Silver Triflate/*p*-TSA Co-Catalysed Synthesis of 3-Substituted Isocoumarins from 2-Alkynylbenzoates

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ABSTRACT: In this paper, we describe the silver triflate/*p*-toluensulfonic acid co-catalysed synthesis of seventeen isocoumarins and two thieno[2,3-c]pyran-7-ones starting from 2-alkynylbenzoates and 3-alkynylthiophene-2-carboxylates, respectively. The reactions proceed with absolute regioselectivity under mild reaction conditions and low catalyst loading, to give the desired products in good to excellent yields. A conceivable reaction mechanism is proposed and supported by isotope-exchange tests, ^{1}H NMR studies and ad-hoc experiments.

INTRODUCTION

Isocoumarin nucleus[1] is the core of numerous biologically active molecules.[2] The most abundant category of naturally occurring isocoumarins is characterized by the presence of a carbo-substituent in 3-position. Great efforts have been devoted to the synthesis of isocoumarins both by metal-free[3] or metal-catalysed[4] approaches. In this regard, the d-block of the periodic table have been widely browsed: titanium, chromium, iron, ruthenium, rhodium, iridium, nickel, palladium, copper, silver, gold, and zinc salts or complexes have been exploited as catalysts for the synthesis of these heterocycles, although palladium and copper based catalysts remain the most studied and used among all the transition metals.[5]

A possible synthetic strategy to build the pyran-2-one moiety of isocoumarin nucleus involves the cyclization of γ-alkynyl carboxylic acids or esters under metal free conditions.[6] One of the main problem of these reactions is the regioselectivity, i.e. 6-*endo-dig* vs 5-*exo-dig* cyclization mode. In 2006 Uchiyama investigated the relationship between regioselectivity and acidic or alkaline reaction conditions, by analysing in depth a model reaction. Whereas a basic environment favoured the 5-exo-

dig cyclization mode, the formation of the pyran-2-one ring was selectively obtained at rt using strong acids as solvents or in refluxing toluene in the presence of catalytic amounts of acid.[6a] Alami[6b,c] widened the scope for the synthesis of isocoumarins by a microwave-assisted cyclization reaction of 2-alkynylbenzoic esters in ethanol at 160 °C in the presence of 20-30 mol% of *p*-toluenesulfonic acid. Some interesting examples of this kind of metal free approaches require the presence of an additional electrophile.[7] Beside the seminal works on electrophilic lactonization reported by Biagetti and Rossi in 2002[7a] and Larock in 2003,[7b] among the most recent papers are worth noting the iodolactonization in ionic liquids reported by Mancuso and Gabriele[7c] and the oxoborilation of 2-alkynylbenzoic esters published by Blum,[7d] yielding the corresponding 4-iodo and 4-borylated isocoumarins, respectively.

Moreover, the cyclization of γ-alkynyl carboxylic acids or esters have been also investigated under Lewis acid or transition metal catalysis.[8] In some cases, an inter/intramolecular electrophile is introduced in the position 4 of the isocoumarin nucleus. One of the earliest interesting example of that was reported by Zeni in 2011.[8a] A series of 4-Se, Te, S substituted isochromenones were synthesized by cyclization of o-alkynyl benzoic esters at rt in the presence of 1 equiv. of $FeCl_3$ and different diorganyl dichalcogenides. Interestingly, in the absence of diorganyl dichalcogenide, the corresponding 4 unsubstituted-isocoumarins were selectively obtained in good yields. One year later Hashmi[8d] studied the gold catalysed conversion of 2-alkynylbenzoic esters into the corresponding isocoumarin using in situ-generated Au(I) triflate (5 mol%). In these reactions, the allyl alcoholic moiety of the ester can act as intramolecular electrophile. A more recent study on regioselective gold(I)-catalyzed synthesis of 8-hydroxy-3-substituted isocoumarins from 2,2-dimethyl-5-(alkynyl)-4H-benzo[d]-[1,3]dioxin-4-ones has been described by Mohapatra.[8c] Regarding Pd catalysis, a cascade cyclization/oxidative olefination of *tert*-butyl 2-alkynylbenozates was reported in 2012 by Han and Li,[8d] whereas inter- and intra-molecular cascade cyclohexane/addition of methyl vinyl ketone[8e] or alkyne-tethered carbonyls[8f] have been studied by Lu and Han. More expensive metal catalysts, such as Re,[8g] have been also recently tested.

In the latter years, some synthesis of isocoumarins have been also described directly starting from *o*-halobenzoic acid/esters and terminal alkynes by means of domino coupling/annulation sequences.[9] The more recent reactions are generally catalysed by copper-based catalysts (10-20 mol%), require the presence of a base and heating[9b,d] or ultrasound activation.[9c] A further improvement of these domino approaches is represented by the direct CH bond-activation/annulation sequence starting from benzoic acids and internal alkynes, so yielding 3,4-disubstituted isocoumarins.[10] For these purposes expensive Ru,[10a,b] Ir[10c] catalyst were employed (2.5-10 mol%). Very recently, a similar Pd catalysed approach that involves bromoalkynes as reaction partner, so allowing the formation of 4-

unsusbstituted isocoumarins, has been reported.[11] In some cases the above mentioned strategies involving a CH activation step, require high reaction temperatures (120 °C).[10b,11]

All these approaches are interesting and valuable, but in some cases, they display some limitations, such as moderate product yields, regioselectivity issues, limited scope, the requirement of harsh conditions and high temperatures, the need for more-than-stoichiometric amount of promoters or sub-stoichiometric catalyst loadings, the need of expensive catalytic systems. For these reasons, the development of alternative approaches based on less explored and cheap catalysts, such as silver salts, is still an interesting challenge for synthetic organic chemists. In this regards, Wakamatsu[12] in 1995, Bellina[13] in 2000, and Shindo[14] in 2009 reported the only three examples of silver promoted synthesis of 3-substituted isocoumarins or pyran-2-ones starting from the corresponding γ-alkynyl carboxylic acids. In all these works the scope was not extensively explored, the amount of metal catalyst used (as Ag(I) salts or Ag powder) was relatively high (10-20 mol%) and some regioselectivity complications were encountered.

In the last decade, we spent many efforts in the study of new advantageous silver catalysed approaches for the synthesis of oxygen containing heterocycles starting from alkyne derivatives.[15] We were pleased to report here our results on the AgOTf/p-TSA co-catalysed synthesis of isocoumarins starting from 2-alkynyl benzoic ester derivatives. To explore the robustness of the approach, it was also applied to the preparation of two thieno[2,3-c]pyran-7-ones[16] starting from methyl 3-alkynylthiophene-2-carboxylates. The strong advantages of our approach are mild reaction conditions, selectivity, low catalyst loading, high yields. Finally, the mechanism was in-depth investigated by ^{1}H NMR studies, isotope-exchange experiments and tests under controlled conditions.

RESULTS and DISCUSSION

The cyclization of methyl 2-(p-tolylethynyl)benzoate **1a** was chosen as model reaction to screen among different silver-based catalytic systems and to find the optimal reaction conditions (Table 1). We made the firsts attempts in some solvents with different relative polarity[17] (i.e., toluene, dichloroethane, tetrahydrofuran and ethanol) in the presence of 10 mol% of silver triflate at room temperature (Table 1, entries 1-4). Under these conditions, the starting product **1a** was detected by tlc analysis unmodified after 24 h reaction. Then, 30 mol% of p-TSA· H_2O was added in each of the four reactions and the progress of the reactions was monitored by tlc after 4.5 h. This check revealed that only the reaction in DCE had started (Table 1, entry 2) whereas in the other solvent the reaction seemed to be fixed. Therefore, while the former (Table 1, entry 2) was left to react at rt the other three

(Table 1, entries 1, 3 and 4) were heated at 70 °C. After additional 21 h reaction, we observed that only the reactions performed in DCE and toluene gave the desired isocoumarin **2a** in satisfying yields (Table 1, entries 1 and 2) but the advantage of using DCE was that the reaction proceeded at rt yet. For this reason, DCE was selected as the solvent of choice. Next, we tested three other silver salts with counterions with different coordinating properties,[18] and we verified that a more coordinating anion such as nitrate gave worse results (Table 1, entry 5), whereas weaker anions as hexafluoroantimonate and tetrafluoborate (Table 1, entries 6 and 7) were slightly less effective than triflate. The concentration of the substrate seemed to have a little effect on the course of the reaction (Table 1, entries 8 and 9), as expected for an intramolecular transformation, although under dilute conditions yields are a little lower. Afterwards, we tried to reduce the amount of catalyst and additive (Table 1, entries 10-13). Although it became necessary a slight rise of temperature to 60 °C to speed up the reaction, we were pleased to find that the silver catalyst loading could be reduced from 10 mol% to 1 mol% without sensible reduction of yields (Table 1, entries 10 and 11). Conversely, the reduction of Brønsted acid amount from 30 to 10 mol% resulted in a drop of yields both at rt and at 60 °C (Table 1, entries 12 and 13). A simultaneous reduction of the amount of the silver salt and the acid to 2 mol% strongly hampered the reaction (Table 1, entry 14). Finally, performing the reaction directly at 60 °C under these optimized reaction conditions isocoumarin **2a** was obtained in 85% isolated yield in only 2 h (Table 1, entry 15).

As control experiments, we performed five reactions under special conditions (Table 1, entries 16-20). In the absence of silver triflate, both at rt and at 60 °C (Table 1, entries 16 and 17), the cyclization product **2a** was obtained in lower yields and only after a one day reaction time, thus confirming the dramatic effect of the silver on the reaction rate and product yield. The reaction was also tried with the Brønsted acid alone or the silver catalyst alone, in the presence one equivalent of ethanol as proton shuttle (Table 1, entries 18 and 19), but also under these conditions the reaction gave scarce results or completely failed, respectively, even after a 24h reaction time. Finally, to exclude a possible direct involvement of triflic acid eventually generated in situ by reaction of silver triflate and DCE[19] a control experiment was made in the presence of 1 mol% of the superacid, but also in this case the yields are limited and the reaction is slow. All these evidences seem to confirm the importance of a fine-tuned *cooperative* action of the silver catalyst and the *p*-toluenesulfonic acid.[20]
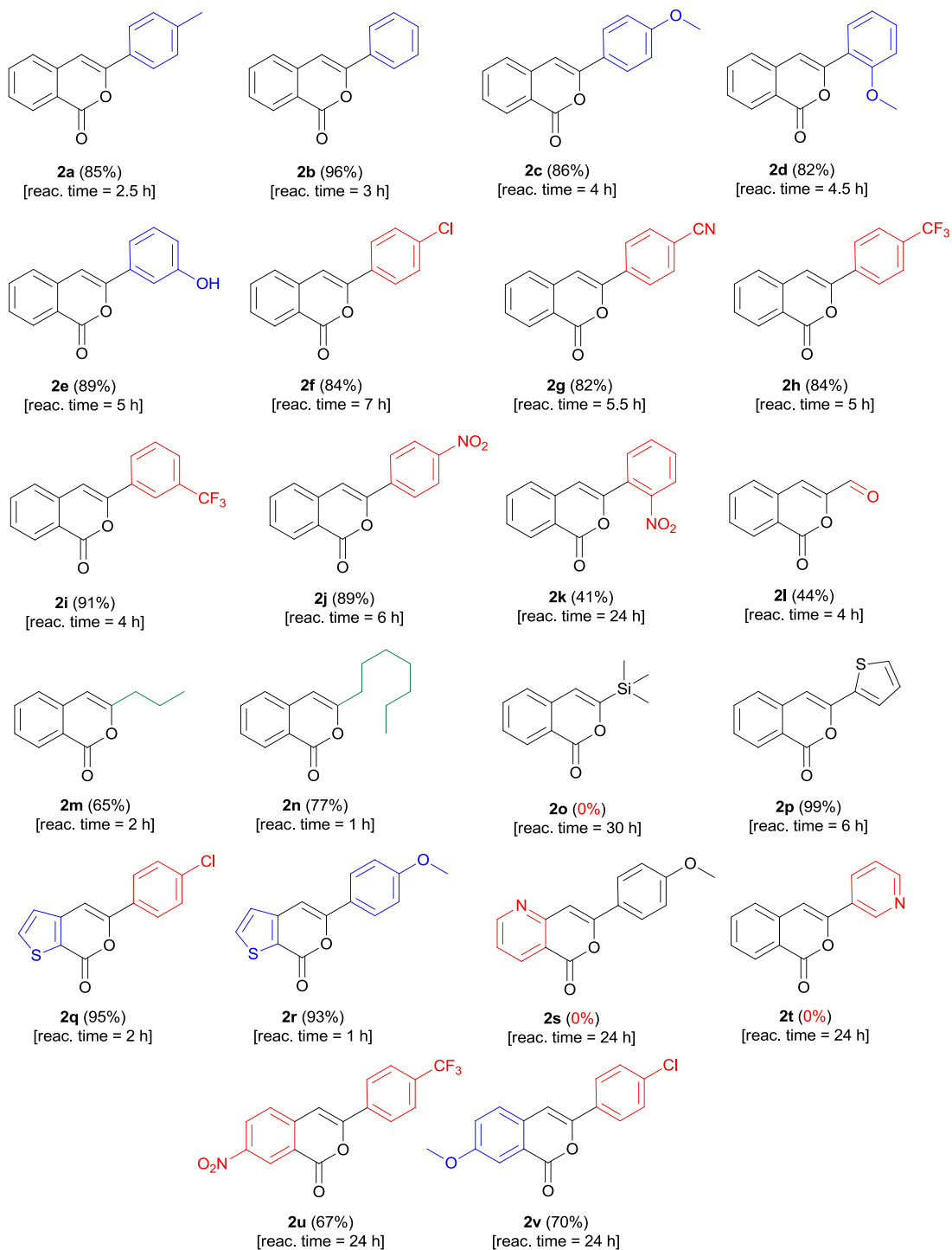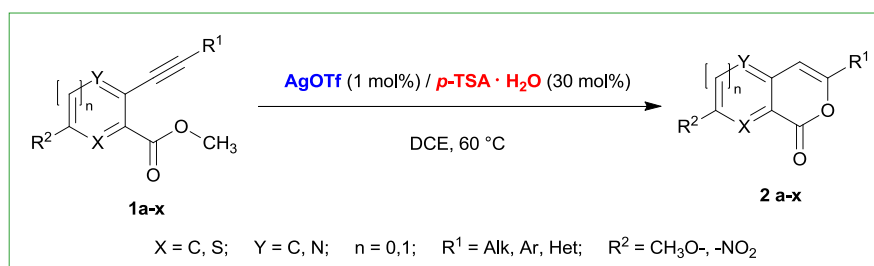
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Table 1. Optimization of the reaction conditions.
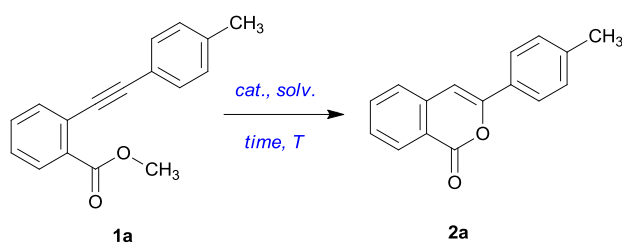
Entry	[1a] M	Catalyst (mol%)	p-TSA·H_2O (mol%)	Solvent	T (°C) / t (h)	2a yield[a] (%)	1a rec. yield[a] (%)
1	0.250	AgOTf (10)	(30)[b]	Toluene	rt/4.5 → 70/21	90	9
2	0.250	AgOTf (10)	(30)[b]	DCE	rt/4.5 → rt/21	87 (75)	6
3	0.250	AgOTf (10)	(30)[b]	EtOH	rt/4.5 → 70/21	16	82
4	0.250	AgOTf (10)	(30)[b]	THF	rt/4.5 → 70/21	-	-
5	0.250	AgNO$_3$ (10)	(30)	DCE	rt/21	28	72
6	0.250	AgSbF$_6$ (10)	(30)	DCE	rt/21	79	13
7	0.250	AgBF$_4$ (10)	(30)	DCE	rt/21	70	30
8	0.125	AgOTf (10)	(30)	DCE	rt/21	78	21
9	0.500	AgOTf (10)	(30)	DCE	rt/21	90	9
10	0.250	AgOTf (5)	(30)	DCE	rt/24 → 60/15	91	9
11	0.250	AgOTf (1)	(30)	DCE	rt/24 → 60/15	94	3
12	0,250	AgOTf (10)	(10)	DCE	rt/21	38	58
13	0.250	AgOTf (10)	(10)	DCE	60/17	35	57
14	0.250	AgOTf (2)	(2)	DCE	60/24	9	90
15	**0.250**	**AgOTf (1)**	**(30)**	**DCE**	**60/2**	**90 (85)**	**8**
16	0.250	-	(30)	DCE	rt/24	31	68
17	0.250	-	(30)	DCE	70/24	56	43
18	0.250	-	(30)	DCE[c]	60/24	(22)	(65)
19	0.250	AgOTf (1)	-	DCE[c]	60/24	-	(96)
20	0.250	HOTf (1)	(30)	DCE	60/24	(45)	(20)

[a] Yields calculated via ^1H NMR using dibromomethane (3 µL, 0,043 mmol) as internal standard. In parenthesis yields of pure isolated product. [b] Added after 24 h reaction at rt. [c] With 1 equiv. of ethanol.

Next, we tested scope and limitations of the approach under the best reaction conditions achieved (Table 1, entry 15). We selected some methyl 2-alkynyl-(hetero)arylcarboxylate derivatives characterized by the presence on the alkyne moieties of alkyl or (hetero)aryl group with different substituent with electron-donating or electron withdrawing properties (**1a-u**). Compounds **1a-u** were synthesized by means of a typical Sonogashira coupling[21] in good to excellent yields starting from methyl 2-alkynyl-(hetero)arylcarboxylate and suitable terminal acetylenes (see Supporting Information). Starting material **1a-u** were reacted under optimized conditions and the results are reported in Scheme 1. In most cases, the reactions gave the desired products in very good yields. The approach well tolerated the presence of EDGs (**2a-e**) as well as EWGs (**2f-j**) in all the positions of the aryl terminus of the alkyne moiety, except for the bulky nitro group in the ortho position that resulted in lower yield of isocoumarin **2k**. Notably, also an unprotected hydroxy substituent (**2e**) and the unusual nitrile group (**2g**) did not affect with the reaction course. Starting from methyl 2-(3,3-diethoxyprop-1-yn-1-yl)benzoate **1l**, the corresponding 1-oxo-*1H*-isochromene-3-carbaldehyde **2l** was directly obtain in 44% yields. Such result is remarkable for its potential application as a one-step total synthesis of artemidinal, a natural isocoumarin isolated from the epigeal part of *Artemisia dracunculus*.[22] Alkyl alkynes derivatives (**2m, n**) were obtained in slightly lower yields, while the reaction of the trimethylsilylacetylene derivative (**1o**) gave a mixture of unidentified products even after a prolonged reaction time.[23] Thiophene substituted methyl 2-alkynylbenzoate and methyl 3-(arylethynyl)thiophene-2-carboxylates reacted quickly to give the corresponding *2H*-pyran-2-one cyclization products in excellent yields (**2p-r**). Conversely, the presence of a pyridine as substituent on the methyl 2-alkynylbenzoate moiety or as methyl 2-(arylethynyl)nicotinate completely forbid the reaction (**2s,t**), and the starting materials were quantitatively recovered unreacted. The pyridine ring and heteroaromatic analogues are known to strongly coordinate Lewis acids such as silver triflate. We envisaged that a complete protonation of the pyridine ring could have left the catalyst free to coordinate the triple bond. However, also rising the amount of *p*-TSA to 1.3 equiv. the desired products were not obtained, and the starting materials were quantitatively recovered. On the other hand, we were pleased to find that also substitutions with ED or EW groups on the benzoic acid ring are well tolerated, but the reactions require a prolonged reaction time (**2u,v**).

Scheme 1. Scope and limitations of the approach (isolated yields)**.**

X = C, S;   Y = C, N;   n = 0,1;   R^1 = Alk, Ar, Het;   R^2 = CH$_3$O-, -NO$_2$

2a (85%)
[reac. time = 2.5 h]

2b (96%)
[reac. time = 3 h]

2c (86%)
[reac. time = 4 h]

2d (82%)
[reac. time = 4.5 h]

2e (89%)
[reac. time = 5 h]

2f (84%)
[reac. time = 7 h]

2g (82%)
[reac. time = 5.5 h]

2h (84%)
[reac. time = 5 h]

2i (91%)
[reac. time = 4 h]

2j (89%)
[reac. time = 6 h]

2k (41%)
[reac. time = 24 h]

2l (44%)
[reac. time = 4 h]

2m (65%)
[reac. time = 2 h]

2n (77%)
[reac. time = 1 h]

2o (0%)
[reac. time = 30 h]

2p (99%)
[reac. time = 6 h]

2q (95%)
[reac. time = 2 h]

2r (93%)
[reac. time = 1 h]

2s (0%)
[reac. time = 24 h]

2t (0%)
[reac. time = 24 h]

2u (67%)
[reac. time = 24 h]

2v (70%)
[reac. time = 24 h]

A particular behavior has been observed reacting alkyne **1w** (Scheme 2). Under the standard reaction condition the only product obtained was the α,β-unsaturated ketone **3a**, resulting from a Lewis-acid catalysed Meyer-Schuster rearrangement.[24]

Scheme 2. Reactivity of 1w.
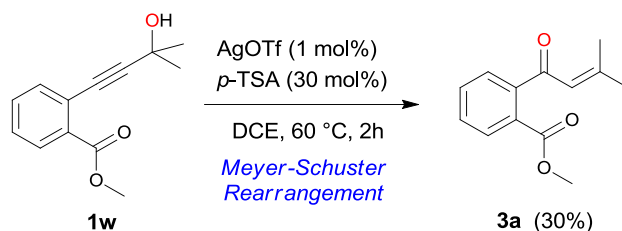
Finally, to test the scalability of the approach, the model reaction was performed in gram scale (1g of **1a**, 4 mmol) obtaining the desired product **2a** in 93% isolated yields, in 3 h. Moreover, the scale-up allowed a further reduction of an half of the catalyst loading (0.5 mol% AgOTf).

Based on our results and previous literature findings, we suggest a plausible reaction mechanism, as depicted in Scheme 3. The first step involves the coordination of the triple bond by silver that enhances the electrophilicity of alkyne. The following regiospecific *6-endo-dig* intramolecular nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne forms the isochromenylium cation[25] (**A, A'**), stabilized by resonance. The adventitious water removes the methyl group from intermediate **A'** to give the silver σ-complex **B** and a molecule of protonated methanol,[26] which is probably responsible for the regeneration of the *p*-TSA required for the formation of the final product **2** by protodemetallation.

Scheme 3. Proposed mechanism.
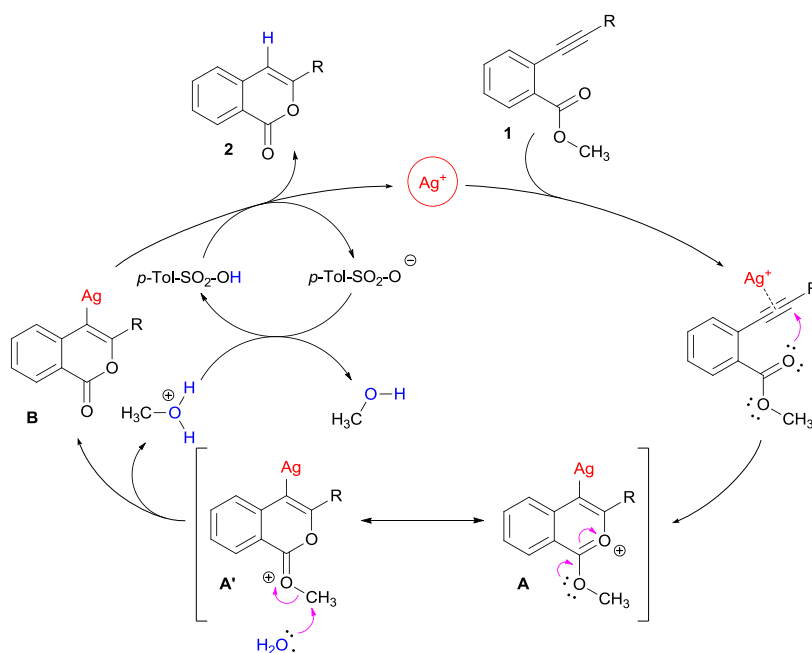
To gain insight into the mechanism, ^{1}H NMR studies have been performed. The reaction of **1a** was carried out in the presence of AgOTf (1 mol%) and *p*-TSA· H_2O (30 mol%) at 25 °C in deuterated dichloromethane in a NMR test tube, and a number of spectra were recorded at regular intervals during 18 hours (Figure 1). Confirming our mechanistic hypothesis, the analysis of the spectra reveals the appearance of the signal of the methyl group of methanol between 3.46-3.56 ppm. The small variation of chemical shift observed for this signal during the course of the reaction suggested and validate the presence of related protonated species in equilibrium under the acidic conditions. As comparison, the spectra of methanol and protonated methanol were recorder and reported in the bottom of figure 1. At the same time, the signals of the methoxy ester of **1a** at 3.98 ppm decreased while the C4-H signal of isocoumarin **2a** at 7.05 ppm appeared and raised. Also for this latter signal, the very small deviation of chemical shift during the course of the reaction could be related to the presence of equilibria between protonated species of **2a** (Figure 1).
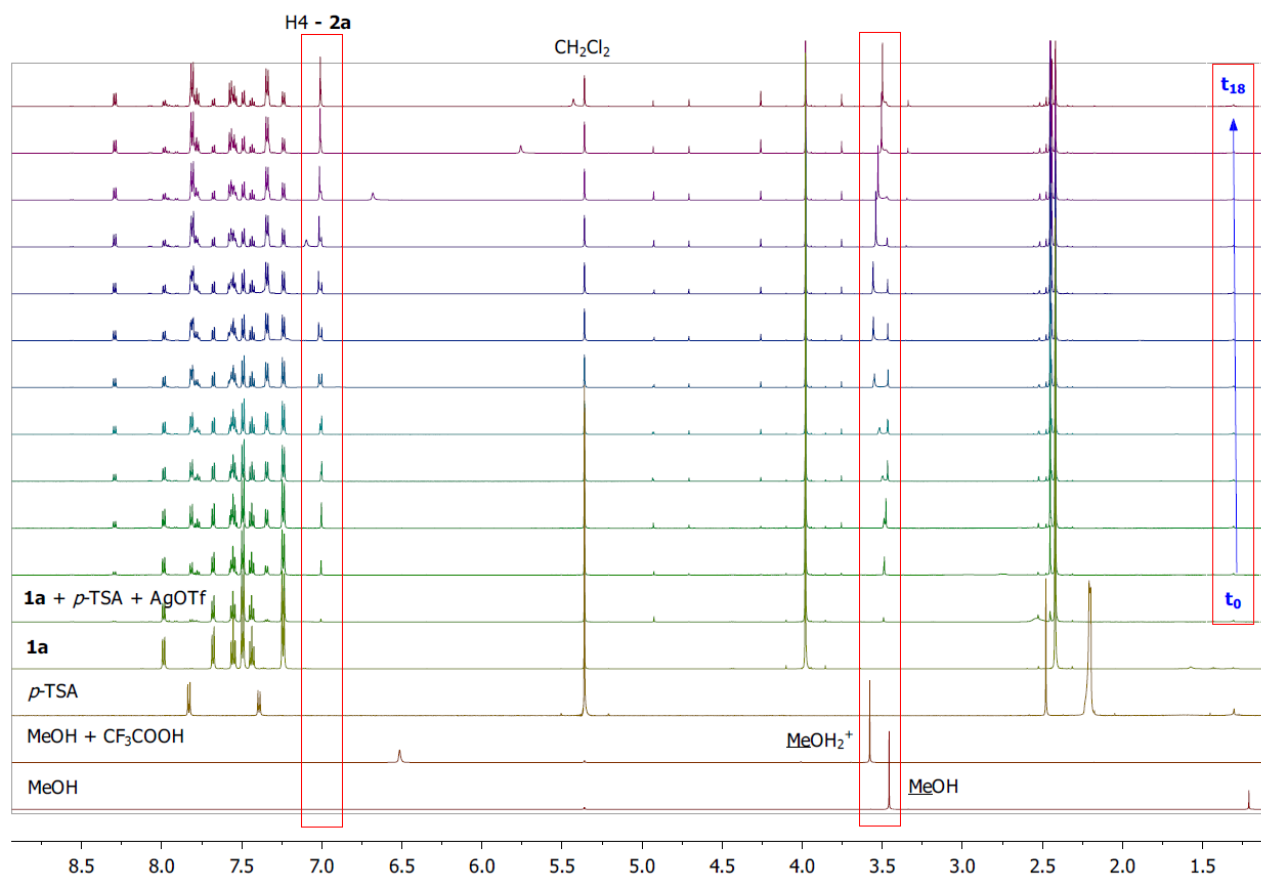
Figure 1. ^{1}H NMR study.

Afterward, the role of Brønsted acid in the protodemetallation step was verified by reacting the alkyne **1a** under standard condition with 30 mol% of deuterated of *p*-TSA-d · D_2O.[27] The reaction was complete in 7 h at 60 °C to give **2a** in 86% yields. The analysis of the ^{1}H-NMR spectra of the purified

product **2a** showed a strong reduction (-50%) of the integral of the signal at 6.91 ppm, which is associated to the resonance of the proton bonded in position 4 of the isocoumarin nucleus (Figure 2).
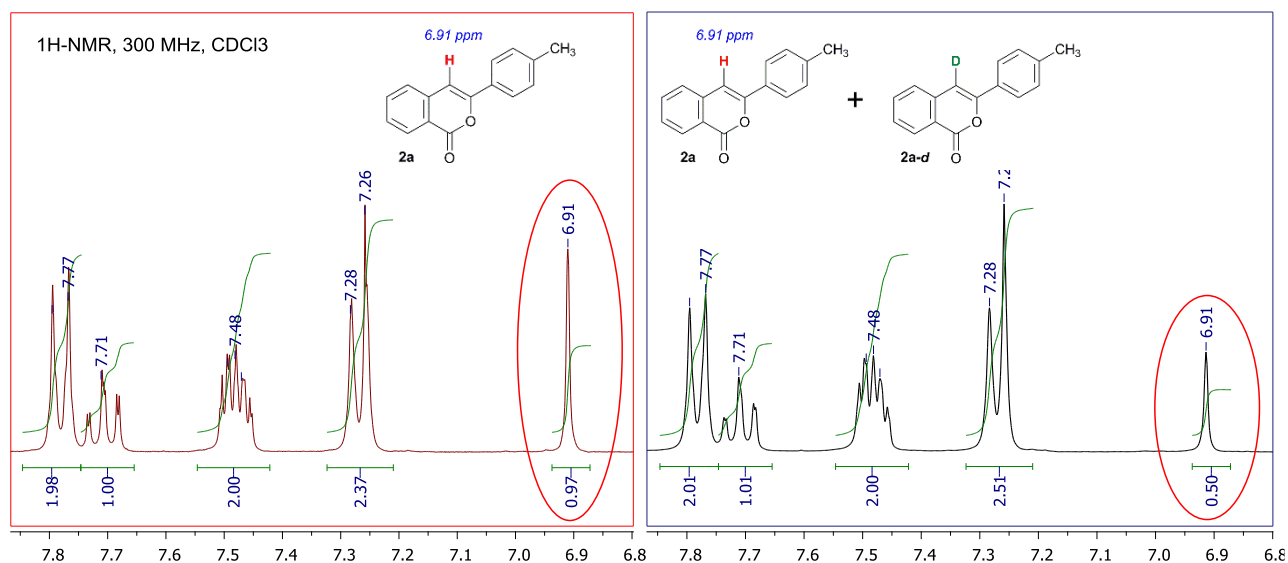
Figure 2. Isotope exchange study.

Finally, the key role of adventitious water was confirmed by carrying-out the model reaction under anhydrous conditions (nitrogen atmosphere, *p*-TSA previously dried by treatment with 4 Å molecular sieves and the presence 4 Å molecular sieves in the reaction mixture). The reaction became very slow and only about 35% of product **2a** was obtained after a prolonged reaction time (21 h), beside about 60% of unreacted **1a** (yields calculated via ^{1}H NMR using CH_2Br_2 as internal standard).

CONCLUSIONS

We reported herein a useful synthesis of isocoumarins by a AgOTf/*p*-TSA co-catalysed cyclization of 2-alkynyl benzoic ester derivatives. The reaction occurs in a 6-*endo-dig* regiospecific fashion and it is characterised by mild reaction condition, broad scope, low metal catalyst loading and in general very good yields. The versatility of the approach was also briefly explored by the synthesis of two thieno[2,3-c]pyran-7-ones starting from methyl and methyl 3-alkynylthiophene-2-carboxylates. The reaction was unsuccessful only in the presence of pyridine derivatives (probably due to a strong complexation of the metal catalyst) or trimethylsililacetylene group. The synthesis demonstrated to be easily scalable to gram scale allowing an additional reduction of silver catalyst loading. The mechanism was investigated by ^{1}H NMR studies, isotope exchange tests, and experiments under controlled conditions. By this way, the importance of a fine-tuned ratio among Lewis (AgOTf) and

Brønsted (*p*-TSA) acids has been pointed out and their peculiar cooperative action has been established.

CONFLICTS OF INTEREST: There are no conflicts to declare.

ELECTRONIC SUPPLEMENTARY INFORMATION (ESI) AVAILABLE: General experimental details, procedures, characterization data, and NMR spectra.

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