A polymer-supported alkyl methyl sulfide as an efficient promoter of the Khand cyclisation reaction

William J. Kerr,* David M. Lindsay, Mark McLaughlin and Peter L. Pauson

Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, Scotland, UK G1 1XL

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A readily prepared polymer-supported alkyl methyl sulfide has been shown to be a recyclable, practically convenient, and efficient promoter of the Khand cyclisation reaction, affording good to excellent yields of cyclopentenones.

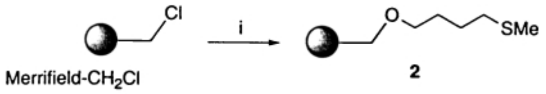
In recent years the Khand cycloaddition reaction has been developed into a highly utilisable method for generating cyclopentenone systems.[1] This cobalt carbonyl mediated annulation involving an alkyne, an alkene and carbon monoxide, was first described in 1971 and was originally conducted under thermal conditions.[2] With few exceptions, the technique of simply heating the reactants led to reaction mixtures from which the desired cyclopentenone products could only be separated in low to moderate yield after careful chromatography. Consequently, great efforts have been made to find more efficient procedures by which this valuable cycloaddition process can be carried out.[3]

Although promotion by ultrasound[4] and dry state adsorption conditions[5] have provided improvements in product yields in certain instances, it has undoubtedly been the introduction and thorough investigation of the use of amine *N*-oxides as promoters[6] that has led to the most significant advances in overall Khand reaction applicability and efficiency. More specifically, studies in our own laboratory have developed amine *N*-oxide promoted Khand techniques for use with gaseous olefins[7] and gaseous olefin equivalents,[8] and have exploited the same class of *N*-oxide promoted cyclisations within total synthesis programmes.[9] Additionally, the use of non-racemic chiral amine *N*-oxides has led to the establishment of direct asymmetric Khand cyclisation strategies.[10]

As part of an on-going optimisation of the asymmetric process, we have synthesised a novel polymer-linked amine *N*-amine *N*-oxide and shown this to be a good solid phase promoter of the Khand reaction.[11] As well as forming the basis for the construction of a potentially structurally diverse library of supported chiral amine *N*-oxides, this work also demonstrated that the widely recognised benefits associated with the technique of employing a solid phase reagent[12] could be realised within the arena of Khand cyclisation chemistry. Indeed, a major advantage offered by this resin-based *N*-oxide method is in the simplification of product isolation procedures; by routine filtration the desired cyclopentenone is removed from the (organometallic) by-products in remarkably pure form. With this knowledge, we have now gone on to further extend and widen the overall scope of this immobilised Khand reaction promoter strategy.

Sugihara has recently reported that *n*-butyl methyl sulfide was the optimum sulfide promoter of a number that were tested and provided good to excellent yields in both intra- and intermolecular Khand cyclisations.[13]† Indeed, this reaction additive is particularly notable for its ability to promote some Khand reactions which had previously failed completely or proceeded only very poorly under alternative conditions. On the other hand, we considered the use of *n*-butyl methyl sulfide to have certain drawbacks. More specifically, as a low molecular weight sulfide, the *n*-butyl methyl derivative has a very unpleasant odour and imparts a lachrymatory effect. Furthermore, it is relatively expensive and, under the developed techniques, cannot be readily recycled. Therefore, we sought to develop a reusable polymer-supported analogue of *n*-butyl methyl sulfide and examine its ability to promote the Khand annulation reaction.

To initiate this work, the supported sulfide was synthesised in a single step, using standard chemistry, from commercially available Merrified gel-type resin‡ and 4-(methylthio)butan-1-ol **1**, *via* formation of a chemically robust ether link (Scheme 1). The derivatised polymer **2** obtained was odour-free and possessed sulfide functionality which is similar to the optimum solution phase promoter. Elemental analysis and infrared spectroscopy confirmed complete displacement of all chloride atoms from the starting material and gave the expected sulfur content for the new polymer.

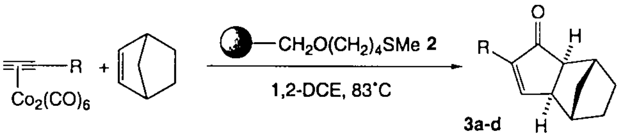


Scheme 1 *Reagents and conditions*: i, HO(CH$_2$)$_4$SMe **1** (3 equiv.), NaH (6 equiv.), THF, Δ, 72 h.

Having established a simple preparation of our new solid phase reagent, we turned our attention to the study of its effectiveness as a promoter of the Khand reaction. The cyclisation of a series of alkyne substrates with norbornene was investigated and to our delight these reactions were complete in only 30 min at 83 °C in the presence of 3.5 equiv. of the supported sulfide and using 1,2-dichloroethane (1,2-DCE) as solvent.§ As shown in Table 1, very good to excellent yields of the desired cyclopentenones **3** were obtained. Furthermore, work-up of these reactions was rendered expedient by the fact that the cobalt residues produced were sequestered by the resin and merely involved filtration of the reaction mixture followed by minimal chromatographic purification. This feature of the novel promoter **2** confers a tangible practical benefit over the alternative Khand cyclisation methods.¶

In due course, using dimethylpropargyl alcohol as the alkyne substrate, we conducted several reactions using alternative alkenes. These reactions also proceeded entirely satisfactorily (Table 2); the modest yields of cyclopentenone products from the reactions of cyclopentene and 2,5-dihydrofuran reflect the lower reactivity of these olefins in Khand cyclisations.

Table 1 Solid phase sulfide promoted Khand reactions



R	*t*/min	Product	Yield (%)
Me$_2$(OH)C-	30	**3a**	92
Ph-	30	**3b**	97
Me$_3$Si-	30	**3c**	83
t-Bu-	30	**3d**	89

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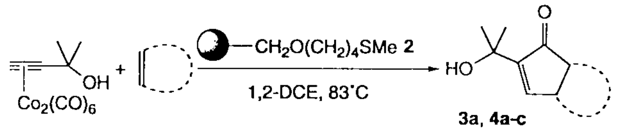
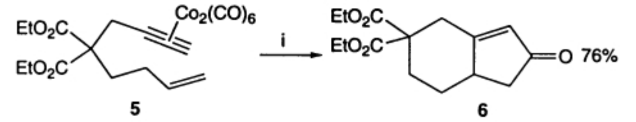
Table 2 Khand reactions with a selection of alkenes



Alkene	*t*/min	Product	Yield (%)
Norbornene	30	**3a**	92
Norbornadiene	30	**4a**	91
2,5-Dihydrofuran	30	**4b**	47
Cyclopentene	90	**4c**	50

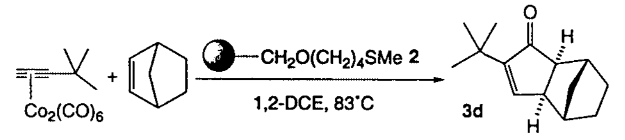
In order to further extend the substrate applicability of this new solid-phase technique, an intramolecular Khand cyclisation was examined using enyne complex **5**. This example furnished the requisite bicyclic compound **6** in 76% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: i, Resin **2** (3.5 equiv.), 1,2-DCE, 83 °C, 30 min.

A further important observation from this study was that, at the conclusion of all reactions the recovered polymer resin could be cleaned very easily by washing with a THF–aqueous 2 M HCl mixture. This enabled us to investigate the potential of recycling the resin. For this study the *tert*-butylacetylene–norbornene reaction was chosen. As illustrated in Table 3, the excellent yield of **3d** and short reaction time is maintained through five cycles. This aspect of the new promoter is particularly noteworthy in that, unlike our previously disclosed supported amine *N*-oxide techniques,[11] no chemical transformation is necessary for regeneration of the active solid phase promoter. Moreover, in contrast to the solution phase analogue, expense is minimised by the recyclable nature of the immobilised sulfide.

Table 3 Khand reactions using recycled resin **2**



Run	1	2	3	4	5
t/min	30	30	30	30	30
Yield (%)	89	92	87	86	88

Finally, two additional *tert*-butylacetylene–norbornene cyclisations were carried out in which the quantity of the polymeric reagent used was reduced in order to determine if the 3.5 equiv. of sulfide (as established in the Sugihara solution phase studies[13] and employed throughout this work) were absolutely necessary. With 2 equiv. of resin **2** an 86% cyclisation yield was achieved, whereas 1 equiv. of **2** delivered cyclopentenone **3d** in 88% yield. Therefore, in both cases the product yield was not significantly lowered. However, it should be noted that with successive reduction in quantity of resin there was a stepwise drop in the efficiency of the cobalt residue retention.

In conclusion, a relatively cheap, commercially available gel-type resin was readily modified to afford an odourless, supported alkyl methyl sulfide. This novel solid phase reagent can be used to promote both intra- and intermolecular Khand cycloaddition reactions in a highly efficient and practical manner. Isolation of the cyclopentenone products is facilitated by the resin's ability to retain undesired cobalt residues and, furthermore, the resin can be easily and rapidly regenerated by a mildly acidic wash.

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Notes and references

† It should be noted that the promoting effect of suitably spaced methyl sulfide groups when tethered to the alkene[14] or alkyne[6d,15] was first discovered and reported by Krafft.

‡ The 1% cross-linked Merrifield resin was purchased from NovaBiochem with a chloride loading of 1.1 mmol g^{-1}.

§ Respresentative experimental procedure; To a solution of hexacarbonyl(3,3-dimethylbut-1-yne)dicobalt (34.0 mg, 0.092 mmol) and norbornene (56.0 mg, 0.596 mmol) in 1,2-DCE (2.5 ml) was added sulfide resin **2** (0.29 g, 0.29 mmol) and the mixture was stirred at 83 °C for 30 min. The solvent was drained and the resin washed with CH_2Cl_2 (10×2 ml) and THF (5×2 ml). The combined filtrates were evaporated *in vacuo* to afford a residue which was chromatographed on silica using 5% Et_2O in petrol as eluant. The product **3d** was obtained as a white crystalline solid (16.7 mg, 89%).

¶ 4-(Methylthio)butan-1-ol was also tested as a solution phase promoter using Sugihara's conditions in the *tert*-butylacetylene–norbornene reaction and provided an 89% yield of cyclopentenone **3d**. However, this additive suffers from an undesirable odour and lacks the potential to be readily recycled.

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