

CHEMISTRY A European Journal



WILEY-VCH

Accepted Article Title: Divergence in Ynone Reactivity: Atypical Cyclization by 3,4-Difunctionalization versus Rare Bis(cyclization) Authors: Pedro Almendros, Benito Alcaide, Carlos Lázaro-Milla, and Patricia Delgado-Martínez This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article. To be cited as: Chem. Eur. J. 10.1002/chem.201800630 Link to VoR: http://dx.doi.org/10.1002/chem.201800630 **Supported by** ACES

CHEMISTRY A European Journal Full Paper

Synthetic Methods

Divergence in Ynone Reactivity: Atypical Cyclization by 3,4-Difunctionalization versus Rare Bis(cyclization)

Benito Alcaide, *^[a] Pedro Almendros, *^[b] Carlos Lázaro-Milla,^[a] and Patricia Delgado-Martínez^{[c],§}

Dedication ((optional))

Abstrac: Functionalized ynones can be activated by in situ generated $Tf_2C=CH_2$ to form zwitterionic species, which were trapped in an intramolecular fashion by several nucleophiles to generate in a divergent way two main types of triflones. Through fine-tuning the temperature, bis(triflyl)-6-membered-or (triflyl)-5-membered-fused-heterocycles were achieved in reasonable yields in a totally selective manner. In this way,

bis(triflyl)flavones,

bis(triflyl)thioflavones,

bis(triflyl)selenoflavones, (triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles were built. Conceivable mechanistic proposals were suggested based in the isolation of several intermediates and control experiments.

Introduction

Tuning selectivity in organic synthesis is difficult considering the usual inherent preference for the creation of a specific type of product. In some cases, a divergent synthesis can be achieved through modification of the promoter, additive, and reagent. Consequently, the discovery of novel strategies for divergent reactions is appealing. Ynones, a versatile acetylenic platform readily available from acyl chlorides and metal acetylides, have a great potential in organic synthesis in nucleophilic additions, cycloadditions, and condensation reactions.^{[1],[2]} However, less conventional reactivities are underexplored. The presence of

 [a] Prof. Dr. Benito Alcaide, Carlos Lázaro-Milla Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química Universidad Complutense de Madrid 28040 Madrid (Spain) Fax: (+34) 91-3944103 E-mail: alcaideb @quím.ucm.es

- [b] Prof. Dr. Pedro Almendros Instituto de Química Orgánica General Consejo Superior de Investigaciones Científicas, IQOG-CSIC Juan de la Cierva 3, 28006 Madrid (Spain) Fax: (+34) 91-5644853 E-mail: Palmendros@iqog.csic.es
- [c] Dr. P. Delgado-Martínez CAI Difracción de Rayos X Facultad de Química Universidad Complutense de Madrid
- § Responsible for X-ray crystal-structure determination.

Supporting information for this article and ORCIDs for the authors can be found under http://dx.doi.org/10.1002/chem.2018xxxxx.

fluoroorganic moieties in organic compounds notably influences the physicochemical properties.^[3] This modification usually results in alteration of the pharmacological properties of the fluorinated derivatives. Particular attention has been paid to the strong electron-withdrawing triflyl functionality, which also exhibited mild lipophilicity with the subsequent bioavailability improvement. In this context, the group of Yanai has recently developed an innovative methodology disclosing the use of 2-(pyridinium-1-yl)-1,1-bis(perfluoroalkylsulfonyl)ethan-1-ides as a stable source of $Tf_2C=CH_2$,^[4] while we developed a route for the preparation of bis(triflyl)cyclobutenes^[5] (Scheme 1a). Based on these previous observations, we decided to study the reactivity of functionalized ynones. Unexpectedly, divergent paths with respect to previous results were encountered. A detailed study of this chemistry unveiled novel aspects of the unique reactivity of ynones, allowing the direct preparation of various heterocyclic cores decorated with fluorinated moieties (Scheme 1b).

CHEMISTRY A European Journal Full Paper

DOI: 10.1002/chem.201xxxxx

Previous literature (a)

ChemPubSoc



Scheme 1. Background and current design for the synthesis of triflones using 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide.

Results and Discussion

To explore the feasibility of the use of ynones as precursors, 1-[2-(methylthio)phenyl]-3-phenylprop-2-yn-1-one 2a^[2a] was treated with 2-(2-fluoropyridinium-1-yl)-1,1bis[(trifluoromethyl)sulfonyl]ethan-1-ide 1 in acetonitrile at room temperature. Interestingly, the formation of bis(triflyl)thioflavone 3a was observed (Scheme 1) rather than Friedel-Crafts-type bis(triflyl)alkylation or cyclobutene construction. It should be noted the mild formation of a carbon-sulfur (C-S) bond,[6] which is present in a vast array of natural products and bioactive molecules such as thioflavones. The organofluorine substituent is also incorporated in the same step under metal free conditions via dual functionalization of the alkyne moiety. With these cyclization conditions in hand, we examined the scope of MeSfunctionalized ynones susceptible to thioflavone generation. First, the scope and limitations were evaluated through different substitution patterns at the alkyne site. Various substituents in the aromatic ring at the terminal akyne, such as methoxy, methyl and bromo were well tolerated, providing the desired fluorinated thioflavones 3a-d in isolated yields of 41% to 77% (Scheme 2). Besides, naphthalene-, indole-, thiophene-, and ferrocene-linked alkynes 2e-i were prone to suffer the thiacyclization/functionalization sequence (Scheme 2). Compounds 3a-i easily dissociate the acidic hydrogen and provide the corresponding metal salts 3a-i-Na after column chromatography.^[7] The highly deactivating 4-NO₂C₆H₄ and 4-CF₃C₆H₄ moieties attached to the alkyne group did not afford the corresponding thioflavones 3j and 3k. Unfortunately, alkynones bearing an alkyl substituent at the alkyne such as 21 were also inert in the presence of zwitterion 1.



3k-Na (EWG = CF₃, 0%, 24 h)

Scheme 2. Controlled preparation of bis(triflyl)thioflavones 3a-i.

The generality of the reaction was also explored through modification of the MeS-alkynone tether. Variation of the benzene linker was viable, with pyridine-, cyclohexene-, indole-, and thiophene-tethered alkynones all affording the desired organofluorine thioflavones 3m-q in reasonable yields (Scheme 3).

ChemPubSoc

CHEMISTRY A European Journal Full Paper





Taking into account the rich chemistry and the important biological properties of organoselenium compounds, the nature of the nucleophile was investigated by replacing the –SMe group for a –SeMe. Noticeably, starting from (methylseleno)-alkynones **4a**–**c** and zwitterion **1** the desired fluorinated selenoflavones **5a–c** were smoothly obtained as the exclusive products (Scheme 4).



Scheme 4. Controlled preparation of bis(triflyl)selenoflavones 5a-c.

The nature of the nucleophile could also be modified to oxygen derivatives with (methoxy)-alkynones **6a–e-Me** and (hydroxy)-alkynones **6a–e** both found to be feasible cyclization precursors. The preparation of bis(triflyl)flavones **7a–e** was accomplished in yields ranging from 56% to 84% (Scheme 5). Unfortunately, the amide functionality in HN-Ac, HN-Ms, HN-Ts, and HN-CO₂Me protected amido-alkynones **8** was unreactive under the above conditions, not providing access to fluorinated quinolin-4-ones. It should be noted the lack of the signal corresponding to the highly acidic hydrogen on the sulfone alphacarbon (Tf₂CH) in the ¹H NMR spectra of compounds **3**, **5**, and **7**, which should be attributed to chromatographic purification without re-acidification. Ishihara et al. reported that the purification of

strong acidic compounds by column chromatography on silica gel gives their calcium salts.^[7a] Yanai has reported that Tf₂CH-bearing compounds were strongly acidic and eluted as the corresponding Ca²⁺ salts during silica gel chromatography.^[7b] In our case, the metal cation is sodium, as we previously reported in a related cyclobutenyl-[Tf₂CCH₂]-Na⁺ derivative based in its X-ray crystallographic analysis.^[5c] In addition, sodium was detected in representative flavone derivatives such as **3m-Na**, **5c-Na**, and **7b-Na** through the use of two different analytical techniques, namely SEM-EDX and ²³Na NMR (see Supporting Information for details).



6a–e-Me _(Z = Me) 6a–e _(Z = H)

DOI: 10.1002/chem.201xxxxx





(74%, 2 h; from 6b-Me)

(79%, 1 h; from 6b)



(73%, 3 h; from 6c-Me)

(78%, 3 h; from 6c)

)Me

o^{Tf}

7e-Na

(84%, 1 h; from 6e)

(76%, 1 h; from 6e-Me)

___Tf

Na⊕

(56%, 4 h; from **6a-Me**) (61%, 3 h; from **6a**)



(67%, 3 h; from **6d-Me**) (81%, 2 h; from **6d**)



Scheme 5. Controlled preparation of bis(triflyl)flavones 7a-e.

Having probed the feasibility of this cyclization/functionalization sequence, and tested several structural variations within the acyclic precursors, investigations into a tunable reactivity were initiated moving towards variation in the solvent and temperature. Initially, MeS-alkynone 2a was treated with zwitterion 1 in acetonitrile at 80° C, resulting in a bis(triflyl)thioflavone mixture (2:1)of 3a and 3-[(trifluoromethyl)sulfonyl]-2H-benzo[4,5]thieno[3,2-b]pyran 9a. With this promising result in hand, we hope that fine tuning of this reaction outcome might be achieved and would result in the sole construction of tricycle 9a. Zwitterion 1 is almost unsoluble in apolar or halogenated solvents at rt, but can be used in these solvents at reflux temperature. Replacing acetonitrile by another solvents was found to be useful. To our satisfaction, upon adding



DOI: 10.1002/chem.201xxxxx

CHEMISTRY A European Journal Full Paper

zwitterion 1 at one time to a boiling solution of alkynone 2a in toluene the tricycle 9a was exclusively obtained without any trace of bicycle 3a (Scheme 6). Noticeably, simple temperature and solvent alterations give rise to the divergent formation of two entirely distinct fluorinated heterocyclic cores from a common cyclization precursor. This second domino process allows a direct metal-free access to a tricyclic framework with the simultaneous formation of C-S, C-O, and C-C bonds. A variety of MeSalkynones 2 bearing various functional groups and tethers were also submitted to bis(cyclization). Various fused thieno[3,2b]pyrans 9 were achieved with exquisite selectivity in reasonable yields, with the exception of ferrocene derivative 9i which was obtained in a decreased 22% yield (Scheme 6). The reaction was even extended to the symmetrical bis(MeS-alkynone) 2s in which a two-fold sequence takes place to afford benzothiophene-linked bis(tricycle) 9s (Scheme 6). To the best of our knowledge, a general access to fused tricyclic benzothienopyrans from acyclic precursors in one synthetic operation seems to be lacking in the literature. The structure of tricycle 9a was confirmed through its X-ray crystallographic study (Figure 1).^[8]



Scheme 6. Controlled preparation of tricyclic triflyl-benzothienopyrans **9**. [a] Partial decomposition during chromatographic purification.



Figure 1. ORTEP drawing of 3-[(trifluoromethyl)sulfonyl]-2*H*-benzo[4,5]thieno[3,2-*b*]pyran **9a**. Thermal ellipsoids shown at 50% probability.

We conceived that bicycles of type **3** could be converted into fused tricycles **9** at elevated temperature. However, the treatment of a toluene solution of bicycle **3a** at 110 °C resulted in absence of reaction. Even more puzzling would appear the obtention of cyclobutenes **10p** and **10q** in almost quantitative yields from thiophene-tethered MeS-alkynones **2p** and **2q** under the optimized conditions for the formation of tricycles **9**. Fortunately, the treatment of an acetonitrile solution of **10p** and **10q** in a sealed tube at 110 °C resulted in full conversion towards 6-(triflyl)-7*H*-thieno[2',3':4,5]thieno[3,2-*b*]pyrans **9p** and **9q** (Scheme 7). Therefore, it may be inferred that cyclobutenes **10** and not bicycles **3** are intermediates in the formation reaction of fused pyrans **9**.



Scheme 7. Controlled preparation of bis(triflyl) cyclobutenes **10p,q** and triflyl-(bis-thieno)pyrans **9p,q**.

It should be important to extend the current method for the synthesis of tricyclic thienopyrans to other relevant heterocyclic cores. For example, replacement of the S atom for a bulkier Se normally increases the semiconducting properties of the resulting less aromatic selenophenes in comparison with their thiophene counterparts. We initiated our study by variation of the alkynone partner to (methylselanyl)phenyl-propynones **4a–c**. Gratifyingly, the use of heat did allow the efficient synthesis of 3-(triflyl)-2*H*-benzo[4,5]selenopheno[3,2-*b*]pyrans **11a–c** (Scheme 8). Consequently, MeSe-alkynones were proven to be excellent substrates for the bis(cyclization) because changing the heteroatom from S to Se has not effect on the reactivity pattern.

ChemPubSoc

CHEMISTRY A European Journal Full Paper



DOI: 10.1002/chem.201xxxxx

Scheme 8. Preparation of triflyl-benzoselenophenopyrans 11.

The reaction of zwitterion 1 with substrates 6-Me, containing a methoxy group at the alkynone side, in toluene at 110° C gave rise to an intractable mixture of products. A beneficial effect is provoked by moving from the MeO moiety of 6-Me to hydroxyalkynones 6. The treatment of hydroxy-alkynones 6 with zwitterion 1 in boiling toluene did not allow a direct preparation of the expected tricycles, because several unstable products were formed. Interestingly, in one case we were able to isolate a putative intermediate, namely, spirocyclic cyclobutene 12d (Scheme 9). Fortunately, the reaction of hydroxy-alkynones 6 was encountered to be suitable in the presence of a base, which probably enhances the nucleophilicity of the oxygenated functionality. Among several bases tested, potassium carbonate provided best results. In this way, (hydroxy)-alkynones 6a-e suffer a rearrangement reaction to form adducts 14a-e (Scheme 9). Surprisingly, the expected tricycles 13 were not obtained. Compounds 14 bearing an open-chain conjugated dienone structure, as confirmed by X-ray diffraction analysis of 14e (Figure 2),^[9] were formed instead. The occurrence of such unanticipated result could be tentatively explained invoking bond lengths. The C-S and the C-Se bonds are larger than the C-O bond, which may disfavour the final cyclization in this last case. Interestingly, adducts 14 are (triflyl)vinyl aurones, a group of flavonoids. When the proposed intermediate 12d was heated in acetonitrile at 110° C in a sealed tube, compound 14d was formed (Scheme 9); thus confirming the intermediation of spirocyclic cyclobutene species of type 12.





 Figure
 2.
 ORTEP
 drawing
 of
 (E)-2-(1-(thiophen-2-yl)-2-((trifluoromethyl)sulfonyl)allylidene)benzofuran-3(2H)-one
 14e.
 Thermal ellipsoids shown at 50% probability.

Next, we used amido-alkynone substrates **8** hoping that they proved applicable to the preparation of fused indoles. In the event, derivatives **8** did not give the desired aza-tricycles at rt in presence of zwitterion **1**, because the reaction did not proceed. Fortunately, under similar conditions as developed for the preparation of functionalized aurones **14**, various aza-tricycles **15** were obtained in synthetically valuable yields (Scheme 10). Consequently, both heat as well as the presence of a base are crucial for the success of the cyclization/rearrangement sequence.



DOI: 10.1002/chem.201xxxxx



The PMP group in **15a** could be replaced with naphthyl, thienyl, or phenyl, without attenuation in reaction efficiency. Besides, our protocol could accommodate different *N*-protected functionalities, including acetamides and sulphonamides. The tricyclic structure of 2,5-dihydropyrano[3,2-*b*]indole **15b** was confirmed by X-ray diffraction analysis (Figure 3).^[10] In order to obtain direct evidence of the intermediacy of a cyclobutene-type product, the reactions between amido-alkynones **8a–c** and **1** were carried out at 110° C with suppression of the base treatment. We were lucky enough to isolate cyclobutene derivatives **16a–c** in good yields. Providentially, a thermal treatment of strained derivatives **16a–c** in acetonitrile under basic conditions (K₂CO₃) resulted in the formation of tricycles **15a–c** (Scheme 10), suggesting that adducts **16** are key intermediates.







(64%; i) 20 min, ii) 10 min)



Scheme 10. Controlled preparation of triflyl-2,5-dihydropyrano[3,2-*b*]indoles 15a-e and cyclobutenes 16a-c. purification.



Figure 3. ORTEP drawing of 1-(4-(thiophen-2-yl)-3-((trifluoromethyl)sulfonyl)pyrano[3,2-*b*]indol-5(2*H*)-yl)ethan-1-one **15b**. Thermal ellipsoids shown at 50% probability.

A possible pathway for the metal-free formation of bicyclic triflones 3, 5, and 7 is outlined in Scheme 11. Formation of 1,1bis((trifluoromethyl)sulfonyl)ethene I from 2-(2-fluoropyridinium-1yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide 1 would trigger the nucleophilic attack of the C2 carbon atom of propynones 2, 4, and 6 to the terminal carbon atom of alkene I. The so-formed zwitterionic species II would suffer a selective intramolecular heterocyclization to generate bicycles 3, 5, and 7 (path A). From common intermediate II, a different path which implies a carbocyclization reaction to generate intermediate cyclobutenes III could be operative (path B). This alternative cyclobutene formation is not achievable at rt. Next, the regioselective nucleophilic addition of a -SMe, -SeMe, -OH, or -NHP functionality C1 carbon to the atom of bis((trifluoromethyl)sulfonyl)cyclobut-1-en-1-yl)methanones Ш occurs to form spirocyclic cyclobutene intermediates IV. Subsequent rearrangement with cyclobutene ring-opening gives rise to dienone intermediates V. Final 6n-electrocyclic ringclosure afford tricyclic triflones 9, 11, and 15. This second path must be driven by alleviation of the ring strain linked to the cyclobutene moiety, on forming deeply conjugated dienone intermediates V. Although the obtention of cyclobutenes 10p,q (Scheme 7) and 16a-c (Scheme 10), spirocyclic cyclobutene 12d (Scheme 9), and dienones 14a-e (Scheme 9) was serendipitous, these finding are in agreement with the mechanism of Scheme 11, because detectable intermediates were isolated.



Scheme 11. Rationalization for the formation of bicyclic triflones 3, 5, 7 and tricyclic triflones 9, 11, 15.

Conclusion

In summary, we have unveiled the reaction of $Tf_2C=CH_2$ with ynones, giving rise to a divergent preparation of two main kinds of triflone-



DOI: 10.1002/chem.201xxxxx

based products. The selectivity of the product can be completely switched through adjusting the reaction temperature. In this way, bis(triflyl)flavones, bis(triflyl)thioflavones, bis(triflyl)selenoflavones, (triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles were built. Based on control experiments and the trapping of several intermediates, we have proposed two conceivable reaction mechanisms.

Experimental Section

General methods: ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in CDCI₃ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (¹H, 0.0 ppm), or CDCI₃ (¹H, 7.27 ppm; ¹³C, 76.9 ppm), or C₆D₆ (¹H, 7.16 ppm; ¹³C, 128.0 ppm), or acetone-d₆ (¹H, 2.05 ppm; ¹³C, 206.3 ppm), or CD₃CN (¹H, 1.94 ppm; ¹³C, 118.2 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphitemonochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. All commercially available compounds were used without further purification.

General procedure for the reaction between alkynones 2a–q, 4a–c, 6a–e, and 6a–e-Me with pyridinium salt 1 at room temperature. Preparation of bis(triflyl)thioflavones 3a–i, 3m–q, bis(triflyl)selenoflavones 5a–c, and bis(triflyl)flavones 7a–e. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1bis[(trifluoromethyl)sulfonyl]ethan-1-ide 1 (0.2 mmol) was added at room temperature to a solution of the appropriate alkynone 2a–q, 4a–c, 6a–e, and 6a–e-Me (0.2 mmol) in acetonitrile (4 mL). The reaction was stirred at room temperature until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures followed by further disolution in Et₂O, precipitation with hexanes and filtration, gave analytically pure compounds. Spectroscopic and analytical data for adducts 3a–i-Na, 3m– q-Na, 5a–c, and 7a–e-Na follow.^[11]

Bis(trifluoromethylsulfonyl)thioflavone 3b. From 40 mg (0.14 mmol) of alkynone **2b**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et₂O and precipitation with hexanes) gave compound **3b-Na** (57 mg, 70%) as a colorless solid; mp 219–221 °C; ¹H NMR (300 MHz, CD₃CN, 25 °C): δ = 8.51 (m, 1H, CH^{Ar}), 7.73 (m, 2H, 2CH^{Ar}), 7.60 (m, 1H, CH^A), 7.32 (m, 2H, 2CH^{Ar}), 7.04 (m, 2H, 2CH^{Ar}), 3.90 (s, 3H, OCH₃), 3.67 (s, 2H, CH₂); ¹³C NMR (75 MHz, CD₃CN, 25 °C): δ = 181.3 (C=O), 161.4 (*C*^{Ar-q}-OMe), 152.1 (S-C=C), 138.3 (*C*^{Ar-q}), 132.4 (CH^{Ar}), 132.2 (S-C=C), 131.8 (2CH^{Ar}), 131.5 (*C*^{Ar-q}), 129.4 (CH^{Ar}), 128.2 (CH^{Ar}), 126.4 (CH^{Ar}), 122.0 (q, *J_{CF}*= 328.9 Hz, 2CF₃), 114.3 (2CH^{Ar}), 63.5 (CTf₂), 55.9 (OCH₃), 27.6 (CH₂); ¹⁹F NMR (282 MHz, CD₃CN, 25 °C): δ = -80.4 (s, 6F, 2CF₃); IR (CH₃CN): v = 1723 (C=O), 1379, 1110 (O=S=O), 1215 (C-F) cm⁻¹; HRMS (ES): calcd for C₂₀H₁₅F₆O₆S₃[*M*+ H]⁺: 560.99295; found: 560.99056.

Bis(trifluoromethylsulfonyl)selenoflavone 5b. From 30 mg (0.079 mmol) of alkynone **4b**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et₂O and precipitation with hexanes) gave compound **5b-Na** (35 mg, 65%) as a colorless solid; mp 196–198 °C; ¹H NMR (500 MHz, acetone-d₆, 25 °C): δ = 8.50 (dd, 1H, *J* = 8.1, 1.3 Hz, CH^{Ar}), 7.86 (s, 1H, CH^{Ar}), 7.81 (m, 2H, 2CH^{Ar}), 7.76 (d, 1H, *J* = 7.9 Hz, CH^{Ar}),

7.57 (m, 1H, CH^{Ar}), 7.46 (m, 2H, 2CH^{Ar}), 7.31 (d, 1H, J = 2.4 Hz, CH^{Ar}), 7.16 (dd, 1H, J = 8.9, 2.6 Hz, CH^{Ar}), 3.90 (s, 3H, OCH₃), 3.76 (s, 2H, CH₂); ¹³C NMR (125 MHz, acetone-d₆, 25 °C): $\delta = 183.5$ (C=O), 159.7 (C^{Ar-q} -OMe), 151.8 (S-C=C), 137.7 (C^{Ar-q}), 135.8 (C^{Ar-q}), 135.0 (S-C=C), 134.5 (C^{Ar-q}), 133.6 (C^{Ar-q}), 132.2 (CH^{Ar}), 131.5 (CH^{Ar}), 130.9 (CH^{Ar}), 129.2 (C^{Ar-q}), 129.2 (CH^{Ar}), 128.5 (CH^{Ar}), 128.1 (2CH^{Ar}), 127.5 (CH^{Ar}), 122.4 (q, $J_{CF} = 329.7$ Hz, 2CF₃), 120.4 (CH^{Ar}), 106.8 (CH^{Ar}), 64.2 (CTf₂), 55.9 (OCH₃), 28.8 (CH₂); ¹⁹F NMR (282 MHz, acetone-d₆, 25 °C): $\delta = -79.8$ (s, 6F, 2CF₃); ⁷⁷Se-NMR (95 MHz, CDCl₃, 25 °C) δ : 400.3 (s, 1Se, Se); IR (acetone): v = 1726 (C=O), 1371, 1110 (O=S=O), 1211 (C-F) cm⁻¹; HRMS (ES): calcd for C₂₄H₁₇F₆O₆S₂Se [M + H]⁺: 658.95308; found: 658.95286.

Bis(trifluoromethylsulfonyl)flavone 7b. From 20 mg (0.08 mmol) of alkynone **6b**, and after flash chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent (with further disolution in Et₂O and precipitation with hexanes) gave compound **7b-Na** (36 mg, 79%) as a colorless solid; mp 223–225 °C; ¹H NMR (300 MHz, CD₃CN, 25 °C): δ = 8.22 (dd, 1H, *J* = 8.0, 1.5 Hz, CH^{Ar}), 7.80 (m, 1H, CH^{Ar}), 7.57 (d, 1H, *J* = 8.0 Hz, CH^{Ar}), 7.46 (m, 3H, 3CH^{Ar}), 7.06 (m, 2H, 2CH^{Ar}), 3.91 (s, 3H, OCH₃), 3.67 (s, 2H, CH₂); ¹³C NMR (75 MHz, CD₃CN, 25 °C): δ = 179.7 (C=O), 165.2 (O-C=C), 162.0 (C^{Ar-q}-OMe), 156.8 (C^{Ar-q}-O), 134.7 (CH^{Ar}), 122.0 (2CH^{Ar}), 126.5 (C^{Ar-q}), 126.1 (CH^{Ar}), 125.7 (CH^{Ar}), 123.6 (C^{Ar-q}), 121.9 (q, *J_{CF}* = 328.3 Hz, 2CF₃), 119.4 (O-C=C), 118.8 (CH^{Ar}), 114.2 (2CH^{Ar}), 63.4 (CTf₂), 56.0 (OCH₃), 25.4 (CH₂); ¹⁹F NMR (282 MHz, CD₃CN, 25 °C): δ = -80.5 (s, 6F, 2CF₃); IR (CH₃CN): v = 1719 (C=O), 1376, 1109 (O=S=O), 1209 (C-F) cm⁻¹; HRMS (ES): calcd for C₂₀H₁₅F₆OrS₂ [*M* + H]⁺: 545.01579; found: 545.01488.

General procedure for the reaction between alkynones 2a–i, 2n–s, and 4a–c with pyridinium salt 1 at 110 °C. Preparation of triflyl-benzothienopyrans 9a–i, 9n–s, and triflyl-benzoselenophenopyrans 11a–c. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide 1 (0.2 mmol) was added to a hot solution (110 °C) of the appropriate alkynone 2a–i, 2n–s, and 4a–c (0.2 mmol) in refluxing toluene (4 mL). The reaction was stirred at 110 °C until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Adducts 2p and 2q required an extra heating in acetonitrile in sealed tube at 110 °C because after the initial heating in toluene, cyclobutenes 10p and 10q were isolated. Chromatography of the residue eluting with hexanes/ethyl acetate or hexanes/toluene mixtures gave analytically pure compounds. Spectroscopic and analytical data for adducts 9a–i, 9n–s, and 4a–c follow.

TriflyI-benzothienopyran 9b. From 40 mg (0.14 mmol) of alkynone **2b**, and after flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **9b** (49 mg, 82%) as a yellow solid; mp 155–157 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.89 (m, 1H, CH^{Ar}), 7.71 (m, 1H, CH^{Ar}), 7.47 (m, 2H, 2CH^{Ar}), 7.33 (m, 2H, 2CH^{Ar}), 6.98 (m, 2H, 2CH^{Ar}), 5.37 (s, 2H, OCH₂), 3.88 (s, 3H, OCH₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 161.0 (*C*^{Ar-q}-OMe), 155.3 (*C*^{Ar-q}), 154.9 (*C*^{Ar-q}), 142.2 (*C*^{Ar-q}), 130.4 (2CH^{Ar}), 128.9 (CH^{Ar}), 128.5 (*C*^{Ar-q}), 125.2 (CH^{Ar}), 123.3 (CH^{Ar}), 122.9 (CH^{Ar}), 120.0 (q, *J_{CF}*= 326.8 Hz, CF₃), 119.9 (*C*=C-Tf), 113.2 (CH^{Ar}), 105.0 (*C*=C-Tf), 67.4 (OCH₂), 55.3 (OCH₃); ¹⁹F NMR (282 MHz, CDCl₃, 25 °C): δ = -79.0 (s, 3F, CF₃); IR (CHCl₃): v = 1379, 1110 (O=S=O), 1209 (C-F) cm⁻¹; HRMS (ES): calcd for C₁₉H₁₄F₃O₄S₂ [*M*+H]⁺: 427.02801; found: 427.02737.

TriflyI-benzoselenophenopyran 11b. From 30 mg (0.079 mmol) of alkynone **4b**, and after flash chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **11b** (39 mg, 91%) as a yellow oil; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.94 (m, 1H, CH^{Ar}), 7.78 (m, 4H, 4CH^{Ar}), 7.45 (m, 3H, 3CH^{Ar}), 7.22 (m, 2H, 2CH^{Ar}), 5.44 (d, 1H, *J* = 12.7 Hz, OC*H*H), 5.38 (d, 1H, *J* = 12.7 Hz, OCH*H*), 3.96 (s, 3H, OCH₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ =

A European Journal

Full Paper



DOI: 10.1002/chem.201xxxxxx

CHEMISTRY A European Journal Full Paper

158.8 (C^{Ar-q} -OMe), 156.8 (C^{Ar-q}), 156.4 (C^{Ar-q}), 142.7 (C^{Ar-q}), 135.1 (C^{Ar-q}), 131.3 (C^{Ar-q}), 130.0 (CH^{Ar}), 129.0 (CH^{Ar}), 127.9 (CH^{Ar}), 127.7 (C^{Ar-q}), 126.3 (CH^{Ar}), 126.2 (CH^{Ar}), 126.1 (CH^{Ar}), 125.6 (CH^{Ar}), 125.0 (CH^{Ar}), 120.1 (q, J_{CF} = 326.9 Hz, CF₃), 119.9 (C=C-Tf), 119.7 (CH^{Ar}), 105.8 (CH^{Ar}), 105.6 (C=C-Tf), 67.0 (OCH₂), 55.4 (OCH₃); ¹⁹F NMR (282 MHz, CDCl₃, 25 °C): δ = -78.9 (s, 3F, CF₃); ⁷⁷Se-NMR (95 MHz, CDCl₃, 25 °C) δ : 441.7 (s, 1Se, Se); IR (CHCl₃): ν = 1371, 1109 (O=S=O), 1210 (C-F) cm⁻¹; HRMS (ES): calcd for C₂₃H₁₆F₃O₄SSe [M+ H]*: 524.98819; found: 524.98730.

General procedure for the reaction between alkynones 6a–e and pyridinium salt 1 at 110 °C. Preparation of triflyl-allylidenebenzofuranones 14a–e. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1ide 1 (0.2 mmol) was added to a hot solution (110 °C) of the appropriate alkynone 6a–e (0.2 mmol) in refluxing toluene (4 mL). The reaction was stirred at 110 °C until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Next, K₂CO₃ (2 equiv.) was added to a stirred solution of the above crude reaction in acetonitrile (4.0 mL). The resulting mixture was heated at 110 °C (typically 15 min) in a sealed tube. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for adducts 14a–e follow. After the first reaction step, spirocyclic cyclobutene 12d was isolated and fully characterized.

TriflyI-allylidenebenzofuranone 14b. From 20 mg (0.08 mmol) of alkynone **6b**, and after flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **14b** (25 mg, 78%) as a yellow solid; mp 178–180 °C; ¹H NMR (700 MHz, Cl₂DC–CDCl₂, 60 °C): δ = 7.79 (d, 1H, *J* = 7.5 Hz, CH^{Ar}), 7.70 (m, 3H, 3CH^{Ar}), 7.35 (d, 1H, *J* = 8.3 Hz, CH^{Ar}), 7.29 (t, 1H, *J* = 7.4 Hz, CH^{Ar}), 7.05 (m, 2H, 2CH^{Ar}), 6.74 (s, 2H, =CH₂), 391 (s, 3H, OCH₃); ¹³C NMR (175 MHz, Cl₂DC–CDCl₂, 60 °C): δ = 164.6 (*C*^{Ar-q}-O), 161.2 (*C*^{Ar-q}-OMe), 145.2 (*C*^{Ar-q}), 136.8 (CH^{Ar}), 131.9 (2CH^{Ar}), 124.6 (*C*^{Ar-q}), 124.1 (CH^{Ar}), 123.9 (CH^{Ar}), 121.5 (*C*=C), 119.8 (q, *J*_{CF}= 328.1 Hz, CF₃), 114.4 (2CH^{Ar}), 113.0 (CH^{Ar}), 99.6 (*C*-Tf), 55.6 (OCH₃); ¹⁹F NMR (282 MHz, Cl₂DC–CDCl₂, 25 °C): δ = -75.3 (s, 3F, CF₃); IR (CH₂Cl₂): v = 1703 (C=O), 1365, 1106 (O=S=O), 1209 (C-F) cm⁻¹; HRMS (ES): calcd for C₁₉H₁₄F₃O₅S [*M*+ H]⁺: 411.05086; found: 411.05121.

General procedure for the reaction between alkynones 8a-e and pyridinium salt 1 at 110 °C. Preparation of triflyl-2,5-dihydropyrano[3,2b]indoles 15а-е. 2-(2-Fluoropyridin-1-ium-1-yl)-1,1bis[(trifluoromethyl)sulfonyl]ethan-1-ide 1 (0.2 mmol) was added to a hot solution (110 °C) of the appropriate alkynone 8a-e (0.2 mmol) in refluxing toluene (4 mL). The reaction was stirred at 110 °C until disappearance of the starting material (TLC), and then the mixture was concentrated under reduced pressure. Next, K₂CO₃ (3 equiv.) was added to a stirred solution of the above crude reaction in acetonitrile (4.0 mL). The resulting mixture was heated at 90 °C (typically 15 min) in a sealed tube. The reaction was allowed to cool to room temperature, concentrated under vacuum, and purified by flash column chromatography eluting with ethyl acetate/hexanes mixtures. Spectroscopic and analytical data for adducts 15a-e follow. After the first reaction step, cyclobutenes 16a-c were isolated and fully characterized.

TriflyI-2,5-dihydropyrano[3,2-b]indole 15b. From 35 mg (0.06 mmol) of alkynone **8b**, and after flash chromatography of the residue using hexanes/ethyl acetate (9:1 → 8:2) as eluent gave compound **15b** (22 mg, 83%) as a yellow solid; mp 152–154 °C; ¹H NMR (700 MHz, CDCl₃, 50 °C): δ = 8.34 (d, 1H, *J* = 8.6 Hz, CH^{Ar}), 7.78 (d, 1H, *J* = 7.9 Hz, CH^{Ar}), 7.67 (d, 1H, *J* = 5.0 Hz, CH^{Ar}), 7.64 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.52 (d, 1H, *J* = 1.9 Hz, CH^{Ar}), 7.40 (t, 1H, *J* = 7.6 Hz, CH^{Ar}), 7.17 (dd, 1H, *J* = 4.9, 3.4 Hz, CH^{Ar}), 5.35 (s, 2H, OCH₂), 1.91 (s, 3H, CH₃); ¹³C NMR (175 MHz, CDCl₃, 50 °C): δ = 170.0 (NC=O), 156.9 (*C*^{Ar-q}), 155.8

 $\begin{array}{l} (C^{Ar-q}), \ 142.2 \ (C^{Ar-q}), \ 135.1 \ (CH^{Ar}), \ 132.5 \ (CH^{Ar}), \ 131.7 \ (CH^{Ar}), \ 127.3 \ (CH^{Ar}), \\ 124.7 \ (CH^{Ar}), \ 122.6 \ (C=C-Tf), \ 120.9 \ (CH^{Ar}), \ 120.3 \ (q, \ {\it J_{CF}}=\ 327.2 \ Hz, \ CF_3), \\ 117.7 \ (C^{Ar-q}), \ 116.8 \ (CH^{Ar}), \ 100.1 \ (C=C-Tf), \ 69.6 \ (OCH_2), \ 25.5 \ (CH_3); \ ^{19}F \ NMR \\ (282 \ MHz, \ CDCI_3, \ 25 \ ^{\circ}C): \ \delta = -78.5 \ (s, \ 3F, \ CF_3); \ IR \ (CHCI_3): \ v = 1665 \ (C=O), \\ 1362, \ 1108 \ (O=S=O), \ 1209 \ (C-F) \ cm^{-1}; \ HRMS \ (ES): \ calcd \ for \ C_{18}H_{13}F_3NO4S_2 \\ [M+H]^{+}: \ 428.02326; \ found: \ 428.02427. \end{array}$

Acknowledgements

Support for this work by the MINECO and FEDER (Projects CTQ2015-65060-C2-1-P and CTQ2015-65060-C2-2-P). C. L.-M. thanks MINECO for a predoctoral grant.

Keywords: alkynes • cyclization • fluorine • heterocycles • synthetic methods

- a) X. Zeng, Z. Lu, S. Liu, G. B Hammond, B. Xu, Adv. Synth. Catal. 2017, 359, 4062; b) Y. Liu, X. Fan, Z. H. Li, H. Wang, Chem. Commun. 2017, 53, 10890; c) K. B. Hamal, W. A. Chalifoux, J. Org. Chem. 2017, 82, 12920; d) H.-L. Cui, J.-F. Wang, H.-L. Zhou, X.-L. You, X.-J. Jiang, Org. Biomol. Chem. 2017, 15, 3860; e) X. Kong, G. Zhang, S. Yang, X. Liu, X. Fang, Adv. Synth. Catal. 2017, 359, 2729; f) N. D. Rodea, A. Arcadia, M. Chiarini, F. Marinelli, Synthesis 2017, 49, 2501; g) R. Samineni, J. Madapa, S. Pabbaraja, G. Mehta, Org. Lett. 2017, 19, 6152; h) J. Ametovski, U. Dutta, L. Burchill, D. Maiti, D. W. Lupton, J. F. Hooper, Chem. Commun. 2017, 53, 13071; i) M. Meng, G. Wang, L. Yang, K. Cheng, C. Qi, Adv. Synth. Catal. 2018, 360, DOI: 10.1002/adsc.201701469 and references therein.
- [2] a) B. Alcaide, P. Almendros, E. Busto, F. Herrera, C. Lázaro-Milla, A. Luna, Adv. Synth. Catal. 2017, 359, 2640; b) V. Dwivedi, M. Rajesh, R. Kumar, R. Kantc, M. S. Reddy, Chem. Commun. 2017, 53, 11060; c) D. Zhai, L. Chen, M. Jia, S. Ma, Adv. Synth. Catal. 2018, 360, 153; d) X. Gao, Z. Li, W. Yang, Y. Liu, W. Chen, C. Zhang, L. Zheng, H. Guo, Org. Biomol. Chem. 2017, 15, 5298; e) Z. Yan, J. Xie, C. Zhu, Adv. Synth. Catal. 2017, 359, 4153; f) Y. Zhao, Y. Yuan, M. Xu, Z. Zheng, R. Zhang, Y. Li, Org. Biomol. Chem. 2017, 15, 6328; g) P. Fedoseeva, E. Van der Eycken, Chem. Commun. 2017, 4, 2392; i) R. Samineni, J. Madapa, P. Srihari, G. Mehta, Org. Lett. 2017, 19, 3119.
- a) L. K. San, S. N. Spisak, C. Dubceac, S. H. M. Deng, I. V. Kuvychko, M. A. Petrukhina, X.-B. Wang, A. A. Popov, S. H. Strauss, O. V. Boltalina, *Chem. Eur. J.* 2018, *24*, 1441 and references therein; b) W. Miao, Y. Zhao, C. Ni, B. Gao, W.; Zhang, J. Hu, *J. Am. Chem. Soc.* 2018, *140*, 880 and references therein; c) D. L. Orsi, R. A. Altman, *Chem. Commun.* 2017, *53*, 7168 and references therein; d) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donelly, N. A. Meanwell, *J. Med. Chem.* 2015, *58*, 8315 and references therein.
- [4] a) H. Yanai, R. Takahashi, Y. Takahashi, A. Kotani, H. Hakamata, T. Matsumoto, *Chem. Eur. J.* 2017, *23*, 8203; b) H. Yanai, T. Yoshino, M. Fujita, H. Fukaya, A. Kotani, F. Kusu, T. Taguchi, *Angew. Chem.* 2013, *125*, 1600; *Angew. Chem. Int. Ed.* 2013, *52*, 1560; c) H. Yanai, Y. Takahashi, H. Fukaya, Y. Dobashi, T. Matsumoto, *Chem. Commun.* 2013, *49*, 10091; d) H. Yanai, H. Ogura, H. Fukaya, A. Kotani, F. Kusu, T. Taguchi, *Chem. Eur. J.* 2011, *17*, 11747; e) H. Yanai, M. Fujita, T. Taguchi, *Chem. Commun.* 2011, *47*, 7245.
- [5] a) B. Alcaide, P. Almendros, I. Fernández, C. Lázaro-Milla, Chem. Commun. 2015, 51, 3395; b) B. Alcaide, P. Almendros, C. Lázaro-Milla, Chem. Eur. J. 2016, 22, 8998; c) B. Alcaide, P. Almendros, C. Lázaro-Milla, Adv. Synth. Catal. 2017, 359, 2630.
- [6] For a review on C–S bond formation under metal-free conditions, see: D.-Q. Dong, S.-H. Hao, D.-S. Yang, L.-X. Li, Z.-L. Wang, *Eur. J. Org. Chem.* 2017, 6576.
- [7] a) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, Angew. Chem. 2010, 122, 3911; Angew. Chem. Int. Ed. 2010, 49, 3823; b) H. Yanai, S. Egawa,



ChemPubSoc Europe

DOI: 10.1002/chem.201xxxxx

K. Yamada, J. Ono, M. Aoki, T. Matsumoto, T. Taguchi, Asian J. Org. Chem. 2014, 3, 556.

- [8] CCDC 1528521 contains the supplementary crystallographic data for compound 9a in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.
- [9] CCDC 1815354 contains the supplementary crystallographic data for compound 14e in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [10] CCDC 1817363 contains the supplementary crystallographic data for compound 15b in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [11] Experimental procedures as well as full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information. It contains compound characterization data, experimental procedures, and copies of NMR spectra for all new compounds.

Received: ((will be filled in by the editorial staff)) Revised: ((will be filled in by the editorial staff)) Published online: ((will be filled in by the editorial staff))



DOI: 10.1002/chem.201xxxxxx



Entry for the Table of Contents

FULL PAPER

Herein, we describe the unique use of $Tf_2C=CH_2$ as a Tf source in the reaction with functionalized ynones to form zwitterionic species, which were trapped in an intramolecular fashion by several nucleophiles to generate in a divergent way two main types of fluoroorganic moieties, namely, bis(triflyl)-6-membered- or (triflyl)-5-membered-fused-heterocycles, through the simultaneous formation of several carbon–carbon and carbon–heteroatom bonds.



Synthetic Methods

B. Alcaide, * P. Almendros, * Carlos Lázaro-Milla, and Patricia Delgado-Martínez



Divergence in Ynone Reactivity: Atypical Cyclization by 3,4-Difunctionalization versus Rare Bis(cyclization)