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Fluoroalkylated α,β-Unsaturated Imines as Synthons for the Preparation of Fluorinated Triazinane-2,4-diones and Dihydropyrimidin-2(1*H*)-ones

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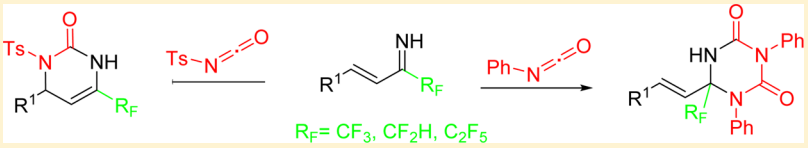
Supporting Information



ABSTRACT: A regioselective addition of isocyanates to fluoroalkylated α,β-unsaturated imines **1** is described. Fluoroalkyl-substituted triazinane-2,4-diones **4** are obtained by the reaction of phenyl isocyanate with fluorinated imines **1**, while fluorinated dihydropyridin-2(1*H*)-ones **7** are prepared when tosyl isocyanate is used. Tetrahydro-pyridin-2(1*H*)-one **10** is obtained by catalytic reduction of dihydropyridin-2(1*H*)-one **7**. Computational studies are performed to explain the different behaviors of both isocyanates and the mechanisms of the processes.

INTRODUCTION

α,β-Unsaturated imines (**I**, Scheme 1), also called 1-azadienes, are a versatile family of compounds with a wide range of applications in preparative organic chemistry.[1] These substrates are used not only for the preparation of six-membered heterocycles through the well-known aza-Diels−Alder reaction (ADAR, compounds **II**, Scheme 1)[2] but also for the construction of five-membered heterocycles by means of the [4 + 1] cycloadditions for the synthesis of pyrroles[3] or the [3 + 2] cycloadditions for the preparation of both β-lactams[4a] and highly fuctionalizad cyclopentenes.[4b] Moreover, owing to their ambident electrophilic character, α,β-unsaturated imines can either undergo 1,2[5] or conjugate 1,4[6] nucleophilic addition processes (compounds **III** and **IV**, Scheme 1). However, controlling the regioselectivity is generally difficult, and very often the double-nucleophilic addition products are obtained.[7] Dihydropyrimidin-2(1*H*)-ones (DHPMs) are important heterocycles[8,9] that form the core of a wide number of biologically active derivatives,[10] such as antihypertensive,[11] anticancer,[12] antioxidant,[13] antimicrobial,[14] anti-HIV activities,[15] NaI symporter[16] or enzyme inhibitors,[17] calcium channel blockers,[18] and selective A2B adenosine receptor antagonists.[19]

In this context, fluoroorganic compounds have received a great deal of attention since the incorporation of a fluorine containing group into an organic molecule dramatically alters its physical, chemical and biological properties.[20] Due to the unique properties of the fluorine atom, fluorinated molecules occupy a significant place[21] in pharmaceutical/medicinal,[22] agrochemical,[23] and material sciences.[24]

In recent years, an elegant and efficient preparation of DHMPs has been developed from isocyanates and α,β-unsaturated imines,[25] and when alkenyloxazolines[26] were used the preparation of bicyclic DHMPs was reported. We have been involved in the chemistry of heterodienes derived from amino acids and have developed synthetic methodologies for the preparation of 1-azadienes such as α,β-unsaturated imines, hydrazones, or oximes. We also reported an efficient procedure for the synthesis of electron-poor 1-azadienes derived from α-amino acids or α-aminophosphonates using an aza-Wittig approach, as well as successful normal ADA reactions of α,β-unsaturated *N*-arylimines, hydrazones, and ADA reaction of α,β-unsaturated sulfinylmines with electron-rich dienophiles and Michael additions (1,4 addition) of α,β-unsaturated *N*-arylimines. In the development of new fluorinated substrates, we prepared the first stable N-unsubstituted α,β-unsaturated imine[27] **Ia** (Scheme 2) from primary fluorine-substituted enaminophosphonates,[28,29] and we used these derivatives for the preparation of vinylogous α-aminonitriles **IIIa**,[30] β-aminonitriles **IIIb** (X = CN),[30] and β-aminoesters **IIIb** (X = CO_2Et),[31] obtained by 1,2-addition of trimethylsilyl cyanide, acetonitrile, or ethyl acetate, while the regioselective Michael addition of α-carbanions derived from carboxylic esters and nitriles to fluorinated imines **I** may afford functionalized pyridine derivatives **IV**.[31,32]

In this context, the development of new methods for the preparation of fluorine-substituted heterocycles is an interesting goal in synthetic organic chemistry not only because of their use in medicinal chemistry[22] but also for the development of active ingredients for crop protection[23] and materials.[24] Continuing with our interest in the chemistry of fluorinated derivatives as well as 1-azadienes, here we report the

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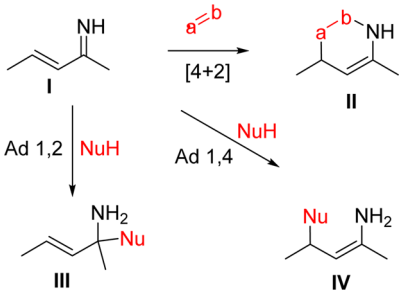
Scheme 1. Reactivity Pattern of α,β-Unsaturated Imines I



preparation of novel fluoroalkyl-substituted triazinane diones **V** and DHPMs **VI** (Scheme 2).

RESULTS AND DISCUSSION

Synthesis of Fluoroalkylated Triazinane-2,4-diones 4. Unsaturated imines **1** were prepared in good yields by olefination reaction of phosphorated enamines and aldehydes,[27a,28] and DHPMs are a class of important heterocycles used not only in preparative organic chemistry[8] but also in medicinal chemistry.[11−19] Our initial approach to fluorinated DHPMs was based on the ADA reaction of 1-azadiene **1** and phenyl isocyanate.[25] However, the treatment of α,β-unsaturated imine **1a** (R^1 = *p*-$CH_3C_6H_4$, R_F = CF_3) with phenyl isocyanate **2a** at room temperature did not give the fluorinated DHPMs **3a**, and the corresponding vinylogous triazinane-2,4-dione **4a** (R^1 = *p*-$CH_3C_6H_4$, R_F = CF_3, Scheme 3) was obtained instead in a regioselective fashion in low yield. This compound **4a** was characterized on the basis of spectroscopic data. The high-resolution mass spectrum (HRMS, M^+ 451.1508) is consistent with the incorporation of two molecules of phenyl isocyanate **2a** into fluorinated azadiene **1** (1:2 cycloadduct).

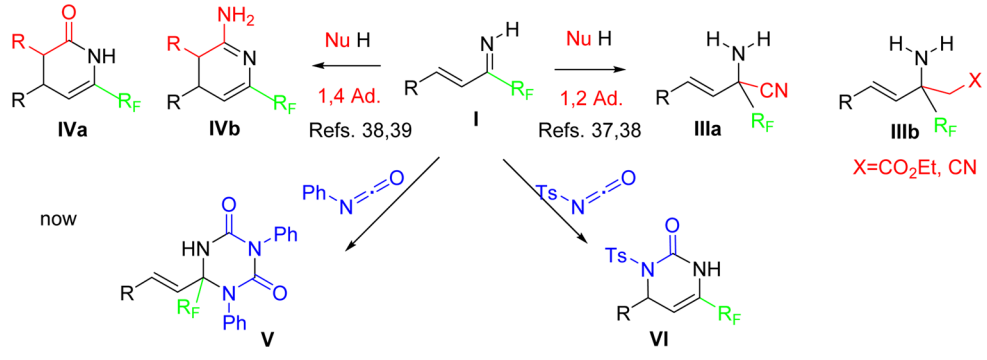
This behavior prompted us to reexamine the process in order to improve the low yield obtained initially. When 2 equiv of phenyl isocyanate **2a** was used, the isolation of the triazinane-2,4-dione **4a** in good yield (85%, Scheme 3, Table 1, entry 1) was achieved. The process was also extended to trifluoromethyl- and difluoromethyl-substituted imines **1b−e** (R_F = CF_3, CHF_2) containing aromatic (R = *p*-$NO_2C_6H_4$) or heteroaromatic (R^1 = 2-furyl) substituents, and the corresponding heterocycles **4b−e** were obtained in good yields (Scheme 3, Table 1, entries 2−5).

The formation of these heterocycles **4a−e** could be explained as outlined in Scheme 3. Addition of phenyl isocyanate **2a** to unsaturated imines **1a−e** may give initially the corresponding zwitterionic intermediate **5**, which by addition of a second equivalent of phenyl isocyanate **2a**, followed by cyclization, afforded triazinane derivatives **4a−e**. A second pathway is possible whereby the first zwitterionic intermediate by an 1,3-H-shift could give nonisolated monoadduct **6**, which by addition of a second equivalent of phenyl isocyanate **2a** followed by ring closure can similarly afford the six-membered heterocycles **4a−e**. Formally, the process may be considered as a [2 + 2 + 2] cycloaddition involving the very reactive C═N double bond from the imines **1** and both C═N bonds from the two molecules of isocyanate **2a**. Similar [2 + 2 + 2] cycloaddition processes involving two molecules of phenyl isocyanate and the C═N of aldimines,[33a] ketimines,[5a] hydrazones,[33b] isoquinolines,[33c] or acetimidates[33d] have been described. Although triazinane-2,4-dione heterocycles have been used in herbicidal formulations[34] and in pharmaceutical compositions,[35] few examples of preparation of the triazinane-2,4-dione heterocycles have been reported.[33] This process represents, as far as we know, the first example of preparation of fluorinated triazinane-2,4-diones **4**.

To have a better understanding of factors controlling the process, we computationally examined the reactions between azadienes **1a** (R^1 = *p*-$CH_3C_6H_4$, R_F = CF_3), **1c** (R^1 = *p*-$NO_2C_6H_4$, R_F = CF_3), **1d** (R^1 = 2-furyl, R_F = CF_3), **1e** (R^1 = 2-furyl, R_F = CHF_2), and **1f** (R^1 = *p*-F-C_6H_4, R_F = CF_3) and phenyl isocyanate **2a** (see the Supporting Information for details).[36−42] Thus, the approach of 1-azadienes **1a,c−f** to phenyl isocyanate could take place preferentially in the configuration *s-trans*-1*Z*,3*E* (see Figure 1 in the Supporting Information) through transition states **TS1a,c−f** or **TS2a,c−f** which could lead to two different zwitterion intermediates **M1a,c−f** or **M2a,c−f**. respectively (Scheme 4). Computational results indicate that in the presence of THF, the activation barriers corresponding to the approach 1-azadienes **1a,c−f** through transition structures **TS2a,c−f** are very similar to activation barriers corresponding to transition structures **TS1a,c−f** and calculated free energy differences indicate that zwitterionic intermediates **M2a,c−f** are more stable than **M1a,c−f** (see Table 1 and Figures 2 and 3 in the Supporting Information for a comparative of results), although all the processes are slightly endothermic, with reaction energies for the formation of **M2a,c−f** ranging from 1.8 kcal/mol (for **M2e**, R^1 = 2-furyl, R_F = CHF_2) to 6.5 kcal/mol (for **M2c**, R^1 = *p*-$NO_2C_6H_4$, R_F = CF_3).[43] As an example in Figure 1, the energy profile for the reaction of **1a** with **2a** to give **M1a** and **M2a** is shown.

Next, we studied the second step of the reaction for the generation of vinylogous triazinane derivatives **4** (1:2 cycloadducts) vs the alternative DHPMs **3** (1:1 cycloadducts). The

Scheme 2. Nucleophilic Reactions (1,2 vs 1,4) of Fluorinated α,β-Unsaturated Imines I and Reactions with Isocyanates



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Scheme 3. Synthesis of Fluoroalkylated Triazinane-1,3-diones 4

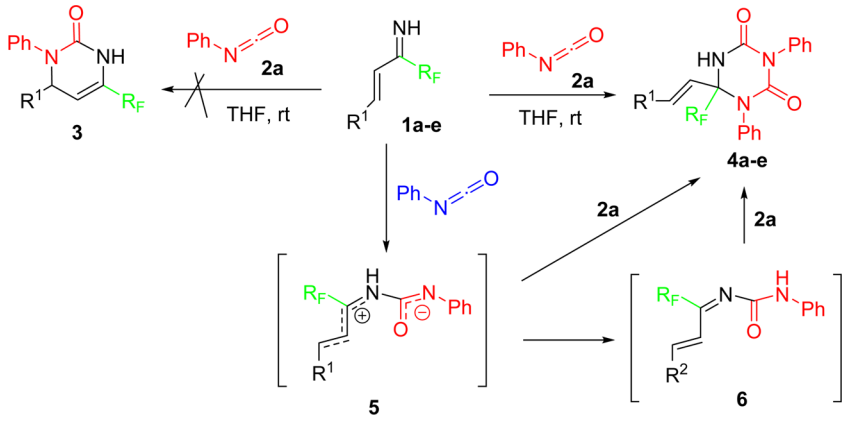


Table 1. Fluoroalkylated Triazinane-2,4-diones 4

entry	compd	R^1	R_F	yield[a] (%)
1	**4a**	*p*-$CH_3C_6H_4$	CF_3	85
2	**4b**	*p*-$NO_2C_6H_4$	CHF_2	75
3	**4c**	*p*-$NO_2C_6H_4$	CF_3	83
4	**4d**	2-furyl	CF_3	92
5	**4e**	2-furyl	CHF_2	90

[a]Yield of isolated purified compounds obtained from **1a−e**.

hypothetical formation of DHPMs **3** could be explained by direct intramolecular cyclization of the more stable zwitterionic intermediates **M2a,c−f**. However, the formation of triazinane compounds **4a,c−f** may involve the addition of a second molecule of isocyanate **2a** to intermediates **M2a,c−f** to give, through transition structures **TS5a,c−f**, new zwitterionic intermediates **M3a,c−f**, that finally cyclize to triazinane products **4**, through transition structures **TS6a,c−f** (see Scheme 4). Alternatively, nonisolated monoadducts **6a,c−f** may be generated from the first zwitterionic intermediates **M2a,c−f** through a **TS4a,c−f**. The addition of a second

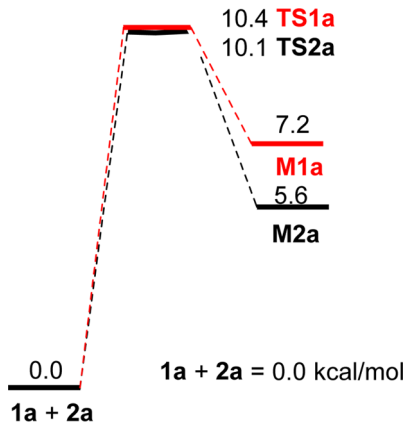
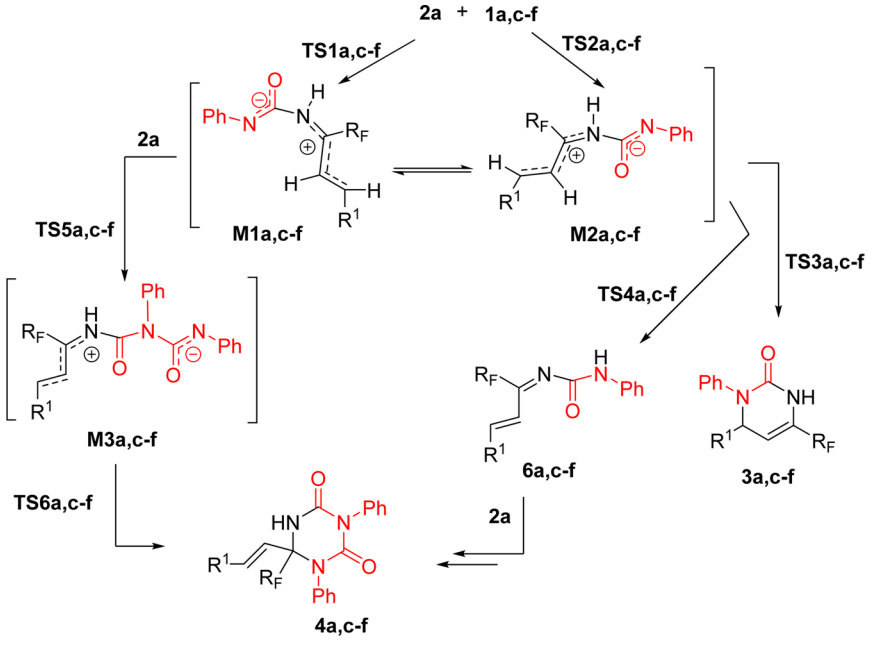


Figure 1. Energy profile for transformation from reactants **1a** and **2a** to zwitterionic intermediates **M1a** and **M2a** at the M06-2X(PCM)/6-311+G**//B3LYP/6-31G* + ΔZPVE level (unit: kcal/mol) using tetrahydrofuran as solvent.

Scheme 4. Different Pathways for the Reaction of 1a,c−f with 2a



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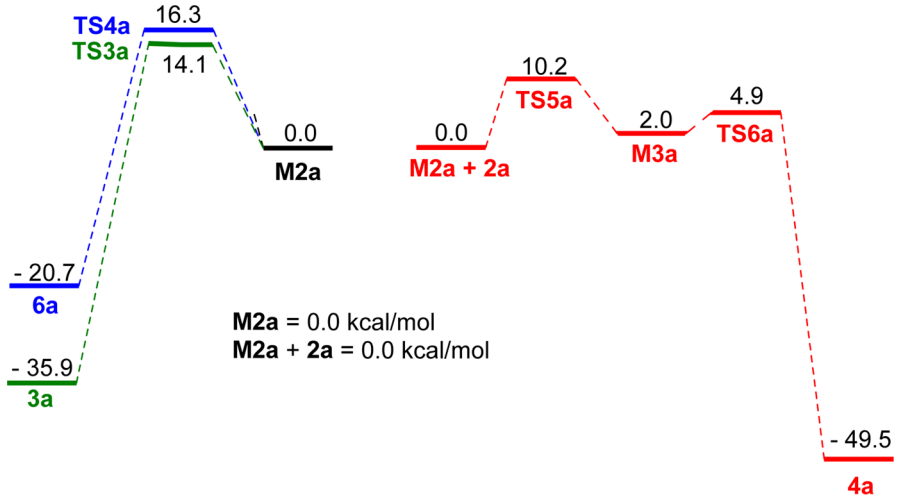

Figure 2. Energy profile for transformation from zwitterionic intermediate **M2a** to the products **3a**, **4a**, and **6a** at the M06-2X(PCM)/6-311+G**//B3LYP/6-31G* + ΔZPVE level (unit: kcal/mol) using tetrahydrofuran as solvent.

equivalent of phenyl isocyanate **2a** followed by ring closure would lead to heterocycles **4a,c–f**. Thus, we studied and compared, (i) the formation of **M3a,c–f** through **TS5a,c–f**, (ii) the formation of **3a,c–f** through **TS3a,c–f**, and (iii) the formation of **6a,c–f** through **TS4a,c–f** (Scheme 4).

In all cases, in the presence of THF as the solvent, computational results indicate that the pathways involving transition structures **TS5a,c–f** for the formation of zwitterionic intermediates **M3a,c–f** exhibit the lowest activation barriers (see Table 2 and Figure 4 in the Supporting Information for details).[43] The processes for the formation of **3** and **6** are exothermic, but it is very important to note that the activation barriers associate with the cyclization of **M3a,c–f** to give **4a,c–f** through **TS6a,c–f** are very low (in THF lower than 5 kcal/mol in all cases), reflecting that the reaction is very facile and the cyclization is very fast. Moreover, in all cases, the formation of **4a,c–f** from **M3a,c–f** is much more exothermic (around 20 kcal/mol in all cases) than the formation of **3a,c–f** and also (around 30 kcal/mol in all cases) for the formation of **6a,c–f**. As an example in Figure 2, the energy profile for the formation of compounds **3a**, **4a**, and **6a** from **M2a** is shown (for full comparisons of energetics, see the Supporting Information).

These computational results indicate that the formation of **4a,c–f** in solution of THF is favored kinetically and thermodynamically and is in agreement with the experimental results. As an example see Figure 4 in the Supporting Information, which summarizes the stationary points found in the reaction of **2a** and **1f**. These results are consistent with those previously described[44] for the [2 + 2] reaction of isocyanates with electron withdrawing groups and olefins with electron donanting groups, because the reaction is very effective, but takes place through zwitterionic intermediates in a two-step process favored by the presence of a solvent. Similarly, a stepwise process with the participation of zwitterionic intermediates is used in a computational study to understand the mechanisms of three-component reaction between imidazoles, isocyanates and cyanophenylacetylene to generate imidazole carboxamides.[45] Therefore, the mechanism proposed in Scheme 3 is consistent with both experimental and computational results.

Synthesis of Fluoroalkylated 3,4-Dihydro- 7 and 3,4,5,6-Tetrahydropyridin-2(1*H*)-ones 10. Taking into account the observed versatility of *α,β*-unsaturated imines **1** as starting materials for the preparation of acyclic compounds and nitrogen heterocycles, we extended the study of the reactivity to isocynates containing an electron-withdrawing group, such a tosyl group, in order to test if the presence of this group might drive the process to fluorinated DHPM-monoadducts. The addition of tosyl isocyanate **2b** to fluorinated unsaturated imine **1a** (R^1 = *p*-$CH_3C_6H_4$, R_F = CF_3) in THF at rt gave the corresponding cycloadduct **7a** (R^1 = $CH_3C_6H_4$, R_F = CF_3, Scheme 5, Table 2, entry 1) in good yield.

Fluoroalkylated 3,4-dihydropyrimidin-2(1*H*)-one **7a** was characterized based on its spectroscopic data. HRMS (M^+ 410,0912) is consistent with the incorporation of one molecule of tosylisocyanate **2b** into azadiene **1a** and formation of monoadduct **7a**. ^{1}H NMR spectra of conpound **7a** also show a well-resolved doublet at δ_H = 5.76 ppm with a coupling constant of $^3J_{HH}$ = 6.0 Hz, corresponding to the 4-H of the dihydropyridone ring, as well as a double quadruplet at δ_H = 6.09 ppm with coupling constants $^4J_{FH}$ = 1.6 Hz and $^3J_{HH}$ = 6.0 Hz for 5-H, while only one signal appears in ^{19}FNMR as a single peak at δ_F = −70.6 ppm. The scope of the process is very wide, given that heterocycles **7** containing not only aromatic substituent (R^1 = *p*-FC_6H_4, Table 2, entry 2) and heteroaromatic substituent (R^1 = 2-furyl, Table 2, entries 3–5) but also trifluoromethyl (R_F = CF_3, Table 2, entries 2 and 3)

Scheme 5. Synthesis of Fluoroalkylated 3,4-Dihydropyridin-2(1*H*)-ones 7 and 3,4,5,6-Tetrahydropyridin-2(1*H*)-one 10.

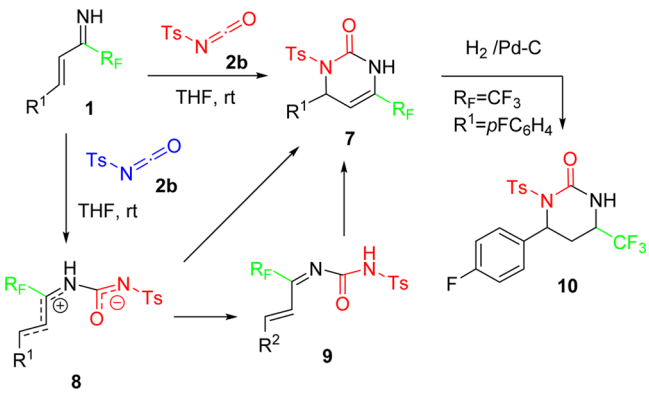

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Table 2. Fluoroalkylated 3,4-Dihydropyrimidin-2(1*H*)-ones 7 and 4-(Trifluoromethyl)tetrahydropyrimidin-2-one 10

entry	compd	R^1	R_F	yield[a] (%)
1	**7a**	*p*-$CH_3C_6H_4$	CF_3	78
2	**7f**	*p*-FC_6H_4	CF_3	68
3	**7d**	2-furyl	CF_3	75
4	**7e**	2-furyl	CHF_2	71
5	**7g**	2-furyl	C_2F_5	72
6	**10**			86[b]

[a]Yield of isolated purified compounds obtained from **1**. [b]Yield obtained from **7f**.

and difluoromethyl (R_F = CHF_2, Table 2, entry 4) and pentafluoroethyl (R_F = C_2F_5, Table 2, entry 5) derivatives may also be prepared (Scheme 5).

Formation of fluoroalkylated DHPMs **7** may be explained via the pathway depicted in Scheme 5. The process may be initiated by a nucleophilic attack from the NH of the imino group from unsaturated imine **1** to the C=N double bond of tosyl isocyanate **2b** to give a zwitterionic intermediate **8** followed by an intramolecular cyclization to give DHPMs **7**. Likewise, a 1,3-H-rearrangement from intermediate **8** may give monoadduct **9**, and subsequent intramolecular nucleophilic addition may lead to DHPMs **7**. However, another pathway involving a concerted [4 + 2] cycloaddition (DA reaction) involving unsaturated imines **1** (1-azadiene) and isocyanate **2a** (dienophile) could also explain the formation of fluorinated DHPMs **7**.

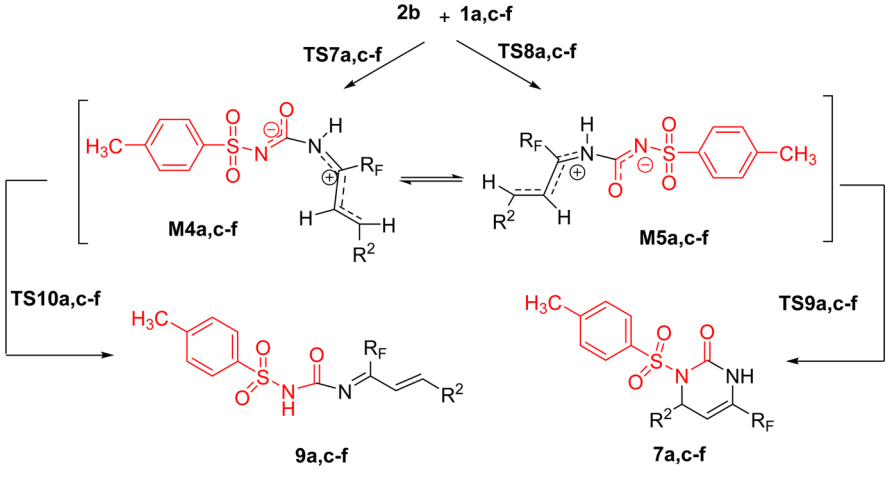
For this reason, a computational study[46] was performed to explain the different behavior observed when tosyl isocyanate **2b** vs phenyl isocyanate **2a** reacted with fluorinated imines **1** and to determine the most favored mechanism of the processes. It is also interesting to note that all our attempts to locate a transition state corresponding to the DA reaction that would lead to the formation of the products **7** through a concerted process met with no success. All of the starting geometries converged to either a transition structure where the bond *N*-imimic−C-isocyanate (with a distance *N*-isocyanate−C-4aza-diene higher than 3 Å) began to form or a transition structure with the bond N-imimic−C-isocyanate formed, where the bond *N*-isocyanate C-4-azadiene began to be created upon the optimization at the B3LYP/6-31G* + ZPVE level. This feature was also observed for the reaction of alkenyloxazolines with isocyanates.[26a]

As was the case for **2a**, the approximation of azadienes **1a,c−f** to isocyanate **2b** in a nonconcerted process will take place preferentially in configuration *s-trans*-1*Z*,3*E* through transition states **TS7a,c−f** or **TS8a,c−f**, and therefore, the different approach could lead to two different zwitterion intermediates **M4a,c−f** or **M5a,c−f** (Scheme 6). In all cases, in the presence of THF as the solvent, the activation barriers corresponding to the approach of dienes **1a,c−f** through transition structures **TS7a,c−f** are very similar to activation barriers corresponding to transition structures **TS8a,c−f**, and as expected its values decrease relative to the gas phase. As an example, in Figure 3, the energy profile for the reaction of **1a** with **2b** to give **M4b** and **M5a** is shown. Moreover, all the processes are exothermic, and calculated free energy differences indicate that zwitterionic intermediates **M5a,c−f** are more stable than **M4a,c−f** (see Table 3 and Figures 5 and 6 in the Supporting Information for a comparison of results).

Therefore, the formation of **M5a,c−f** in a solution of THF is favored kinetically and thermodynamically. In addition, these results indicate that **TS7a,c−f** and **TS8a,c−f** are very early, the activation energy of this first step is very low (ranging from 1 to 5 kcal/mol, computing a B3LYP(PCM)/6-311 +G** +ΔZPVE level of theory using tetrahydrofuran as solvent) and supports the idea that not only is this step of the reaction very straightforward but also that the formation of **M5a,c−f** is very rapid. Thus, isocyanate **2b** is probably completely consumed before the second step of the reaction (see the Supporting Information for a comparison of results).

Concerning the second step of the process, in the presence of THF the cyclization of more stable zwitterionic intermediate **M5a,c−f** to give **7a,c−f** exhibit, in all cases, lower activation barriers (around half in all cases),[47] through transition structures **TS9a,c−f**, than those involving transition structures **TS10a,c−f** for the formation of acyclic monoadduct **9a,c−f**. As an example, in Figure 4, the energy profile for the formation of compounds **7a** and **9a** from **M5a** is shown. Both processes are exothermic, but the formation of DHPMs **7a,c−f** is much more exothermic (more than 15 kcal/mol in all cases),[47] than the formation of monoadduct **9a,c−f**. These results indicate that kinetically and thermodynamically the formation of fluoroalkylated 3,4 dihydropyrimidin-2(1*H*)-ones **7** is favored and is in

Scheme 6. Different Pathways for the Reaction of 1a,c−f with 2b



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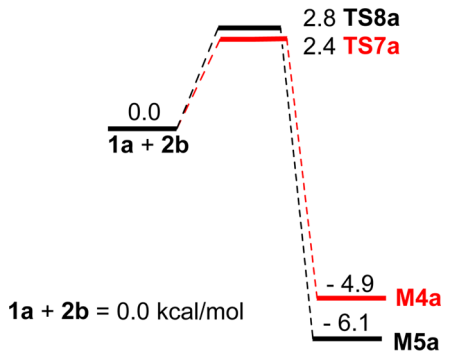

Figure 3. Energy profile for transformation from reactants **1a** and **2b** to zwitterionic intermediates **M4a** and **M5a** at the M06-2X(PCM)/6-311+G**//B3LYP/6-31G* + ΔZPVE level (unit: kcal/mol) using tetrahydrofuran as solvent.

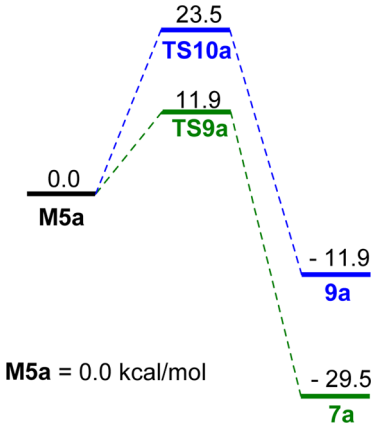

Figure 4. Energy profile for transformation from zwitterionic intermediate **M5a** to the products **7a** and **9a** at the M06-2X(PCM)/6-311+G**//B3LYP/6-31G* + ΔZPVE level (unit: kcal/mol) using tetrahydrofuran as solvent.

agreement with the experimental results and with the tentative proposed mechanism in Scheme 5. As examples, see Figures 7 and 8 in the Supporting Information where the stationary points found in the reaction of **2b** with **1c** and **2b** with **1e**, respectively, are summarized.

Finally, the hydrogenation of fluoroalkylated DHPMs **7f** (R^1 = *p*-FC_6H_4, R_F = CF_3), was explored in order to increase the diversity with new fluorinated heterocycles such as tetrahydropyrimidin-2-ones (THPMs). The reduction of the cyclic enaminic C−C double bond was performed by means of hydrogenation with Pd/C in methanol and afforded the corresponding 4-trifluoromethyl tetrahydropyrimidin-2-one **10** in good yield (86%, Scheme 5, Table 2, entry 6) as a mixture of diastereoisomer (ratio 1/1). This strategy represents, as far as we know, the first example of preparation of fluorinated di- **7** and tetrahydropyrimidin-2-ones **10**.

■ CONCLUSION

In conclusion, this paper describes a simple, mild, and convenient strategy for the preparation of fluoroalkyl-substituted triazene-2,4-diones **4** obtained by regioselective 1,4-addition of two molecules of phenyl isocyanate **2a** to fluoroalkylated *α,β*-unsaturated imines **1**. However, dihydropyrimidin-2(1*H*)-ones **7** may be prepared by the reaction of *α,β*-unsaturated imines **1** with tosyl isocyanate **2b**. Catalyst-mediated hydrogenation of dihydropyrimidin-2(1*H*)-ones **7** may give the corresponding fluoroalkyl-substituted tetrahydropyrimidin-2(1*H*)-one **10**. Computational and experimental studies indicate that fluoroalkylated *α,β*-unsaturated imines **1** reacted through the iminic nitrogen with the electron-deficient carbon of isocyanates **2** leading to zwitterionic intermediates which participate in a stepwise mechanism to give fluorinated heterocycles **4** and **7**. When phenyl isocyanate **2a** is used the nitrogen atom in zwitterionic intermediate **5** is more nucleophilic and therefore may favor the addition of a second equivalent of isocyanate **2a** to give triazinane-2,4-diones **4**. Conversely, the reaction of tosyl isocyanate **2b** and fluoroalkylated *α,β*-unsaturated imines **1** may take place via a nonconcerted process though a zwitterionic intermediate **8**, which is generated very rapidly and is favored kinetically and thermodynamically. Subsequent cyclization to give DHPMs **7** in a second step is also favored kinetically and thermodynamically. The scope of the reaction is not limited to the trifluoromethyl group, given that not only difluoromethyl but also perfluoroethyl groups may be used. Substituted triazinane derivatives **4**,[33−35] dihydro- **7**, and tetrahydropyrimidinones **10**,[8−19] are important building blocks in organic synthesis and in the preparation of biologically active compounds of interest in medicinal chemistry,[22] agricultural,[23] and material sciences.[24]

■ EXPERIMENTAL SECTION

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Melting points are uncorrected. IR−FT spectra were recorded with an infrared spectrometer, and absorbance frequencies are given at maximum of intensity in cm^{-1}. High-resolution mass spectra (HRMS) were obtained using an electron spray ionization (ESI) method with a time-of-flight Q-TOF system. ^1H (300, 400 MHz) and ^{13}C (75, 100 MHz) spectra were recorded on a 300 or 400 MHz spectrometers, respectively, in $CDCl_3$ or CD_3OD, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$ or CD_3OD, as internal standards in a broad band decoupled mode. Chemical shifts for ^{19}F NMR are reported in ppm downfield from fluorotrichloromethane ($CFCl_3$). The abbreviations used are as follows: s, singlet; d, doublet; dd, double-doublet; dq, double-quadruplet; t, triplet; q, quartet; m, multiplet. Flash-column chromatography was carried out using commercial grades of silica gel finer than 230 mesh. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates, and spot visualization was accomplished by UV light (254 nm) or $KMnO_4$ solution. Unsaturated imines **1** were prepared following a literature procedure.[34a,35]

General Procedure for the Synthesis of Fluoroalklated Triazinane-2,4-diones 4. Phenyl isocyanate (2 mmol, 238 mg) was added to a solution of *α,β*-unsaturated imine (1 mmol) in anhydrous THF (15 mL). The reaction was stirred at room temperature until TLC showed the disappearance of the *α,β*-unsaturated imine (16−20 h). Then the reaction was filtered through a glass vacumm filtration funnel with Celite, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (hexane/ethyl acetate).

*6-(4-Methylstyryl)-1,3-diphenyl-6-(trifluoromethyl)-1,3,5-triazinane-2,4-dione (**4a**).* Compound **4a** was obtained as a white solid (383 mg, 85%) from imine **1a** as described in the general procedure: mp 225−227 °C; ^1H NMR ($CDCl_3$) δ 7.63 (br, 1*H*), 7.24−7.45 (m, 10H), 7.16 (d, $^3J_{HH}$ = 16.1 Hz, 1*H*), 7.07 (d, $^3J_{HH}$ 7.9 Hz, 2H), 6.93, (d, $^3J_{HH}$ = 7.9 Hz, 2H), 5.66 (d, $^3J_{HH}$ = 16.2 Hz, 1*H*), 2.34 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 152.7, 151.4, 139.9, 136.6, 136.2, 134.6, 131.8, 131.7, 129.7, 129.3, 129.2, 128.8, 127.4, 122.0 (q, $^1J_{FC}$ = 292.1 Hz), 117.9, 72.7 (q, $^2J_{FC}$ = 30.8 Hz), 21.6 ppm; ^{19}F NMR ($CDCl_3$) δ

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−80.5 ppm; IR ν_{max} 3210, 3089, 1732, 1660 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{20}F_3N_3O_2$ [M$^+$] 451.1508, found [M$^+$] 451.1519.

*6-(Difluoromethyl)-6-(4-nitrostyryl)-1,3-diphenyl-1,3,5-triazinane-2,4-dione (**4b**).* Compound **4b** was obtained as a yellow solid (348 mg, 75%) from imine **1b** as described in the general procedure: mp 232−234 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.00−7.45 (m, 13H), 7.21 (d, $^3J_{HH}$ = 16.2 Hz, 1*H*), 5.99 (t, $^3J_{FH}$ = 54.8 Hz, 1*H*,), 5.83 (d, $^3J_{HH}$ = 17.3 Hz, 1*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 152.9, 151.5, 148.2, 140.9, 136.0, 134.6, 133.8, 131.3, 129.7, 129.6, 129.3, 129.2, 128.8, 128.0, 124.4, 113.9 (t, $^1J_{FC}$ = 254.3 Hz), 72.1 (t, $^2J_{FC}$ = 22.7 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −130.6 (dd, $^2J_{FH}$ = 54.9 Hz, $^2J_{FF}$ = 278.5 Hz), −132.4 (dd, $^2J_{FH}$ = 54.9 Hz, $^2J_{FF}$ = 278.4 Hz) ppm; IRν_{max} 3212, 3112, 1715, 1667 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{18}F_2N_4O_4$ [M$^+$] 464.1296, found [M$^+$] 464.1308.

*6-(4-Nitrostyryl)-1,3-diphenyl-6-(trifluoromethyl)-1,3,5-triazinane-2,4-dione (**4c**).* Compound **4c** was obtained as a yellow solid (400 mg, 83%) from imine **1c** as described in the general procedure: mp 221−223 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (br, 1*H*), 7.99 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 7.40−7.15 (m, 10H), 7.22 (d, $^3J_{HH}$ = 16.5 Hz, 1*H*), 6.87 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 5.72 (d, $^3J_{HH}$ = 16.2 Hz, 1*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 140.7, 135.9, 134.5, 134.4, 131.6, 129.7, 129.6, 129.3, 129.2, 128.6, 128.1, 124.3 (q, $^1J_{FC}$ = 292.9 Hz), 122.3, 72.4 (q, $^2J_{FC}$ = 31.0 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −80.4 ppm; IR ν_{max} 3225, 3112, 1712, 1682 cm^{-1}; HRMS (ESI) m/z Calcd for $C_{24}H_{17}F_3N_4O_4$ [M$^+$] 482.1201, found [M$^+$] 482.1213.

*6-(2-(Furan-2-yl)vinyl)-1,3-diphenyl-6-(trifluoromethyl)-1,3,5-triazinane-2,4-dione (**4d**).* Compound **4d** was obtained as a beige solid (392 mg, 92%) from imine **1d** as described in the general procedure: mp 236−237 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.14 (m, 12H), 6.86 (d, $^3J_{HH}$ = 15.9 Hz, 1*H*), 6.30 (m, 1*H*), 6.17 (m, 1*H*), 5.67 ($^3J_{HH}$ = 15.9 Hz, 1*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 152.2, 151.1, 150.0, 143.9, 135.8, 134.3, 131.3, 129.2, 128.9, 128.5, 124.5 (q, $^1J_{FC}$ = 293.0 Hz), 124.1, 116.5, 112.6, 111.7, 72.5 (q, $^2J_{FC}$ = 30.9) ppm; ^{19}F NMR ($CDCl_3$) δ −80.2 ppm; IR ν_{max} 3189, 3094, 1736, 1650 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{16}F_3N_3O_3$ [M$^+$] 427.1143, found [M$^+$] 427.1148.

*6-(Difluoromethyl)-6-(2-(furan-2-yl)vinyl)-1,3-diphenyl-1,3,5-triazinane-2,4-dione (**4e**).* Compound **4e** was obtained as a beige solid (368 mg, 90%) from imine **1e** as as described in the general procedure: mp 226−228 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 11*H*), 6.91 (br, 1*H*), 6.72 (d, $^3J_{HH}$ = 15.9 Hz, 1*H*), 6.27 (m, 1*H*), 6.17 (d, $^3J_{HH}$ = 3.0 Hz, 1*H*), 5.82 (t, $^3J_{FH}$ = 55.0 Hz, 1*H*), 5.68 (d, $^3J_{FH}$ = 15.9 Hz, 1*H*) ppm; ^{13}C NMR ($CDCl_3$) δ 152.4, 151.5, 150.3, 143.7, 135.9, 134.5, 131.0, 129.2, 129.0, 128.9, 128.8, 128.3, 123.3, 118.7, 113.7 (t, $^1J_{FC}$ = 253.4 Hz), 112.1, 111.6, 72.1 (t, $^2J_{FC}$ = 21.8 Hz) ppm; ^{19}F NMR ($CDCl_3$) δ −130.7 (dd, $^2J_{FH}$ = 54.9 Hz, $^2J_{FF}$ = 272.2 Hz), −133.0 (dd, $^2J_{FH}$ = 54.8 Hz, $^2J_{FF}$ = 272.3 Hz) ppm; IR ν_{max} 3230, 3100, 1717, 1675, 1663 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{17}F_2N_3O_3$ [M$^+$] 409.1238, found [M$^+$] 409.1247.

General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones 7. Tosyl isocyanate (1 mmol, 117 mg) was added to a solution of fluoroalkylated β-unsubstituted imine (1 mmol) in anhydrous THF (15 mL). The reaction mixture was stirred at room temperature until TLC showed the disappearance of the fluorinated α,β-unsaturated imine (20−22 h). Then, a saturated solution of NH_4Cl (10 mL) was added, the reaction mixture was extracted with DCM (3 × 25 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (hexane/ethyl acetate).

*4-(p-Tolyl)-3-tosyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1H)-one (**7a**).* Compound **7a** was obtained as a white solid (320 mg, 78%) from imine **1a** as described in the general procedure: mp 188−190 °C; ^{1}H NMR ($CDCl_3$) δ 8.53 (br, 1*H*), 7.81 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.35 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.0 Hz, 2H,), 7.06 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 6.09 (dq, $^4J_{FH}$ = 1.6 Hz, $^3J_{HH}$ = 6.0 Hz, 1*H*), 5.76 (d, $^3J_{HH}$ = 6.0 Hz, 1*H*), 2.39 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.3, 139.5, 139.4, 136.2, 135.7, 129.5, 128.9, 127.4, 126.6, 125.9 (q, $^2J_{FC}$ = 36.0 Hz), 119.6 (q, $^1J_{FC}$ = 272.5 Hz), 106.8 (q, $^3J_{FC}$ = 4.3 Hz,), 59.1, 21.7, 21.4 ppm; ^{19}F NMR ($CDCl_3$) δ −70.6 ppm; IR ν_{max} 3361, 3116, 2991, 1361, 1175 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{17}F_3N_2O_3S$ [M$^+$] 410.0912, found [M$^+$] 410.0925.

*4-(Furan-2-yl)-3-tosyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1H)-one (**7d**).* Compound **7d** was obtained as a white solid (290 mg, 75%) from imine **1d** as described in the general procedure: mp 205−207 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.43 (br, 1*H*), 7.23 (d, $^3J_{HH}$ = 1.6 Hz, 1*H*), 7.10 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.37 (d, $^3J_{HH}$ = 3.1 Hz, 1*H*), 6.31 (dd, $^3J_{HH}$ = 1.7 Hz, $^3J_{HH}$ = 3.2 Hz, 1*H*), 6.15 (d, $^3J_{HH}$ = 6.1 Hz, 1*H*), 5.66 (d, $^3J_{HH}$ = 6.2 Hz, 1*H*, CH), 2.32 (s, 3H) ppm; ^{13}C NMR (CD_3OD) δ 150.8, 149.0, 145.2, 144.7, 136.4, 129.8, 129.0, 127.2 (q, $^2J_{FC}$ = 35.2 Hz), 116.2 (q, $^1J_{FC}$ = 273.0 Hz), 111.5, 109.8, 104.9 (q, $^3J_{FC}$ = 4.5 Hz), 51.7, 21.7 ppm; ^{19}F NMR ($CDCl_3$) δ −70.7 ppm; IR ν_{max} 3350, 3116, 2989, 1359, 1169 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{13}F_3N_2O_4S$ [M$^+$] 386.0548, found [M$^+$] 386.0557.

*6-(Difluoromethyl)-4-(furan-2-yl)-3-tosyl-3,4-dihydropyrimidin-2(1H)-one (**7e**).* Compound **7e** was obtained as a yellow solid (291 mg, 71%) from imine **1e** as described in the general procedure: mp 191−193 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, $^3J_{HH}$ = 7.8 Hz, 1*H*), 7.24 (d, $^3J_{HH}$ = 7.7 Hz, 2H,), 7.20 (br, 1*H*,), 7.11 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 6.35 (m, 1*H*), 6.29 (d, $^3J_{HH}$ = 1.7 Hz, 1*H*), 6.14 (d, $^3J_{HH}$ = 7.3 Hz, 1*H*), 6.03 (t, $^3J_{FH}$ = 52.7 Hz, 1*H*), 5.42 (d, $^3J_{HH}$ = 7.3 Hz, 1*H*), 2.31 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.0, 149.8, 144.7, 143.4, 135.6, 129.4, 129.1, 111.3 (t, $^1J_{FC}$ = 250.0 Hz), 110.6, 109.0, 102.1 ($^3J_{FC}$ = 10.2 Hz), 52.0, 21.5 ppm; ^{19}F NMR ($CDCl_3$) δ −120.1 (dd, $^2J_{FH}$ = 54.9 Hz, $^2J_{HH}$ = 305.2 Hz), −122.3 (dd, $^2J_{FH}$ = 54.9 Hz, $^2J_{HH}$ = 305.2 Hz) ppm; IR ν_{max} 3349, 3109, 2981, 1352, 1165 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{14}F_2N_2O_4S$ [M$^+$] 368.0642, found [M$^+$] 368.0639.

*4-(4-Fluorophenyl)-3-tosyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1H)-one (**7f**).* Compound **7f** was obtained as a white solid (281 mg, 68%) from imine **1f** as described in the general procedure: mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (br, 1*H*), 7.29 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.23 (dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{FH}$ = 5.3 Hz, 2H), 7.01 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 6.95 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 6.03 (d, $^3J_{HH}$ = 5.8 Hz, 1*H*), 5.67 (d, $^3J_{HH}$ = 5.9 Hz, 1*H*), 2.28 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 161.3 (d, $^1J_{CF}$= 252.3 Hz), 150.1, 144.9, 135.2, 134.8, 129.2, 128.7, 125.5 (q, $^2J_{FC}$ = 36.7 Hz), 119.2 (q, $^1J_{FC}$ = 272.6 Hz), 116.3, 116.0, 106.1 (q, $^3J_{FC}$ = 4.3 Hz), 58.2, 21.5 ppm; ^{19}F NMR ($CDCl_3$) δ −70.6, −111.9 ppm; IR ν_{max} 3354, 3113, 2986, 1359, 1172 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{14}F_4N_2O_3S$ [M$^+$] 414.0661, found [M$^+$] 414.0670.

*4-(Furan-2-yl)-6-(perfluoroethyl)-3-tosyl-3,4-dihydropyrimidin-2(1H)-one (**7g**).* Compound **7g** was obtained as a brown solid (314 mg, 72%) from imine **1g** as described in the general procedure: mp 173−175 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (br, 1*H*), 7.45 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 7.24 (m, 1*H*), 7.10 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 6.35 (d, $^3J_{HH}$ = 3.2 Hz, 1*H*), 6.29 (m, 1*H*), 6.18 (d, $^3J_{HH}$ = 6.2 Hz, 1*H*), 5.61 ($^3J_{HH}$ = 6.3 Hz, 1*H*), 2.30 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.8, 149.5, 144.7, 143.6, 135.3, 129.0, 128.9, 112.0−130.1 (m), 110.5, 109.3, 105.3 (t, $^3J_{FC}$ = 6.5 Hz,), 51.7, 21.5 ppm; ^{19}F NMR ($CDCl_3$) δ −84.5, −120.8 (q, $^2J_{FF}$ = 67.8 Hz) ppm; IR ν_{max} 3346, 3102, 2993, 1352, 1160 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{13}F_5N_2O_4S$ [M$^+$] 436.0516, found [M$^+$] 436.0519.

Procedure for the Synthesis of the Fluoroalkylated Tetrahydropyrimidin-2-(1*H*)-one 10. To a solution of fluoroalkylated 3,4-dihydropyrimidin-2-(1*H*)-one **7f** (1 mmol, 414 mg) and Pd/C (0.1 mmol, 106 mg) in anhydrous methanol (10 mL) was applied 80 psi of hydrogen, and the reaction was stirred until TLC showed the disappearance of the starting material (24 h). Then, a saturated solution of NH_4Cl (10 mL) was added, the reaction mixture was extracted with DCM (3 × 25 mL), dried with anhydrous $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (hexane/ethyl acetate) to afford **10** as a white solid (357 mg, 86%): mp 189−191 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, $^3J_{HH}$ = 8.4 Hz, 4H), 7.32 (d, $^3J_{HH}$ = 8.2 Hz, 4H), 7.15 (d, $^3J_{HH}$ = 8.5 Hz, 4H), 6.92 (d, $^3J_{HH}$ = 8.5 Hz, 4H), 5.70 (m, 2H), 4.78 (br, 2H), 4.08 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 2.55−2.70 (m, 2H) ppm; ^{13}C NMR(DMSO) δ 151.5, 144.9, 142.5, 142.0, 137.3, 130.1, 129.8, 129.6, 129.0, 128.1, 125.2, 115.2, 115.1, 56.7, 50.6 (q, $^2J_{FC}$ = 32.2 Hz), 50.5 (q, $^2J_{FC}$ = 32.2 Hz), 29.6, 21.7, 21.6 ppm; ^{19}F NMR ($CDCl_3$) δ −77.1, −77.2, −114.2

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ppm; IR (NaCl) ν_{max} 3350, 3098, 2990, 1364 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{16}F_4N_2O_3S$ $[M^+]$ 416.0818, found $[M^+]$ 416.0815.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra of compounds **4a−e**, **7a,d−g**, and **10**. Computational Studies: details about structures of stationary points associated with the reactions of **2a** and **2b** with azadienes **1a,c−f**, Cartesian coordinates, harmonic analysis data, and energies for all the stationary points discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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