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Sustainable Synthesis of Vinyl Sulfones Using Copper Catalysis †

Dawid Halka [1], Ignacio Padrón [1], Amparo Luna [1,*] and Pedro Almendros [2,*]

[1] Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain; email1@email.com (D.H.); email2@email.com (I.P.)
[2] Instituto de Química Orgánica General, IQOG, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
* Correspondence: alunac@ucm.es (A.L.); palmendros@iqog.csic.es (P.A.)
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Abstract

Sulfonyl derivatives are very important compounds as they can be found in sulfones and sulfonamides, two classes of compounds with prominent biological and pharmacological activities. This study explores a copper-catalyzed cascade heterocyclization/sulfonylation reaction for the controlled preparation of sulfonyl oxazinones. Surprisingly, in this work we have isolated a great variety of vinyl sulfones with high selectivity instead of the expected cyclization. These sulfones are obtained by the reaction between N-Boc-allenes and aromatic sodium sulfinates. These results emphasize the reactivity of allenes toward the formation of bis(γ-amino-functionalized vinyl sulfones) in the presence of copper salts under radical conditions.

Keywords: allenyl carbamates; allenes; sulfones; copper catalysis

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1. Introduction

Allenamides are a subgroup of allenes that show interesting reactivity because the free electron pair of nitrogen can be delocalized with the amide group, reducing its donating ability towards the allenic center and giving it greater stability compared to other subgroups such as allenamines. Allenyl carbamates is one type of allenamides where the Boc group is used as a protecting group and can be removed under mild conditions. These allenamides are interesting in organic synthesis since they can be used as starting materials in cyclization reactions catalyzed by transition metals and cycloaddition reactions, among others [1].

Sulfonated compounds are of great importance in Organic Chemistry since they exhibit a wide range of biological activities, including antimicrobial, antiviral, antidiabetic, and anticancer properties [2,3].

Vinylsulfones and gamma-amino vinylsulfones (Figure 1) are compounds known for their varied pharmacological activity, such as being reversible inhibitors of many types of cysteine proteases, inhibiting other types of enzymes such as HIV-1 integrase and antibacterial agents, among others [4,5].

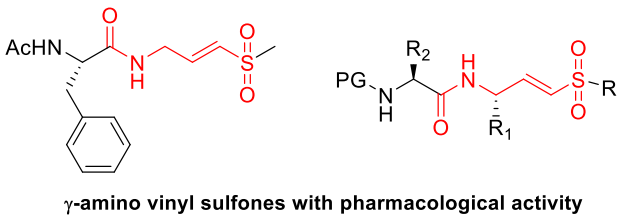
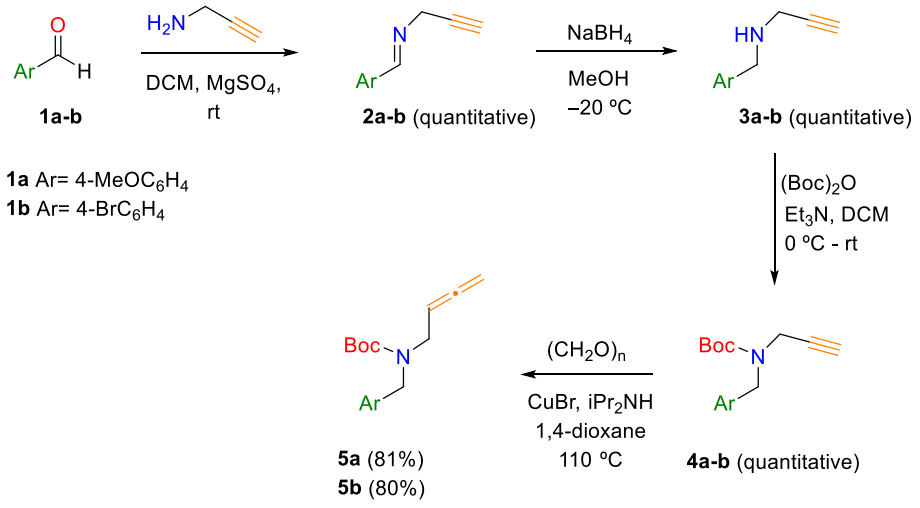


Figure 1. Importance of sulfonated compounds.

Despite their high biological importance, they also play an important role in Organic Synthesis, acting as efficient Michael acceptors and 2π donors in cycloaddition reactions. Our research group has reported a gold(I)-catalyzed cyclization of allenic carbamates to obtain 1,3-oxazinan-2-ones and the synthesis of sulfonated heterocycles from α-allenols by an oxycyclization/sulfonylation reaction [6]. The use of copper salts in organic synthesis is desirable because of low toxicity and low cost. In this context, we decided to study a copper-catalyzed cascade heterocyclization/sulfonylation for the controlled preparation of sulfonyl compounds [7].

2. Results and Discussion

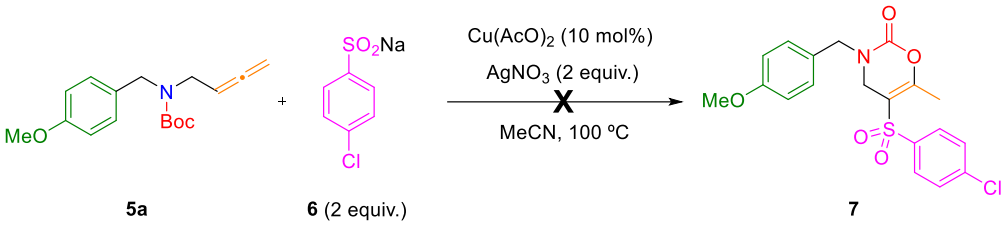
According to our working plan, the preparation of allenyl carbamates **5** was carried out following a procedure described in the literature (Scheme 1) [8]. Thus, alkynyl carbamates **1a–b** were prepared through reductive amination of the appropriate aromatic aldehyde and propargylamine in the presence of anhydrous magnesium sulfate, which acts as a dehydrating agent. The treatment of the corresponding N-substituted prop-2-yn-1-amines with Boc_2O afforded the desired compounds with good yields. Finally, the terminal alkynes **4** were conveniently converted into allenic carbamates **5** by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé homologation reaction).



Scheme 1. Synthesis of allenic carbamates **5**.

Next, when starting materials were synthesized, the study of the cyclization/sulfonylation cascade reaction for obtaining sulfonated oxazinones was developed. The allenyl carbamate **5a** was used as model substrate. The reaction conditions, previously optimized by the research group for cyclization reactions with incorporation of the arylsulfonyl group, were tested (2 equivalents of sodium sulfinate **6a**, 2 equivalents of silver nitrate as the oxidizing agent, and copper(II) acetate as the catalyst) [9]. The solvent used was acetonitrile, and the reaction was achieved in a sealed tube at 100 °C (Scheme 2). However,

after purifying the product and obtaining its ^{1}H-NMR spectrum, it did not correspond to the sulfonated oxazinone **7**.



5a **6** (2 equiv.) **7**

Scheme 2. Oxycyclization/sulfonylation sequence of allene **5a** with benzenesulfinate **6**.

It is important to note that the ^{1}H-NMR spectrum at 25 °C showed more aromatic signals. However, due to overlapping resonance signals, the integration values did not correspond to the heterocyclization/sulfonylation reaction. For this reason, NMR experiments were conducted at different temperatures with the aim to have a good resolution of peaks that were indistinguishable at room temperature (Figure 2). This structure was studied through variable-temperature ^{1}H NMR (300 MHz), including 1D and 2D experiments, in $C_2D_2Cl_4$. The higher resolution of the ^{1}H NMR spectrum at 65 °C compared to 25 °C is clearly visible. The multiplet (6.61 ppm, signal orange) well--resolved signal at 65 °C (t, J = 6.3 Hz) indicates the presence of a double bond. This triplet is expected because the proton couples with two protons, N-**C*H*$_2$**-CH (3.83 ppm, signal green) (d, J = 6.3 Hz).

This experiment revealed a sulfonylation/homodimerization sequence of the allenyl carbamate **5a** and the exact mass spectrum confirmed this dimeric compound.

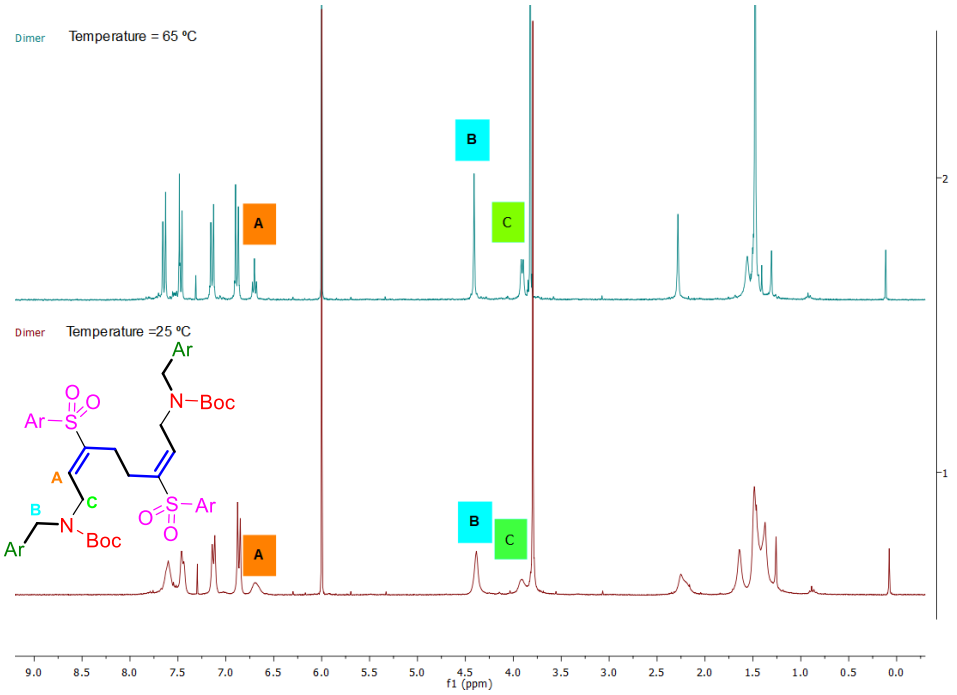
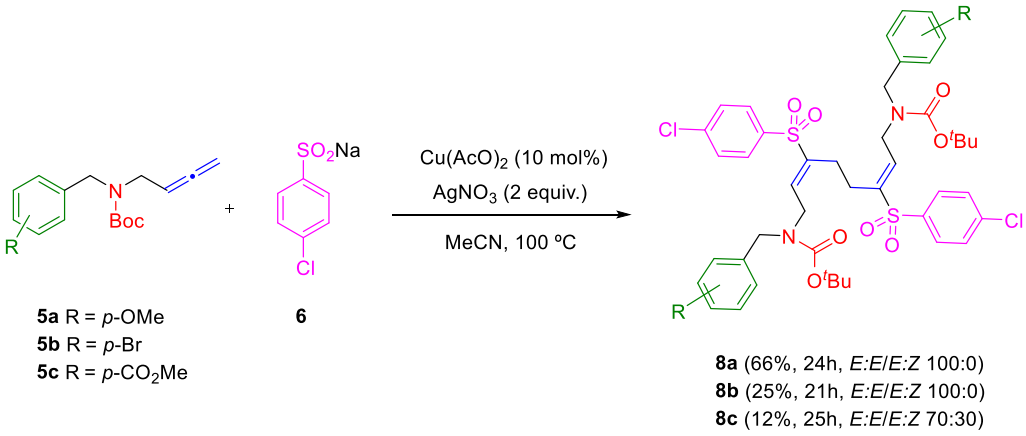


Figure 2. ^{1}H NMR (300 MHz) spectrum of **8a** in $C_2D_2Cl_4$. at 25 °C and 65 °C.

Although the desired compound **7** was not generated, the product obtained has an attractive pharmacological and biological potential as γ-amino vinylsulfone.

The scope of the copper-catalyzed sulfonylation/homodimerization of allenyl carbamates was explored. Allenyl carbamates **5a–c** with electron-donating (MeO), moderately electron-withdrawing (Br) or electron-withdrawing (CO_2Me) substituents at *para* position

of the phenyl ring and sulfinate **6** provided the required homodimeric γ-amino vinyl sulfones **8** in fair yields (Scheme 3).



Scheme 3. Sulfonylation/homodimerization of allenyl carbamates **5a–c**.

The variation in yields was notable for the different products. The highest yield was obtained for product **8a** as single (*E,E*)-isomer (66% yield). Nevertheless, when the ring of the allenyl carbamate **5c** is substituted with an electron-withdrawing group, the dimer **8c** was obtained as a mixture of (*E,E*) and (*E,Z*) isomers. These results show a regioselective synthesis (sulfonylation in the central carbon atom of the allene) and stereoselective synthesis (exclusive or majority formation of the *E:E* isomer) of a variety of bis(γ-amino vinylsulfones) that incorporate different substituents in the aromatic ring with different stereoelectronic effects.

3. Experimental Section

3.1. General Information, Intrumentation and Chemicals

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer. NMR spectra were recorded in $(CCl_2D)_2$ solutions, $(CCl_2D)_2$ (^{1}H, 5.91 ppm; ^{13}C, 74.2 ppm). Low- and high-resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

3.2. General Procedure

To a solution of the appropriate allenyl carbamates **5a–c** (1.0 mmol) in acetonitrile (10 mL) was added $Cu(OAc)_2$ (10 mol %), the corresponding sodium sulfinate **6** (2.0 mmol) and $AgNO_3$ (2.0 mmol). The reaction was stirred at 100 °C in a sealed tube until completion, which was monitored by TLC. The mixture was cooled to room temperature and was diluted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine (3 × 3 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for pure forms of compounds **8** follow.

3.3. Spectral Data

bis(γ-amino vinyl sulfone) 8a. From 25 mg (0.10 mmol) of allene **5a**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound **6ba** (31 mg, 66%) as a colorless solid; mp 147.1–148.6 °C; ^{1}H NMR (300 MHz, $(CCl_2D)_2$, 65

°C): δ = 7.56 (d, 4H, *J* = 8.7 Hz, ArH), 7.39 (d, 4H, *J* = 8.7 Hz, ArH), 7.06 (d, 4H, *J* = 8.7 Hz, ArH), 6.80 (d, 4H, *J* = 8.7 Hz, ArH), 6.61 (t, 2H, *J* = 6.3 Hz, C*H*=), 4.32 (s, 4H, N-CH_2), 3.83 (d, 4H, *J* = 6.3 Hz, N-CH_2-CH), 3.74 (s, 6H, O-CH_3), 2.21 (s, 4H, CH_2-CH_2), 1.39 (s, 18H, *t*-Bu); ^{13}C NMR (75 MHz, ($CCl_2D)_2$, 55 °C): δ = 159.4 (2C), 155.4 (2C), 141.0 (2C), 140.5 (2C), 140.2 (2C), 137.6 (2C), 129.9 (Ar, 4CH), 129.8 (Ar, 4CH), 129.7 (2C), 129.2 (Ar, 4CH), 114.6 (Ar, 4CH), 81.0 (2C), 55.7 (2CH_3-O), 51.2 (2CH_2), 44.8 (2CH_2), 28.7 (6CH_3), 26.2 (2CH_2); IR (AcOEt): ν = 1690 (C=O), 1611, 1247 cm^{-1}; HRMS (ES): calcd for $C_{46}H_{54}Cl_2N_2NaO_{10}S_2$ [*M* + Na]$^+$: 951.2489; found: 951.2517.

bis(γ-amino vinyl sulfones) 8b. From 45 mg (0.13 mmol) of allene **5b**, and after chromatography of the residue using hexanes/ethyl acetate [6:1]⟶[2:1] as eluent gave compound **6ca** (17 mg, 25%) as a white solid; mp 181.1–182.5 °C; ^{1}H NMR (300 MHz, ($CCl_2D)_2$, 65 °C): δ = 7.58 (d, 4H, *J* = 8.3 Hz, ArH), 7.41 (m, 8H, ArH), 7.02 (d, 4H, *J* = 8.1 Hz, ArH), 6.63 (t, 2H, *J* = 6.3 Hz, C*H*=), 4.33 (s, 4H, N-CH_2), 3.87 (d, 4H, *J* = 6.4 Hz, N-CH_2-CH), 2.26 (s, 4H, CH_2-CH_2), 1.38 (s, 18H, *t*-Bu); ^{13}C NMR (75 MHz, ($CCl_2D)_2$, 65 °C): δ = 155.3 (2C), 140.9 (2C), 140.6 (2C), 140.4 (2C), 137.7 (2C), 137.0 (2C), 132.2 (Ar, 4CH), 129.9 (Ar, 4CH), 129.7 (Ar, 4CH), 129.5 (Ar, 4CH), 121.7 (2C), 81.3 (2C), 51.3 (2CH_2), 45.3 (2CH_2), 28.6 (6CH_3), 26.3 (2CH_2); IR (AcOEt): ν = 1690 (C=O), 1475, 1146 cm^{-1}; HRMS (ES): calcd $C_{44}H_{48}Br_2Cl_2N_2NaO_8S_2$ [*M* + Na]$^+$: 1047.0488; found: 1047.0498.

bis(γ-amino vinyl sulfones) 8c. From 49.6 mg (0.16 mmol) of allene **5c**, and after chromatography of the residue using hexanes/ethyl acetate [2:1] as eluent gave compound **8c** (13.2 mg, 12%) as a yellow oil; ^{1}H NMR (300 MHz, ($CCl_2D)_2$, 65 °C): δ = 7.92 (d, 8H, *J* = 8.3 Hz, ArH, M+m), 7.70–7.44 (m, 8H, ArH, M+m), 7.34–7.09 (m, 16H, ArH, M+m), 6.93 (t, 2H, *J* = 6.8 Hz, C*H*=, m), 6.61 (t, 2H, *J* = 6.3 Hz, C*H*=, M), 4.47 (m, 8H, N-CH_2, M+m), 3.84 (m, 8H, N-CH_2-CH, M+m y 12H, O-CH_3, M+m), 2.15 (s, 8H, CH_2-CH_2, M+m), 1.35 (m, 36H, *t*-Bu, M+m); IR (AcOEt): ν = 1696 (C=O), 1595, 1155 cm^{-1}; HRMS (ES): calcd $C_{48}H_{54}Cl_2N_2O_{12}S_2$ [*M*]$^+$: 985.9820. This compounds did not ionize well.

4. Conclusions

In this work the copper-catalyzed cascade heterocyclization/sulfonylation for the controlled preparation of sulfonyl oxazinones from allenyl-carbamates and sodium sulfinates did not take place. Instead, a selective copper-catalyzed synthesis of dimeric vinylsulfones was developed, where the products could present pharmacology activities due to the nature of these compounds.

On the other hand, the electronic nature and the steric hindrance of the substituents of the aromatic ring of the allenyl-carbamates influence the performance and selectivity of the process.

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