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Solvent-dependent behavior of arylvinylketones in HUSY-zeolite: a green alternative to liquid superacid medium

Abdelkarim Sani Souna Sido,[a,b] Stefan Chassaing,[a] Mayilvasagam Kumarraja,[a] Patrick Pale[b,*] and Jean Sommer[a]

[a]*Laboratoire de Physicochimie des Hydrocarbures, Institut de Chimie associé au CNRS (UMR 7177), Université L. Pasteur, 67000 Strasbourg, France*

[b]*Laboratoire de Synthèse et Réactivité Organique, Institut de Chimie associé au CNRS (UMR 7177), Université L. Pasteur, 67000 Strasbourg, France*

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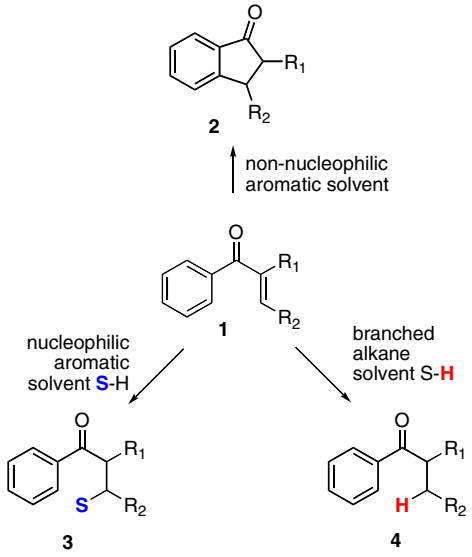
Abstract—Depending on the reaction conditions, arylvinylketones can be directly and efficiently converted using zeolites to indanones by cyclization or to dihydrochalcones through regioselective aryl addition or chemoselective hydride transfer.

Arylvinylketones represent valuable precursors in organic synthesis, offering a diversity point toward a number of pharmaceutically interesting compounds.[1,2] Inter alia, arylvinylketones **1** can be converted in liquid Brönsted-type superacids to different useful products.[3–5]

In order to perform these acid-mediated transformations in a more eco-friendly way, we envisaged to replace liquid superacid media by solid acids. For the last thirty years, zeolites have indeed raised enormous interest as catalyst in hydrocarbon chemistry with a clear environmental benefit.[6] As a result, we recently reported that intramolecular cyclization of arylvinylketones **1** into indanones **2** can be performed using solid acids such as zeolites, sulfated zirconia or heteropolyacid.[7] We now report here that the reactivity of arylvinylketones **1** can be modulated and controlled by the reaction conditions on zeolites. Indeed, either cyclization to indanones **2**, or regioselective aryl addition or chemoselective hydride transfer to, respectively, dihydrochalcones **3** or **4** has been achieved (Scheme 1).

The proposed mechanistic pathways for superacid-induced transformations rely on superelectrophilic solvation[8] via the formation of mono- and dicationic intermediate species such as **I1**–**4** (Scheme 2). The exact nature of the key dicationic species is still under debate, some authors suggesting with some computational support the involvement of 1,2-dications **I3**[3,4,9,10] resulting from O,O-diprotonation while others suggest 1,4-dicationic intermediates **I4**[7] resulting from O,C-diprotonation.



Scheme 1. Zeolite-promoted transformations of arylvinylketones.

Keywords: Zeolites; Arylvinylketones; Cyclization; Arylation; Reduction; Superelectrophile; Dication.
* Corresponding author. Tel./fax: +33 390 241 517; e-mail addresses: ppale@chimie.u-strasbg.fr; sommer@chimie.u-strasbg.fr

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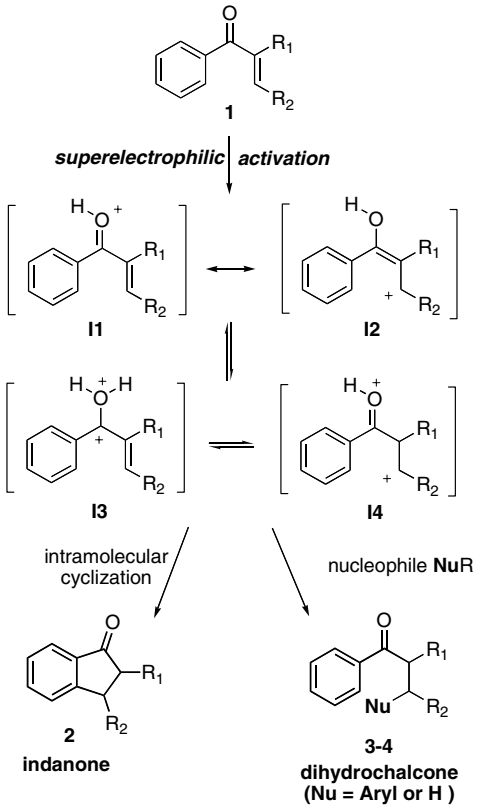


Scheme 2. Superelectrophilic activation of arylvinylketones.

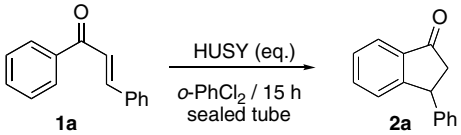
It is nevertheless worth noting that a few O-C-diprotonated 1,4-dications **I4** have already been detected in liquid superacids by NMR spectroscopy.[11]

Despite the controversy about acidity measurement of solid acids,[12] the acidity in zeolite environment is estimated at H_0 -7–9,[13] and therefore, such transient species should not be considered as real dications but rather as protosolvated intermediates, the relatively weaker acidity being compensated by confinement effects.

On these bases and on the analogy between superacids and zeolites, we reasoned that ions such as **I4** should be trapped with various donors, even inside zeolites. We thus explored these possibilities and showed here that this is indeed the case.

The HUSY-induced cyclization of chalcone **1a** into 3-phenylindanone **2a** was initially used to find the more appropriate conditions. The right balance between temperature and the number of acidic sites was investigated in a poor nucleophilic solvent, that is, *ortho*-dichlorobenzene (Table 1). Below or at 130 °C, the use of quantity corresponding to stoichiometric acidic sites[14] or twice this amount did not promote any transformation (entries 1 and 2). However, 5 molar excess of acidic sites clearly appeared as the minimum required to complete the reaction (entry 3 vs entreis 1, 2). Increasing further the ratio acidic sites to substrate showed only a slight effect on the efficiency of the process (entry 4 vs 3). It is worthy to note that chalcone **1a** has been reported to be inert in triflic acid even at 80 °C,[3] highlighting

Table 1. Reaction conditions optimization studies: cyclization



Entry	HUSY[a] (equiv)	Conditions[b]	Conversion (%)	Yield[c] (%)
1	1	*o*-$PhCl_2$, 15 h, 130 °C	—[d]	—[d]
2	2	*o*-$PhCl_2$, 15 h, 130 °C	<5[d]	<5[d]
3	5	*o*-$PhCl_2$, 15 h, 130 °C	100[d]	66
4	10	*o*-$PhCl_2$, 15 h, 130 °C	100[d]	68
5	5	*o*-$PhCl_2$, 15 h, 110 °C	43[e]	32

[a] Based on the theoretical number of acidic sites of HUSY.[14,15]
[b] The reaction was conducted in sealed tubes.
[c] Isolated yields of pure product after complete conversion unless otherwise stated.
[d] Determined by ^1H NMR analysis of the crude mixture.
[e] Based on recovery of starting material after column chromatography.

the promising potential of HUSY-zeolite compared to the classical liquid medium. Temperature also plays a critical role on the reaction conversion as demonstrated by a dramatic loss of efficiency upon a slight decrease of the temperature (entry 5 vs 3).

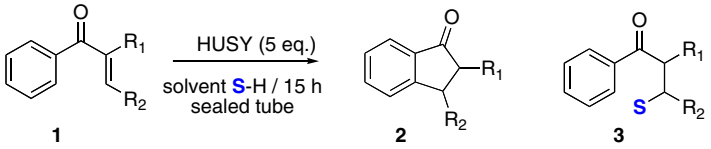
With these reaction conditions in hand (5 molar excess of acid sites at 130 °C), we then studied the behavior of three model phenylvinylketones **1a**–**c** in aromatic solvents having distinct nucleophilic properties (Table 2). In benzene, a mixture of cyclization product **2** and addition product **3** was always observed. However, their relative amount varied upon the precursor nature. Starting from **1b**, indanone **2b** was the major product, while from chalcone **1a**, addition product **3a** was the major one (entry 7 vs 3). With **1c**, this addition product could merely be detected (entry 10 vs entries 3, 7). Interestingly, the structures of addition products **3a**,**b** showed that they correspond to a *regioselective* 1,4-nucleophilic addition of the aromatic solvent.

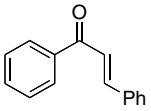
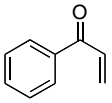
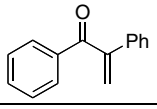
In the less nucleophilic *ortho*-dichlorobenzene, only cyclization products **2a**,**b** were observed (entries 1 and 5). In chlorobenzene, as expected, an intermediate behavior was observed. Only the cyclization products **2b**,**c** were observed with **1b**,**c** (entries 6 and 9), while a mixture of **2a** and **3a** was produced starting from **1a**, the indanone being the major one (entry 2).

In a more nucleophilic solvent such as toluene, the addition was the major process starting from **1a**,**b**, the indanone being scarcely detected (entries 4 and 8). However, with **1c**, the cyclization remained the almost exclusive route (entry 11).

These results showed that for **1a**,**b**, the product distribution appeared to be directly dependent on the nucleophilic character of the solvent, the more nucleophilic the solvent is, the more adduct would be produced (entries 1–4, 5–8). In contrast, such solvent adducts were scarce in reactions with **1c** and the cyclization products were isolated in highest yields (up to 85%).

Table 2. Reaction conditions optimization studies: cyclization versus arylation



Entry	Substrate	Solvent S–H	Yield[a] (%) **2a–c**	Yield[a] (%) **3a–c**
1	 **1a**	*o*-$PhCl_2$	66	—[b]
2		PhCl	46	29[c]
3		PhH	23	47
4		$PhCH_3$	5	42[c]
5	 **1b**	*o*-$PhCl_2$	47	—[b]
6		PhCl	55	—[b]
7		PhH	40	22
8		$PhCH_3$	<5[b]	35[c]
9	 **1c**	PhCl	85	<5
10		PhH	84	<5
11		$PhCH_3$	77	<5

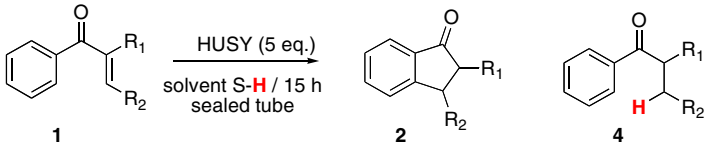
[a] Isolated yields of pure product after complete conversion unless otherwise stated.
[b] Not detected even by ^{1}H NMR analysis of the crude mixture.
[c] Mixture of *ortho*- and *para*-substituted isomers.

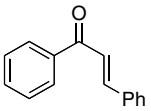
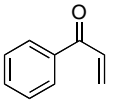
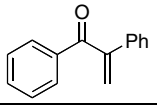
The difference in the reactivity of **1a**,**b** versus **1c** is clearly in favor of a carbocationic pathway. A more stabilized carbocation would have a longer half-life and thus be more prone to intermolecular reactions, this is indeed observed with the arylation described above. The fact that a single adduct regioisomer (the 1,4-adduct) was observed revealed that the cationic center is mainly localized at position 4 (enone numbering, species **I2** or **I4** in Scheme 2). Moreover, the size of the nucleophile does not seem to be important, but rather its nucleophilicity, toluene reacting faster than benzene, itself faster than chlorobenzene, even faster than dichlorobenzene.

With such evidences for a 4-carbocationic species being created within the zeolite, we then tried to trap it with hydrogen donors in order to get a formal regioselective reduction of the enone system.

Alkanes being prone to hydrogen transfer in superacids,[5] we submitted our model arylvinylketones to HUSY in various alkanes (Table 3). In heptane, the reaction was not really efficient yielding around 40% of the products. The major process was cyclization (entries 1 and 5). Interestingly enough, a small amount of the expected reduction product **4a** could be isolated from the reaction

Table 3. Optimization studies of the reaction conditions: cyclization versus hydride transfer



Entry	Substrate	Solvent S–**H**	Yield[a] (%) **2a–c**	Yield[a] (%) **4a–c**
1	 **1a**	Heptane	39	4
2		Cyclohexane	47	29
3		Methylcyclopentane	8	69
4		2,3-Dimethylpentane	—[b]	21[c]
5	 **1b**	Heptane	42	—[b]
6		Cyclohexane	38	5
7		Methylcyclopentane	<5[b]	60
8	 **1c**	Methylcyclopentane	66	14

[a] Isolated yields of pure product after complete conversion unless otherwise stated.
[b] Not detected even by ^{1}H NMR analysis of the crude mixture.
[c] Mixture of unidentified products.

of **1a**. In cyclohexane, this product was now formed in almost 30% in the reaction of **1a**, but still in low amount with **1b** (entries 2 and 6).

Since branched alkanes should be better hydrogen donors, we investigated the effect of methylcyclopentane and 2,3-dimethylpentane. The latter led to a complex mixture of products where the expected product **4a** was the sole compound isolated, although in low yield (entry 4). Fortunately, methylcyclopentane proved to be the best compromise between reactivity and selectivity. In this solvent, the reduction was now the major process with **1a**,**b** (entries 3 and 7), indanone **2b** being barely detectable starting from **1b** (entry 7). Not so surprisingly, cyclization was still the major process with the very reactive **1c** (entry 8).

Therefore, these results showed that *regioselective* reduction of enones is also possible in HUSY. They also revealed that the more branched the alkane is, the more reduction product would be formed (entry 3 vs entries 1, 2).

In summary, we have further expanded the scope of synthetic applications of H-zeolites, demonstrating that either cyclization or *regioselective* aryl addition or *regioselective* reduction of arylvinylketones can be achieved in good yield by zeolite catalysis under the appropriate conditions.

It is worthy mentioning the ease to perform such reactions and to recover the products. Moreover, the zeolite catalyst can be reused three times without significant decrease in yields.

Therefore, zeolites appear as green alternatives to conventional Brönsted acids and superacids.

Further works are now in progress to further explore the scope of these reactions and to apply them in organic synthesis.

Acknowledgments

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References and notes

1. For recent examples of pharmaceutically active indanone derivatives, see Ernst-Russell, M. A.; Chai, C. L. L.; Wardlaw, J. H.; Elix, J. A. *J. Nat. Prod.* **2000**, *63*, 129; Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1998; Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.-i.; Tanakashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932; Alonso, D.; Dorronsoro, I.; Rubio, L.; Munoz, P.; Garcia-Palomero, E.; Del Monte, M.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J.; Castro, A.; Medina, M.; Martinez, A. *Bioorg. Med. Chem.* **2005**, *13*, 6588; Dai, J.; Krohn, K.; Flörke, U.; Draeger, S.; Schulz, B.; Kiss-Szikszai, A.; Antus, S.; Kurtan, T.; van Ree, T. *Eur. J. Org. Chem.* **2006**, *35*, 3498; Das, U.; Gul, H. I.; Alcorn, J.; Shrivastav, A.; George, T.; Sharma, R. K.; Nienaber, K. H.; De Clercq, E.; Balzarini, J.; Kawase, M.; Kan, N.; Tanaka, T.; Tani, S.; Werbovetz, K. A.; Yakovich, A. J.; Manavathu, E. K.; Stables, J. P.; Dimmock, J. R. *Eur. J. Med. Chem.* **2006**, *41*, 577; Giner, J.-L.; Kehbein, K. A.; Cook, J. A.; Smith, M. C.; Vlahos, C. J.; Badwey, J. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2518.
2. For recent examples of pharmaceutically active dihydrochalcone derivatives, see Rezk, B. M.; Haenen, G. R. M. M.; Van Der Vijgh, W. J. F.; Bast, A. *Biochem. Biophys. Res. Commun.* **2002**, *295*, 9; Williams, C. A.; Grayer, R. J. *Nat. Prod. Rep.* **2004**, *21*, 539; Nakatani, N.; Ichimaru, M.; Moriyasu, M.; Kato, A. *Biol. Pharm. Bull.* **2005**, *28*, 83.
3. For liquid superacid-induced intramolecular cyclization of arylvinylketones, see Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774.
4. For liquid superacid-induced arylation of arylvinylketones, see Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364.
5. For liquid superacid-induced reduction of C,C-double bond of arylvinylketones, see Coustard, J. M.; Douteau, M. H.; Jacquesy, J. C.; Jacquesy, R. *Tetrahedron Lett.* **1975**, *25*, 2029.
6. Corma, A. *Chem. Rev.* **1995**, *95*, 559–614.
7. Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2005**, *46*, 8391–8394.
8. Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211.
9. Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767.
10. Nenajdenko, V. G.; Shevchenko, N. E.; Balenkova, E. S.; Alabugin, I. V. *Chem. Rev.* **2003**, *103*, 229–282.
11. Koltunov, K. Y.; Repinskaya, I. B.; Borodkin, G. I. *Russ. J. Org. Chem.* **1994**, *30*, 97; Vasilyev, A.; Walspurger, S.; Haouas, M.; Pale, P.; Sommer, J.; Rudenko, A. P. *Org. Bio. Chem.* **2004**, *2*, 3483–3489; Vasilyev, A.; Walspurger, S.; Sommer, J.; Pale, P. *Tetrahedron* **2005**, *61*, 3559–3564.
12. Farneth, W. E.; Gorte, R. J. *Chem. Rev.* **1995**, *95*, 615–635; Gorte, R. J. *Catal. Lett.* **1999**, *62*, 1–13.
13. Umansky, B. S.; Hall, K. *J. Catal.* **1990**, *124*, 97–108; Umansky, B. S.; Engelhardt, J.; Hall, K. *J. Catal.* **1991**, *127*, 128–140.
14. For a recent method of determination of Brönsted acid sites on zeolites, see Louis, B.; Walspurger, S.; Sommer, J. *Catal. Lett.* **2004**, *93*, 81.
15. Characteristics of HUSY-zeolite: source: Zeolyst International (CBV 500), topology: cage, pore diameter (Å): 7.4×7.4, Si/Al ratio: 2.8.
Typical procedure: Zeolite USY ($SiO_2/Al_2O_3 = 5.64$, CBV 500, Zeolyst International) in NH_4^+ form was activated at 550 °C for 4 h under air. The number of acid sites was estimated to be 4.33 mmol/g.
Synthesis of **2c** *(Table 2, entry 9)*: Activated zeolite (2.52 g, 10.92 mmol sites), chlorobenzene (10 mL), and compound **1c** (454 mg, 2.18 mmol) were successively loaded in 20 mL pressure tube. The resulting suspension was magnetically stirred at 130 °C overnight. After cooling, the mixture was added to 50 mL of MeOH, then stirred at 80 °C for 5 h. After cooling, the catalyst was filtered off and the organic phase was concentrated to provide the crude product (434 mg). A chromatographic purification (silica gel, pentane/ethyl acetate 9:1) gave pure **2c** (387 mg, 85%).