1,4-addition to the resulting enone to produce the piperidones **8a-e**, which were isolated by filtration from the released sulfinate resin,** evaporation of the solvent and final flash chromatography on silica gel.***

Because of their widespread occurrence in nature and their wide-ranging biological activity,[7] there has been considerable interest in the development of synthetic routes to substituted piperidine derivatives.[8]

In conclusion, a new solid-phase synthesis of 2-substituted piperidin-4-ones has been described which provides an interesting framework for combinatorial libraries using diverse pools of aldehydes and amines.

Further applications of these functionalized frameworks to the synthesis of biologically active compounds are in progress in our laboratories. We are currently attempting to use a phenol-sulfide solid-phase instead of the Merrifield resin to attach **1**. This will allow us to investigate the chemistry connected with the dianion of **1**, the sulfone group being directly connected to the aromatic ring thus ensuring a site-specific generation of the α-sulfonyl anion.

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REFERENCES and NOTES

1. a) Fruchtel, J.S.; Jung, G., *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 17-42; b) Balkenhohl, F.; Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C., *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2288-2337; c) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D., *Tetrahedron*, **1996**, *52*, 4257-4254; d)

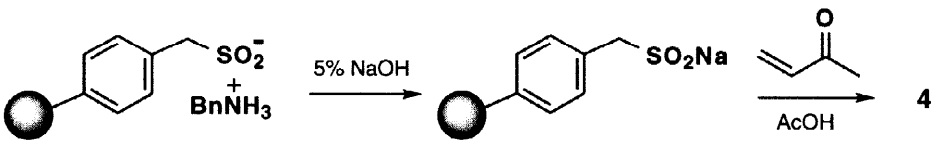
Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D., *Tetrahedron*, **1997**, *53*, 5643-5678; e) Bristol J.A., *Tetrahedron.*, **1997**, *53*, 6573-6706; e) Lam, S.K.; Lebl, M.; Krchnák, V., *Chem. Rev.*, **1997**, *97*, 411-448.

2. Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V., *Tetrahedron Lett.*, **1998**, *39*, 1973-1976.
3. Tietze, L.F., *Chem. Rev.*, **1996**, *96*, 115-136 and references cited therein.
4. Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M., *Tetrahedron Lett.*, **1996**, *37*, 2809-2812.

* Workup: filtered resin was repeateadly washed with the employed solvent at the end of each step, then with diethyl ether and finally dried.

5. Yamada, M.; Miyajima, T.; Horikawa, H., *Tetrahedron Lett.*, **1998**, *39*, 289-292.
6. Kroll, F.E.K.; Morphy, R.; Rees, D.; Gani, D., *Tetrahedron Lett.*, **1997**, *38*, 8573-8576.

. Treatment of the resin with 5% NaOH solution converts the resin into the corresponding sulfinate sodium salt allowing its easy recyclization. In fact, its reaction with 3-butenone in acetic acid furnished the resin-bound compound addition product **4 which displayed a carbonyl streching at 1718 cm^{-1} and can be reutilized.



*** **8a**: oil; 75%; ^{1}H NMR: δ 1.16 (d, 3H, J=6.39), 2.35 (m, 3H), 2.54 (m, 2H), 3.0 (m, 2H), 3.42 (d, 1H, J=13.3), 3.95 (d, 1H, J=13.3), 7.3 (m, 5H); **8b**: oil; 55%; δ 0.86 (t, 3H, J=6.3), 1.1-1.5 (m, 16H), 2.23 (m, 3H), 2.7 (m, 2H), 3.0 (m, 2H), 3.6 (d, 1H, J=13.5), 3.9 (d, 1H, J=13.3), 7.31 (m, 5H); **8c**: oil; 50%, ^{1}H NMR data see ref.8a; **8d**: oil; 55%, ^{1}H NMR data see ref.8b; **8e**: 1 :3 mixture of diastereomers, 76% (overall yield); less polar isomer (SiO_2, 1:2 EtOAc/cyclohexane), $[\alpha]_D^{25} = +3.09°$ ($CHCl_3$, c 2.07); δ 1.34 (s, 3H), 1.4 (s, 3H), 2.19 (dd, 1H, J=14.7, J=5), 2.4 (m, 2H), 2.6 (dd, 1H, J=14.7, J=5), 2.8 (dt, 1H, J=6.4, J=12.7), 3.15 (m, 2H), 3.7 (t, 1H, J=7.8), 3.82 (d, 1H, J=13.7), 4.0 (t, 1H, J=6.3), 4.05 (d, 1H, J=13.7), 4.3 (q, 1H, J=6.4), 7.3 (m, 5H); more polar isomer (SiO_2, 1:2 EtOAc/hexane), $[\alpha]_D^{25} = 8.79$ ($CHCl_3$, c 6.5); δ 1.28 (s, 3H), 1.32 (s, 3H), 2.4 (m, 4H), 2.95 (m, 1H), 3.1 (m, 2H), 3.58 (dd, 1H, J=7, J=8.3), 3.85 (s, 2H), 4.0 (dd, 1H, J=6.7, J=8.3), 4.3 (dt, 1H, J=6.7, J=4.4), 7.32 (m, 5H).

7. Bailey, P.D.; Millwood, P.A.; Smith, P.D., *Chem. Commun.*, **1998**, 633-640.
8. For alternative approaches and synthetic applications of 4-piperidone derivatives: a) Hattori, K.; Yamamoto, H., *Tetrahedron*, **1993**, *49*, 1749-1760; b) Diez, A.; Voldoire, A.; López, I.; Rubiralta, M.; Segarra, V.; Pagès, L.; Palacios, J.M., *Tetrahedron*, **1995**, *51*, 5143-5156; c) Wang, Y.; Wilson, S.R., *Tetrahedron Lett.*, **1997**, *38*, 4021-4024; d) Chen, C.; McDonald, I.A.; Munoz, B., *Tetrahedron Lett.*, **1998**, *39*, 217-220.