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Aza-Diels–Alder reaction in fluorinated alcohols. A one-pot synthesis of tetrahydroquinolines

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Abstract—Hexafluoroisopropanol and trifluoroethanol are found to promote imino-Diels–Alder reactions of the *N*-aryl aldimine **1** with alkyl vinyl ethers to afford the corresponding tetrahydroquinolines in good yields without Lewis acid under mild and neutral conditions. The reaction is also efficient in a three component process from aldehyde, amine and vinyl ethers. © 2002 Elsevier Science Ltd. All rights reserved.

Aza-Diels–Alder is one of the most powerful synthetic routes for constructing nitrogen containing six-membered heterocycles.[1] Imines derived from aromatic amines can act as heterodienes and undergo an imino-Diels–Alder reaction with various dienophiles, leading to tetrahydroquinolines. Lewis acids ($BF_3{\cdot}Et_2O$, $TiCl_4$, $AlCl_3$, $InCl_3$) are known to catalyze these reactions and replace advantageously Brönsted acids.[2–4] More recently lanthanide triflates ($Yb(OTf)_3$, $Sc(OTf)_3$, $GdCl_3$…) have also been used as catalysts for this reaction.[5,6] More than a stoichiometric amount of Lewis acid is often required, because the acids are trapped by nitrogen[1] of both reactant and product, and these latter could suffer from these strong acidic conditions. Despite of improvement by performing these aza-Diels–Alder reactions in one-pot through coupling with aldehydes, new and milder conditions are still required for these transformations.

In our interest in the use of a fluorous medium in organic synthesis, we showed that hexafluoroisopropanol (HFIP), used as a solvent, could promote epoxide ring opening. Its high ability to give hydrogen bonds ($\alpha = 1.96$),[7] its high ionizing power ($Y = 3.82$) and its low nucleophily allowed to perform oxirane ring opening reactions with aromatic amines and thiols under mild and neutral conditions, avoiding the use of any base, metal or Lewis acid catalysis.[8] These properties of fluoroalkyl alcohols have been exploited in some other organic reactions.[9] To our knowledge, only two examples have been reported where HFIP facilitates a cycloaddition reaction.[10] In this line we investigated the aza-Diels–Alder reaction of aldimines with dienophiles in fluoroalcohols.

N-Benzilidene aniline **1a** was chosen as substrate and was treated with ethyl vinyl ether **2a** in HFIP at room temperature. The aldimine acted as a heterodiene and the reaction proceeded smoothly to afford, after 15 min, the expected tetrahydroquinoline **3a** in 71% yield. Tetrahydroquinoline **3a** was obtained as only one regioisomer and in 90/10 *cis*/*trans* stereoselectivity. The reaction was also investigated in trifluoroethanol. The reaction proceed smoothly in trifluoroethanol (TFE) and was as fast and efficient as in HFIP and provided a 90/10 mixture of **3a**. Reactions with the 2,3-dihydrofuran **2b** and the 3,4-dihydro-2*H*-pyran **2c**, performed in HFIP, afforded tetrahydroquinoline derivatives in good yields but with no stereoselectivity (Table 1). The structures of compounds were determined by IR, ^1H, ^{13}C NMR, and were identical to the literature data.[2e,5,6c] From **2b**, the cycloadduct was also obtained in good yield in TFE. Conversely, dihydropyran **2c** was quite unreactive when the reaction was performed in TFE. HFIP and TFE gave the same results in selectivities with some differences in the reaction times. Except from the dihydrofuran **2b**, where reaction times and yields are similar, with enol ethers **2a** and **2c** in TFE, the reactions were slower than in HFIP. These differences between these fluoroalkyl alcohols were observed to the selective oxidation of sulfides to sulfoxides and ring opening of epoxides with thiols and aromatic amines.[8]

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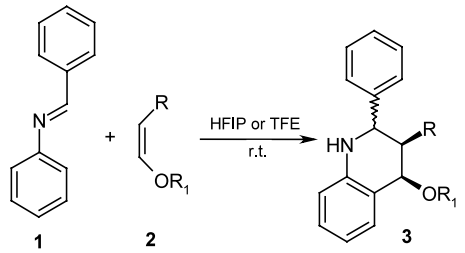
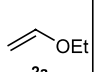
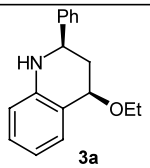
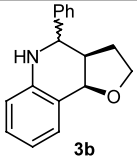
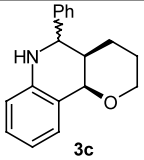
Table 1. Syntheses of tetrahydroquinoline derivatives in HFIP or TFE[a]



1 2 3

Entry	2	3	*Cis/trans*	Rdt (%)[b] in HFIP (time)	Rdt (%)[b] in TFE (time)
1	 **2a**	 **3a**	90/10	71 (0.25h)	92 (1h)
2	 **2b**	 **3b**	50/50	96 (1h)	97 (1h)
3	 **2c**	 **3c**	50/50	91 (4h)	Traces (2 days)

[a] Reactions were performed as follows: imine **1** (1 mmol), enol ether **2** (2 mmol) were placed in 3 mL of HFIP or TFE.
[b] Yield of isolated product.

The great advantages of the present procedure using fluoroalkyl alcohols as promoters of aza-Diels–Alder reaction are the mild and neutral conditions which allow to perform the reaction even with acid sensitive compounds.

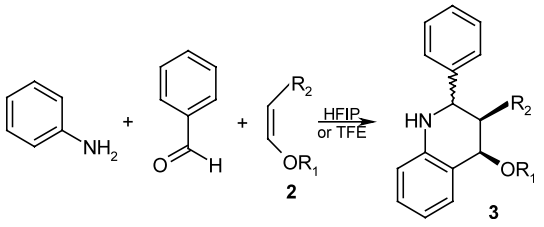
We then investigated the three-component cycloaddition from aldehydes.

Multiple component condensation reactions are powerful tools for the fast assembly of polysubstituted molecules[11] and were largely used in Lewis acid-catalysed hetero-Diels–Alder.[4b,5,6d] In this reaction, the Lewis acid catalysed both the preformation of imine and the cycloaddition.

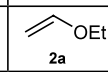
The difficulty would reside in the formation of imine from aldehyde and amine in fluoroalkyl alcohols. We have thus to check if fluoroalkyl alcohols could also promote the formation of aldimine from aldehyde. So far such a reaction has only been studied with the very reactive fluoral.[12]

The three-component coupling reaction has been investigated at room temperature in HFIP and TFE, with 1 equiv. of the benzaldehyde, 1 equiv. of aniline with no addition of drying agent. GC analysis of samples suggested that after 1 h the aldehyde was completely converted into the corresponding imine. The enol ether was then added to the solution and after complete reaction the fluorous alcohol was recovered by distillation from the crude product, and products were purified on silica gel by flash chromatography. In HFIP, the tetrahydroquinolines **3a** and **3b** were isolated in 81% yield after 4 h, and in 96% yield after 2 h, respectively. Similarly benzaldehyde, aniline, and enol ethers **2a** and **2b** reacted efficiently in TFE without drying agent to give tetrahydroquinolines **3a** and **3b** in 76 and 96% yields, respectively (Table 2).

Table 2. One-pot synthesis of tetrahydroquinolines from benzaldehyde, aniline, and enol ethers in HFIP or TFE[a]



2 3

Entry	2	*Cis/trans*	**3** yield (%) in HFIP (time)	**3** Yield (%) in TFE (time)
1	 **2a**	90/10	**3a** 81 (4h)[b]	**3a** 76 (2h)
2	 **2b**	50/50	**3b** 96 (3h)	**3b** 96 (1h)

[a] Reactions were performed as follows: amine (1 mmol), aldehyde (1 mmol) were placed in 3 mL of solvent. After 1 h, enol ether (2 mmol) was added.
[b] 4 eq. of **2a** was required.

In conclusion, we have reported that HFIP and TFE are excellent solvents for the synthesis of tetrahydroquinolines through the imino-Diels–Alder reaction of aldehyde and amine with enol ethers. They are able to promote the formation of imine without drying agent and to promote the cycloaddition reaction without any catalyst. The procedure offers several advantages like mild and neutral reaction conditions, good yields of products, operational simplicity and ease of isolation of the products. The fluorinated solvents could be recovered and reused for other reactions, and there are no effluents after reaction.

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CT 2000-00002) and the COST-Action 'Fluorous Medium' D12/98/0012.

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