ChemPubSoc Europe

DOI: 10.1002/cctc.201901384

CHEMCATCHEM Full Papers

Zeolite-promoted Synthesis of Coumarins and Thiocoumarins

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Acidic zeolites, especially faujasites, efficiently promote the intramolecular cyclization of aryl propynoates and propynethioates, which produces coumarins and thiocoumarins, usually in high yields. Comparison with homogeneous Lewis or BrØnsted acids and with heterogeneous related sieve materials revealed the prevalence of zeolites exhibiting large cage-type pores (H-USY) for such cyclizations. Various substituents proved compatible with the cyclization process, leading to a variety of substituted coumarins and thiocoumarins (20 examples, 30–99%).

1. Introduction

Coumarins, also named *2H*-chromen-2-one or *2H*-1-benzopyran-2-one, encompass a large number of natural products, isolated from a large range of plant sources as well as certain microorganisms and animals.[1] Due to their structural diversity, coumarins are classified into six types according to their substituent nature, and each type exhibit different biological activities. For example, hydroxycoumarins such as fraxetin and hasakol (Figure 1) exhibit antioxidant and antibacterial activities and could be used as antispasmodic, while furocoumarins are used in the treatment of various skin diseases (e.g. psoralen and angelicin in Figure 1). 4-Arylcoumarins often exhibit insecticidal, antiparasitic or antiviral properties, such as isodispar B, which inhibits HIV replication,[2] or the calomelanol family used against malaria (Figure 1).[3] The wide range of biological activities exhibited by coumarins has induced their use as drug scaffold, as well as the production of numerous analogs.[4] Furthermore, coumarins can be fluorescent, a phenomenon which has led to the development of various probes in biology,[5] in environmental[6] and material sciences.[7]

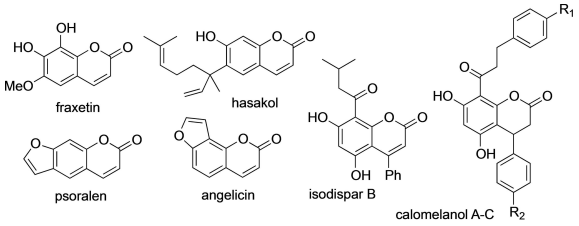
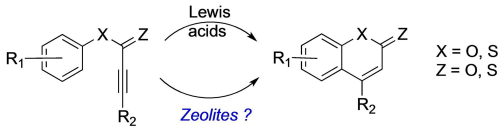


Figure 1. Representative examples of bioactive natural coumarins.

In contrast, the non-natural thiocoumarins are far less represented, although their synthesis could be traced back to 1912.[8] Together with coumarins, they have been developed as low nanomolar selective inhibitors of zinc metalloenzyme carbonic anhydrase,[9] as inhibitors of cell adhesion and of lipid peroxidation.[10] They also have been used as chemodosimeters, highly selective toward Hg^{2+} or Au^{3+} ions due to chromo- and fluorogenic changes in the presence of these ions.[11]

This variety of properties has led to numerous syntheses via very different routes.[12] Among them, the Lewis acid-promoted cyclization of aryl propiolates is one of the most simple and convergent methods (Scheme 1, top arrow).[12a,f] This strategy also offers a large and useful modularity, as the aryl, the propiolate substituent as well as the linkage nature could easily be tuned towards specific properties.

Although very few protic acids,[13] and even superacids,[14] have been investigated for such cyclizations, heterogeneous acids were surprisingly neglected. Extensively used in petro-



Scheme 1. Known routes to coumarins and the new and green proposed route to coumarins and thiocoumarins.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.201901384

chemical industry, heterogeneous acid catalysis, mostly based on zeolites, provides a wide range of building blocks for most chemical industry sectors. Besides their properties, such catalysts are easy to recover, recyclable, made of abundant elements, and they thus comply with some of the Green Chemistry principles.[15]

Within this Green Chemistry context, heterogeneous catalysis is becoming increasingly important in (very) fine chemistry, providing alternative but effective methods while contributing more and more to 'greening' (organic) chemistry.[16]

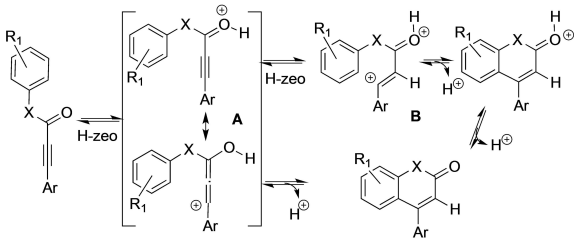
In this context, we are currently developing new methods relying on heterogeneous catalysis, with either acid or metalated catalysts such as polyoxometalates,[17] and zeolites.[18] Due to the intense interest in coumarins and thiocoumarins, we have explored new routes to these compounds based on heterogeneous acid catalysts and we report here that zeolites, especially faujasites, can conveniently promote the cyclization of *O*- and *S*-aryl propyn(thi)oates to the corresponding (thio) coumarins (Scheme 1, bottom arrow).

2. Results and Discussion

As we already demonstrated that aryl vinyl ketones could be cyclized to indanones in the presence of acidic zeolites,[19] we expected that homologous aryl propynoates would react in a similar way. Furthermore, the selectivity pattern gained with different zeolites suggested mechanism involving dicationic intermediates,[19] as in superacid media,[20,21] as well as shape selectivity in transition states. It is thus interesting to study the cyclization of propynoates and propynethioates for comparison and as a new and green way to produce coumarins and thiocoumarins.

For this study, we selected *O*-aryl arylpropynoates and *S*-aryl arylpropynethioates as substrates. The aryl group conjugated to the π-system should stabilize cationic intermediates at the remote acetylenic position (**A** and/or **B** in Scheme 2), according to the expected mechanisms, especially the one derived from our earlier work (via **B**). These readily available substrates (see Supplementary Informations) were submitted to different commercial zeolites of various size and shape pores as well as to related materials in order to look for some selectivity.

Condition set up. In a first series of experiments, the influence of the promoter nature was examined by submitting the challenging 2-methylphenyl 3-phenylpropynoate **1b** to various heterogeneous materials and for comparison purposes, to a few homogeneous Lewis or BrØnsted acid promoters (Table 1). As heterogeneous promoters, microporous materials such as zeolites and purely mesoporous materials, such as molecular sieves, were selected and compared. The role of acidity was also investigated by selecting materials exhibiting increasing Si/Al ratio and thus decreasing acidity.



Scheme 2. Proposed mechanism for the zeolite-promoted cyclization of aryl propynoates to coumarins.

In 1,2-dichloroethane at 85 °C during a short time (1 h), the starting ester **1b** did not evolve without promoter (entry 1), while in the presence of promoter, it was more or less converted to the expected coumarin **2b**, but with very variable conversions and yields depending on the promoter nature (entries 2–14). Under these conditions, typical Lewis acids led to the expected coumarin **2b**, but with a poor efficiency, as only around one third of the starting ester was converted and only half of it as the expected coumarin **2b** (entries 12–13). In contrast, some heterogeneous materials could increase the conversion of **1b**, providing **2b** with up to 40% yield with H-USY zeolites (entries 9–11). Zeolites thus clearly outperformed Lewis acids for the cyclization of aryl propynoates to coumarins.

Zeolites are often considered as heterogeneous equivalents to liquid superacids. We thus compared the behavior of **1b** in triflic acid, one of the most common superacid (entry 14). At room temperature, **1b** was readily converted to an extend of 60% and the expected coumarin **2b** was isolated with 45% yield, together with side products.[23] In terms of conversion and yield, superacid could thus be compared to the more active heterogeneous catalysts. Nevertheless, the latter provided

Table 1. Conversion of the aryl propynoate **1b** upon reaction with various acidic promoters, either homogeneous or heterogeneous materials.[a]

	Promoter	Type	Si/Al	Acidity[b] [mmol H^+/g]	Conv. [%]	Yield[c] [%]
1	–	–	–	–	0	0
2	MOR	Microporous zeolite	10	1.9	16	10
3	BETA	"	14	1.07	9	5
4	MFI	"	25	0.86	2	1
5	FAU (H–Y)	"	37	0.71	30	18
6	MS-1	Mesoporous solid	10	3.0	1	0
7	MS-2	"	25	1.4	3	0
	FAU (H-USY)	Micro- &				
8	CBV 500	meso porous	3.4	3.9	37	15
9	CBV 720	zeolites	21	2.4	55	40[d]
10	CBV 760		41	2.2	50	40[d]
11	CBV 780		57	2.0	39	30[d]
12	$AlCl_3$	homo-geneous	–	–	30	13
13	BF_3	"	–	–	30	17
14	CF_3SO_3H	"	–	–	60[d]	45[e,f]

[a] Conditions: for zeolites, 1 equiv. H^+, 85 °C, 1 h; for Lewis or BrØnsted acids, 5 equiv., 85 °C unless otherwise stated, [b] Determined according to ref. 22, [c] Determined by ^{1}H NMR with internal standard quantification method, [d] Isolated yield, [e] Reaction performed at rt, [f] Vinyl triflates could also be detected.[23]

similar results, without side-product and in a far greener and safer way (entries 9–10 vs 14).

However, heterogeneous materials provided very variable results, with some quite active while others were almost ineffective as promoter (entries 9–11 vs 3–4 and 6–7). Mesoporous molecular sieves only led to very low conversion, up to 3% (entries 6–7), as did MFI zeolite (ZSM-5) having channel pores of small size (entry 4). Related zeolites containing larger channels (MOR, BETA) performed slightly better (9 and 16%; entries 2–3), while those exhibiting large and cage-shaped pores (FAU, *i.e.* Y and USY) provided more than 30% conversion in only one hour (entries 5 and 8–11).

Regarding these materials, no clear correlation between acidity or Si/Al ratio could be observed. Indeed, heterogeneous materials exhibiting similar acidity provided very different results, as revealed by comparing MOR and USY (with acidity of respectively 1.9 and 2.0 mmol H^+/g) which respectively induced 16 and 39% conversion (entry 2 vs 11). The same trend could be seen with MFI, FAU and MS2 of 0.86, 0.71 and 1.4 mmol H^+/g acidity which led to respectively 2, 30 and 3% conversion (entries 4, 5 and 7).

These results clearly showed that acidity is not the key factor in such reaction, but rather the material structuration, and especially its internal porosity. The latter strongly influenced the promoter efficacy for this reaction. The size and shape of the pores within zeolites are thus critical for the success of the transformation, as shown by the higher efficiency of FAU Y and especially USY, both having the largest pore size and a spherical pore shape. Such results are in agreement with the role of confinement, introduced by Derouane,[24] and observed with other organic transformations.[25]

It is nevertheless worth noticing that H-USY with different Si/Al ratios, and thus different acidities, provided different results under the applied conditions, *i.e.* 1 equiv. H^+ at 85 °C for only 1 h. The H-USY exhibiting the largest number of acid sites only led to low yield of coumarin, while H-USYs with lower numbers provided up to 55% conversion and 40% yield (entry 8 vs 9–10). Despite the above-mentioned tendency, these results suggested some effect of acidity *within* the same structural zeolite motif.

It is indeed well known that the smaller the Si/Al ratio, the larger the number of BrØnsted acid sites, especially for high Al-content zeolites, like FAU structure, while the strength of these acidic sites increases with raising Si/Al ratios. the Next Nearest Neighbors (NNN) theory explains that the lability of those protons becomes greater when the Al-atom is surrounded by Si-atoms which are more electronegative. Hence the protons become sufficiently labile, even 'superacidic'[26] to allow an activation of barely reactive chemical bonds.[27]

In an attempt to get more information on such acidity aspects, we then screened the efficacy of these commercially available micro- and mesoporous H-USY having different Si/Al ratios, using 5 H^+ equivalents in order to push conversion to completion (Figure 2). The gained results clearly showed that within a zeolite type, the acidity remains also critical, with a key Si/Al ratio of 30. Below a Si/Al ratio of 20, full conversion was indeed reached, while conversion dramatically dropped at Si/Al ratios higher than 40. However, H-USY (ultrastable Y) zeolites are produced by treatments of H–Y zeolites to create mesoporority, but these usually alkaline or steaming treatments extract *i.a.* Al atoms and thus reduced the framework Al content; a part of it often remains as extra-framework Al species (EFAl), which can diminishes the zeolite pore accessibility. The presence of EFAl species in zeolites in close vicinity to protons may enhance their acid strength and hence the zeolite catalytic performance,[26,28] but they can also act as Lewis acid sites.[29]

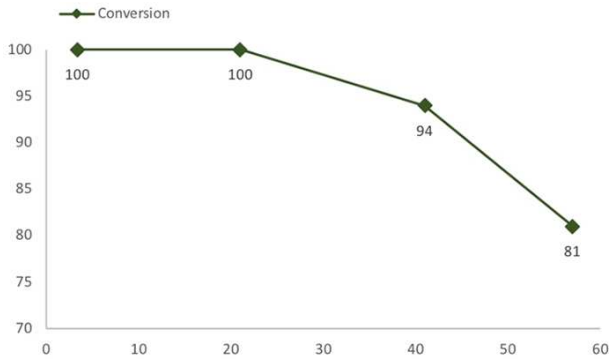


Figure 2. Conversion of **1b** with commercial H-USY of different Si/Al ratios. (DCE, 1 h, 5 equiv. H^+, 85 °C).

To look at such effects on the reactivity and efficiency of the used zeolites, we analyzed them and their BET surface areas, micro- and mesopore volumes, acidities[22] were measured (Table S1 in S.I.) and solid-state ^{27}Al NMR were recorded. Not so surprisingly, EFAL species could be detected by ^{27}Al MAS NMR, and as expected, at higher amounts as the Si/Al ratio raised (Fig S2 in S.I.). It thus seems that the more EFAl is present, the less active is the zeolite, probably by obstructing the pores, as revealed by decreasing pore volumes (From 0.43 to 0.39 cm^3/g; Table S1 in S.I.). Therefore, the efficacy of H-USY in promoting cyclization to coumarin seems to be the result of a subtle balance between the number of BrØnsted acid sites, their strengths and the amount of EFAL. Interestingly, the best result gained in converting **1b** was obtained with the H-USY zeolite CBV 720 exhibiting the largest pore volume and the largest micro- and mesopore volumes (Table S1 in S.I.).

From these results and data, we selected this commercial H-USY CBV 720 with a Si/Al ratio of 21 to set up the best conditions because it appeared as the most relevant regarding porosity parameters, acidity and efficiency (See Table 1, entry 9, and Figure 2).

Not so surprisingly regarding the possible mechanism (see Scheme 2), the amount of zeolite relative to the starting ester was critical under the same conditions. Increasing the equivalent of acid sites gradually increased conversion (Figure 3, blue line). Full conversion was reached after 1 h with an amount of zeolite corresponding to 5 equivalents of proton. Alternatively, full conversion could be achieved with a certain amount of zeolite upon longer reaction time. However, the coumarin isolated yield seemed affected by the amount of zeolite. Despite full conversion using more than 3 equivalents of

proton, the coumarin yield remained modest and even decreased with increasing amount of zeolite (Figure 3, red line). Such behavior suggested that some product could be trapped within the porous solid material.

As optimum isolated yields were observed around 3–4 H^+ equivalents, we selected 3 equivalents as the appropriate H^+ equivalent amount and to further adjust conditions, we extended this study to two other aryl propynoates, *i.e.* phenyl and 4-methylphenyl 3-phenylpropynoate **1a** and **1c**. With such H^+ equivalent amount, conversions were not always complete within 1 h, but increasing reaction time to 2 h allowed reaching full conversion as well as increasing coumarin yields (Figure 4).

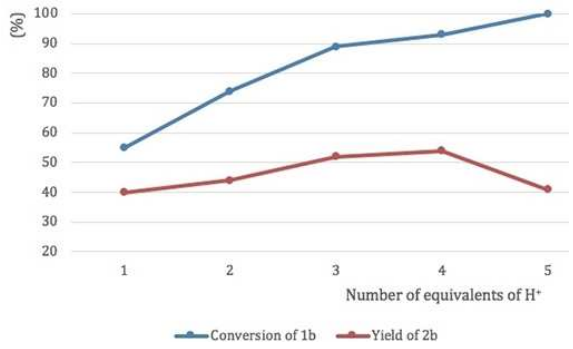


Figure 3. Conversion of **1b** and yield of **2b** relative to the amount of zeolite (H-USY; Si/Al = 21; 1 to 5 eq. H+; DCE, 1 h, 85 °C).

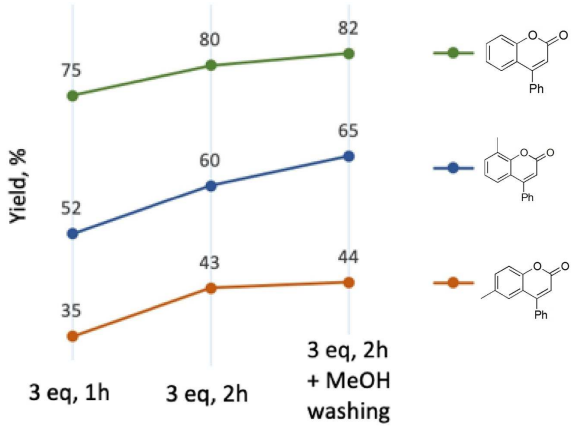


Figure 4. Yield of isolated coumarins **2a-c** upon reaction time and extraction method.

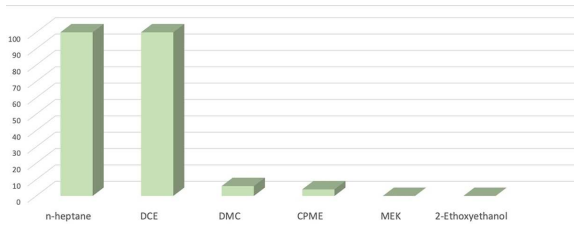


Figure 5. Conversion of **1b** in various solvents (reaction performed with 5 eq of H^+, at 85 °C for 1 h).

Due to differences between conversions and isolated yields (see Figure 3) but also due to the polarity of the so-formed coumarins and of the solvent used, we also wondered if all the organic matter could get out of the zeolite materials.[30] Several work-up protocols were thus evaluated and it turned out that an extensive washing with methanol allowed extracting slightly more organic compounds and thus raised the amount of recovered coumarins (Figure 4).

Solvents in which the reaction could be performed, were also briefly screened, with an emphasis on green solvents (Figure 5). Unfortunately, the latter did not give useful results. Solvents of low polarity provided the best results, while polar ones did not. Among the former, heptane and 1,2-dichloroethane gave full conversion within 1 h.

Recycling. Besides ease of handling and purification, another eco-friendly interesting aspect of heterogeneous catalyst relies on catalyst recovery and recycling. In order to look at this aspect, we performed several times the cyclization of **1a** to **2a** with the same H-USY, the latter being filtered, washed with methanol, calcinated and reused after each run. As shown in Figure 6, the H^I-USY zeolite could be recycled up to five times without significant loss of activity.

Scope and limitation. With the right conditions in hands, we explored the possibilities offered by this zeolite-promoted cyclization of aryl propyn(thi)oates to (thio)coumarins. Esters were first investigated and various electro-donating or withdrawing substituents were introduced at the ester moiety to look at their effects on the cyclization (Table 2).

Interestingly, 3-phenylpropynoates carrying electron-rich or poor substituents on the ester moiety provided the corresponding coumarins in high yields (around 80%), whatever the electronic effect of the substituent (entries 2, 4, 5 or 6 vs 1). Surprisingly, the *para*-tolyl derivative **1c** gave lower yield of coumarin compared to its *ortho* and *meta* isomers (entry 3 vs 2 and 4). This could be due to difficulties to extract the organic product from zeolite (see Fig. 4 and[30]).

Similarly, variations on the phenylpropynoate moiety did not alter much the results, although a slight electronic effect was observed (entries 10–12). The more electrodonating substituent was indeed inducing slightly higher yield of coumarin than electrodeficient substituent (entry 12 vs 10). These results are consistent with an easier protonation of the starting ester in line with an increasing electron density of the alkynyl moiety.

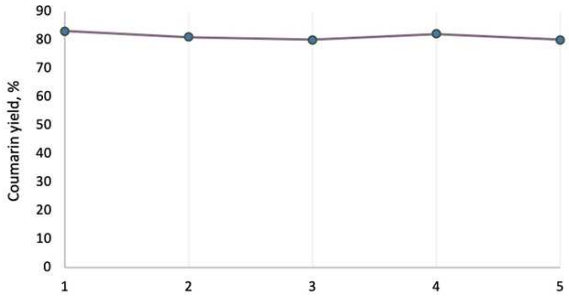
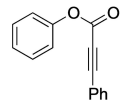
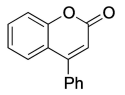
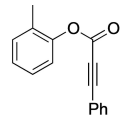
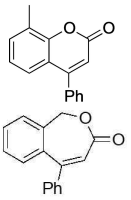
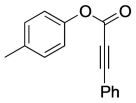
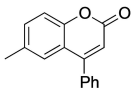
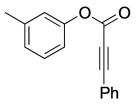
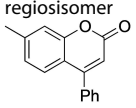
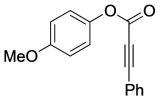
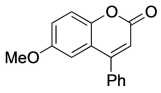
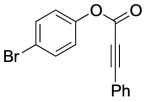
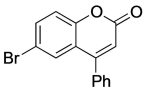
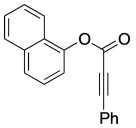
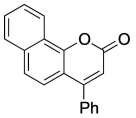
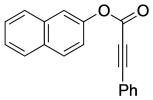
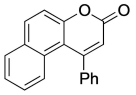
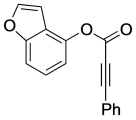
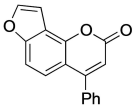
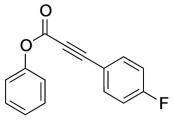
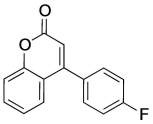
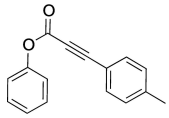
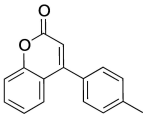
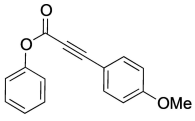
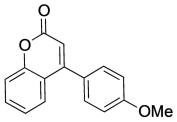


Figure 6. Recycling study of H-USY using **1a** (each run performed with 3 eq of H^+ at 85 °C for 2 h).

Table 2. Zeolite-promoted cyclization of aryl propynoates to coumarins.[a]

	Propynoate	Coumarin		Yield[b]
1		**1a**		**2a** 82
2		**1b**		**2b** 65 **2b′** 14
3		**1c**		**2c** 44[c]
4		**1d**	+ regiosisomer 	**2d** 80 **2d′** (1:0.4)
5		**1e**		**2e** 80[d]
6		**1f**		**2f** 84
7		**1g**		**2g** 28[c,e]
8		**1h**		**2h** 65
9		**1i**		**2i** 33[c,e]
10		**1j**		**2j** 73
11		**1k**		**2k** 80
12		**1l**		**2l** 88

[a] Conditions: H-USY (3 equiv. H^{+}), DCE, 85 °C, 1 h, [b] Isolated yield, [c] Not all organic matter could be extracted from zeolite, [d] Partial demethylation occurred, [e] Formation of unidentified products (degradation occurred).

These results are thus in agreement with the proposed mechanism (see Scheme 2 and below).

It is worth mentioning that unexpected but interesting side-products could be isolated in low yields in a few cases. The *ortho*-tolyl derivative **1b** provided a cyclized compound aside and different of the expected product **2b**. Crystallization of this side product allowed to ascertain its structure, which turned out to be a seven-membered lactone. As the latter includes the former methyl group, a rearrangement must have taken place (see below).

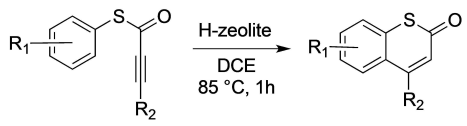
In contrast, naphtyl esters **1g–h** provided different results. The α isomer **1g** gave the expected benzocoumarin **2g** in moderate yield (entry 7), while the β provided the benzocoumarin **2h** as a single regioisomer in good yield (entry 8). The **2h** structure confirmed that cyclization occurred at the more reactive and nucleophilic α-naphtyl position; the latter is thus clearly responsible for the excellent regioselectivy. Interestingly, a benzofuran ester **1i**, analog to the α-naphtyl ester **1g**, also provided the expected product **2i**, which is a phenyl-substituted analog of the naturally occurring compound angelicin (see Figure 1).

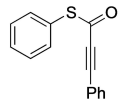
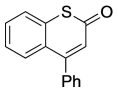
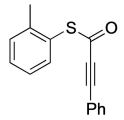
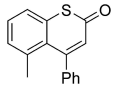
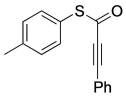
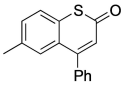
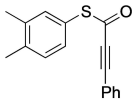
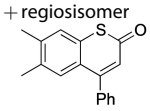
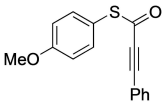
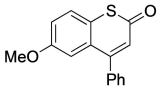
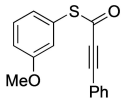
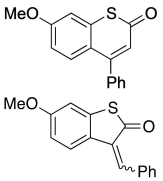
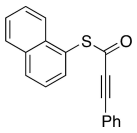
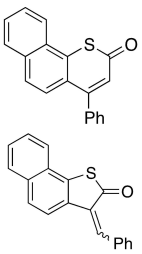
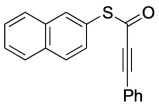
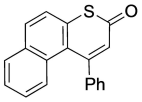
Rewardingly, thioesters **3** also provided the expected thiocoumarins **4** when submitted to the same conditions used for the preceding esters **1** (Table 3). Except for the *meta*-methoxylated compound **3f**, conversions were generally complete and high to quantitative yields of the corresponding thiocoumarins were usually abtained under the conditions set for the corresponding esters.

In contrast to the corresponding esters, the *para*-tolyl thioester **3c** quantitatively gave the corresponding thiocoumarin **4c** (entry 3), while its *ortho* isomer **3b** only provided in modest yield a thiocoumarin (entry 2). However, the structure of the latter did not correspond to the expected one (**4b**), but to the more hindered isomer **4b′**, as confirmed by XRD analysis of crystals grown out of it (See S. I.). Indeed, the methyl of the *ortho*-tolyl group proved to be adjacent to the phenyl group, which implies that a rearrangement took place, as during the reaction of the *ortho*-tolyl ester **1b** (see Table 2, entry 2). The dimethylated thioester **3d** also quantitatively gave the corresponding thiocoumarin, but as a mixture of the two possible regioisomers (entry 4). The less hindered isomer **4d** was predominantly formed, with a 1:0.45 ratio, similar to the ratio gained from the *meta*-tolyl ester **1d** (see Table 2, entry 4).

For the methoxylated thioesters **3e–f**, other unexpected results were obtained. The *para*-isomer **3e** fully reacted, giving the thiocoumarin **4e** in high yield (entry 5), while the *meta* isomer **3f** only gave low yield of the expected thiocoumarin **4f** and a new compound **4f′** in very low yield (entry 6). The latter proved to be the result of an *exo* cyclization rather than a compound issued from the *endo* cyclization observed for all the other examples. A similar *exo* cyclization product was also produced during the reaction of the α-naphtyl thioester **3g**. For the latter, the expected benzothiocoumarin **4g** was obtained in modest yield, as for the α-naphtyl ester (Table 2, entry 7), but together with compound **4g′**, although in a very low yield. In contrast, the β isomer provided almost quantitatively the

Table 3. Zeolite-promoted cyclization of aryl propynethioates to thiocoumarins.[a]



	Propynoate		Coumarin		Yield[b]
1		**3a**		**4a**	84
2		**3b**		**4b′**	40[c]
3		**3c**		**4c**	99
4		**3d**		**4d** **4d′**	99 (1:0.45)
5		**3e**		**4e**	90
6		**3f**		**4f** **4f′**	24[c,d] 8
7		**3g**		**4g** **4g′**	33[c,d] 5
8		**3h**		**4h**	95

[a] Conditions: H-USY (3 equiv. H^+), DCE, 85 °C, 1 h, [b] Isolated yield, [c] Not all organic matter could be extracted from zeolite, [d] Formation of unidentified products (degradation occurred).

expected product **4h** (entry 7 vs 8), the structure of which was ascertained by XRD analysis of crystals (See SI.).

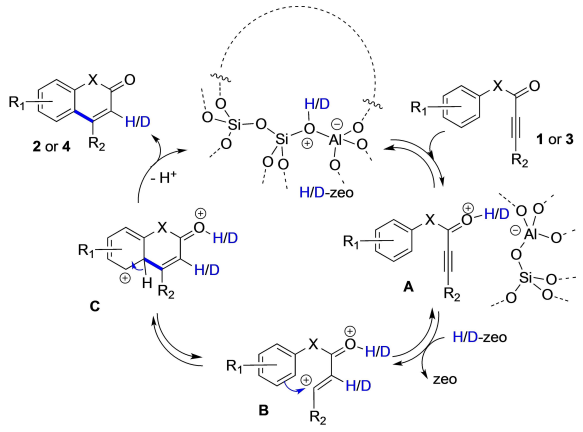
Discussion and Mechanism. Only FAU zeolites having the largest and spherical pores were effective to promote the cyclization of *O*- and *S*-aryl propyn(thi)oates to (thio)coumarins. Such zeolites exhibit some mesopores (mesopore volume: 0.07–0.18 $cm^3 g^{-1}$) of ~13 nm as average diameter and a large microporous system (micropore volume: 0.22-0.25 $cm^3 g^{-1}$) (See Table S1), consisting in the so-called super cage with a diameter of 12 Å. The spherical shape and the size of these cages obviously impose steric constrain to compound entering and exiting such pores, as well as to the transition state during reaction, which can alter reaction outcome.[24,31]

As the starting (thio)esters have on average a 7–8 Å diameter, and due to their flexibility, they most probably can readily enter the microporous system and reach the acid sites within the cages. However, the cyclized products with an average 8–10 Å diameter should suffer from limitations to exit cages. This phenomenon is probably responsible for the problem we encountered to get quantitative yield of products, despite the cleanliness of the reaction. It was necessary to extensively wash the zeolite material with methanol after reaction (see Figure 3).

The strong acidity in zeolites is due to the protonation of the framework oxygen atom, next to an aluminate center (H-zeo in Scheme 3). When a starting (thio)ester encounters such acid sites, the more basic carbonyl oxygen atom must be first protonated (**A** in Scheme 3). Although the resulting intermediate could possibly react, it seems from the Si/Al and stoechiometric requirements (see Figure 2–4) that a second protonation is required.

It is worth noticing that the resulting diprotonated intermediate **B** exhibits a shape more prone to cyclization than the monoprotonated species **A** and more adjusted to the spherical cage shape, with possible stabilization through H-π interaction (Figure 7).[32] Furthermore, this spherical pore shape could force intermediate **B** to adopt a more reactive conformation and thus facilitate the cyclization (Figure 7, right).

With this mechanism, the vinylic proton in the final coumarin should come from the zeolite (blue H, step A to B in Scheme 3). Therefore, using deuterated zeolite instead of protic zeolite should introduce deuterium at that vinylic position. We thus checked this possibility by preparing zeolites with different deuterium contents. Rewardingly, running the cyclization with D-zeolites at different deuteration levels allowed to isolate coumarins deuterated at the expected position and with the same deuteration levels (Scheme 4). These results confirm the



Scheme 3. Mechanism for the zeolite-promoted cyclization of aryl propyn (thi)oates to (thio)coumarins (For clarity, the zeolite cage and its framework are – partially – represented only for the 1st step).

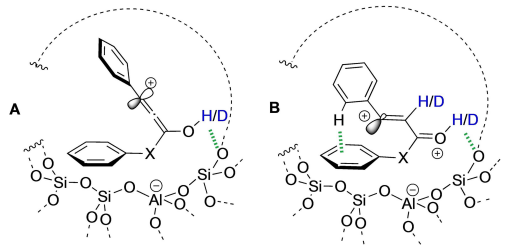
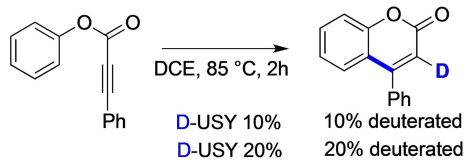


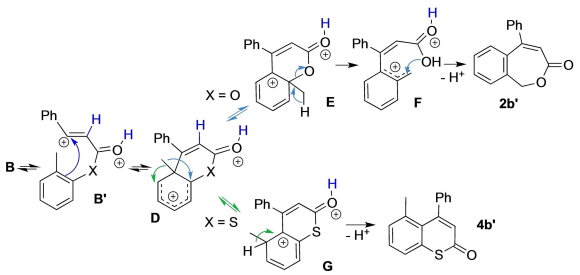
Figure 7. Possible structures and shapes of singly and di-protonated aryl propyn(thi)oates within zeolite cage as intermediates towards (thio)coumarins.



Scheme 4. Control experiments with deuterated zeolite to assess the proposed mechanism.

proposed mechanism, and especially the double protonation of the substrate, which induces the cyclization to coumarin.

Interestingly, this mechanism could also account for the side products observed with a few starting esters and thioesters. Indeed, the *exo*-cyclization products **4f–g′** could simply result from the other regioselectivity during the second protonation. Furthermore, the seven-membered lactone **2b′** and the counter-intuitive thiocoumarinic regioisomer **4b′** could both result from cyclization at the more hindered site and methyl shift due to steric reasons (Intermediate **D** derived from **B** through its rotamer **B′**; Scheme 5). For the *ortho*-tolyl thioester **3b**, this shift could occur away from the large phenyl and sulfur groups, leading to intermediate **G**. The latter would then rearomatize to provide **4b′**. For the *ortho*-tolyl ester **2b**, the methyl shift might be linked to an elimination leading to the departure of the protonated ester moiety, more nucleofugal than the more polarizable thioester. This would lead to the opened intermediate **F**, which could then stabilize by ring closure and thus formation of **2b′**.



Scheme 5. Possible mechanism for the zeolite-promoted formation of the side-reactions occurring during cyclization of aryl propyn(thi)oates to (thio) coumarins.

4. Conclusions

Through the present work, we demonstrated that zeolites, especially faujasites (H-USY), are able to promote the cyclization of aryl propynoates and propynethioates to respectively coumarins and thiocoumarins. Comparison between Lewis or BrØnsted acids and several heterogeneous materials showed that zeolites with large cage-type pores are efficient and greener alternative to acidic conditions, including superacid media.

This zeolite-promoted cyclization of aryl propyn(thi)oates provides a rapid and mild access to coumarins, and especially to the less reported thiocoumarins.

The role of zeolites as useful tool in organic synthesis will be pursued in our group.

Experimental Section

General Information: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300, 400, or 500 instruments. The chemical shifts are given in ppm on the δ scale. The solvent peak was used as reference value. For ^{1}H NMR: $CDCl_3 = 7.26$ ppm. For ^{13}C NMR: $CDCl_3 = 77.16$ ppm. Data are presented as follows; chemical shift, multiplicity (standard abbreviations), coupling constants (J in Hz), integration, and carbons with same chemical shift (x carbons). Assignments were determined either on the basis of unambiguous chemical shifts or coupling patterns, and COSY, HSQC, HMBC experiments were sometimes needed to fully interpret spectra for related compounds. IR spectra were recorded neat on Bruker Alpha ATR instrument. Wavelengths of maximum absorbance are quoted in wave numbers (cm^{-1}). High-resolution mass spectra (HRMS) data were recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ are quoted. Analytical TLC was carried out on silica gel 60 F254 plates with visualization by ultraviolet light, vanillin, anisaldehyde or $KMnO_4$. Chromatography was carried out using silica gel 60 (40–63 μm). Reagents and solvents were purified using standard methods. When necessary, anhydrous reactions were carried out in flame-dried glassware and under an argon atmosphere. Anhydrous CH_2Cl_2, DCE, THF, and MeOH were dried by passing through activated alumina under a positive pressure of argon using GlassTechnology GTS100 devices. All other chemicals were used as received. Zeolites were purchased from Zeolyst.

General procedure: In a tube sealed with a screw cap, was added *O*-aryl or *S*-aryl esters of 3-arylpropynoic acid (45 mg, 1 eq), H-USY (CBV-720 from Zeolyst; 3 eq H^+) and 2 ml of 1,2-DCE. The reaction was performed at 85 °C with stirring during 2 h. At the end of the reaction, the mixture was filtered through nylon membrane (0.2 μm), washed with 2–5 ml DCE. The zeolite from the filter was collected in a 50 ml round bottom flask and stirred with 20 mL of methanol at room temperature for 2 hours. After filtration, the two filtrates were combined and the solvents were removed under reduced pressure. The resulting reaction product was purified by column chromatography on silica gel, with a mixture of eluents (cyclohexane : ethyl acetate 90:10 or 80:20).

Acknowledgements

The authors thank the CNRS, the French Ministry of Research and the Russian Science Foundation (grant no. 18-13-00008). OZ thanks the Russian Science Foundation for a PhD fellowship.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: coumarin · thiocoumarin · zeolite · cyclization

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Manuscript received: July 30, 2019
Revised manuscript received: September 13, 2019
Accepted manuscript online: September 18, 2019
Version of record online: ■■, ■■■

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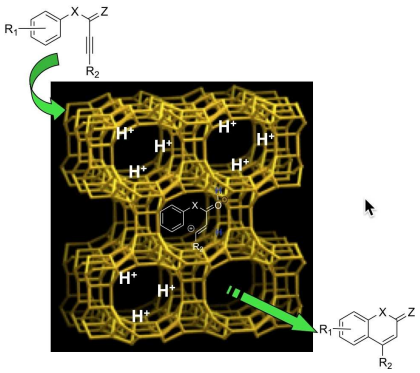
Organic synthesis: Zeolites as Nanoreactors for Green Chemistry and Fine Chemistry : New route to Coumarins and Thiocoumarins



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Zeolite-promoted Synthesis of Coumarins and Thiocoumarins