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A new microwave-assisted thionation-heterocyclization process leading to benzo[*c*]thiophene-1(3*H*)-thione and 1*H*-isothiochromene-1-thione derivatives†

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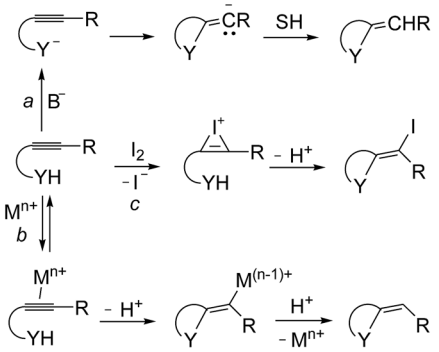
The first example of a tandem thionation/*S*-cyclization process leading to benzo[*c*]thiophene-1(3*H*)-thione and 1*H*-isothiochromene-1-thione derivatives, starting from 2-alkynylbenzoic acids, is reported. The reaction is carried out in CH_2Cl_2 using 1 equiv. of Lawesson's reagent under MW irradiation at 100 °C and 300 W for 1 h. Depending on the nature of the substituent at the distal β carbon of the triple bond, either benzothiophenethiones or isothiochromenethiones were obtained selectively, in high to excellent yields. The structure of the representative compounds has been confirmed by X-ray diffraction analysis.

Heterocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is widely recognized as a methodology of primary importance for the direct preparation of a variety of heterocyclic systems in a regioselective fashion, starting from readily available acyclic precursors.[1] This reaction can be promoted by strongly basic conditions, which favor the deprotonation of the nucleophilic group, followed by intramolecular nucleophilic attack on the triple bond (Scheme 1, pathway a; only the *exo-dig* mode is shown for simplicity). To avoid possible substrate and/or product degradation, the heterocyclization is more conveniently carried out by electrophilic activation of the triple bond, usually ensuing from triple bond coordination to a suitable metal center (as in metal-catalyzed heterocyclizations, Scheme 1, pathway b) or from the interaction with an electrophilic species (such as iodine, as in the case of iodocyclization reactions that lead to iodinated heterocycles, Scheme 1, pathway c).

Compared to the considerable number of examples reported in the literature for the synthesis of O- or N-heterocycles (Scheme 1, Y = O or NR), there are still relatively few examples of heterocyclizations of *S*-containing alkyne substrates leading to sulfur heterocycles (Scheme 1, Y = S). This is probably connected with the relatively low stability of the thiol group as compared to the hydroxyl or the amino group and, in the case of metal-catalyzed heterocyclization, to the "poisoning" effect exerted by the sulfur atom on the metal catalyst, owing to its strong coordinating and adsorptive properties.[2]

Nevertheless, during the last years, several important *S*-cyclization reactions, starting from substrates bearing a free as well as a masked thiol group, have been developed,[1a,3] including several contributions from our research group.[3b,i,j,4]



(YH = heteronucleophile; B^- = strong base; M^{n+} = metal center; SH = protic solvent)

Scheme 1 Possible heterocyclization pathways of acetylenic substrates bearing a heteronucleophilic group (YH) leading to heterocycles (only the *exo-dig* mode is shown for simplicity).

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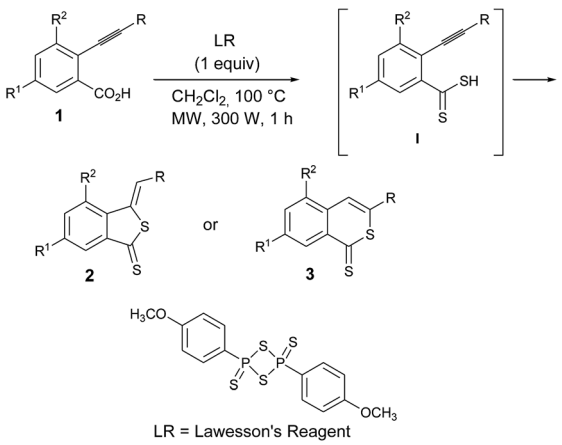
In this work, we report a new thionation-heterocyclization process leading to benzo[*c*]thiophene-1(3*H*)-thione and 1*H*-isothiochromene-1-thione derivatives (**2** and **3**, respectively)[5–7] in one step starting from readily available 2-alkynylbenzoic acids **1**[8,9] (Scheme 2). The tandem process is carried out under microwave (MW) irradiation,[10] in the presence of 1 equiv. of the Lawesson's reagent.[11,12] 2-Alkynylbenzodithioic acids **I**,[13] obtained *in situ* by thionation of **1**, undergo *S*-cyclization to give **2** or **3** without the need for activation from an external electrophilic promoter (Scheme 2).

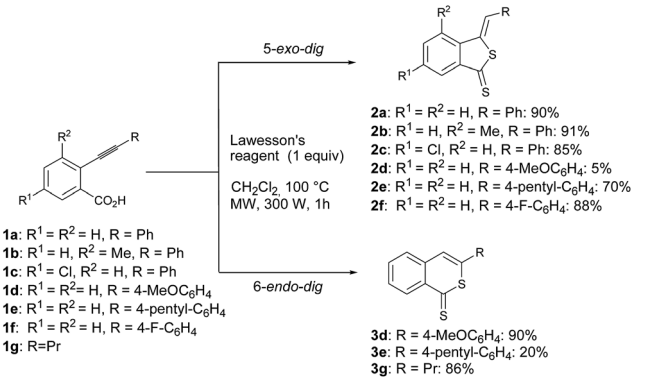
The initial substrate we tested was 2-(2-phenylethynyl)benzoic acid **1a** ($R^1 = R^2 = H$, R = Ph), which was allowed to react with 1 equiv. of the Lawesson's reagent in CH_2Cl_2 at 100 °C under MW irradiation. After 1 h, (*Z*)-3-benzylidenebenzo[*c*]thiophene-1(3*H*)-thione **2a** was obtained in 90% isolated yield, with complete regio- and stereoselectively (Scheme 3).

It is worth noting that the same reaction, carried out under conventional heating (refluxing CH_2Cl_2, 1,2-dichloroethane, toluene or MeCN for 6–24 h) led to the formation of **2a** in only small amounts (0–5%), with partial decomposition of the substrate. A peculiar aspect of our MW-assisted synthetic approach is that the *S*-cyclization of the intermediate 2-alkynylbenzodithioic acids **I** occurs without the need for the presence of an external electrophilic promoter.

The structure of products **2** was elucidated by ^{1}H NMR and ^{13}C NMR spectroscopies and MS spectrometry. In particular, the *Z* stereochemistry around the exocyclic double bond was assigned on the basis of selective 1D NOESY experiments, carried out on compound **2a** (Fig. 1A). When H_4 was irradiated (7.53 ppm), the selective 1D NOESY spectrum clearly showed cross-peaks between H_4 and H_8 (7.94 ppm), H_4 and H_{orto} (7.62 ppm) in the phenyl substituent, as the result of the spatial proximity of these protons, which is only possible if they are in the *Z*-configuration. The *Z* stereochemistry was further confirmed by X-ray crystallographic analysis (Fig. 2, see the ESI† for additional details).[14]



Scheme 2 MW-assisted tandem thionation-heterocyclization of 2-alkynylbenzoic acids **1**, carried out in the presence of 1 equiv. of the Lawesson's reagent, that leads to (*Z*)-3-alkylidenebenzo[*c*]thiophene-1(3*H*)-thiones **2** and 1*H*-isothiochromene-1-thiones **3** through the formation of 2-alkynylbenzodithioic acids **I** as intermediates.



Scheme 3 Synthesis of (*Z*)-alkylidenebenzo[*c*]thiophene-1(3*H*)-thiones **2** and 1*H*-isothiochromene-1-thiones **3**.

Our protocol could be also be successfully applied to substrates substituted in *ortho* or in *para* with respect to the carboxyl group, as in the case of **1b** (R^2 = Me) and **1c** (R^1 = Cl), which led to the corresponding benzo[*c*]thiophene-1(3*H*)-thiones **2b** and **2c** in 91% and 85% yields, respectively (Scheme 3). Moreover, a substrate bearing a *p*-fluorophenyl substituent on the triple bond, such as **1f**, led to the corresponding benzo[*c*]thiophene-1(3*H*)-thione derivative **2f** in high yield (88%, Scheme 3).[15]

Interestingly, 2-alkynylbenzoic acids carrying on the triple bond an alkyl substituent (such as propyl, as in **1g**) or a phenyl group substituted in the *para* position with a strong π-donating group (such as methoxyl, as in **1d**) selectively underwent, after *in situ* thionation, a 6-*endo-dig* rather than a 5-*exo-dig* cyclization, to give the corresponding 1*H*-isothiochromene-1-thiones **3g** and **3d**, respectively, in excellent yields (Scheme 3).[16] The structure of products **3** was confirmed by MS spectrometry, ^{1}H NMR and ^{13}C NMR spectroscopies (in particular, no NOESY effect was observed by irradiation of proton H_4 in compound **3d**, see Fig. 1B), and confirmed by X-ray crystallographic analysis (Fig. 2; see the ESI† for additional details).[14]

Quite consistently, a substrate bearing on the triple bond a phenyl group substituted in *para* position with a weakly electron-donating substituent (such as the *n*-pentyl, as in **1e**) afforded (*Z*)-3-(4-pentylbenzylidene)benzo[*c*]thiophene-1(3*H*)-thione **2e** as the major product (70% yield) together with 3-(4-pentylphenyl)-1*H*-isothiochromene-1-thione **3e** in 20% yield (Scheme 3). The observed change in regioselectivity moving from an electron-withdrawing substituent to an electron-

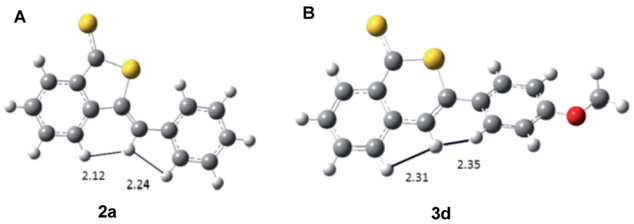


Fig. 1 Molecular structure of compounds **2a** (A) and **3d** (B) optimized by Gaussian at 6-31g**b3lyp level.

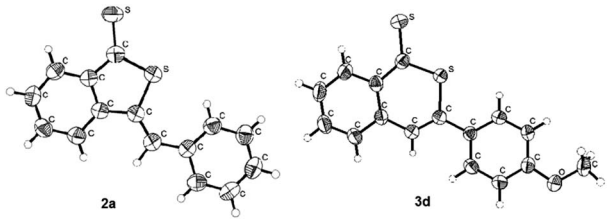
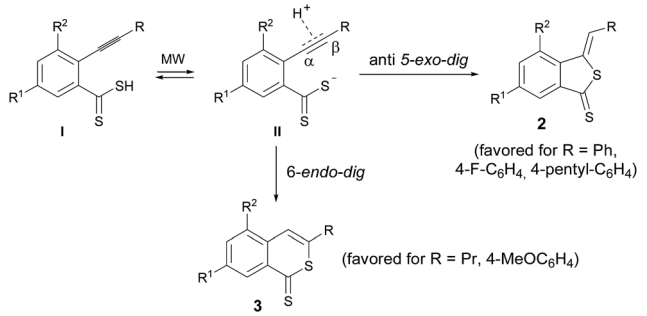


Fig. 2 X-ray crystal structures of products **2a** and **3d**, showing 50% probability ellipsoids for non-H atoms and spheres of arbitrary size for H atoms.



Scheme 4 Proposed mechanism for the heterocyclization of 2-alkynylbenzodithioic acids **I**: the initial MW-induced dissociation of the dithiocarboxyl group, with simultaneous proton coordination by the triple bond, is followed by *anti* 5-*exo-dig* or by 6-*endo-dig* intramolecular nucleophilic attack of the dithiocarboxylate group to the electrophilically-activated triple bond.

donating substituent on the triple bond is in agreement with the results previously obtained in other heterocyclizations of functionalized alkynes.[17]

Mechanistically, the cyclization process may start with MW-induced dissociation of the dithiocarboxyl group[18] of **I** with simultaneous proton coordination by the triple bond, with formation of intermediate **II**, as shown in Scheme 4. This intermediate, according to the electronic nature of the triple bond, can lead to compound **2** or **3**. In particular, the presence of an electron withdrawing group at the β carbon of the triple bond promotes the protonation on this carbon followed by the *anti* 5-*exo-dig* intramolecular nucleophilic attack of the dithiocarboxylate group, leading to the formation of compound **2**. An *anti* intramolecular attack is in perfect agreement with the observed *Z* stereochemistry of the final product **2**. Alternatively, the presence of an electron releasing group on the β carbon of the triple bond promotes the 6-*endo-dig* cyclization, with protonation on the more negative carbon of the triple bond (β carbon), thus leading to the formation of 1*H*-isothiochromene-1-thione derivatives **3**.

Conclusions

In summary, we have reported the first example of tandem thionation/heterocyclization of 2-alkynylbenzoic acids **1**. The process occurs using 1 equiv. of the Lawesson's reagent as the thionation agent under MW irradiation (100 °C at 300 W) in CH_2Cl_2 for 1 h, and leads to (*Z*)-benzothiophenethiones **2** or isothiochromenethiones **3**, depending on the nature of the substituent at the distal β position of the carbon–carbon triple bond. In particular, compounds **2** were regio- and stereoselectively obtained starting from substrates bearing an aryl group (Ph, 4-F-C_6H_4, or 4-pentyl-C_6H_4) as substituent on the carbon–carbon triple bond, through thionation followed by a 5-*exo-dig* cyclization, while substrates carrying an alkyl group (such as Pr) or an electron-rich aryl substituent (such as *p*-$MeOC_6H_4$) at the same position selectively underwent a 6-*endo-dig* cyclization to yield **3**. The study of the bioactivity of the newly synthesized *S*-heterocycles is currently underway and will be reported in due course.

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13 Thioacids are a well-established and versatile class of organic compounds which, due to their nucleophilicity, have found broad applications. For representative examples, see: (*a*) D. Crich, K. Sana and S. Guo, *Org. Lett.*, 2007, **9**, 4423; (*b*) K. N. Barlett, R. V. Kolakowski, S. Katukojvala and L. J. Williams, *Org. Lett.*, 2006, **8**, 823; (*c*) A. K. Mapp and P. B. Dervan, *Tetrahedron Lett.*, 2000, **41**, 9451.

14 CCDC 1442210 (**2a**) and 1442211 (**3d**) contain the supplementary crystallographic data for this paper.

15 The selectivity toward the 5-*exo-dig* products **2a–c** and **2f** was virtually complete; in fact, no detectable amounts of the isomeric products deriving from a 6-*endo-dig* cyclization mode were observed in the reaction crudes by GLC and GLC/MS analyses.

16 The selectivity toward the 6-*endo-dig* product **3g** was practically complete, while small amounts of the 5-*exo-dig* cyclization product **2d** (5%) were observed in the reaction mixture deriving from **1d**.

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