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Synthesis of 3,4-Dihydropyridin-2-ones via Domino Reaction under Phase Transfer Catalysis Conditions

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Abstract: 3,4-dihydropyridin-2-ones are of considerable importance due to the large number of these core structures exhibiting a diverse array of biological and pharmacological activities. The Michael-type addition of 1,3-dithiane-2-carbothioates to α,β-unsaturated *N*-tosyl imines, followed by intramolecular annulation driven by a sulfur leaving group, provides a practical reaction cascade for the synthesis of a variety of substituted 3,4-dihydropyridin-2-ones. In this work, the reaction was carried out under solid–liquid phase transfer catalysis (SL-PTC) conditions at room temperature, in short reaction times in the presence of cheap $Bu_4N^+HSO_4^-$ and solid KOH. The new PTC method exhibited adequate functional group tolerance, proving to be a green and reliable method and easy to scale up to furnish rapid access to 3,4-dihydropyridin-2-ones after desulfurization from simple, readily available starting materials.

Keywords: tandem reaction; S-2,2,2-trifluoroethyl 1,3-dithiane-2-carbothioate; 3,4-dihydropyridin-2-ones; Michael addition; acyl anion equivalent; phase transfer catalysis

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1. Introduction

Multi-substituted dihydropyridinones are privileged frameworks, found in many biologically active natural compounds [1,2] and are included in the structures of a number of synthetic molecules with therapeutic properties [3–5]. Moreover, they can be easily converted into highly valuable derivatives [6] and employed as precursors in the synthesis of natural molecules with biological activity [7].

In particular, 3,4-dihydropyridinones constitute the core of Lanicepine A (Figure 1), a natural molecule extracted from *Saussurea* plants, known as "snow lotus", used to treat various disorders [8].

The 3,4-dihydropyridinone skeleton embodies the core of a series of potent P2X7 inhibitors which play important roles in several inflammatory, immune, neurological and musculoskeletal disorders (Figure 1) [9–12].

They are also present in a series of selective α_{1a} receptor antagonists, showing a possible application for the benign prostatic hyperplasia [13]. Derivatives of 3,4-dihydropyridinones play a critical role as ROCK1 inhibitors for the treatment of hypertension and related disorders [14]. A series of compounds based on 3,4-dihydropyridinone core have been found to show hypolipidemic and 5α-reductase inhibitory activities [15]. Moreover, the six-membered lactams and their derivatives such as piperidines are valuable building blocks [16–18].

The wide pharmacological activity of the 2-pyridinone derivatives has encouraged the research of efficient synthetic methodologies under mild and safe conditions. Typically, the methods reported in the literature take advantage of multicomponent processes (MCR) [19–21], or one-pot synthesis via tandem reactions.

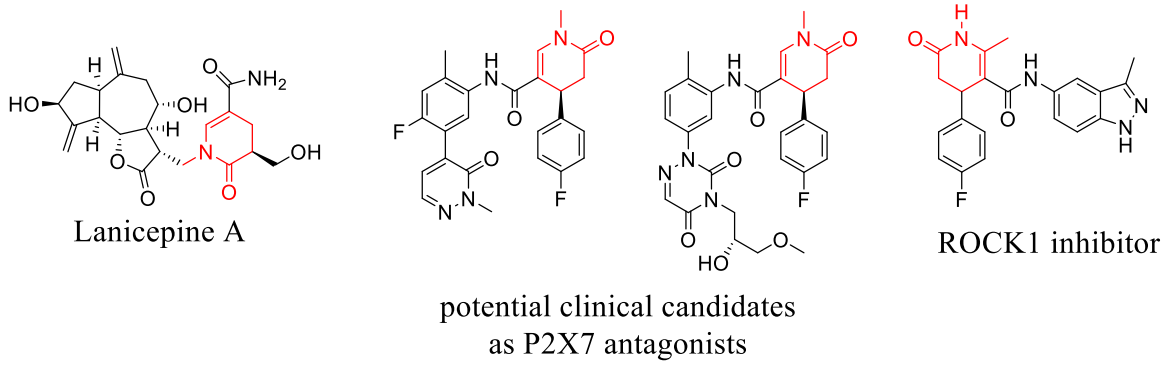
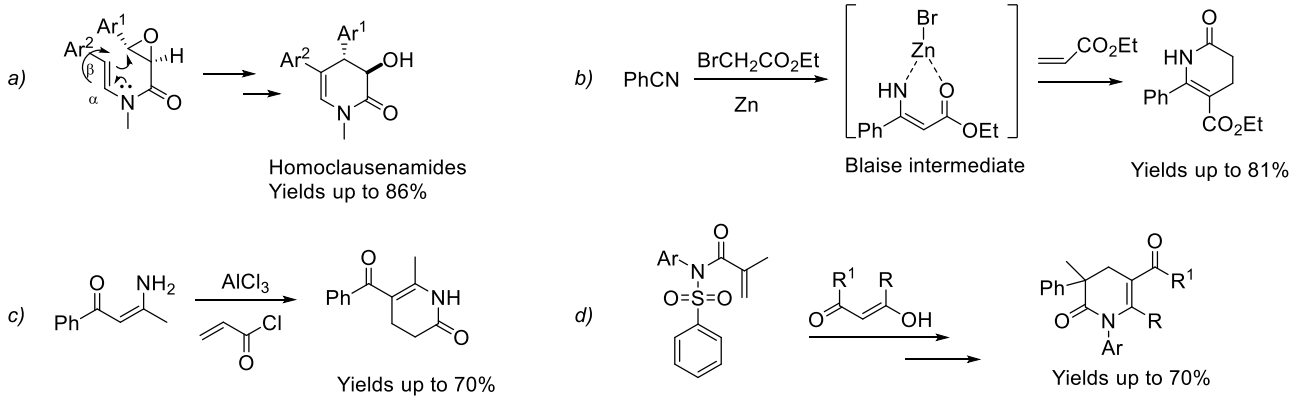


Figure 1. Natural and synthetic biologically active 3,4-dihydropyridinones.

The cyclization of suitable substrates in a one-pot tandem reaction is an attractive approach for the synthesis of dihydropyridinones. Nonetheless, these methods require pre-functionalized molecules, which are often troublesome to access and need expensive or toxic catalysts or harsh reaction conditions (Scheme 1).



Scheme 1. (**a**–**d**) One-pot tandem processes for the preparation of 3,4-dihydropyridin-2-ones.

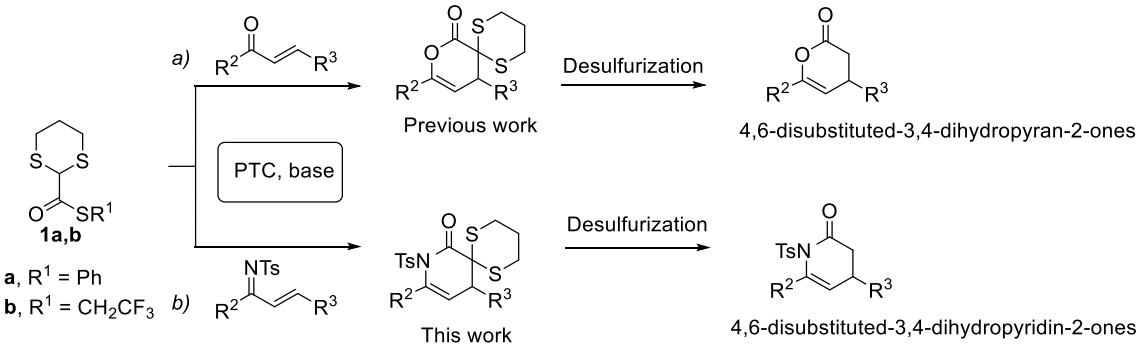
Wang reported a trifluoroacetic acid-mediated stereospecific intramolecular cyclization reaction of oxirane-containing enamides to produce homoclausenamide analogs [22]. Zhao developed a one-pot protocol for the access to 3,4-dihydropyridin-2-ones via a tandem Michael-type addition followed by cyclization between Blaise intermediates, obtained from nitriles and α-haloesters (1.5 eq.) in the presence of Zn (2 eq.), and α,β-unsaturated carboxylic esters (2 eq.), catalyzed by boron trifluoride [23]. Liu achieved the title compounds by the domino reaction of NH_2-based enaminones and acryloyl chloride (2 eq.) in the presence of aluminum trichloride (2 eq.) in water/THF as the reaction media, at room temperature for 12 h [24]. A silver catalyzed one-pot radical reaction cascade from *N*-(arylsulfonyl)-acrylamides and 1,3-dicarbonyl compounds (2 eq.) for the unprecedent regioselective formation of 3,3-disubstituted-2-dihydropyridinones was developed by Nevado [25].

The dihydropyridine-2-one skeleton could also be generated in a stereoselective fashion through benzyl bromide carbonylation followed by isothiourea promoted formal [1 + 1 + 4] annulation with α,β-unsaturated *N*-tosyl ketimines [26]. Moreover, *N*-heterocyclic carbenes could also be successfully used to form the desired motif through activation of α,β-unsaturated esters with enamides [16].

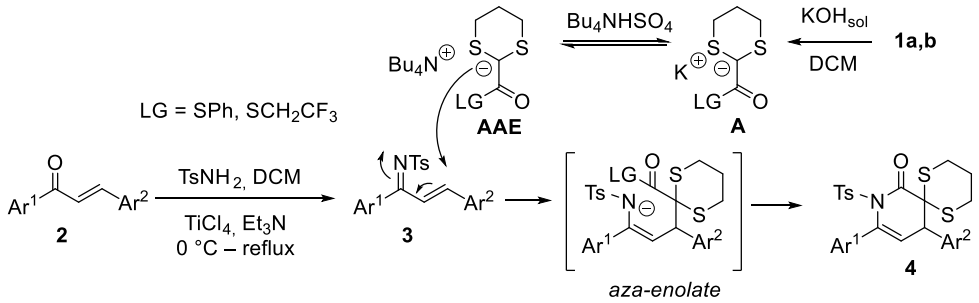
Although all these methods can provide various types of the 3,4-dihydropyridin-2-one skeleton, they suffer from the use of excess reagents, need metals or anhydrous solvents and/or inert atmosphere, or involve the use of NaH as a base. Thus, it seemed reasonable to investigate alternative protocols to generate the target compounds using a more practical procedure.

As part of our interests in the development of simple and efficient methodologies under PTC conditions for the synthesis of heterocycles with potential biological activity [27–30], we envisioned the possibility to obtain six-membered enol lactams according to our recently published one-pot tandem procedure for the preparation of analogous enol lactones (Scheme 1, path a) [31].

The synthetic plan involves the conjugate addition of the acyl anion equivalent (**AAE**), generated by deprotonation of 1,3-dithiane-2-carbothioates **1a,b** under SL-PTC conditions, on the β position of α,β-unsaturated *N*-tosyl imines **3** (Scheme 2, path b). These compounds could be easily generated from the corresponding chalcones **2** by using 4-toluenesulfonamide in the presence of $TiCl_4$. In the second step, the resulting reactive aza-enolate generates the six-membered lactams through an intramolecular addition/elimination pathway (Scheme 3).



Scheme 2. Synthetic scheme for dihydropyran-2-ones (path **a**) and dihydropyridine-2-ones (path **b**).



Scheme 3. Proposed reaction mechanism.

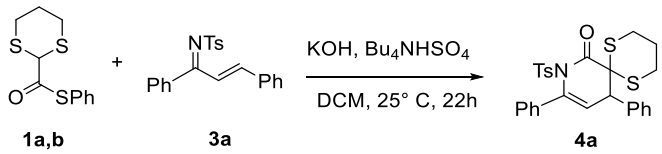
Indeed, 1,3-dithiane-2-derivatives are known acyl anion equivalents due to the stabilization of the carbanion adjacent to the two sulfur atoms as a consequence of delocalization of the negative charge into the contiguous vacant sulfur d-orbitals [32]. Moreover, the additional carbothioate group contributes to decreasing the pKa with respect to the unsubstituted 1,3-dithiane, thus enriching the reactivity profile [33]. In our case, the thioate moiety has a crucial role acting as a suitable leaving group, thus enabling the cyclization to give the desired dihydropyran-2-one skeleton. Noteworthy, in the literature, different methodologies are reported to easily remove the 1,3-dithiane group in the final product. 1,3-dithiane-2-carbothioates have also been successfully used by one of the authors of this work in the stereoselective 1,4-addition to nitroalkenes [34] and enones [35].

2. Results

In a first set of experiments, we investigated the feasibility of the synthetic plan by using *S*-phenyl 1,3-dithiane-2-carbothioate (**1a**) and *N*-[(1*E*,2*E*)-1,3-diphenylallylidene]-4-methylbenzenesulfonamide (**3a**) as model compounds.

When thioester (**1a**) was reacted with imine **3a** (1.05 eq) in the presence of solid KOH (1.1 eq.) and $Bu_4N^+HSO_4^-$ (0.1 eq., $TBAHSO_4$) in DCM for 22 h at room temperature, the corresponding enol lactam **3a** was formed in 51% yield (Table 1, entry 1).

Table 1. Optimization of reaction conditions [a].



1a,b **3a** **4a**

Entry	Thioester	3a (eq.)	Cat. (0.1 eq.)	Base (eq.)	Solvent	t (h)	4a (Yield %) [b]
1	**1a**	1.05	$TBAHSO_4$	KOH (1.1)	DCM	22	51
2	**1a**	1.05	TEBA	KOH (1.1)	DCM	22	50
3	**1a**	1.25	$TBAHSO_4$	KOH (1.1)	DCM	22	61
4	**1a**	1.25	$TBAHSO_4$	KOH (1.5)	DCM	22	62
5	**1a**	1.25	$TBAHSO_4$	K_2CO_3 (1.5)	DCM	22	38
6	**1a**	1.25	–	KOH (1.1)	DCM	22	13
7 [c]	**1a**	1.25	$TBAHSO_4$	–	DCM	22	20
8	**1b**	1.25	$TBAHSO_4$	KOH (1.5)	DCM	5	85
9 [d]	**1b**	1.25	$TBAHSO_4$	KOH (1.5)	DCM	5	88
10 [e]	**1b**	1.25	$TBAHSO_4$	KOH (1.5)	toluene	5	38
11 [e]	**1b**	1.25	$TBAHSO_4$	KOH (1.5)	2MeTHF	5	44
12 [e]	**1b**	1.25	$TBAHSO_4$	KOH (1.5)	CH_3CN	5	54
13 [e]	**1b**	1.25	$TBAHSO_4$	KOH (1.5)	1,2,3-trimethylbenzene	5	47
14	**1b**	1.15	$TBAHSO_4$	KOH (1.5)	DCM	5	77
15	**1b**	1.15	$TBAHSO_4$	–	DCM	5	0
16 [e]	**1b**	1.15	–	KOH (1.5)	DCM	5	33

[a] All reactions were carried out on a 0.2 mmol scale by using 0.2 mL of the indicated solvent at 25 °C. [b] Isolated yield. [c] At 40 °C. [d] Using 0.2 eq. of $TBAHSO_4$. [e] The yield was calculated by ^1H NMR of the reaction mixture after usual work-up by using 1,4-dinitrobenzene as internal standard.

Under the same reaction conditions, benzyl triethylammonium chloride (TEBA) afforded similar yield (Table 1, entry 2). In both cases, some unreacted thioester **1a** was recovered; therefore, it was chosen to increase the amount of imine **3a**. Better yields could be obtained by using 1.25 molar equivalents of **3a** (Table 1, entry 3), whereas similar results were obtained by using more solid KOH (Table 1, entry 4). On the other hand, a milder base such as solid, anhydrous K_2CO_3 furnished a lower yield of **3a** (Table 1, entry 5). Both KOH and $TBAHSO_4$ were needed to ensure high yields of the desired product **4a**. Actually, very low conversions and yields were observed when the reaction was carried out without a base or $TBAHSO_4$ (Table 1, entries 6,7). These results confirm that the reaction proceeds through a PTC mechanism even though the background reaction occurs to some extent [36,37].

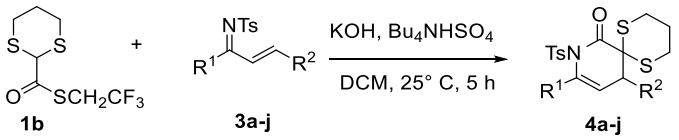
In a second set of experiments, we used *S*-2,2,2-trifluoroethyl-1,3-dithiane-2-carbothioate (**1b**) for further optimization since previous results [31] showed that the presence of the powerful electron-withdrawing *S*-2,2,2-trifluoroethyl group facilitates such domino processes.

We were pleased to find that the reaction reached completion in 5 h only, affording the desired **4a** in 85% isolated yield (Table 1, entry 8). The amount of PT catalyst (0.1 eq) was shown to be optimal since only a slightly increased yield could be obtained by increasing the amount of $TBAHSO_4$ to 0.2 molar equivalents (Table 1, entry 9). Lower yields were obtained when dichloromethane (DCM) was replaced by toluene, 2-methyltetrahydrofuran, acetonitrile or 1,2,3-trimethylbenzene (Table 1, entries 10–13).

Similar results could be obtained with a slightly reduced amount of imine **3a** (Table 1, entry 14), whereas the reaction did not proceed in the absence of base (Table 1, entry 15) and gave 33% yield only without PT catalyst (Table 1, entry 16). This behavior might be ascribed to a limited solubility of the thioate potassium salt **A** in DCM that makes possible the reaction with the *N*-tosyl-imine **2a**. However, the reaction is remarkably more efficient in the presence of the PTC catalyst. Indeed, the exchange of the potassium cation in **A** with the ammonium cation of the catalyst generates the highly reactive ammonium acyl anion equivalent **AAE**, triggering a fast reaction cascade and leading to the desired heterocycle **4a**. When the same reaction was carried out without $TBAHSO_4$ by using a greater excess of both KOH (3 eq.) and *N*-tosylimine **2a** (2 eq.), the dihydropyran-2-one **4a** could be obtained in a 62% yield. Moreover, this reaction provided **4a** in a complex mixture with other byproducts, and the latter reaction conditions are remarkably less efficient from the atom economy point of view.

The reaction scope has been investigated by reacting a variety of substituted imines **3a–j** either bearing electron-poor or electron-rich substituents with thioester **1b** under optimized conditions (Table 2). Both electron-withdrawing and electron-donating substituents in the *para* position of the aromatic rings gave adequate yields of 3,4-dihydropyridin-2-ones **4**. On the other hand, the less reactive imine **3g** bearing a nitro group was not suitable to generate the expected compound under the present conditions. The reaction works with imines bearing the sterically encumbered bromo atom both in *ortho* and *para* positions. The current method was also suitable when the heteroaromatic furyl and thienyl rings replaced the phenyl ring in position three of the starting imine.

Table 2. Synthesis of 3,4-dihydropyridin-2-ones **4a–j** [a].



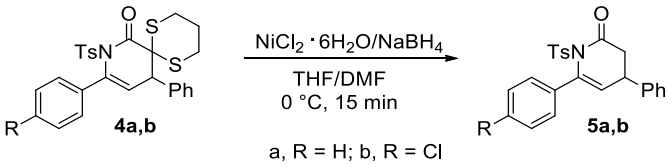
	R^1	R^2	Yield (%)
3a,4a	Ph	Ph	85
3b,4b	4-C_6H_4-Cl	Ph	62
3c,4c	4-C_6H_4-Br	Ph	64
3d,4d	4-C_6H_4-OMe	4-C_6H_4-OMe	60 [b]
3e,4e	Ph	4-C_6H_4-OMe	59
3f,4f	Ph	4-C_6H_4-Me	70
3g,4g	Ph	4-C_6H_4-NO_2	–
3h,4h	Ph	2-C_6H_4-Br	50
3i,4i	Ph	3-methylthienyl	72
3j,4j	Ph	2-methylfuryl	76

[a] Reaction conditions: **1b** (0.30 mmol), **3** (0.375 mmol), KOH_{solid} (0.45 mmol), $TBAHSO_4$ (0.03 mmol), DCM (0.30 mL) at rt for 5 h. [b] The yield was 70% when the reaction was carried out with 1.25 mmol of **1b** under otherwise identical conditions.

The reaction could be easily carried out on a preparative scale under the same reaction conditions. Increasing the reaction scale by 4-fold gave 496 mg of dihydropyridin-2-one **4d** (70% isolated yield) after the same reaction time by using the same 1 M concentration.

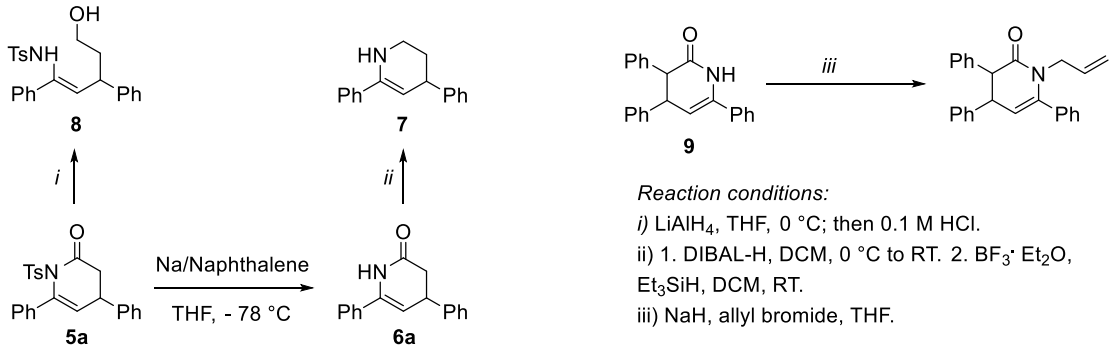
The 1,3-dithiane moiety of dihydropyridin-2-ones **4** could be easily removed by reductive desulfurization, as demonstrated by the clean conversion of **4a,b** to the corresponding 4,6-diaryl-1-tosyl-3,4-dihydropyridin-2-ones **5a,b** with the nickel boride approach (Scheme 4) [38,39]. The reaction was carried out by portion-wise addition of $NaBH_4$ to a stirred solution of the substrate in the presence of nickel chloride hexahydrate. The

dihydropyridin-2-ones **5a,b** were isolated in 70% yield, showing analytical and physical properties identical to those previously reported [40].



Scheme 4. Desulfurization of dihydropyridin-2-ones.

The 3,4-dihydropyridin-2-ones derivatives **5** are useful building blocks for several further derivatizations (Scheme 5). In our hands, the *N*-detosylation of **5a** using the sodium naphthalenide protocol afforded a 82% yield of **6a**. The latter has been previously converted to the corresponding piperidine **7** by a two-step procedure involving a carbonyl to alcohol DIBAL-H reduction followed by deoxygenation [16]. Moreover, the amide nitrogen of **9** could also be successfully subjected to *N*-allylation [26], whereas the heterocyclic ring could be opened to sulfonamide **8** with $LiAlH_4$ at 0 °C.



Scheme 5. Derivatization of 3,4-dihydropyridin-2-ones.

3. Conclusions

In summary, an efficient synthesis of 3,4-dihydropyridin-2-ones **4** was accomplished via the addition of 1,3-dithiane-2-carboxy thioesters **1** to *α*,*β*-unsaturated ketimines **2** under SL-PTC conditions, followed by in situ cyclization driven by the thioate leaving group. The reaction could be carried out under mild conditions with bench stable and cheap substrates. The method is tolerant of different substituents on the aromatic groups of the ketimines and does not need to be carried out under inert atmosphere. The process can be easily carried out to scale. The 1,3-dithiane group on the final products **5** can be easily removed by reductive desulfurization.

This new procedure competes well with previous methods. In particular, the previous procedures [16,40] to generate 3,4-dihydropyridin-2-ones **4,5** described herein require working under deoxygenated and inert atmosphere in 20-fold more diluted conditions for significantly longer reaction times. The PTC approach also seems promising to develop the asymmetric version of the procedure.

4. Materials and Methods

All commercially available compounds were purchased from Merck Life Science S.r.l., 20149 Milano, Italy or TCI Europe, Boereveldseweg 6-Haven 1063, 2070 Zwijndrecht, Belgium.

Melting points were determined with a BÜCHI 535 (BÜCHI Labortechnik AG Meierseggstrasse 40, Postfach, 9230 Flawil, Switzerland) and were corrected. NMR spectra were recorded on a Bruker AC 300 (Bruker, Billerica, MA, USA) operating at 300.13 MHz for ^{1}H NMR, 75.3 MHz for ^{13}C NMR and 282 MHz for ^{19}F NMR. Chemical shifts were reported by using $CHCl_3$ (7.24 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR) and $CFCl_3$ (0 ppm for ^{19}F

NMR) as external standards. APT experiments were used in the assignment of carbon spectra. Column chromatography on silica gel (230–400 mesh) was performed by the flash technique or by using MPLC. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 (Merck KGaA, Darmstadt, Germany) were used and compounds were visualized by irradiation with UV light.

*4.1. Synthesis of S-2,2,2-Trifluoroethyl 1,3-dithiane-2-carbothioate (***1b***)*

To a solution of dithiane carboxylic acid (0.67 g, 5 mmol) in dry dichloromethane (25 mL), hydroxybenzotriazole (0.71 g, 5.25 mmol) was added at 0 °C, and the resulting solution was stirred for 10 min at the same temperature. 1-ethyl-3-carbodiimide hydrochloride (1.01 g, 5.25 mmol) was added at 0 °C and the mixture was stirred for 30 min at the same temperature. Finally, 2,2,2-trifluoroethanethiol (0.64 g, 5.50 mmol) was added at 0 °C, and the mixture was allowed to warm to room temperature. After being stirred overnight, the reaction mixture was diluted with dichloromethane (10 mL) and water (30 mL) was added. The aqueous layer was extracted with dichloromethane (2 × 15 mL) and the organic phases were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated in vacuo to give the title compound as pale yellow solid. Crude **1b** was recrystallized from dichloromethane-petroleum ether to give 1.00 g of pure **1b**, yield 80%, mp 56–57 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96–2.20 (m, 2 H), 2.60–2.68 (m, 2 H), 3.16–3.24 (m, 2 H), 3.62 (q, *J* = 9.8 Hz, 2 H) 4.27 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (CH_2), 26.4 (2 CH_2), 31.8 (q, *J* = 1.4 Hz, CH_2), 49.5 (CH), 124.0 (q, *J* = 272.0 Hz), 192.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ =− 67.2. $C_7H_9F_3OS_3$ (262.34): calcd. C, 32.05, H, 3.46; found C, 32.14, H, 3.47.

4.2. General Procedure for N-Tosylimine **3** *Synthesis*

To a stirred dry DCM (75 mL) solution of chalcone **2** (0.015 mol) and 4-toluenesulfonamide (3.08 g, 0.018 mol) cooled to 0 °C, Et_3N (5.46 g, 0.054 mol) and $TiCl_4$ (3.41 g, 0.018 mol) were added in sequence. After heating at reflux overnight, the resulting solution was cooled to room temperature, followed by the addition of water and extraction with DCM. The combined organic phase was evaporated to dryness and subjected to column chromatography or directly purified through crystallization with AcOEt-hexane 1:1 to generate pure compounds **3** in 50–70% yield with physical and spectroscopic data identical to those reported in literature [41–43].

The following imines are new:

4-methyl-*N*-((*E*)-3-(3-methylthiophen-2-yl)-1-phenylallylidene)benzenesulfonamide (**3i**) ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, 2H, *J* = 8.1 Hz), 7.63 (d, 2H, *J* = 7.5 Hz), 7.55–7.42 (m, 6 H), 7.32 (d, 2H, *J* = 8.1 Hz), 7.26 (d, 1H, *J* = 15.6 Hz), 6.90 (d, 1H, *J* = 5.1 Hz), 2.49 (s, 3H), 2.22 (s, 3H).

^{13}C (75 MHz, $CDCl_3$) δ = 177.4 (C), 143.3 (C), 140.2 (CH), 139.0 (C), 134.5 (C), 131.6 (CH), 131.5 (CH), 129.9 (CH), 129.6 (CH), 129.4 (CH), 128.3 (CH), 127.2 (CH), 109.8, 49.8 (CH), 27.8 (CH_2), 27.7 (CH_2), 24.3 (CH_2), 21.7 (CH_3). Mp 173–175 °C. $C_{21}H_{19}NO_2S_2$ (381.51): calcd. C, 66.11; H, 5.02; N, 3.67; found C, 66.12; H, 5.00; N, 3.68.

4-methyl-*N*-((*E*)-3-(5-methylfuran-2-yl)-1-phenylallylidene)benzenesulfonamide (**3j**) ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (d, 2H, *J* = 7.6 Hz), 7.59 (d, 2H, *J* = 7.6 Hz), 7.53–7.31 (m, 6 H), 6.79 (d, 1H, *J* = 15.6 Hz), 6.60 (d, 1H, *J* = 3.6 Hz), 6.15 (d, 1H, *J* = 3.3 Hz), 2.44 (s, 3H), 2.43 (s, 3H).

^{13}C (75 MHz, $CDCl_3$) δ = 177.4 (C), 157.7 (C), 149.6 (C), 143.1 (C), 139.0 (C), 135.1 (CH), 131.2 (CH), 129.7 (CH), 129.2 (CH), 128.2 (CH), 127.0 (CH), 119.4 (CH), 109.8 (CH), 21.4 (CH_3), 14.0 (CH_3). Mp 142–143 °C. $C_{21}H_{19}NO_3S$ (365.45): calcd C, 69.02; H, 5.24; N, 3.83; found C, 69.01; H, 5.23; N, 3.84.

4.3. General Procedure for the Synthesis of 3,4-Dihydropyridin-2-ones **4a**–**j**

Well-crushed KOH (25,2 mg, 0.45 mmol) was added under vigorous stirring at room temperature to a solution of thioester **1b** (109 mg, 0.30 mmol), imine **3** (0.37 mmol) and $TBAHSO_4$ (10.2 mg, 0.03 mmol) in dichloromethane (0.30 mL). After 5 h, the reaction mixture was added with 10% aq NH_4Cl, the organic phase was separated and the aqueous phase was extracted with DCM (2 × 5 mL). The combined organic phases were dried over

Na_2SO_4 and evaporated to dryness at reduced pressure. The crude obtained was purified by flash chromatography to afford dihydropyridin-2-ones **4a**–**j**. The eluant, yield, physical and spectroscopic data of **4a**–**j** are as follows.

9,11-Diphenyl-8-oxa-1,5-dithiaspiro[5.5]undec-9-en-7-one (**4a**)

Et_2O/hexane 1:6, (129 mg, 85%), white solid, mp 186–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.87 (d, 2H, *J* = 8.4 Hz), 7.36–7.28 (m, 12 H), 5.74 (d, 1H, *J* = 6.3 Hz), 3.95 (d, 1H, *J* = 6.3 Hz), 3.49–3.29 (m, 2H), 2.63–2-59 (m, 2H), 2.49 (s, 3H), 2.11 (m, 1H), 1.75 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.4 (C), 145.1 (C), 140.2 (C), 137.1 (C), 136.4 (C), 135.2 (C), 129.6 (CH), 129.5 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 126.2 (CH), 118.1 (CH), 55.4 (C), 49.8 (CH), 27.8 (CH_2), 27.7 (CH_2), 24.3 (CH_2), 21.7 (CH_3). $C_{27}H_{25}NO_3S_3$ (507.68): calcd. C, 63.88, H 4.96; found C 63.90, H 5.00.

9-(4-chlorophenyl)-11-phenyl-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4b**)

Et_2O/hexane 1:5, (101 mg, 62%), white solid, mp 180–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.89 (d, 2H, *J* = 8.4 Hz), 7.32–7.27 (m, 11H), 5.73 (d, 1H, *J* = 6.6 Hz), 3.93 (d, 1H, *J* = 6.6 Hz), 3.49–3.31 (m, 2H), 2.63–2.55 (m, 2H), 2.50 (s, 3H), 2.14–2.10 (m, 1H), 1.78–1.71 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.2 (C), 145.3 (C), 139.1 (C), 136.1 (C), 135.7 (C), 129.5 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 118.5 (CH), 55.2 (C), 49.7 (CH), 27.83 (CH_2), 27.79 (CH_2), 24.3 (CH_2), 21.8 (CH_3). $C_{27}H_{24}ClNO_3S_3$ (542.12): calcd. C, 59.82; H, 4.46; found C, 59.81; H, 4.45.

9-(4-bromophenyl)-11-(phenyl)-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4c**)

Et_2O/hexane 1:4, (113 mg, 64%), white solid, mp 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90 (d, 2H, *J* = 7.9 Hz), 7.49 (d, 2H, *J* = 8.0), 7.37–7.23 (m, 9H), 5.73 (d, 1H, *J* = 6.3 Hz), 3.92 (d, 1H, *J* = 6.3 Hz), 3.49–3.27 (m, 2H), 2.63–2.59 (m, 2H), 2.50 (s, 3H), 2.15–2.10 (m, 1H), 1.80–1.70 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.1 (C), 145.3 (C), 139.1 (C), 136.2 (C), 134.9 (C), 131.4 (C), 129.5 (CH), 129.2 (CH), 128.4 (CH), 127.7 (CH), 126.4 (CH), 122.3 (C), 118.5 (CH), 55.2 (C), 49.7 (CH), 27.79 (CH_2), 27.77 (CH_2), 21.7 (CH_3). $C_{27}H_{24}BrNO_3S_3$ (586,58): calcd. C, 55.29; H, 4.12; found C, 56.00; H, 4.12.

9,11-bis(4-methoxyphenyl)-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4d**)

EtOAc/hexane 1:6, (102 mg, 60%), white solid, mp 203–204 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.87 (d, 2H, *J* = 8.4 Hz), 7.32–7.22 (m, 6H), 6.89–6.83 (m, 4H), 5.66 (d, 1H, *J* = 6.6 Hz), 3.88 (d, 1H, *J* = 6.6 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 3.48–3.29 (m, 2H), 2.62–2.58 (m, 2H), 2.48 (s, 3H), 2.14–2.09 (m, 1H), 1.74–1.62 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.5 (C), 145.3 (C), 139.1 (C), 136.2 (C), 134.9 (C), 131.4 (C), 129.5 (CH), 129.2 (CH), 128.4 (CH), 127.7 (CH), 126.4 (CH), 122.3 (C), 118.5 (CH), 55.2 (C), 49.7 (CH), 27.8 (CH_2), 27.7 (CH_2), 21.6 (CH_3). $C_{29}H_{29}NO_5S_3$ (567.73) calcd. C, 61.35 H, 5.15; found C, 62.56; H, 5.16.

11-(4-methoxyphenyl)-9-phenyl-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4e**)

Et_2O/hexane 1:4, (95 mg, 59%), white solid, mp 176–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 (d, 2H, *J* = 8.1 Hz), 7.34–7.25 (m, 9H), 6.84 (d, 2H, *J* = 8.1 Hz) 5.73 (d, 1H, *J* = 6.6 Hz), 3.91 (d, 1H, *J* = 6.6 Hz), 3.82 (s, 3H), 3.50–3.27 (m, 2H), 2.62–2.59 (m, 2H), 2.49 (s, 3H), 2.15–2.10 (m, 1H), 1.76–1.71 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 163.5 (C), 159.5 (C), 145.0 (C), 140.1 (C), 137.2 (C), 130.7 (CH), 129.5 (CH), 129.2 (CH), 128.3 (CH) 128.2 (CH), 126.1 (CH), 118.4 (CH), 113.8 (CH), 55.2 (CH_3), 48.9 (CH), 27.8 (CH_2), 24.4 (CH_2), 21.8 (CH_3). $C_{28}H_{27}NO_4S_3$ (537.71) calcd. C, 62.54; H, 5.06; found C, 62.55; H, 5.06.

9-phenyl-11-(p-tolyl)-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4f**)

Et_2O/hexane 1:4, (110 mg, 70%), white solid, mp 169–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.85 (d, 2H, *J* = 6.1 Hz), 7.34–7.30 (m, 7 H), 7.19 (d, 2H, *J* = 5.9 Hz), 7.10 (d, 2H, *J* = 5.9 Hz), 5.71 (d, 1H, *J* = 4.7 Hz), 3.90 (d, 1H, *J* = 4.7 Hz), 3.46–3.30 (m, 2H), 2.61–2.57 (m, 2H), 2.47 (s, 3H), 2.33 (s, 3H), 2.11–2.08 (m, 1H), 1.76–1.66 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.5 (C), 145.1 (C), 140.0 (C), 138.2 (C), 137.2 (C), 136.4 (C), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 126.1 (CH), 118.4 (CH), 55.4 (C), 49.3 (CH), 27.9 (CH_2), 27.8 (CH_2), 24.3 (CH_2), 21.8 (CH_3), 21.2 (CH_3). $C_{28}H_{27}NO_3S_3$ (521.71): calcd. C 64.46, H 5.22; found C 64.39, H 5.21.

11-(2-bromophenyl)-9-phenyl-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4h**)

Et_2O/hexane 1:6, (106 mg, 60%), white solid, mp 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 (d, 2H, *J* = 8.3 Hz), 7.63–7.60 (m, 1H), 7.35–7.28 (m, 8H), 7.19–7.16 (m,

2H), 5.77 (d, 1H, *J* = 6.7 Hz), 4.64 (d, 1H, *J* = 6.7 Hz), 3.59–3.49 (m, 1H), 3.35–3.26 (m, 1H), 2.66–2.62 (m, 2H), 2.49 (s, 3H), 2.16–2.11 (m, 1H), 1.84–1.71 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.3 (C), 145.1 (C), 140.2 (C), 137.1 (C), 136.2 (C), 133.0 (C), 129.8 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.3 (C), 128.2 (C), 127.7 (CH), 125.9 (CH), 125.5 (C), 117.0 (CH), 55.0 (C), 47.6 (CH), 27.8 (CH_2), 27.6 (CH_2), 21.7 (CH_3). $C_{27}H_{24}BrNO_3S_3$ (586,58): calcd. C, 55.29; H, 4.12; found C, 55.29; H, 4.11.

11-(3-methylthiophen-2-yl)-9-phenyl-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4i**)

Et_2O/hexane 1:4, (114 mg, 72%), white solid, mp 193–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 7.84 (d, 2H, *J* = 8.4 Hz), 7.33–7.28 (m, 7H), 7.20 (d, 1H, *J* = 5.1 Hz), 6.83 (d, 1H, *J* = 5.1 Hz), 5.68 (d, 1H, *J* = 5.7 Hz), 4.37 (d, 1H, *J* = 5.7 Hz), 3.46–3.37 (m, 2H), 2.68–2.57 (m, 2H), 2.46 (s, 3H), 2.33 (s, 3H), 2.16–2.11 (m, 1H), 1.80–1.75 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) 168.4 (C), 145.1 (C), 140.1 (C), 137.2 (C), 136.7 (C), 131.9 (C), 129.4 (CH), 129.2 (CH), 128.4 (CH), 128.2 (CH), 126.5 (CH), 124.4 (CH), 118.8 (CH), 45.9 (C), 42.4 (CH), 27.7 (CH_2), 27.6 (CH_2), 24.3 (CH_2), 21.7 (CH_3), 14.8 (CH_3). $C_{26}H_{25}NO_3S_4$ (527,73) calcd. C, 59.18 H, 4.78; found C, 62.56; H, 5.16.

11-(5-methylfuran-2-yl)-9-phenyl-8-tosyl-1,5-dithia-8-azaspiro[5.5]undec-9-en-7-one (**4j**)

Et_2O/hexane 1:4, (117 mg, 76%), white solid, mp 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 7.76 (d, 2H, *J* = 8.4 Hz), 7.30–7.25 (m, 7H), 6.25 (d, 1H, *J* = 3.0 Hz), 5.94 (m, 1H), 5.68 (d, 1H, *J* = 7.2 Hz), 3.94 (d, 1H, *J* = 6.9 Hz), 3.67–3.62 (m, 1H), 3.21–3.17 (m, 1H), 2.72–2.62 (m, 2H), 2.46 (s, 3H), 2.33 (s, 3H), 2.18–2.15 (m, 1H), 1.80–1.56 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ = 168.8 (C), 153.1 (C), 146.0(C), 144.7 (C), 140.7 (C), 137.0 (C), 136.8 (C), 129.3 (CH), 129.0 (CH), 128.1 (CH), 126.4 (CH), 115.4 (CH), 110.8 (CH), 106.3 (CH), 54.3 (C), 43.4 (CH), 27.9 (CH_2), 27.6 (CH_2), 21.7 (CH_3), 13.7 (CH_3). $C_{26}H_{25}NO_4S_3$ (511.67) calcd. C, 61.03 H, 4.93; found C, 61.04; H,4.93.

4.4. General Procedure for the Synthesis of 3,4-Dihydropyridin-2-ones **5a–b**

A solution of **4** (0.25 mmol) in THF (2 mL) was added to a stirred solution of $NiCl_2 \cdot 6\ H_2O$ (950 mg, 4.00 mmol) in DMF (1 mL). After cooling to 0 °C, $NaBH_4$ (302 mg, 8.0 mmol) was added in portions. The reaction mixture was stirred at 0 °C for 15 min, then filtered through a Celite pad and washed with AcOEt. The organic solution was dried over $MgSO_4$ and concentrated in vacuum to afford a crude residue that was purified by flash column chromatography to give desulfurized dihydropyranones **5a,b**.

Eluant, yield and physical spectroscopic data of **5a,b** are as follows:

4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2-one (**5a**)

AcOEt/hexane 1:12, (71 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 (d, 2H, *J* = 8.4 Hz), 7.45–7.12 (m, 12 H), 5.96 (d, 1H, *J* = 4.5 Hz), 3.91–3-85 (m, 1H), 2.82 (d, *J* = 8.2 Hz 2H), 2.42 (s, 3H).

6-(4-clorophenyl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2-one (**5b**)

AcOEt/hexane 1:12, (71 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (d, 2H, *J* = 8.4 Hz), 7.40–7.22 (m, 9 H), 7.20–7.15 (m, 2 H) 5.98 (d, 1H, *J* = 4.5 Hz), 3.92–3.83 (m, 1H), 2.82 (d, *J* = 8.2 Hz 2H), 2.43 (s, 3H).

*4.5. Synthesis of 4,6-Diphenyl-3,4-dihydropyridin-2-one (***6a***)*

To a stirred solution of **5a** (71 mg, 0.18 mmol) in THF (3 mL) at −78 °C under nitrogen atmosphere, a freshly prepared sodium naphthalenide solution in dry THF (10 mL) (sodium (33 mg, 1.44 mmol) and naphthalene (185 mg, 8 mmol)) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and quenched with saturated NaCl aqueous solution. The mixture was allowed to reach room temperature and extracted with Et_2O. The aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried, evaporated to dryness under reduced pressure and subjected to column chromatography (AcOEt/hexane 1:6) to generate **6a** (37 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45–7.21 (m, 10 H), 5.56 (dd, 1H, *J* = 4.0, 1.3 Hz), 4.0–3.89 (m, 1H), 2.88 (dd, *J* = 16.2, 6.9 Hz 1H).

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