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

Leyre Marzo, Ignacio Pérez, Francisco Yuste, José Alemán,* José Luis García Ruano*

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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 compounds1 (Figure 1). In the latter field, they are present in large number of products with biological activity like carlina oxide (I) with antimicrobial properties, the metabotropic glutamate receptor II,1 related to the learning and memory processes, or the dopamine receptor (III)2 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′,6′-dithiophene-acetylene moiety is present in the IKK-2 inhibitors VI7 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 AuI as the catalyst11 (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 SiPr3 alkynyl derivatives11 and the oxidative cross-coupling12 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 alkynylation 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 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 ArSO2 moiety to allow the alkynylation of lithiated Csp2 or Csp3 (equation a, Scheme 2).14 These transition-metal free methodology was applied regardless
the source of the organolithiums (alkyl-lithium derivatives\textsuperscript{14b} or arenes with activated C-H\textsuperscript{13c}). Our goal in this work is the use of this methodology to the preparation of different alkynyl heterocycles (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-phenylethenyl heterocycles 3Aa, 3Ba, and 3Ca (Table 1)\textsuperscript{14a}. Typically, the α-lithiation had been performed with \( n\)-BuLi or \( t\)-BuLi in THF or ether at 0 °C, and the alkylation with the sulfone 1a at -78 °C in THF.\textsuperscript{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.** Alkylation of different heterocycles (2A-M) based in their C-H activation with \( t\)-BuLi or \( n\)-BuLi.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfone</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (R = ( C_6H_5 ))</td>
<td>3Aa</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>1b (R = ( p)-MeO-( C_6H_4 ))</td>
<td>3Ab</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>1c (R = ( p)-CF(_3)-( C_6H_4 ))</td>
<td>3Ac</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>1d (R = ( o)-Cl-( C_6H_4 ))</td>
<td>3Ad</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>1e (R = Cy)</td>
<td>3Ae</td>
<td>-\textsuperscript{a}</td>
</tr>
<tr>
<td>6</td>
<td>1f (R = ( t)-Bu)</td>
<td>3Af</td>
<td>-\textsuperscript{a}</td>
</tr>
<tr>
<td>7</td>
<td>1g (R = TIPS)</td>
<td>3Ag</td>
<td>54</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All the reactions were performed with 0.2 mmol of 1a-g and 0.4 mmol of 2A. \textsuperscript{b} Reaction mixtures mainly containing Michael addition products.

The absence of 2,5-dialkynylfurans in the reaction mixtures obtained from unsubstituted heterocycles 2 (Tables 1 and 2)\textsuperscript{16} 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).\textsuperscript{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 thioephene 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 alkylnylated at -78 °C, 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 °C (Scheme 4) and was followed by the addition of 1a at -78 °C that cleanly afforded 3Ka in almost quantitative yield.\(^\text{17}\)

**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 °C, 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 °C). However, the formation of the organolithiums from 3Ka and 3Ca was easier (-78 °C) than for 3C (0 °C to rt).\(^\text{18}\)

It suggests an stabilizing influence of the alkynyl group on the organolithium, that decreases its reactivity.\(^\text{19}\) 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.\(^\text{20}\)

**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 heteroarylolithiums. We fix our attention in sulfones containing the thiophene ring, like 1i\(^\text{1}\) 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 °C 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 heteroarylithiiums derived from 2M-2O were even less fruitful.\(^\text{40}\)

These results suggest 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 than organolithium compounds,\(^\text{22}\) we studied the reaction of 1i with PhMgCl (Mg-2L). The reaction did not work at -78 °C and 0 °C 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 °C 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 3Oa at 50 °C) 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\(^\text{15}\) (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.\(^\text{23}\)

**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\(^\text{24}\) 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


4.  thanks Conacyt-México and DGAPA-UNAM for a sabbatical

5. gratefully acknowledged. J. A. thanks the MICINN for “Ramon y Cajal”

6. fellowship. L.M. thanks for a FPU fellowship to the Spanish government.

7. Notes and references

8.  A. Hopper, A. Sams, M. Graven; K. Gittem


15. These yields were obtained starting from 0.2 mmol of 2A-2C but the reaction 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 was 15 minutes. Longer reaction times for the Br-Li exchange gave an equilibrium of 3-Li2K and 2-Li2K, and consequently the corresponding mixture of monoalkynylated derivatives were formed.

18. This was confirmed by studying deuterium reactions at ~78 °C of the Li carbanions 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 °C 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 °C produces its 2-Li derivative (unsensitive to the opening), which is quantitatively deuterated with ND3.

19. It can be explained by assuming a ~1 effect of the alkynyl group (weaker for longer distance) that stabilizes the lithium carbanion but reduces its reactivity. The complete regioselectivity observed in the alkynylation reaction of 3Ka indicates that this stabilization is clearly higher for (C2)-Li than for (C5)-Li, which supports the above statement. Another possible explanation of this regioselectivity would involve the formation of a mixture of (C2)-Li and (C5)-Li derivatives of 3Ka, with the first one being the most reactive. Nevertheless this could be discarded by the exclusive deuteration at C-2 observed by protonation with ND3Cl (see ref. 18).


21. Sulfone 11 was prepared in two steps from the commercially available 3-ethylthiophene by reaction with sodium toluene sulfinate and Na in the presence of CAN, followed by reaction with K2CO3 in refluxing aceton, according to the procedure reported by Nair et al (V. Nair, A. Augustine and T. D. Suja, Synthesis 2002, 2259). Other heteroarylsulfonyl acetylenes could not be prepared by this procedure, because the starting ethynyl derivatives are not commercially available. We have tried to prepare them, but in the isolation step we found serious problems due to their high volatility.


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

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