A practical synthesis of 2,3-dihydro-1,5-benzothiazepines

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2,3-Dihydro-1,5-benzothiazepines have been obtained through a domino process involving a Michael addition of 2-aminothiophenols to chalcones, followed by in situ cyclization. Up to 98% chemical yields have been obtained at room temperature under essentially neutral conditions by using hexafluoro 2-propanol as an efficient medium.

Introduction

The synthesis of heterocyclic compounds has received a great deal of attention, most notably for the construction of the 1,5-benzothiazepine scaffolds owing to their multiple pharmacological and biological activities, such as calcium antagonist, antihypertensive, antiarrhythmic, antibacterial, and antidepressant.[1]

The commonly adopted strategy to construct the ring skeleton of 2,3-dihydro-1,5-benzothiazepine **4** is the reaction of *ortho*-aminothiophenol (**2a**) with α,β-unsaturated ketones **1** (chalcones) in a two steps domino process. The most general accepted mechanism entails the 1,4-conjugate addition by the thiol group of **2** on chalcones **1** leading to a thia-Michael adduct **3** followed by the intramolecular nucleophilic attack of the amino group on the carbonyl to install the imino group (Scheme 1).
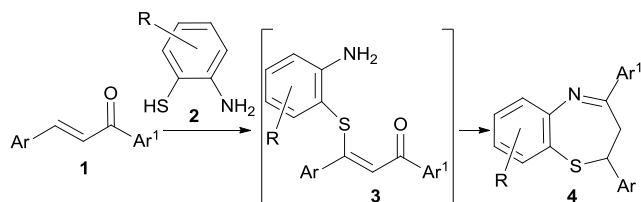
Scheme 1. Thia-Michael/imine cyclization domino approach to 2,3-dihydro-1,5-benzothiazepines **4**.

Traditional methods are carried out under harsh reaction conditions including high temperature, the use of toxic, difficult to recover organic solvents (DMF, toluene, DCE), corrosive acids (AcOH, TFA, HCl), bases (pyridine, piperidine), or electrophilic activation by Lewis acids. Moreover, the use of both Brønsted and Lewis acids releases polluting waste or poisonous metals.

Some of the more recent procedures reported in the literature involve Lewis acids such as Er(OTf)$_3$ in CH$_3$CN,[2] cerium(IV) ammonium nitrate in ethanol at 60-65 °C under ultrasonic irradiation,[3] Mg(ClO$_4$)$_2$ in DCE under reflux,[4] Ga(OTf)$_3$ in CH$_3$CN at 60 °C,[5] Brønsted acids such as glacial acetic acid in toluene under reflux[6] or in DMF by a microwave promoted process.[7]

Two papers deal with the use of ionic liquids, 1-octyl-3-methyl imidazolium isothiocyanate ([omim]SCN) at 60 °C for 18 h[8] and N-methylimidazolium nitrate ([hmim]NO$_3$) at 80 °C for the synthesis of a series of 1,5-benzothiazepines.[9]

As an alternative to homogeneous catalysis, several methods take advantage of strong acids adsorbed on solid supports such as fluoroboric acid[10] or perchloric acid[11] adsorbed on silica-gel (HBF$_4$-SiO$_2$/HClO$_4$-SiO$_2$) in methanol. Mesoporous materials such as MCM-41 in refluxing toluene[12] or Pd nanoparticle decorated nanocrystalline ZSM-5 catalyst in toluene at 85 °C[13] were also employed. However, a general drawback of these methods is the high catalyst loading in order to obtain good results.

Despite several procedures available for the synthesis of benzothiazepines **4**, we decided to explore the possibility to develop a more practical approach avoiding the use of any promoting agent.

Here we report the results of a study on the use of hexafluoro 2-propanol (HFIP) as an efficient medium for this two-component domino process.

In recent years, fluorous solvents have attracted increasing interest as catalysts, solvents or co-solvents in organic synthesis owing to their unique features.

They allow to carry out reactions, which usually require strong Lewis or Brønsted acids and high temperatures, under mild, neutral conditions at moderate temperature. Compared to other fluorinated solvents, HFIP is unique due to its high ionization power, strong hydrogen bond ability, low nucleophilicity and mild acidic character.[14] The fields of application of HFIP range from oxidations, nucleophilic oxirane ring openings, cycloaddition reactions of imines,[15] electrophilic aromatic substitution reactions,[16] aza- and sulfa-Michael reactions,[17,18] to cite only a few. Also, in some cases, the selectivity of the reaction can be modified and finely tuned by

HFIP in comparison to other solvents.[18-19] Recently the critical role of HFIP in a number of enantioselective processes has been widely recognized.[17,20] Although HFIP cannot be described as a cheap solvent, it can be easily recovered during work-up and recycled owing to its low boiling point. As reported in ESI of the manuscript, the amount of consumed HFIP is very low and does not have a significant impact on process economy.[16]

In particular, the acidity of HFIP (pKa = 9.2) seemed to be tailored to activate both the Michael acceptor during the conjugate addition and the carbonyl group in the cyclization step. On the other hand, it cannot deactivate the amino group by protonation.

Thus, the property of this solvent was exploited to carry out the synthesis of 2,3-dihydro-1,5-benzothiazepines **4** in the absence of catalysts.

Results and discussion

At the onset of the study equimolar amounts of *trans*-chalcone **1a** and *ortho*-aminothiophenol (**2a**) were stirred at 28 °C in HFIP without any catalyst. After 2 hours the chromatographic purification of the crude mixture gave the 2,4-diphenyl-2,3-dihydro-1,5-benzothiazepine (**4a**) in a 55% yield along with minor amounts of the Michael adduct **3a**, the starting chalcone **1a**, and 2,2'-diaminodiphenyl disulfide (**5**) (Scheme 2).
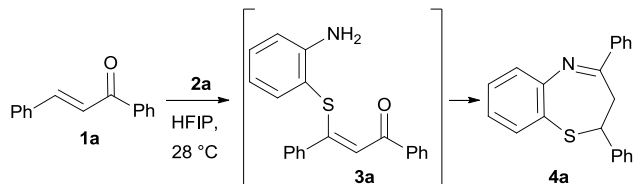
Scheme 2. Domino approach to 2,4-diphenyl-2,3-dihydro-1,5-benzothiazepine (**4a**).

The formation of disulfide **5** was not surprising in view of the known HFIP ability to promote the oxidation of thiols.[21] Also, in our case, the oxidation process was meaningfully accelerated by the presence of the electro-donating *ortho* amino group on the aromatic ring of the thiol.[22] When a small excess of **2a** (1.2 eq) was employed in order to minimize the effect of the competitive oxidation, the yield of the desired benzothiazepine **4a** could be increased to 72% (Table 1, entry 1).§ The addition of sodium sulfite or sodium hydroxymethanesulfinate (rongalite) or ascorbic acid in order to reduce *in situ* the disulfide, did not work, likely owing to their negligible solubility in the reaction medium.

Table 1. Optimization of the synthesis of 2,3-dihydro-1,5-diphenylbenzothiazepine 4a.[a]

Entry	**2** (eq)	Solvent	t (h)	Yield **3a** (%)	Yield **4a** (%)
1	1.2	HFIP	3	-	72
2	1.5	HFIP	3	-	70
3[c]	1.2	HFIP	3	-	71
4	2	HFIP	3	-	86
5[c]	2	HFIP	3	-	84
6	1.2	HFIP/DCM 1-4	24	15	45
7	2	HFIP/DCM 1-4	24	29	56
8[d]	1.2	HFIP/DCM 1-9	24	15	45
9	1.2	DCM	24	59	-
10[c]	1.2	HFIP/DCM 1-4	24	-	50
11[c]	2	HFIP/DCM 1-4	24	-	80
12	1.2	HFIP/acetone 1-4	24	77	< 5
13	1.2	HFIP/CH$_3$CN 1-4	24	88	< 5
14	1.2	HFIP/AcOEt 1-4	24	87	< 5
15	1.2	HFIP/dioxane 1-4	24	2	3
16	1.2	HFIP/DMF 1-4	24	13	15

[a] Reaction conditions: 1a (0.125 mmol), HFIP (0.15 mL, 11 eq), 28 °C. [b] Unless otherwise noted the yields were determined by ^{1}H NMR in the presence of internal standard. [c] In the presence of 4Å molecular sieves. [d] HFIP (1.1 eq).

In order to ascertain if HFIP could be employed as a co-solvent, we used different 1:4 V/V mixtures HFIP/organic solvent as reaction medium.

Among the solvents examined, only the combination HFIP/DCM led to the formation of benzothiazepine **4a**, although in lower yield and longer reaction time compared to our previous conditions (Table 1, entry 6). The amount of HFIP in the mixture can be decreased without affecting the reaction outcome (Table 1, entry 8).

Notably, when the reaction has been carried out in DCM only, 59% yield of the Michael adduct **3a** was isolated without formation of benzothiazepine **4a** (Table 1, entry 9). On the other hand, when the Michael adduct **3a** was stirred in HFIP/DCM mixture under the usual conditions (28 °C, 24 h) the benzothiazepine **4a** could be recovered in quantitative yield.

A significant amount of starting chalcone **1a** was recovered both in neat HFIP and in the mixture HFIP/DCM due to the formation of 2,2'-diaminodiphenyl disulfide (**5**) (Table 1, entry 1,6). These results show that the competitive oxidation plays an important role. It is interesting to note that the intermediate Michael adduct **3a** was completely converted to benzothiazepine **4a** only in neat HFIP (Table 1, entry 1), whereas in neat DCM **4a** is not formed at all (Table 1, entry 9). An intermediate situation is obtained in the mixture HFIP/DCM (Table 1, entry 6).

When a larger excess (2 eq) of thiol **2a** was used, chalcone **1a** was almost completely converted in neat HFIP affording 86% of benzothiazepine **4a** after HFIP removal by distillation and chromatographic purification (Table 1, entry 4). The excess of thiol **2a** was mostly recovered as the corresponding disulfide. The latter can also be reduced by treatment with LiCl/NaBH$_4$ in order to recycle **2a**.[23]

A similar chalcone conversion was also observed in the DCM/HFIP mixture although a lower yield of **4a** was obtained due to the presence of uncyclized Michael adduct **3a** (Table 1, entry 7).

When the reaction was carried out by using 2 equivalents of **2a** in DCM (24 h), followed by addition of HFIP (3 h), 36% of **3a** was obtained along with 33% of **4a**. In addition, the reaction performed in HFIP at 4 °C for 3 h furnished a 1.65/1 mixture of **3a/4**.

These evidences highlight that in the first step the amount of thiol is the most important parameter, whereas HFIP is essential in accelerating the cyclization step that require carbonyl activation, thus behaving as a hydrogen bond donor.[24] Notwithstanding, HFIP is also capable to accelerate the first step of the process by a dual interaction with both aminothiophenol **2** and chalcones **1**. In fact, as previously reported, HFIP might behave as a proton shuttle promoting the proton shift from the thiol to the first anionic Michael adduct (Scheme 3).[17]
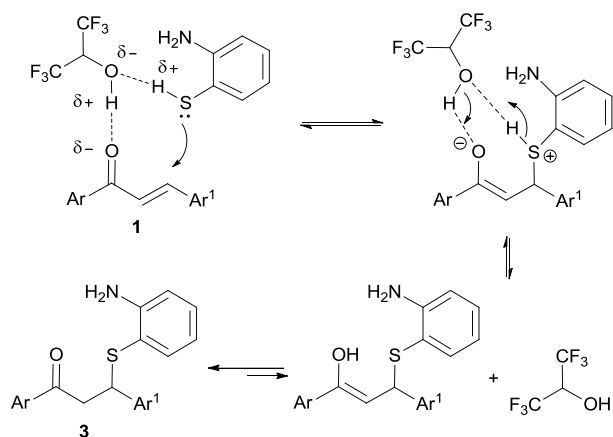

Scheme 3. Proton shuttle strategy in the Michael addition step

Solvents different from DCM gave unsatisfactory results. In particular, when acetone, acetonitrile or ethyl acetate have been used, the Michael adduct **3a** has been recovered with yields of 77%, 88% and 87%, respectively, whereas the benzothiazepine **4a** was formed in less than 5% yield (Table 1, entries 12-14). On the other hand, the use of dioxane or DMF provided only low yields of almost equimolar mixtures of **3a** and **4a** (Table 1, entries 15,16). In order to investigate the influence of water on the reaction outcome, 4Å molecular sieves were added. When the reaction was carried out in neat HFIP, no improvement had been observed (Table 1, entries 1,3). However, when the mixture HFIP/DCM was used in the presence of molecular sieves, the Michael adduct had been completely converted to benzothiazepine (Table 1, entries 6,10 and 7,11).

Under the best reaction conditions described above the reaction scope was shown by reacting *ortho*-aminothiophenol (**2a**) with a series of substituted chalcones **1a-p** under the optimized conditions generating the corresponding benzothiazepines **4a-p** in up to 98% yield (Table 2). The reaction was found to be tolerant to a number of electron withdrawing or electron donating substituents such as NO_2, OH, OCH_3, $OCOCH_3$, Cl, Br. Heteroaromatic chalcones **1l-n** were also shown to be good substrates for the reaction although the yield was moderate in the case of benzothiazepine **4l** (Table 2, entry 12-14).

The 2-aminothiophenol scope was investigated by using as nucleophilic partners substituted 2-aminothiophenols bearing electron-withdrawing or electron-releasing substituents in the reaction with chalcone **1a** under the optimized conditions (Scheme 4).
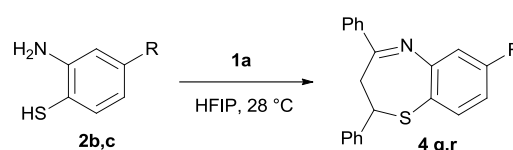
2b, **4q**; R = Cl, 7 h, 35% yield
2c, **4r**; R = Me, 3 h, 93% yield

Scheme 4. Use of substituted 2-aminothiophenols

As expected, excellent result was obtained by using 4-methyl-2-aminothiophenol (**2c**), bearing the electron-releasing methyl group, whereas lower yield was obtained with 4-chloro-2-aminothiophenol (**2b**), bearing the electron-withdrawing chlorine substituent (Scheme 4).

Less nucleophilic *ortho*-aminophenol and *ortho*-phenylene diamine failed to give the corresponding cyclized products also after longer reaction times (66 h) at 45 °C.

We never observed imine intermediates by ^{1}H-NMR analysis of the crude reaction mixtures. These results represent a strong evidence in favor of a reaction pathway consisting of a 1,4 conjugate addition followed by ring closure, according to the mechanism generally reported in the literature.[6,8,15,25]

In order to access the feasibility of the procedure on larger scale a few experiments have been carried out by recovering and recycling HFIP in subsequent runs using chalcone **1a**. The yield of 2,3-dihydro-1,5-benzothiazepine **4a** remained unchanged and only less than 10% of HFIP was added in order to restore identical initial conditions.[&]
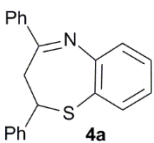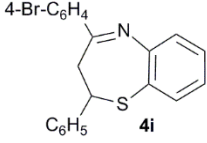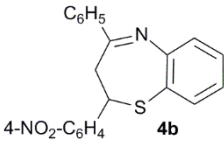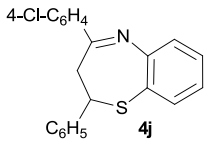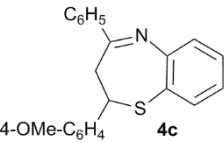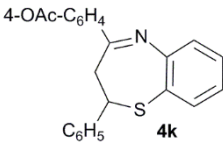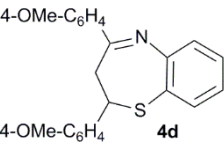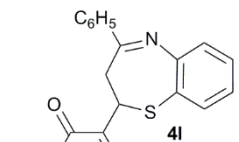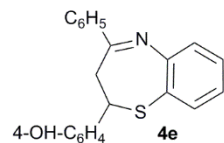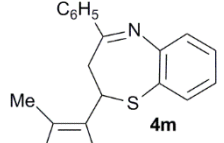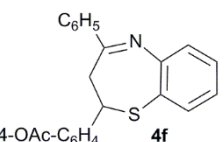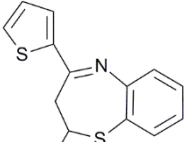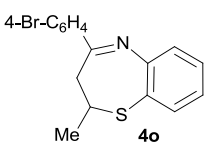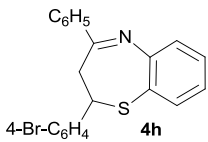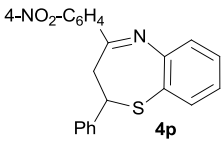
The method was successfully applied to the synthesis of 2-(4-methylphenyl)-4-(4-bromophenyl)-2,3-dihydro-1,5benzothiazepine (**4o**) which has recently been used to modulate the activity of store-operated calcium channels (SOCs).[26] The regulation of SOCs enables to treat diverse disorders including autoimmune, liver and kidney diseases.
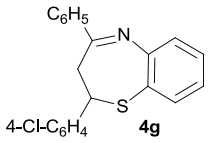
Benzothiazepine **4n** has been investigated for antioxidant activity.[2]

Conclusion

In summary, we have used for the first time hexafluoro-2-propanol as an efficient medium for the synthesis of 2,3-

Table 2. Benzothiazepine **4a-p.**[a]

Entry	t (h)	Benzothiazepine	Yield[b] (%)	Entry	t (h)	Benzothiazepine	Yield[b] (%)
1	3	**4a**	86	9	6	**4i**	75
2	3	**4b**	98	10	4	**4j**	91
3	6	**4c**	81	11	5	**4k**	70
4	6	**4d**	72	12	6	**4l**	41
5	3.5	**4e**	87	13	11	**4m**	60
6	4	**4f**	90	14	12	**4n**	63
7	3	**4g**	73	15	6	**4o**	65
8	3	**4h**	74	16	4	**4p**	69

[a] Reaction conditions: **2** (2 eq), 28 °C, HFIP (11 eq). [b] Isolated yields.

dihydro-1,5-benzothiazepines **4a-r** under neutral conditions, at room temperature, in short reaction times.

We have demonstrated that our novel protocol allows to employ a variety of chalcones and 2-aminothiophenols bearing both electron-donor or electron-withdrawing substituents to provide a simple access to benzothiazepines.

We anticipate that the mild conditions employed in the new procedure will allow it to be used for the large-scale synthesis of a large number of benzothiazepines.

In addition, hexafluoro-2-propanol can be easily recovered by distillation and recycled in further reactions.

Conflicts of Interest

There are no conflicts of interest to declare.

Notes and references

§ The use of an excess of cheap chalcone **1a** was unpractical owing to its cumbersome separation from benzothiazepine **4a** by chromatography.

& See ESI for details.

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