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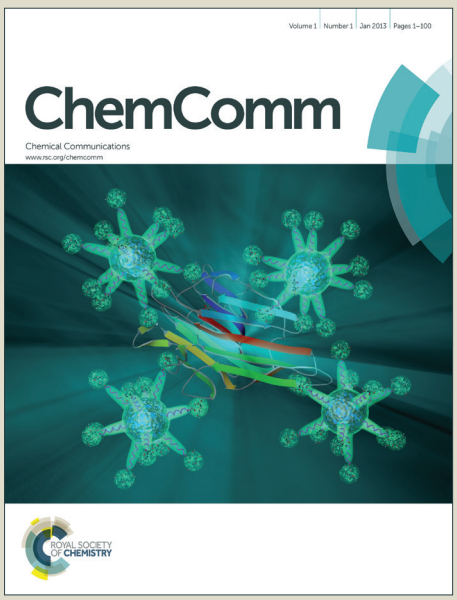

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A Straightforward Alkynylation of Li and Mg Metalated Heterocycles with Sulfonylacetylenes†,‡

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Coupling of alkynyl moieties to heterocyclic rings, without using transition metals, can be easily performed by reaction of aryl or heteroaryl sulfonylacetylenes with heteroaryl-Li compounds or their corresponding less reactive magnesium derivatives.

Heteroarylated acetylenic structures are widely spread in the field of the material science, as well as in many biologically interesting compounds[1] (Figure 1). In the latter field, they are present in large number of products with biological activity like carlina oxide[2] (**I**) with antimicrobial properties, the metabotropic glutamate receptor **II**,[3] related to the learning and memory processes, or the dopamine receptor (**III**)[4] which is used against schizophrenia. Particularly interesting are diheteroarylated acetylenic moieties, like those containing a thienyl residue, which are also present in pharmacologically interesting compounds. Thus, thiophene and furane rings are joined to the triple bond in the tryptase inhibitor **IV**,[5] used for treating allergic or inflammatory disorders, whereas thiophene and thiazol take part of the structure of the mGlu5 receptors **V**.[6] In addition, a 2,3´-dithiophene-acetylene moiety is present in the IKK-2 inhibitors **VI**[7] and in the anti-tumour agent **VII**.[8]

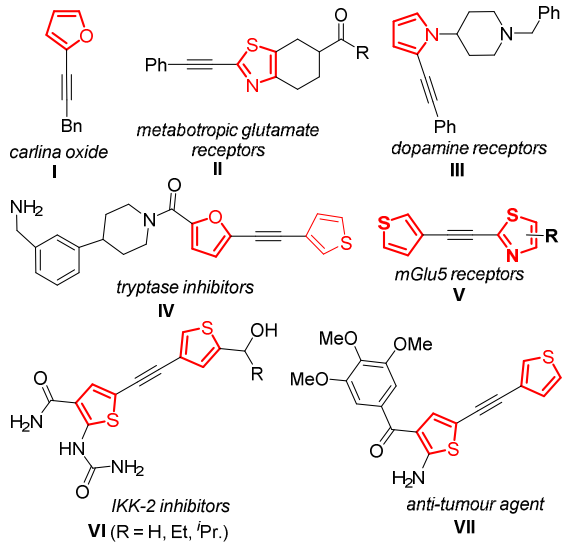
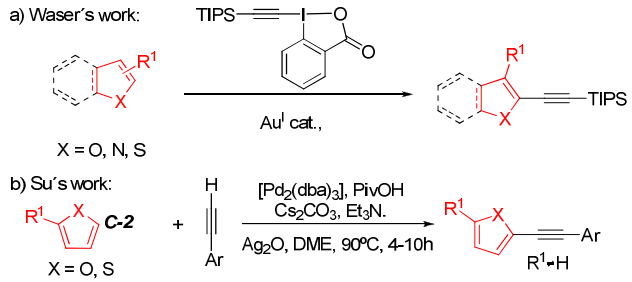


Figure 1. Heteroaryl alkynes with biological interest.

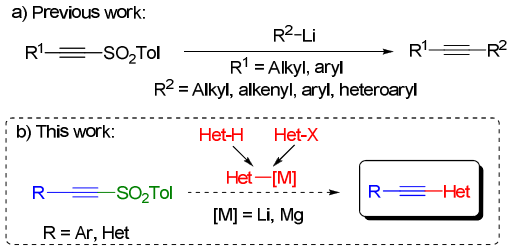
The most employed methodology for the synthesis of heteroaryl acetylenes involve the use of the well-known Sonogashira reaction,[9] starting from heterocyclic halides and aryl or heteroaryl acetylenes and using palladium as the catalyst. As alternative, the direct alkynylation of heteroaromatic compounds with alkynyl halides was developed (inverse Sonogashira),[10] but it is restricted to very activated C-H heterocycles (e.g. thiazol). Very recently, other strategies like the use hipervalent iodine reagents with Au^I as the catalyst[11] (equation a, Scheme 1), and the oxidative cross-coupling of terminal alkynes with heteroarenes,[12] have been reported (equation b, Scheme 1). However, the use of the hypervalent iodine is only valid for preparing Si*i*Pr$_3$ alkynyl derivatives[11] and the oxidative cross-coupling[12] is mainly circumscribed to the synthesis of 2-arylalkynyl 5-substituted thiophenes (rather modest yields were obtained with furane and pyrrol derivatives). Thus, these methods preclude the synthesis of monosubstituted heterocycles, bearing only the alkynyl moiety, which is the case of many of the compounds shown in Figure 1. Moreover, these alternative methods cannot be used for incorporating acetylenic chains to the less activated positions or the heterocyclic rings and therefore cannot be considered as a general alternative to the Sonogashira's reaction for alkynylating heterocycles.



Scheme 1. Recent approaches for the direct alkynylation of heterocycles.

All these methodologies require the use of transition metals for the formation of the Csp-Csp^2 bond, which was recognized as a handicap for the pharmaceutical companies,[13] which indicated the convenience of finding alternative methods for the C-C coupling, avoiding the use of transition metals as catalysts. In 2012, our group reported the unexpected electrophilic behavior of arylsulfonylacetylenes that undergoes through an unusual α-attack (*anti*-Michael addition) in reactions with organolithiums, followed by elimination of the $ArSO_2^-$ moiety to allow the alkynylation of lithiated Csp^2 or Csp^3 (equation a, Scheme 2).[14] These transition-metal free methodology was applied regardless

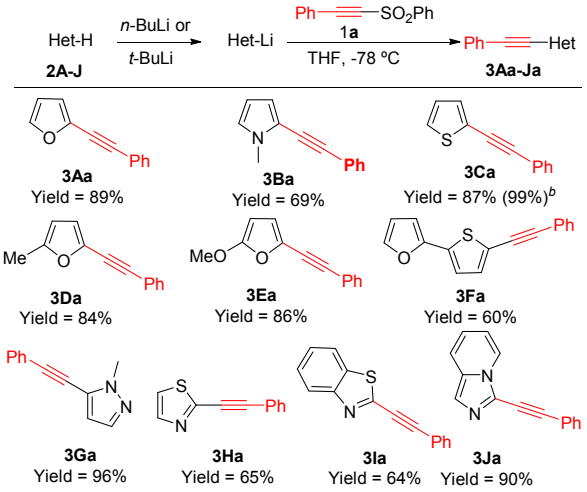
the source of the organolithiums (alkyl-lithium derivatives[14b] or arenes with activated C-H[14a]). Our goal in this work, is the use of this methodology to the preparation of different alkynyl heterocyles (equation b, Scheme 2), including special attention to the regioselective synthesis of dialkynyl heterocycles (useful in material science) and diheteroaryl acetylenes (present in pharmacologically interesting compounds, see Figure 1). As some of the studied substrates were not stable in the presence of organolithiums, the behavior of the less reactive Grignard reagents was studied, which provided surprisingly good results.



Scheme 2. Previous report and present work.

We initiated our study by considering the results previously obtained in the preparation of the 2-phenylethynyl heterocycles **3Aa**, **3Ba**, and **3Ca** (Table 1).[14a] Typically, the α-lithiation had been performed with *n*-BuLi o *t*-BuLi in THF or ether at 0 ºC, and the alkynylation with the sulfone **1a** at -78 ºC in THF.[15] Similar conditions were successful to prepare the alkynyl derivatives **3Da** and **3Ea**, from the 2-substituted furanes **2D** and **2E**, in excellent yields (Table 1). At this point, we studied the behavior of **2F** and observed the exclusive formation of **3Fa** in 60% yield (Table 1), evidencing that the activation provided by the thiophene was clearly higher than that of the furane ring. The preparation of other monoalkynylated heterocycles (Table 1), like those derived from *N*-methylpyrazol (**3Ga**), thiazol (**3Ha**), benzothiazol (**3Ia**), and imidazopyridine (**3Ja**), gave excellent yields in smooth conditions. In all the cases, the incorporation of the alkynyl residue only took place to the more activated position.

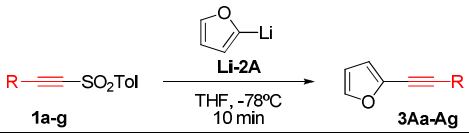
Table 1. Alkynylation of different heterocycles (**2A-M**) based in their C-H activation with by *t*-BuLi or *n*-BuLi.[a]



[a] All the reactions were performed with 0.2 mmol of **1a** and 0.4 mmol of **2A-J**. [b] Reaction carried out at 2.34 mmol scale.

Our next step was to study the influence of the substituents at the aryl group of *p*-tolylsulfonylacetylenes **1a-g** on the reactivity of the *anti*-Michael addition. For this study 2-Li furan (Li-**2A**) was chosen for reacting with different alkynylsulfones under the standard conditions shown in Table 1 (THF, -78 ºC) in 10 min reaction (Table 2). Electron donating groups decreased the reactivity (58% yield of **3Ab**, compare entries 1 and 2), whereas electron-withdrawing groups increased it (95% yield of **3Ac**, compare entries 1 and 3), which is not unexpected taking into account the effect of these groups on the electrophilic character of the triple bond. The reaction was also compatible with the presence of *ortho*-substituents (76% yield of **3Ad**, entry 4). The donating character of the alkyl groups could explain the failure of the reactions with **1e** and **1f** to obtain the *anti*-Michael products **3Ae** and **3Af** (entries 5 and 6). A negative influence of the steric effects of these susbtituens must be less relevant because the even larger TIPS group, present at **1g**, was not a handicap in its reaction with Li-**2A** (**3Ag** is formed in 54% yield, entry 7), probably due to its favourable electronic effects (see later). Compound **3Ag** is important because it can be deprotected and functionalized, thus making possible the preparation of alkyl acetylenes that cannot be obtained by direct reaction.

Table 2. Reactions of Li-**2A** with the *p*-tolylsulfonylacetylenes **1a-g**.



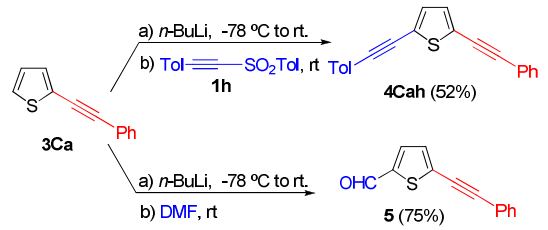
Entry	Sulfone	Product	Yield (%)
1	**1a** (R = C_6H_5)	**3Aa**	89
2	**1b** (R = *p*-MeO-C_6H_4)	**3Ab**	58
3	**1c** (R = *p*-CF_3-C_6H_4)	**3Ac**	95
4	**1d** (R = o-Cl-C_6H_4)	**3Ad**	76
5	**1e** (R = Cy)	**3Ae**	--[a]
6	**1f** (R = *t*-Bu)	**3Af**	--[a]
7	**1g** (R = TIPS)	**3Ag**	54

[a] All the reactions were performed with 0.2 mmol of **1a-g** and 0.4 mmol of **2A**. [b] Reaction mixtures mainly containing Michael addition products.

The absence of 2,5-dialkynylfuranes in the reaction mixtures obtained from unsubstituted heterocycles **2** (Tables 1 and 2) suggests the lower reactivity of their monoalkynyl derivatives **3** and allows their use as starting materials in subsequent functionalization processes based on the C-H activation of the other α–position (C-5).[16] In this sense, starting from **3Ca**, we were able to prepare 2,5-dialkynylthiophenes like **4Cah**, bearing two different acetylenic moieties at the activated positions (equation b, Scheme 3), which is not easily obtained with other methodologies. The introduction of other electrophiles like CHO, by reaction with DMF (**5** in Scheme 3) was also possible. In both cases, the reactions of the monoalkynyl thiophene **3Ca** with the electrophiles were performed at rt (at lower temperatures the reactions did not work), which revealed its lower reactivity with respect to the unsubstituted thiophene **2C**, which could be alkynylated at -78 ºC, as it was indicated in Table 1.

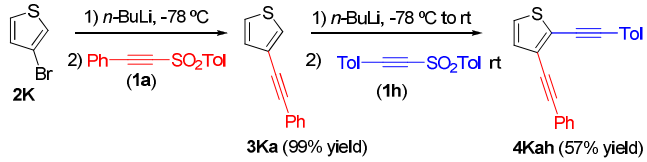
At this point, we investigated the possibilities of our reaction for introducing the alkynyl moieties into the non-activated

positions of the heterocycles, starting from the appropriate haloderivative and generating the corresponding organolithium by lithium-halogen exchange Thus, starting from 3-bromothiophene (**2K**), the Li-Br exchange with *n*-BuLi took place quickly (less than 15 minutes) at -78 ºC (Scheme 4) and was followed by the addition of **1a** at -78 ºC that cleanly afforded **3Ka** in almost quantitative yield.[17]



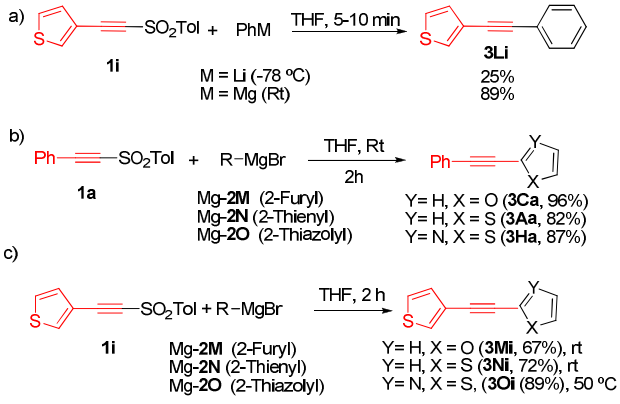
Scheme 3. Functionalization of monoalkynyl heterocycles.

The incorporation of a second alkynyl group to the heteroaryl ring of **3Ka**, with two activated C-H (at C-2 and C-5) would yield dialkynyl thiophenes, being possible the formation of two regioisomers. To our delight, deprotonation of **3Ka** with *n*-BuLi at -78 ºC, followed by reaction with the sulfone **1h** at rt, only yielded the 2,3-dialkynyl derivative **4Kah** (57% yield) in a completely regioselective way. The reactivity of **3Ka** and **3Ca**, both monoalkynyl derivatives, was lower (reactions with **1** require rt) than that of the thiophene **2C** (reaction with **1** took place at -78 ºC). However, the formation of the organolithiums from **3Ka** and **3Ca** was easier (-78 ºC) than for **3C** (0 ºC to rt).[18] It suggests an stabilizing influence of the alkynyl group on the organolithium, that decreases its reactivity.[19] The properties and reactivity associated to the spatial proximity of the two acetylenic moieties on C-2 and C-3 of the thiophene ring has been useful in material science and bionatural products.[20]



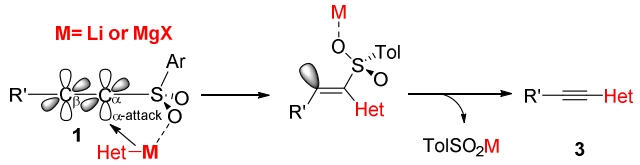
Scheme 4. Double alkynylation of the 3-bromo thiophene.

Once checked the potential of our method in the synthesis of heteroaryl aryl acetylenes, our next goal was to obtain diheteroaryl acetylenes. The synthesis of these compounds required the preparation of heteroaryl alkynyl sulfones to be used as starting products in reactions with the heteroaryllithiums. We fix our attention in sulfones containing the thiophene ring, like **1i**,[21] which would give access to the skeleton of the diheteroaryl acetylenes **IV-VII** shown in Figure 1. Reaction of **1i** with PhLi (Li-**2L**) at –78 ºC in THF provided the expected acetylene **3Ka**, but in low yield (25%), along with a large number of unidentified byproducts (equation a, Scheme 5). Reactions with other heteroaryllithiums derived from **2M-2O** were even less fruitful. These results suggests that the **1i** is not stable in the presence of organolithiums. Taking into account that Grignard reagents are less reactive and, in some cases, more selective too than organolithium compounds,[22] we studied the reaction of **1i** with PhMgCl (Mg-**2L**). The reaction did not work at -78 ºC and 0 ºC but **3Ka** was afforded in an excellent 89% yield when it was conducted at rt (equation a, Scheme 5). Then we explored the reactivity of different heteroaryl Grignard derivatives (Mg-**2M-O**) with the phenylethynylsulfone **1a**. These reactions were very clean in all the cases (only one product was detected by NMR in the reaction crudes) yielding alkynes **3Aa**, **3Ca**, and **3Ha** in excellent yields after 2h at rt (equation b, Scheme 5). It reveals that the Grignard reagents, working at rt, are as efficient as the organolithiums at -78 ºC in their *anti*-Michael reactions with alkynyl sulfones. Thus, Grignard compounds Mg-**2M**, Mg-**2N**, and Mg-**2O** provided the corresponding diheteroaryl acetylenes (**3Mi**, **3Ni** at rt and **3Oi** at 50 ºC) in good yields (decomposition products were not detected), which confirmed the potential of our methodology for preparing diheteroaryl acetylenes (equation c, Scheme 5).



Scheme 5. Reaction of sulfone **1a** and **1i** with Grignard compounds.

The mechanism proposed for the *anti*-Michael reactions of RLi with substituted sulfonylacetylenes[15] (Scheme 6), supported by theoretical calculations, involves the association of the lithium to the sulfinyl oxygens as a previous step of the intramolecular α-attack of the R group to the triple bond and the subsequent elimination of the metal sulfonate (Scheme 6). The ability of the R' to stabilize the carbanionic intermediate would explain the behaviour of the different substrates shown in Table 2. The lower reactivity and chelating ability of Grignard derivatives Mg-**2** with respect to that of the Li-**2** could explain that the first ones require higher temperatures to obtain good conversions. Moreover, these differences in reactivity also support the nucleophilic character of the α-attack.[23]



Scheme 6. Mechanistic proposal for the reaction of sulfonylacetylenes **1** with organolithium and organomagnesium reagents.

In conclusion we have demonstrated that the *anti*-Michael addition of RLi or R-MgX[24] to sulfonylacetylenes constitutes an efficient methodology to obtain different aryl-heteroaryl and diheteroaryl acetylenes under very mild conditions. The broad scope, excellent yields, and simplicity of the experimental procedure, that does not require transition metals, are the main

features of this methodology. The present work can be considered as a general alternative to the Sonogashira's reaction in alkynylation reactions of heterocycles without using transition metals.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental

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15 These yields were obtained starting from 0.2 mmol of **2A-2C** but the reaciton can be scale up (**3Ca** was obtained in 95% yield in a 2.34 mmol scale).

16 Other C-H functionalizations are not selective strategies and mixture of the two activated positions would be found. Therefore, only substituted thiophenes in the 2 position (with the 2´position free to be activated) can be used as starting material (see e.g. reference 12).

17 The standard reaction time for the Br-Li exchange process was 15 minutes. Longer reaction times for the Br-Li exchange gave an equilibria of 3-Li-**2K** and 2-Li-**2K**, and consequenly the corresponding mixture of monoalkynyl derivatives were formed.

18 This was confirmed by studying deuteration reactions at -78 ºC of the Li carbaniones generated from **3Ca** and **3Ka** at the same temperature. They result in the exclusive formation of the **5-D** and **2-D** derivatives respectively. The reaction of thiophene with n-BuLi at -78 ºC only yielded decomposition products, presumably due to the opening of the ring with the organolithium (see e.g. K. Chernichenko, N. Emelyanov, I. Gridnev, V. G. Nenajdenko, *Tetrahedron*, 2011, **67**, 6812), whereas the reaction at 0 ºC produce its 2-Li derivative (unsensitive to the opening), which is quantitatively deuterated with ND_4Cl.

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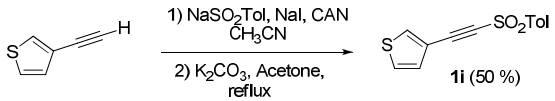

1i (50 %)

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24 We are currently working in a full article concerning the use of the Grignard reagents in alkynylation reactions with sulfonyl acetylenes, which will be published in the near future.