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THE SCOPE OF A NEW MASKED MICHAEL REACTION INVOLVING A PUMMERER INTERMEDIATE

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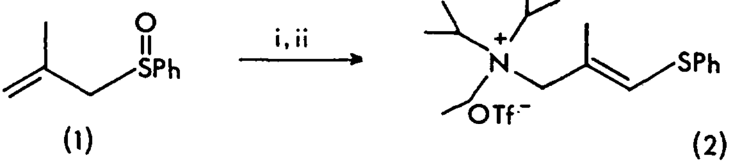
Abstract: Hünig's base has been found to compete as a nucleophile in the alkylation of Pummerer generated vinylthionium ions. This discovery has been used in extending the scope of the novel masked Michael addition reaction.

Over the years, the Pummerer[1] reaction has proved to be extremely versatile for functionality transfer from sulphur to carbon extending to O, N, S and halogen nucleophile incorporation.[1,2,3,4] In the realm of carbon-carbon bond formation most success has been achieved using intramolecular olefinic[5] interception of the Pummerer thionium ion intermediate, and in this respect the β-ketosulphoxide functionality has proved to be the electrophilic partner of choice. Far fewer examples exist for intermolecular[6] interception and the main problem to be overcome is competing reaction by other nucleophiles in the medium. In relation to using a silyl enol ether as the nucleophile, two sets of conditions have appeared recently for the reaction, namely stannous triflate[7] with N-trimethylsilyimidazole as base and trimethylsilyl triflate[8] with diisopropylethylamine. We have recently shown that the latter set of conditions can be used for reaction with phenyl allyl sulphoxides furnishing masked Michael adducts.[8] However, the maximum yields obtainable were always around the 70% mark and use of a less reactive silyl enol ether gave even lower yields e.g. dimethyl malonate (25%). In this communication we uncover the reason for the drop in yield and demonstrate the application of this discovery to the masked Michael reaction.

We have now established that the drop in yield is due to competing interception of the vinyl thionium ion intermediate by Hünig's base. Furthermore, in the absence of silyl enol ether the quaternary ammonium salt can be obtained in high yield. Scheme 1.

Scheme 1

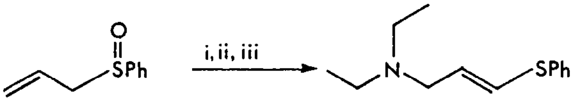


i) $(i\text{-}Pr)_2NEt / CH_2Cl_2$ / 0°C; ii) TMSOTf

A typical experimental procedure is as follows: To a stirred solution of methallyl phenyl sulphoxide (1), (1 mmole) in dry methylene chloride (3 mls) at 0°C, was added diisopropylethylamine (2,1 mmole) and trimethylsilyl triflate (2 mmole). The reaction was allowed to stir at 0°C for fifteen minutes before being quenched (1M HCl) and extracted (3 x 25 mls CH_2Cl_2). Drying and evaporation of solvent furnished the product (2) in high purity by ^1H NMR. The salt may be purified further by washing with ethyl acetate to obtain a white solid (91% yield) (m.pt. 107 - 109°C). The structure of the product was assigned using ^{13}C, ^1H NMR data and the stereochemistry designated as E- on the basis of an N.O.E. experiment. Scheme 1.

Other pyramidal tertiary amines also undergo the reaction including triethylamine and N,N-diethyltrimethylsilylamine. In the latter case using allyl phenyl sulphoxide as substrate and a mildly acidic work up, the masked Mannich derivative (3) could be obtained in 90% yield. Scheme 2. Use of the more hindered base heptamethyldisilazane ($(TMS)_2NMe$) also failed to inhibit the addition reaction and required a higher temperature (0°C) for reaction. By comparison DBN gave no reaction even at reflux temperature, (CH_2Cl_2 as solvent), nor in the presence of a silyl enol ether suggesting that deprotonation to the vinyl thionium ion does not occur. The full implications of choice of base for this reaction will be reported elsewhere.

Scheme 2



(3)

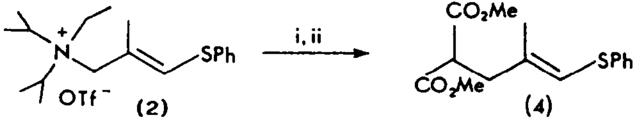
i) $(Et)_2NTMS / CH_2Cl_2$ / 0°C
ii) TMSOTf
iii) NH_4Cl / H_2O

Although it is known that strongly electrophilic alkenes do react with tertiary amines to afford quaternary ammonium salts, this variation significantly extends the use of allyl sulphoxides as electrophilic partners for nitrogen nucleophiles[2] using Pummerer conditions and may well be of use in the alkaloid area. Furthermore, to our knowledge this is the first example of Hünig's base participating as a nucleophile in a formal Michael addition[9]. Regarding the mechanism of this reaction we favour a single electron transfer (SET)[10] mechanism involving a radical ion pair which then recombine at the least hindered position in preference to one involving sigmatropic rearrangement of an S,N ylide[11] or direct conjugate addition at carbon. However, more experimental work must be done to distinguish these possibilities.

With regard to the masked Michael addition using silyl enol ethers previously reported by us, the cometitive participation by Hünig's base is clearly a limitation of the reaction in certain cases. However, the allylic quaternary ammonium salt (2), (1 mmole) regioselectively allylates[12] sodium dimethyl malonate (5 mmole) in THF at room temperature using tetrakis (triphenylphosphine) palladium (0) (0,04 mmole) to afford the masked Michael adduct (4) as a mixture of isomers (E:Z = 6:1) in 60% yield. Scheme 3.

This alternative sequence now extends the versatility of the masked Michael reaction towards a range of nucleophiles.

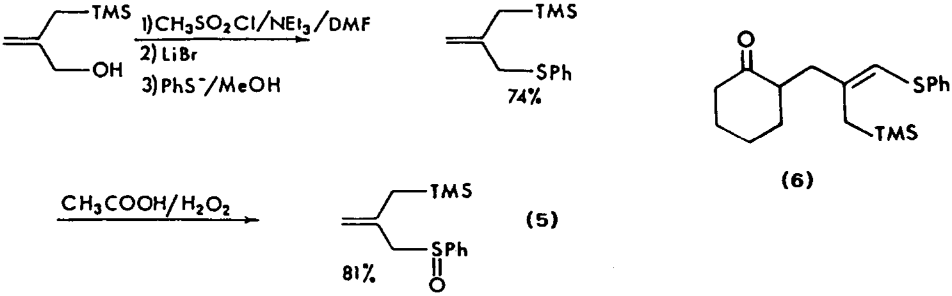
Scheme 3



i) Pd $(PPh_3)_4$ / THF / RT
ii) $Na^+ \, {}^-CH(CO_2Me)_2$

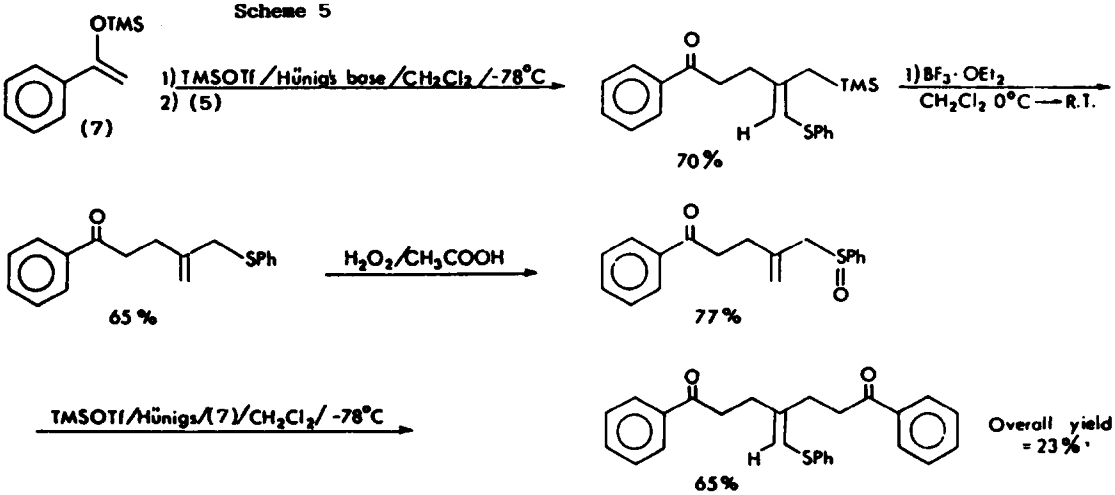
In extending the scope of the reaction further we have also examined condensation with the novel bifunctional[13] reagent 3-phenylsulphinyl-2-(trimethylsilylmethyl) propene (5). The latter could be readily prepared from the known alcohol[14] via the sulphide. Scheme 4.

Scheme 4



Reaction with the silyl enol ether of cyclohexanone furnished the expected functionalised vinyl sulphide (6) as the Z - isomer in 75% yield without affecting the allyl silane. However, all attempts ($TiCl_4$, TMSOTf, $Bu_4N^+F^-$, LDA/HMPA) to cyclise this molecule failed. The reagent can also be used in an iterative masked Michael reaction sequence using the silyl enol ether of acetophenone (7) as a model nucleophile allied with the protio-desilylation reaction of the allyl silane. Scheme 5.

Scheme 5



Further work on the scope of this novel reaction is in progress.

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