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One-pot, Pd/Cu-catalysed synthesis of alkynyl-substituted 3-ylidene-dihydrobenzo[*d*]isothiazole 1,1-dioxides

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A B S T R A C T

Enyne-substituted benzoisothiazole derivatives have been synthesised under one-pot, operationally simple conditions using 2-iodo-*N*-(trimethylsilylethynyl)benzenesulfonamides and terminal alkynes as starting materials and a palladium–copper-based catalytic system. The structure of these heterocycles has been demonstrated by NMR spectroscopy and confirmed by X-ray crystallographic analysis. A plausible reaction mechanism has been proposed.

Keywords:
Alkynes
Cyclisation
Heterocycles
Isothiazole 1,1-dioxides
Palladium

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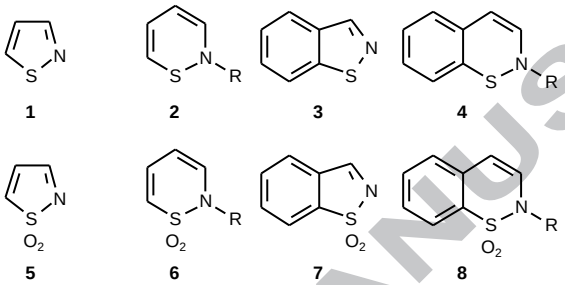
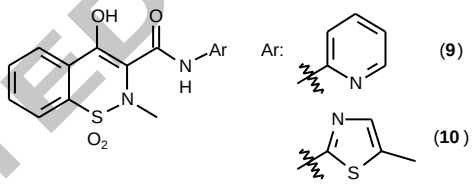
Isothiazole (**1**, Scheme 1) (1,2-thiazole), 2-R-2*H*-1,2-thiazines (**2**), and their benzo-analogues (**3** and **4**, respectively) are privileged heterocyclic frameworks that occur in a large

number of compounds that exhibit extensive biological activities. In particular, 1,1-dioxide (sultam) derivatives (**5**–**8**) inhibit various enzymes[1–8] and are antiproliferative agents against vascular smooth muscle cells,[2] rat aortic myocites,[9] and several cancer cell lines.[10,11] 1,2-Benzothiazine dioxide derivatives also exhibit potent anti-HIV-1[11] and excellent anti-inflammatory and analgesic activities.[12] They are known as oxicams,[13] and piroxicam (**9**, Scheme 2), meloxicam (**10**), droxicam, and ampiroxicam are marketed world-wide under many brandnames.

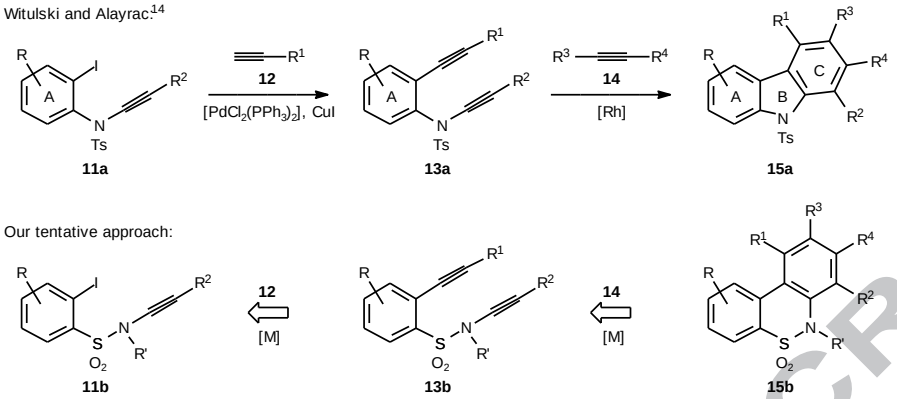


Scheme 1. General structure of 1,2-thiazole (**1**), 1,2-thiazine (**2**), and of their benzo- (**3** and **4**) and 1,1-dioxide derivatives (**5**–**8**).



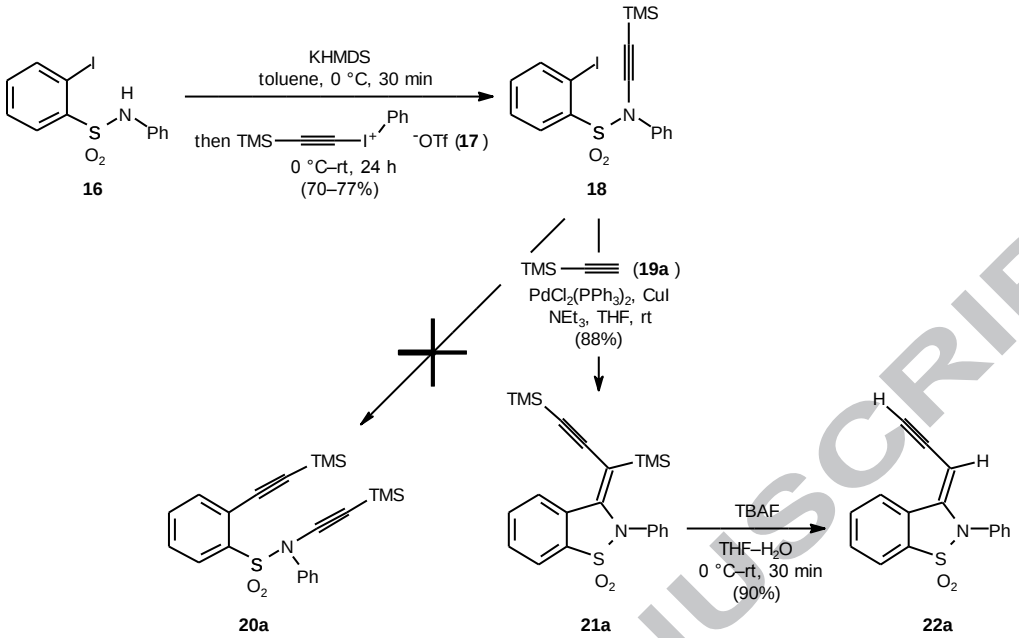
Scheme 2. Molecular structure of piroxicam (**9**) and meloxicam (**10**).

We recently became interested in the synthesis of 6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide derivatives **15b** (Scheme 3) containing two benzene rings fused with the thiazine dioxide motif. To this end, we were inspired by the strategy designed by Witulski and Alayrac[14] for the assembly of the carbazole nucleus **15a** by an A→ABC ring-formation approach based on the synthesis of functionalised tosylynamides **11a**, the reliability of the Sonogashira reaction, and the efficiency of transition-metal-catalysed alkyne cyclotrimerisation. By analogy, we anticipated that 2-iodobenzenesulfonynamides **11b** would be suitable precursors of diynes **13b** (Scheme 3). Contrary to our expectations, application of the Sonogashira coupling to iodides **11b** did not afford the intermediates **13b**. Instead, alkynyl-substituted 3-ylidene-dihydrobenzo[*d*]isothiazole 1,1-dioxides **21** were formed (Scheme 4), which is the subject of the present communication.



Scheme 3. A→ABC ring-formation approach to substituted carbazoles (**15a**) or dibenzothiazine 5,5-dioxides (**15b**) by transition-metal-catalysed alkyne cyclotrimerisation.

We first synthesised ynamide **18** from the precursor *N*-phenyl 2-iodobenzenesulfonamide **16** by adapting the route described by Feldman and Witulski as shown in Scheme 4.[15,16] Thus, deprotonation of sulfonamide **16** with potassium hexamethyldisilazane (KHMDS) in toluene, followed by addition of the readily available trimethylsilylethynyliodonium triflate **17**[17b] gave a 70–77% yield of the desired ynamide **18**, as isolable, colourless crystals that were fully characterised by spectroscopy and by single crystal X-ray diffraction (See Supplementary Data). Then, as mentioned above, treatment of **18** with trimethylsilylacetylene (**19a**) under classical Sonogashira conditions[14,15] failed. Despite several attempts, indeed, the expected diyne **20a** did not form, but enyne-substituted isothiazole derivative **21a** in 88% yield resulting from a 5-*exo*-dig cyclisation. Finally, desilylation with tetrabutylammonium fluoride (TBAF) in wet THF[14–16] furnished **22a** in 90% yield.



Scheme 4. Synthesis of benzoisothiazole 1,1-dioxide **22a**.

The elucidation of the structure of compound **21a** was not an easy task. The IR spectrum includes the typical absorption band of only one alkyne functional group and the shift of the C≡C stretch to 2111 cm^{-1} might be attributed to conjugation. In addition, the bands for the symmetric and asymmetric vibrations of the SO_2 group appear at 1179 and 1340 cm^{-1}, respectively. The ^{1}H and ^{13}C NMR spectra contain the characteristic signals for two trimethylsilyl groups, a doublet at 9.27 ppm assignable to C(7)*H* shifted downfield by the neighbouring SO_2 group, and a set of peaks attributed to unsaturated carbons and the corresponding hydrogens that are difficult to draw any firm information. Fortunately, the exact molecular structure of **21a** was unambiguously assured by X-ray analysis (Fig. 1),[18] which featured a benzoisothiazole 1,1-dioxide core with a *Z*-configured 1,3-bis(trimethylsilyl)prop-2-yne-1-ylidene substituent at position 7 (Fig. 1). The C7–C14 and C18–C19 distances are characteristic of carbon–carbon double and triple bonds, respectively. The geometrical parameters around the vinylic atoms C7 and C14 are in good agreement with sp^2 hybridisation. Only slight deviations of 6.9° (C19–C18–C14) and 1.8° (Si2–C19–C18) to 180° for acetylenic carbons C18 and C19, respectively, are observed, indicating that there is no constraint in the binding of the trimethylsilylacetylene fragment to the vinyl group. Sultam **21a** is a sterically demanding compound and the dihedral angle of 69.8° between the planes (C1→C6) and (C8→C13) (Fig. 1) shows that both aromatic rings are almost perpendicularly oriented in the solid state. This conformation is likely stabilised by the trimethylsilyl group *via* intramolecular interactions between C15–H15C and π (C8→C13) aromatic ring, and weak

intramolecular H-bonds between C16–H16C and nitrogen atom N1 (Fig. 1) (See also Supplementary Data). However, in solution at room temperature, the *ortho* (9 and 13) and *meta* (10 and 12) carbons and hydrogens are equivalent in NMR spectroscopy, indicating that the phenyl group is freely rotating around the N1–C8 bond.

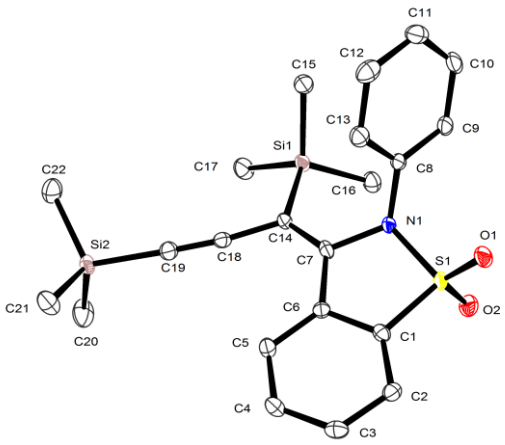
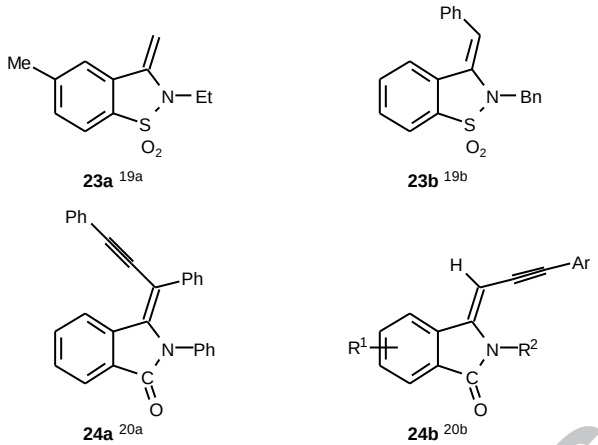
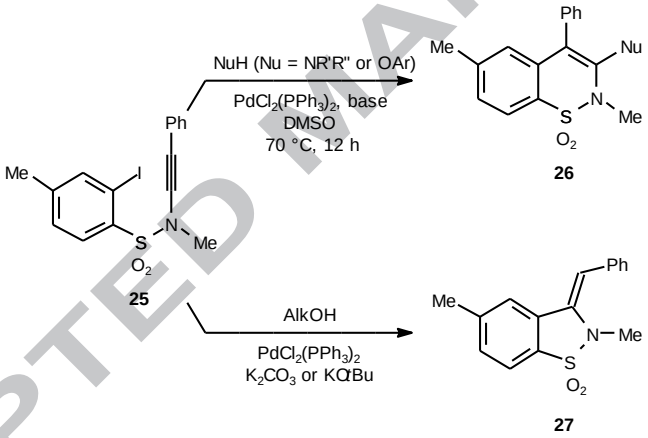


Figure 1. ORTEP representation of isothiazole **21a**, with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms were removed for clarity.

To the best of our knowledge, enyne-containing benzoisothiazole 1,1-dioxides **21** have a structure hitherto unknown. Only the syntheses of related sultams **23**[19] and isoindolin-1-ones **24**[20] (Scheme 5) have been reported, albeit using different methodologies. It has also been reported recently by Kumara Swamy *et al.*[25] that when 2-iodobenzenesulfonynamide **25** was treated with a variety of nitrogen (amines and sulfonamides), carbon and oxygen (phenols) nucleophiles in the presence of a palladium catalyst, 1,2-benzothiazine 1,1-dioxides **26** were synthesised through a 6-*endo*-dig tandem cyclisation (Scheme 6). By contrast, the use of alcohols as nucleophiles resulted in a 5-*exo*-dig cyclisation, without incorporation of the nucleophile.[25] In the present case, in the absence of nucleophile and using a Pd/Cu catalytic system, addition of a terminal alkyne to 2-iodobenzenesulfonynamide **18** led to the formation of enyne-substituted isothiazoles **21**, which might result from the so-called tandem Heck–Sonogashira reaction[21d,i] or alkynylation–carbopalladation reaction,[22c] a process that has been rarely described in the past, notably in the coupling of certain vinyl or aryl halides with terminal alkynes[21] or as a side reaction.[22] In many respects, this process is very similar to the 5-*exo*-dig cyclisation of 2-iodobenzynamides through a tandem palladium-catalysed Heck–Suzuki–Miyaura coupling reaction with arylboronic acids, leading to 3-(arylmethylene)isoindolin-1-ones.[20c,d]



Scheme 5. Structures of representative substituted 3-methylenebenzoisothiazole dioxides **23** and enyne-containing isoindolinones **24**.

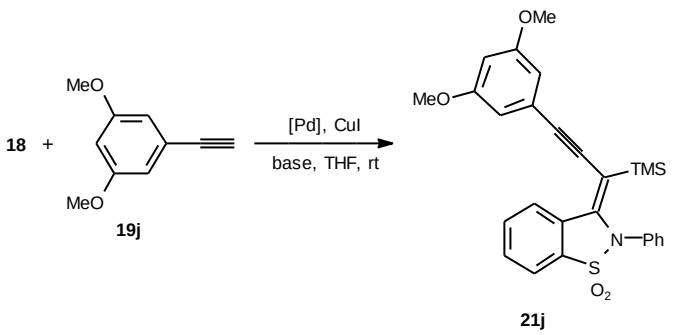


Scheme 6. Reactions of 2-iodobenzenesulfonynamide **25** with nitrogen and oxygen nucleophiles.

Having established the structure of compound **21a**, we next carried out the reaction of ynamide **18** with terminal alkyne **19j** in the presence of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, CuI and NEt_3 in THF at room temperature (Table 1). The yield of isothiazole **21j** was higher (80%) from the reaction with $PdCl_2(PPh_3)_2$ than that from the reaction with $Pd(PPh_3)_4$ (70%).[23] Furthermore, in the absence of CuI, the yield of **21a** or **21j** dropped to 5–10%. When the reaction was carried out only with CuI, without any palladium catalyst, the yields were equally low (< 10%). We also found that triethylamine was a base of choice as was observed previously.[23] The effect of other bases, *e.g.* K_2CO_3 and Cs_2CO_3, was also investigated (Table 1). The use of Cs_2CO_3 instead of NEt_3 under the same reaction conditions afforded a lower yield (55–60%), whereas in the presence of K_2CO_3 the yields dropped again to 40–55%.

Table 1

Influence of both the palladium source and the base on the synthesis of benzoisothiazole dioxide **21j**[a]



Catalyst	Yield,[b,c] %		
Base:	NEt_3	K_2CO_3	Cs_2CO_3
$PdCl_2(PPh_3)_2$	80[b]	42[c]	54[c]
$Pd(PPh_3)_4$	70[c]	55[c]	58[c]

[a] Reaction conditions: ynamide **18**, 1.1 mmol; alkyne **19j**, 1.2 mmol; [Pd], 0.055 mmol; CuI, 0.11 mmol; base, 36 mmol; THF, 5 mL. The resulting reaction mixture was stirred at room temperature and followed by TLC until the reaction was complete.

[b] Isolated yield.

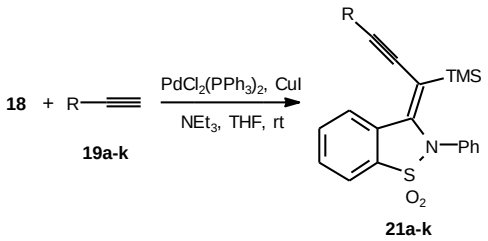
[c] Determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard.

We next explored the substrate scope of terminal alkynes **19** (Table 2). In some cases, in particular when R was an alkyl group (1-propyne (Entry 2) and 1-hexyne (Entry 3)), low yields of 30–40% were obtained. The yield was even lower with propiolic acid (Entry 5) whereas propargylic alcohol (Entry 4) gave an appreciable yield of 72%. When R was the phenyl group (Entry 6) or a phenyl derivative (Entries 7–11), the yields ranged from 58% to 80%, irrespective of the stereoelectronic properties of the substituents on the phenyl ring. However, with only 25% yield, 2,4,6-trimethylphenylacetylene (Entry 7) was a notable

exception. It should also be noted that some benzoisothiazole 1,1-dioxides **21** are not very stable and that signs of decomposition were observed during their purification (Table 2, footnote c).

Table 2

Influence of the terminal alkyne **19a**–**k** on the synthesis of benzoisothiazole dioxides **21a**–**k**[a]



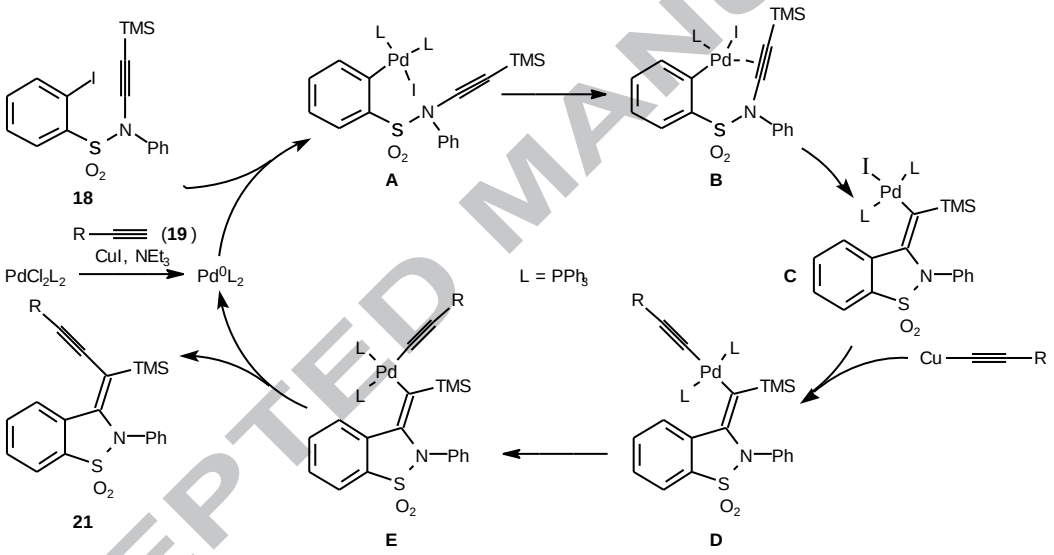
Entry	**21**	R	Yield, %
1	**21a**	TMS	88[b]
2	**21b**	Me	40[b]
3	**21c**	*n*-Bu	30[b,c]
4	**21d**	CH_2OH	72[b,c]
5	**21e**	CO_2H	22[b,c]
6	**21f**	Ph	61[b]
7	**21g**	2,4,6-Me_3-C_6H_2	25[b,c]
8	**21h**	2-MeO-C_6H_4	68[b]
9	**21i**	4-MeO-C_6H_4	58[b,c]
10	**21j**	3,5-$(MeO)_2$-C_6H_3	80[b]
11	**21k**	4-CF_3-C_6H_4	68[b,c]

[a] Reaction conditions: ynamide **18**, 1.1 mmol; alkyne **19**, 1.2 mmol; $PdCl_2(PPh_3)_2$, 0.055 mmol; CuI, 0.11 mmol; NEt_3, 10 mL; THF, 5 mL. The resulting reaction mixture was stirred at room temperature and followed by TLC until the reaction was complete.

[b] Isolated yield.

[c] This compound was partly contaminated by some unidentified degradation products.

In light of these results and of mechanisms proposed by Dougherty *et al.* for the synthesis of enyne-substituted fluorenes[21a] and by Teply *et al.* for the synthesis of enyne-substituted isochromene derivatives,[21c] we propose the mechanism sketched in Scheme 7.[21d,e] Oxidative addition of phenyl iodide **18** to an *in situ* generated Pd(0) species[24] provides the σ-arylpalladium(II) intermediate **A**, which then inserts into the tethered alkyne to form the σ-vinylpalladium(II) 5-*exo*-dig cyclisation intermediate **C**. Transmetallation with alkynyl copper generated *in situ* from terminal alkyne **19** provides the σ-alkynylpalladium(II) intermediate **D**, which after reductive elimination affords enyne-substituted isothiazole **21**. Another mechanism cannot be excluded *a priori*, although it is less likely: an intermolecular addition of a terminal alkyne **19** to the triple bond of the substrate **18**, followed by cyclisation.[22e,26]



Scheme 7. Plausible mechanism for the synthesis of enyne-substituted benzoisothiazole dioxides **21**.

If the mechanism outlined above proves to be correct, it then becomes easy to explain the difference in reactivity between tosylynamide **11a** (Scheme 3) and benzenesulfonynamide **18** (Scheme 4) when both substrates are treated with a terminal alkyne under the same Sonogashira conditions: In contrast to compound **18**, tosylynamide **11a** cannot undergo a 4-*exo*-dig cyclisation to yield the corresponding highly strained 4-membered ring, and that is likely the major reason why here the Sonogashira coupling works so well to provide diynes **13a** (Scheme 3).[14,26] However, 5-*endo*-dig cyclisations with **11a** were reported after activation by a nucleophile.[27]

In conclusion, our initial aim was to access the 6*H*-dibenzo[c,e][1,2]thiazine 5,5-dioxide scaffold **15b**. We have shown, however, that the desired diyne precursor **13b** was not formed under classical Sonogashira conditions, in marked contrast to the related tosylamide system **13a**, but alkynyl-substituted 3-ylidene-dihydrobenzo[*d*]isothiazole 1,1-dioxide **21**, most probably *via* a tandem Heck–Sonogashira reaction. Their structure was confirmed by X-ray crystallographic studies. Work is currently underway in our laboratory to expand the scope of this reaction and to get some mechanistic insight.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, characterisation, ^{1}H, ^{13}C, and IR spectra of compounds, and X-ray structure of compounds **18**, **21a**, **21h**, and **21j**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.xx.yyy.

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One-pot, Pd/Cu-catalysed synthesis of alkynyl-substituted 3-ylidene-dihydrobenzo[*d*]isothiazole 1,1-dioxides

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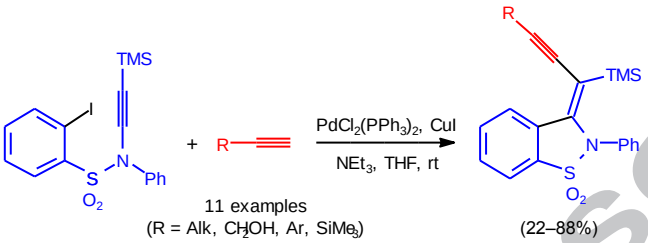

Highlights

A one-pot, Pd/Cu-catalysed approach to enyne-substituted benzoisothiazole 1,1-dioxides is described.

A plausible mechanism involves a rarely described tandem Heck–Sonogashira coupling reaction.

This method can be applied to access new molecular scaffolds of interest in medicinal chemistry.