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Transition-Metal-Free Synthesis of Aryl-Substituted *tert*-Butyl Ynol Ethers through Addition/Elimination Substitution at an sp Centre

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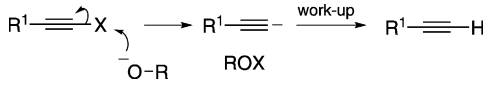
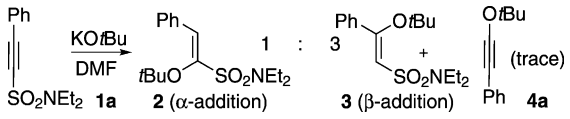
Dedicated to Professor William B. Motherwell on his retirement

Ynol ethers are one of the most interesting functional groups for the preparation of more complex molecules and the development of new synthetic methodology.[1] In particular, *tert*-butyl ynol ethers are particularly desirable as precursors to ketenes by the liberation of isobutene on warming.[2] Although a number of ynol ethers have been prepared (mainly by halogenation and subsequent elimination of enol ethers, because the reaction of alkoxide nucleophiles with haloalkenes is rarely synthetically useful),[3] access to more complex systems has been limited by their arduous and costly synthetic routes that typically employ starting materials, complexity of which exceed that of the product ynol ether. Although transition-metal-mediated processes have been used to give ynamides and related compounds[4] from haloalkynes with oxygen nucleophiles, the X-philic reaction tends to dominate, giving only the parent alkyne (Scheme 1).[5]



Scheme 1. X-philic behaviour of acetylinic halides.

During the course of on-going research in our laboratory, it was found that exposure of the sulfonamide **1a** to potassium *tert*-butoxide in standard grade DMF gave a small amount of ynol ether **4a** as well as the two addition products **2** and **3** (Scheme 2). The observation of the α-product **2** in addition to the β-product **3** was unexpected. Therefore, we compared the total-energy differences of molecules **2** and **3** in DMF by using DFT approaches and found that **2** is 0.8 kcal mol^{-1} more stable than **3**. The α-product is surprisingly stable due in part to the formation of a weak intramolecular hydrogen bond between a H in the R group and SO_2NEt_2, which causes the conjugated carbon framework to remain planar. In contrast, there is no intramolecular hydrogen bond in the β-product, and it adopts a non-planar structure.



Scheme 2. Addition of KO*t*Bu to aryl acetylinic sulfonamides.

These experimental results immediately suggested to us the possibility that the addition of alkoxide anions to these species might be a reversible process, which generates two transient vinyl anions (**2a** and **3a**) with four possible fates as outlined in Figure 1. These fates are following: 1) protonation of the anion adjacent to the phenyl group giving **2**; 2) protonation of the anion adjacent to the sulfonamide giving **3**; 3) elimination of SO_2 to form the ynol ether **4a**; and 4) elimination of alkoxide to regenerate **1** and KO*t*Bu.

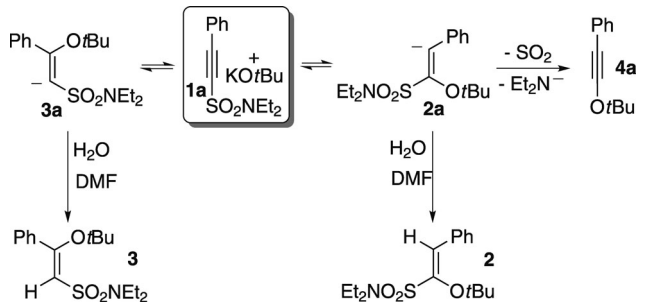


Figure 1. Proposed mechanistic pathway for the formation of products **2**, **3** and **4a**.

We reasoned that rigorous exclusion of water or any proton source from the reaction mixture would therefore demonstrate our hypothesis and improve the yield of **4a**. To our delight, employing dried DMF as the solvent gave ynol ether **4a** as the sole product in good yield (Scheme 3). Substitutions of this type at sp centres with carbon nucleophiles are known,[6] however, examples of heteroatomic nucleophiles are scarce.

Because sulfonyl groups can behave as radical-leaving groups in certain circumstances,[7] we were keen to demon-

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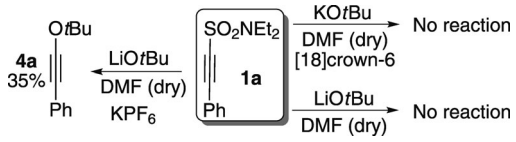


Scheme 3. Reactivity of acetylinic sulfonamides.

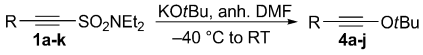
strate whether a radical mechanism was in operation. Addition of a radical inhibitor ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl, TEMPO) to the reaction mixture had no effect on the reaction, so we concluded that a radical process was unlikely to be operating in this case.

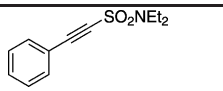
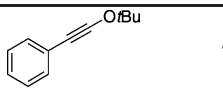
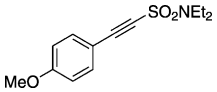
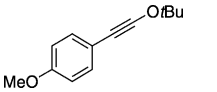
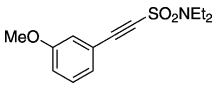
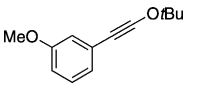
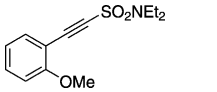
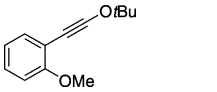
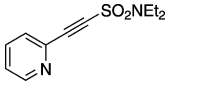
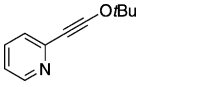
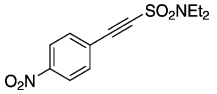
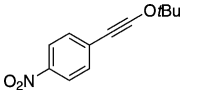
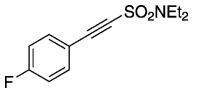
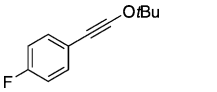
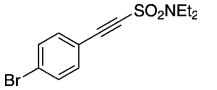
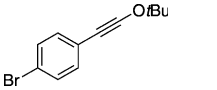
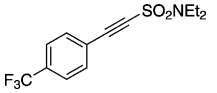
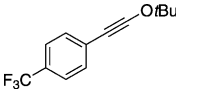
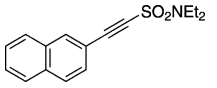
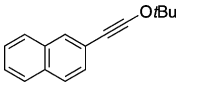
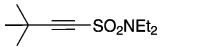
One of the intriguing features of this process is the unique role of the potassium counterion in facilitating the reaction. Employing lithium, sodium, aluminium, magnesium and barium *tert*-butoxides resulted in no reaction, although the reaction can be initiated by employing a soluble potassium salt with any of the above-mentioned metal *tert*-butoxide (Scheme 3). Aware of many recent reports of reactions specific to KO*t*Bu and the current debate regarding whether trace metals actually catalyse the reactions,[8] we employed both standard reagent grade KO*t*Bu and the freshly sublimed reagent in our reaction. No improvement or deterioration in reaction rate, yield or efficiency was observed by using either reagent. We concluded from this that the potassium ion must be playing a critical role, possibly coordinating to the sulfonamide, alkyne or aromatic ring (or even all or a combination of the three components) and activating the molecule towards nucleophilic attack by the alkoxide anion.[9] To demonstrate the significance of the counterion, an experiment, in which the crown ether [18]crown-6 was included in the reaction mixture, was performed. No reaction was observed in this case (Scheme 3). A second experiment conclusively demonstrated the necessity of potassium ions in the reaction. Thus, addition of lithium *tert*-butoxide to **1** in dry DMF resulted in no reaction even after several hours. However, addition of KPF_6 to the reaction mixture almost immediately caused a reaction to occur and the ynol ether was isolated in moderate yield.

To probe the role of the potassium, we turned once more to DFT modelling and found that potassium provides a facile source of nucleophilic *tert*-butoxide in comparison to lithium and sodium. Calculations showed short bond lengths (1.70–2.05 Å), and that there is significant covalent character between the alkal metal and oxygen in LiO*t*Bu and NaO*t*Bu. However, in the case of KO*t*Bu/KOR, the potassium–oxygen bond length is 2.46 Å indicating a relatively weak binding, and analysis of the charge distribution showed much greater charge transfer from the potassium (i.e., the formation of an ion pair) than in the lithium and sodium compounds. In fact, we see that KO*t*Bu spontaneously dissociates in the presence of **1**, resulting in the barrierless attack of $tBuO^-$ to form the anion intermediate or **2**/**3**. For LiO*t*Bu and NaO*t*Bu, the stronger metal–oxygen bond gives rise to a barrier that hinders heterolytic dissociation and presumably explains their inertness.

At this juncture, we were keen to see if the methodology to the synthesis of a range of new *tert*-butyl ynol ethers can be applied and to demonstrate their reactivity in liberating ketenes at elevated temperatures. A range of alkynyl sulfonamides (**1a–j**) were prepared by standard techniques (see the Supporting Information) and exposed to potassium *tert*-butoxide in dry DMF.[10] The results are outlined in Table 1

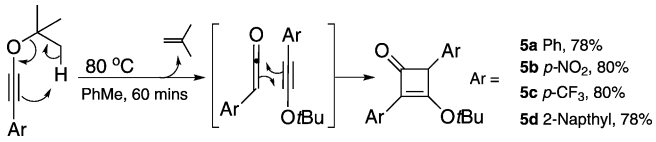
Table 1. Synthesis of ynol ethers from alkynyl sulfonamides.



Entry	Sulfonamide **1a–k**	Ynol ether **4a–j**	Yield [%][a]
1			70
2			68
3			76
4			70
5			69
6			69
7			61
8			59
9			60
10			93
11		–	0 [b]

[a] Isolated yields. [b] Recovered starting material.

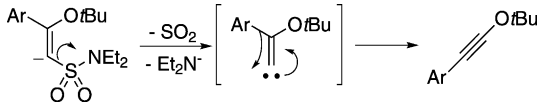
(ynol ethers **4a–j**). The versatility of this new reaction regime is signalled by the good yield of ynol ethers with electron-rich and electron-deficient aromatics, although so far, aliphatic examples have not been successful (entry 11). By following preparation, the ynol ethers can undergo dimerization to give cyclobutenones in excellent yield. Structures with this molecular architecture are very desirable synthetic intermediates due to their ability to undergo facile rearrangements to form a variety of highly functionalised molecules with numerous synthetic applications (Scheme 4).[11] Although there are other methods of preparing these mole-



Scheme 4. Thermal decomposition and [2+2] dimerization of *tert*-butyl ynol ethers giving cyclobutenones **5a**–**d**.

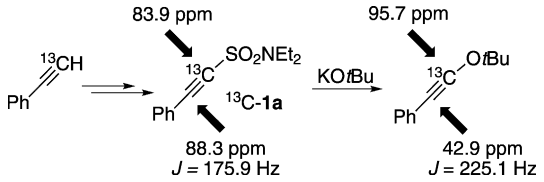
cules,[12] this method offers a complementary approach to these reactive compounds.

Although the addition/elimination mechanism outlined in Scheme 2 seemed to be most likely (particularly, given the elegant mechanistic work by Poisson and co-workers),[13] we could not rule out the possibility of a carbene intermediate resulting in a Fritsch–Buttenberg–Wiechell (FBW) rearrangement[14] involving the sulfonyl group acting as a leaving group (Scheme 5).[15]



Scheme 5. The Fritsch–Buttenberg–Wiechell rearrangement.

To understand fully, which mechanism was in operation, a simple ^{13}C-labelling experiment outlined in Scheme 6 was carried out. Treatment of 2-^{13}C-labelled **1a** with potassium

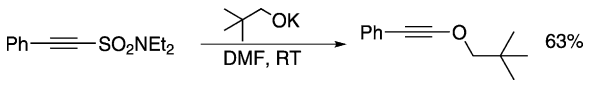


Scheme 6. ^{13}C-labelling experiment.

tert-butoxide gave the 2-labeled ynol ether exclusively (easily observed in the ^{13}C NMR spectrum by the enhanced signal at $\delta = 95.7$ ppm) and supported our hypothesis that the mechanism was proceeding through an addition/elimination pathway. We also note that a comparison of the total DFT energies of the α- and β-anions from Scheme 1 showed that the β intermediate is more stable than α by 5.2 kcal mol^{-1} in sharp contrast to the near identical energies found for products **2** and **3** in wet conditions. The large energetic penalty for forming the α anion coupled with the evidence from NMR analysis strongly indicates that the FBW mechanism is unlikely to be in operation.

Our attention has so far focused on the *tert*-butyl ethers, because KO*t*Bu is commercially available and easy to purify. Our work with other alkoxides is in its early stages, however, employing potassium neopentyl oxide (prepared from the parent alcohol and potassium metal) gave the corresponding ynol ether in good yield, giving us confidence that the scope of the reaction and synthetic utility of the products will be broadened (Scheme 7).

In conclusion, a new synthesis of *tert*-butyl ynol ethers from acetylinic sulfonamides that proceeds through a one-pot nucleophilic addition/elimination pathway at the sp centre was described. The reaction mechanism was established by isotopic-labelling studies supported by insights from DFT modelling. A unique dependence on the potassium counterion has also been demonstrated. With a clear understanding of the reaction mechanism and the critical role of the potassium counterion, research into extending the scope and applicability of the reaction to the synthesis of other more challenging ynol ethers is now underway in our laboratory.



Scheme 7. Synthesis of a neopentyl ynol ether.

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Keywords: alkynes · elimination · sp substitution · sulfonamides · synthetic methods

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