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SO₂F₂-mediated *N*-alkylation of imino-thiazolidinones

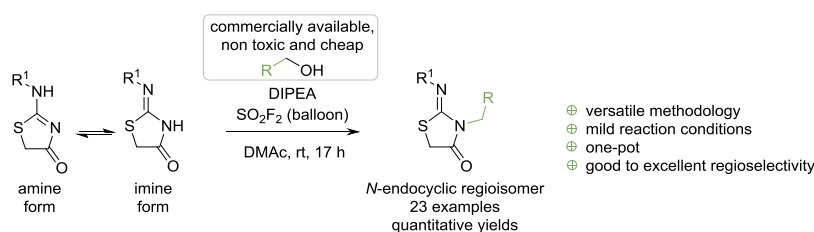
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Supporting Information Placeholder



ABSTRACT: The *N*-alkylation of ambident and weakly nucleophilic imino-thiazolidinones has been developed *via* substitution with alkyl fluorosulfonates. These reactive electrophiles are obtained through the transformation of non-toxic, economic, and commercially available alcohol derivatives on exposure to SO₂F₂ gas. The use of electron-withdrawing groups and DMAc as solvent affords a (*Z*)- and *N*-endocyclic selectivity for the easy introduction of a variety of alkyl and polyfluoroalkyl chains.

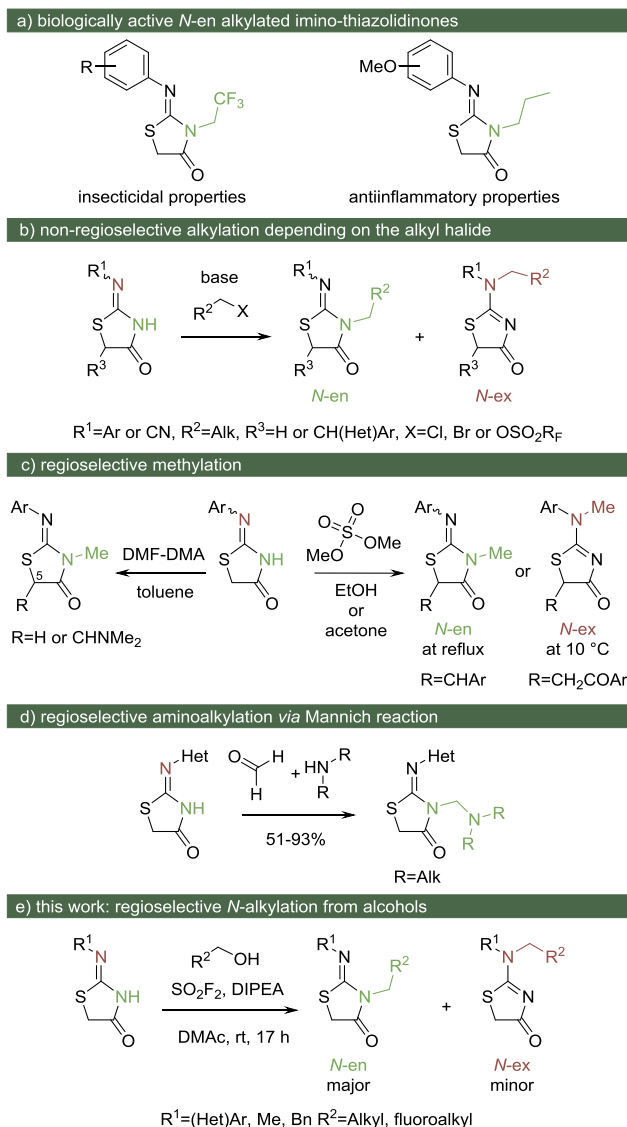
INTRODUCTION

The imino-thiazolidinone core is arousing widespread interest due to its presence in diverse synthetic biologically active compounds.¹ Free NH imine and amine tautomers are well studied and described, and the modulation of their substituents can provide anti-cancer, antimicrobial, anti-inflammatory, and anticonvulsant properties as well as act as hypertensive agents.^{1,2} Despite these potent activities, to the best of our knowledge, very few active compounds of this family bearing a substituted nitrogen are known, including *N*-endocyclic trifluoroethylated species with insecticidal and acaricidal properties and *N*-endocyclic alkylated imino-thiazolidinones which have the potential to reduce local inflammation (Scheme 1, a).^{3–7} This scarcity could be explained by the poor nucleophilicity of the nitrogen atoms and the potential disadvantageous presence of both *N*-endocyclic and *N*-exocyclic regioisomers (hereafter named *N*-en and *N*-ex) which can be a liability for industrialization. To circumvent this drawback, the main approach is to resort to already *N*-alkylated thiourea synthons before ring closure by using chloroacetyl chloride.^{3,8} However, introduction of diversity on the nitrogen atom requires to go two steps backwards. Hence, the direct and regioselective alkylation of free NH imino-thiazolidinone is challenging. Many attempts using alkyl halides have been made for the *N*-alkylation, however, high temperature is required and the regioselectivity strongly depends on the alkylating species (b).^{9–14} Regarding trifluoroethylation using

polyfluorinated fluorosulfonates, no regioselective transformation was obtained (b). In addition to the poor atom economy of this methodology, triflate and perfluorobutane-1-sulfonate are obtained from expensive triflic anhydride or by reaction of sulfolane *via* electrochemical fluorination.¹⁵ For the methylation, two regioselective methods have been developed. Endocyclic *N*-methylation can be achieved by intermolecular condensation of DMF-DMA on the enolic form of imino-thiazolidinone followed by intramolecular rearrangement. Though, a dimethylamino group will thus be introduced on position 5 of imino-thiazolidinone.^{16,17} On the other hand, methylation with dimethyl sulfate can be regioselective depending on the reaction conditions. Indeed, a reaction carried out under reflux of acetone favored endocyclic *N*-methylation while the one at low temperature in EtOH favored exocyclic *N*-methylation (c).^{18,19} The last method is a Mannich-type reaction between formaldehyde and secondary amines which allowed formation of the *N*-en isomer of the dialkylaminomethylated product with moderate to excellent yields (d).²⁰ A major obstacle reported in the literature on alkylation of free NH imino-thiazolidinone is the lack of diversity on the newly introduced alkyl chain. Knowing that there is a strong demand for a handy late-stage introduction of alkyl groups on this type of scaffold, we decided to turn our attention to the development of a method that would be simple, economical, and versatile. For this purpose, we identified an activating agent that fulfilled all these criteria, namely

sulfonyl fluoride (SO_2F_2), through the formation of fluorosulfonate intermediates (ROSO_2F) starting

Scheme 1. Alkylation of Imino-Thiazolidinones

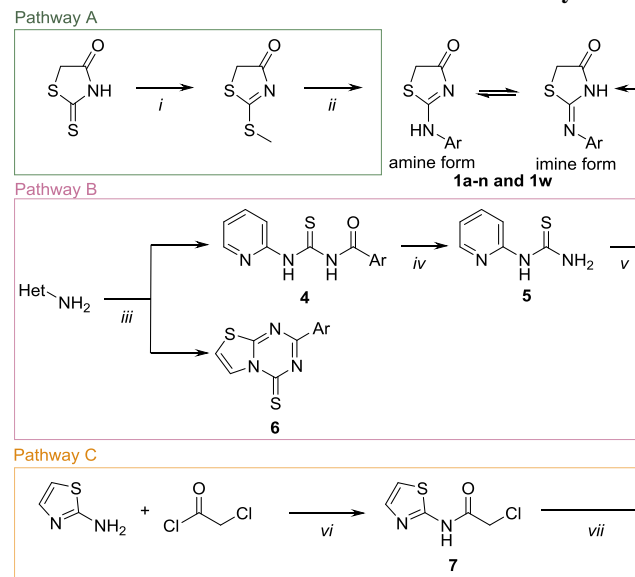


from simple alcohols. Over the last decade, there has been a growing interest in the use of SO_2F_2 as fluorosulfonate precursor, since the fluorosulfonyl group can be involved in reactions as good leaving group or be considered as a connecting functionality.^{21,22} In 2018, Sammis *et al.* developed the *N*-alkylation of rather basic primary and secondary aliphatic amines with polyfluoroalkyl fluorosulfonates.²³ However, in the case of imino-thiazolidinones, the whole process would probably be rougher due to the poor nucleophilicity of both nitrogen atoms which are involved in various mesomeric effects. Indeed, the endocyclic nitrogen can be expected to exhibit reactivity similar to that of an amide, while the exocyclic nitrogen similar to that of an aniline. Herein, we describe a useful method to generate a diverse library of *N*-alkylated imino-thiazolidinones from commercially available, and inexpensive alcohols. Atom economic and affordable SO_2F_2 was used to generate electrophilic alkyl fluorosulfonates *in situ*, which can react with easily accessible free NH imino-thiazolidinones. Considering the ambident reactivity of the reactant, an investigation of the *N*-en regioselectivity was performed.

RESULTS AND DISCUSSION

The synthesis of free NH imino-thiazolidinones was published *via* several routes.^{24–26} The first pathway we applied was the *S*-methylation of rhodanine followed by reaction with a variety of *ortho* and *para* substituted anilines, to form a library of aromatic imino-thiazolidinones **1a–l** and **1w** (Scheme 2, pathway A).^{24,26} Unfortunately, for the imines bearing a pyridine or a thiazole on the exocyclic nitrogen, the targeted imino-thiazolidinones were obtained in yields up to only 35%. As an alternative route, 2-aminopyridine was condensed with benzoyl isothiocyanate to furnish thiourea **4** in 87% yield (Scheme 2, pathway B). Then, deprotection with NaOH to provide **5** followed by a ring closure with ethyl bromoacetate led to targeted compound **1m** in 85% yield.^{25,27} For the synthesis of the 2-aminothiazole derivative, in the first step, the unintended product **6** was obtained through the formation of an unstable intermediate followed by intramolecular rearrangement.²⁸ The desired imino-thiazolidinone **1n** was finally obtained with 74% yield by reaction of *N*-(1,3-thiazol-2-yl)-chloroacetamide **7** with ammonium thiocyanate (Scheme 2, pathway C).^{29,30}

Scheme 2. Free NH Imino-thiazolidinone Synthesis



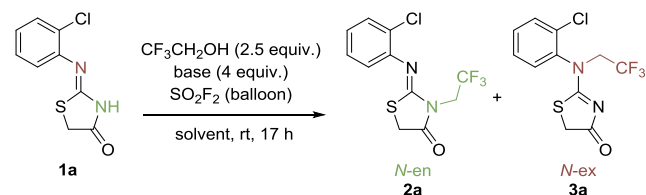
Reagents and conditions: (i) MeI (1.1 equiv.), NaOH, water, 17 h, r.t. (ii) Ar-NH₂ (1.1 equiv.), AcOH, 9 h, reflux. (iii) PhCOCl (1 equiv.), NH₄SCN (1.1 equiv.), acetone, 1 h, reflux. (iv) NaOH, H₂O, 1 h, reflux. (v) BrCH₂CO₂Et (1.1 equiv.), NaOAc (1.3 equiv.), ACN, 17 h, r.t. (vi) ClCH₂COCl (1 equiv.), TEA (1.2 equiv.), DMF,

2 h, r.t. (vii) NH₄SCN (2 equiv.), acetone, 3 h, reflux.

Once the library of free NH imino-thiazolidinones completed, we focused our attention on the optimization of the reaction conditions for the addition of trifluoroethanol. To do so, we initiated our investigation with the trifluoroethylation of *ortho*-chlorophenylimino-thiazolidinone (**1a**) using trifluoroethanol and SO_2F_2 (Table 1). As a starting point, 1 equiv. of **1a** and 1 equiv. of trifluoroethanol were mixed with 2 equiv. of DIPEA as a base in DMAc as solvent. The *in situ* generation of trifluoroethyl fluorosulfonate ($\text{CF}_3\text{CH}_2\text{OSO}_2\text{F}$)

was achieved by slow bubbling of SO_2F_2 in the reaction mixture. Trifluoroethylation succeeded with a moderate conversion of 48% and a good regioselectivity of 92:8 for *N*-en (**2a**) and *N*-ex (**3a**) products respectively after 17 h (Table 1, entry 1). The *N*-en product (**2a**) was always isolated as the *Z*-diastereomer (*vide infra*).

Table 1. Optimization of Reaction Conditions for the Trifluoroethylation of 1a^a



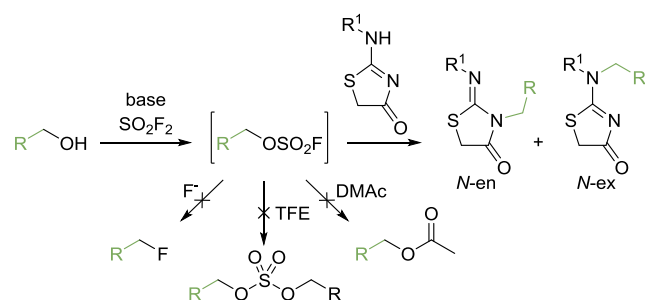
entry	base	solvent	temp. (°C)	NMR ratio 2a:3a	conv. (%)
1 ^b	DIPEA	DMAc	20	92:8	48
2	DIPEA	DMAc	20	92:8	quant.
3	DIPEA	DMAc	0	91:9	70
4	DIPEA	DMAc	40	92:8	quant.
5	Et_3N	DMAc	20	92:8	56
6	KF	DMAc	20	92:8	63
7	DBU	DMAc	20	92:8	quant.
8	DIPEA	toluene	20	41:59	93
9	DIPEA	ACN	20	83:17	76
10	DIPEA	EtOAc	20	60:40	78

^aReaction conditions: **1a** (0.44 mmol), $\text{CF}_3\text{CH}_2\text{OH}$ (1.10 mmol) and base (1.76 mmol) were mixed in the solvent (5 mL), and SO_2F_2 was bubbled through the mixture. ^{19}F or ^1H NMR ratios are reported. ^bWith 1 equiv. of $\text{CF}_3\text{CH}_2\text{OH}$ and 2 equiv. of DIPEA.

Pleasingly, the targeted regioisomer **2a** was predominantly obtained. Nonetheless, the amount of trifluoroethanol and DIPEA were respectively increased to 2.5 equiv. and 4 equiv. to improve the conversion. Thereupon, **1a** was fully converted and the regioselectivity was upheld (Table 1, entry 2). By working at 0 °C, a similar ratio of 91:9 was obtained although the conversion slightly decreased (Table 1, entry 3). A temperature of 40 °C also did not affect the regioselectivity (Table 1, entry 4). Subsequently, the effect of the base was investigated. Triethylamine (Table 1, entry 5) and the inorganic base KF (table 1, entry 6) lowered the conversion but still allowed a good regioselectivity of 92:8. The sterically hindered DBU (Table 1, entry 7) led to the completion of the reaction in only 2 h with preservation of the ratio. This base has already been investigated to increase the reaction rate of alkyl fluorosulfonates with amines.³¹ As DBU is more expensive and toxic, DIPEA was used as an alternative for the alkylation studies. Interestingly, the nature of the solvent had a significant impact on the regioselectivity as previously described in the literature.^{18,19} Non-polar solvents such as toluene favored the *N*-ex regioisomer **3a** (Table 1, entry 8) while more polar ones, such as acetonitrile or ethyl acetate gave lower ratios of

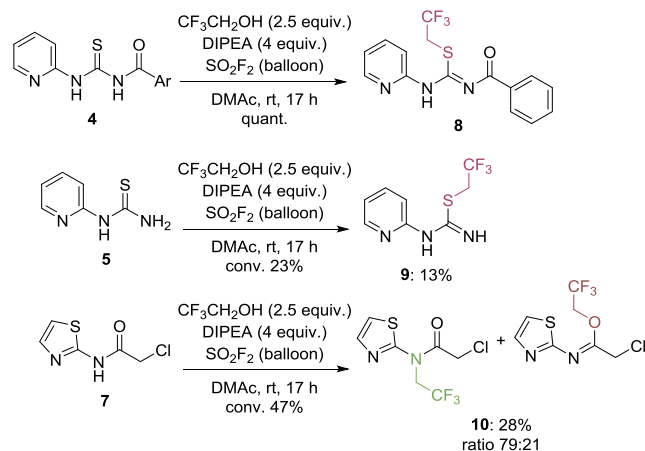
83:17 and 60:40 respectively (Table 1, entries 9 and 10). Finally, the most fruitful outcome was the use of 2.5 equiv. of trifluoroethanol and 4 equiv. of DIPEA as a base in DMAc with a reaction at 20 °C for 17 h (Table 1, entry 2). Interestingly, all along this optimization we never observed side products coming from competitive nucleophilic attacks of the free fluoride, of the substrate itself to form the bis-(trifluoroethyl)sulfate,²³ or from the solvent (DMAc)³² on the trifluoroethyl fluorosulfonate intermediate (Scheme 3).

Scheme 3. Tentative Mechanism and Possible Undesired Side Reactions



In the quest for regioselective *N*-alkylation, intermediates obtained from the synthesis of free NH imino-thiazolidinone **1m** and **1n** were studied under the best reaction conditions for trifluoroethylation, as shown above (Scheme 4). Unfortunately, protected thiourea **4** was quantitatively alkylated at the sulfur atom (**8**). Likewise, *S*-alkylation of pyridyl thiourea **5** was detectable. For the chloroacetamide derivative **7**, dimerization was observed along with a mixture of *O*- and *N*-trifluoroethylation (**10**). These results finally convinced us to carry out the late-stage functionalization of easily accessible free NH imino-thiazolidinones, which occurs regioselectively at the *N*-endocyclic amide.

Scheme 4. Trifluoroethylation of Thioureas and Chloroacetamide Derivatives^a

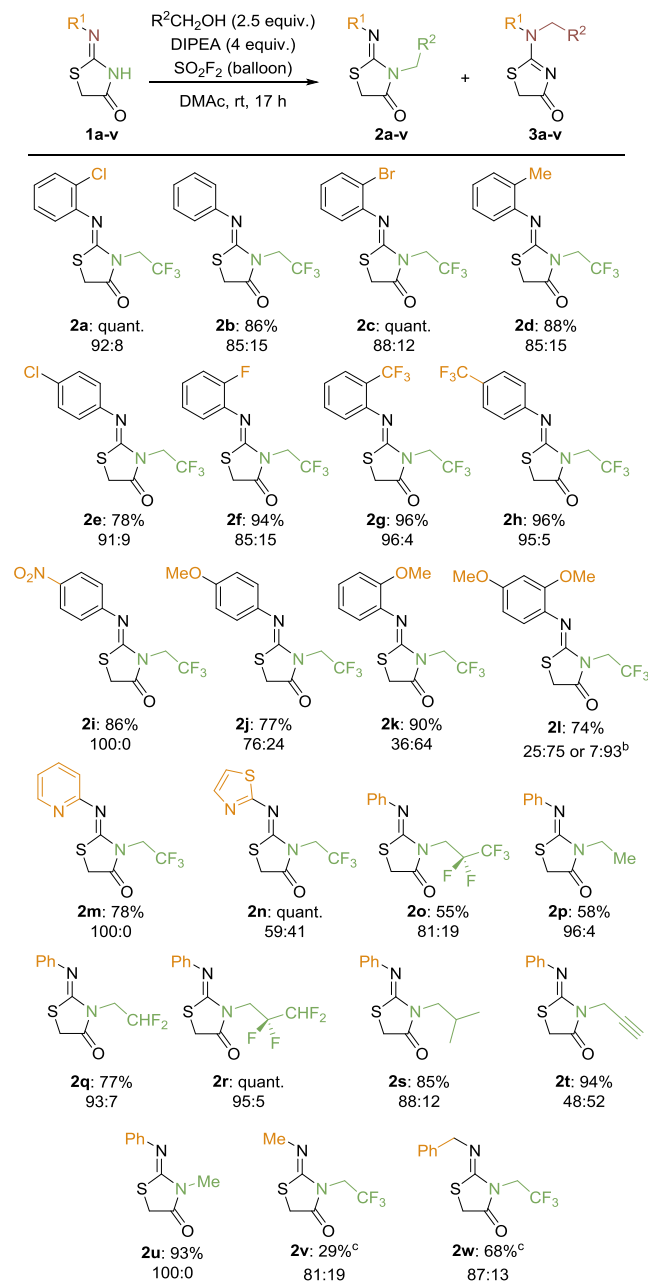


^aYields reported are isolated yields. Ratio and conversions were calculated with ^{19}F NMR.

With these optimized conditions in hands, the effect of the substituent on the aromatic ring R^1 attached to the exocyclic nitrogen was investigated with trifluoroethanol as the alkylating agent (Scheme 5). The alkylation of the non-substituted

phenylimino-thiazolidinone **1b** afforded a mixture of regioisomers in a ratio of 85% of *N*-en product **2b** and 15% of *N*-ex product **3b** with 86% yield. This lower regioselectivity compared to **1a** shows a positive repercussion of the chlorine atom due to its steric or electronic effect. Besides, *ortho* substitution with a methyl group in **2d** afforded a ratio similar to that of phenyl derivative **2b**. The *ortho*-bromo product **2c**, which is more sterically hindered and for which the electron-withdrawing inductive effect is weaker than for chlorine, afforded a slightly better ratio of 88:12 in comparison to the phenyl derivative **2b**. These preliminary results suggest that the electronic effect of chlorine may be responsible for the good regioselectivity rather than steric hindrance, as evidenced by the attempt with the chlorine atom in *para* position. Indeed, **2e** was obtained with a good regioselectivity of 91:9. Thus, the electron-withdrawing inductive effect^{33,34} of halogens results in a less nucleophilic exocyclic nitrogen and thereby less exocyclic *N*-trifluoroethylation. We could have expected that fluorine would increase this effect due to its strong electronegativity. Unfortunately, the ratio for **2f** was only of 85:15. This can be explained by the donating resonance effect of fluorine which can be more important on a phenyl ring.³⁴

Scheme 5. Scope of Alkylation of Imino-thiazolidinones^a



^aYields reported are isolated yields of pure mixtures of regioisomers **2** and **3**. ¹⁹F or ¹H NMR ratios are reported following **2a-w**:**3a-w**. ^bIn toluene as solvent. ^cWith DBU as a base.

In order to corroborate the electronic effect of substituents, we studied the effect of a trifluoromethyl group as an electron-withdrawing group in the *ortho* position (**2g**) and *para* position (**2h**). Nicely, both afforded excellent ratios up to 96:4. The strong negative mesomeric effect of the nitro group in *para* position gave only the desired *N*-en regioisomer **2i** in 86% yield. Conversely, a methoxy group as electron-donating group in the *para* position (**2j**) caused a dramatic decrease of the ratio to 76:24. Surprisingly, in *ortho* position the methoxy group favored the *N*-ex compound **3k** with a ratio of 36:64. The presence of an additional methoxy group in *para* position, in order to further enrich the aromatic ring and enhance the nucleophilicity of the exocyclic nitrogen, favored even more

the *N*-ex isomer **3i** with a *N*-en/*N*-ex ratio of 25:75. As shown in Table 1, the choice of solvent had a strong influence on regioselectivity. In toluene, **1i** allowed the exocyclic *N*-trifluoroalkylation with an excellent regioselectivity of 7:93 with a yield of 42% due to a slow conversion to product **3i**. We also tested the trifluoroethylation of two heterocyclic derivatives. Pyridine, an electron-poor heterocycle, gave only regioisomer **2m** in 78% yield. Thiazole, a five-membered electron-rich heterocycle, afforded a ratio of 59:41 with a quantitative yield of the mixture of **2n** and **3n**.

Next, we explored the effect of the alcohol with phenylimino-thiazolidinone **1b**. Going from trifluoroethanol to the more fluorinated derivative pentafluoropropanol decreased the ratio to 81:19 for **2o**. While using non-fluorinated ethanol an excellent ratio of 96:4 was obtained for **2p**. This trend could presume that the presence of fluorine atoms facilitates the approach to the exocyclic nitrogen over attack of the endocyclic one. Accordingly, difluoroethanol provides a better ratio than trifluoroethanol from 85:15 to 93:7 for **2q**. Unexpectedly, the 2,2,3,3-tetrafluoropropanol derivative **2r** was obtained with an excellent ratio of 95:5 despite the more heavily fluorinated chain. The good results with polyfluoroalkyl fluorosulfonates bearing a difluoromethyl group could be due to the ability of the CHF₂ moiety to engage in H-bonding with the amide.^{35,36} This interaction may explain the better *N*-endocyclic regioselectivity. Isobutyl alcohol with a steric hindrance similar to the one of trifluoroethanol gave rise to **2s** in a ratio of 88:12, proving that steric hindrance also controls the regioselectivity of the alkylation. Propargyl alcohol, which can allow post-functionalization, gave an excellent yield of 94% of **2t**. However, the alkylation was non-regioselective with a ratio of 48:52. Methylation of **1b** worked with an excellent yield and was fully *N*-endocyclic regioselective. To the best of our knowledge, this example stands for the first regioselective *N*-methylation of imino-thiazolidinones under mild conditions.

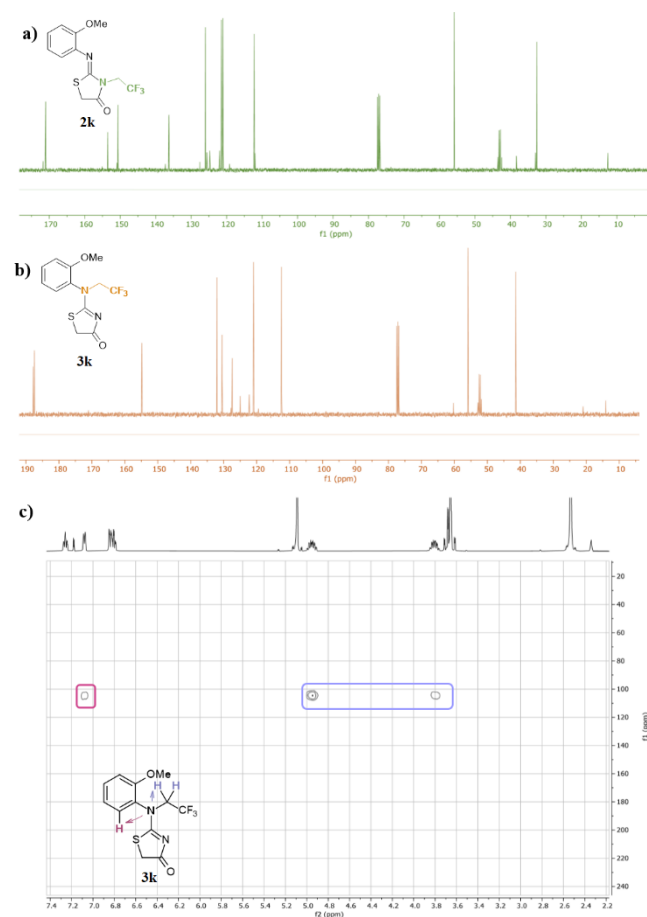
After understanding the importance of the substituents on the aromatic ring, we also tested methylimino-thiazolidinone **1v** and benzylic derivative **1w**. As these derivatives achieved slow conversion with DIPEA, DBU was used as it reduces the reaction time (Table 1, entry 7). By analogy with the nucleophilicity parameter determined by Mayr *et al.* for primary amines in acetonitrile MeNH₂(15.19) > BnNH₂(14.29) > PhNH₂(12.64),^{37,38} the methyl derivative **2v** afforded an anticipated ratio of 81:19 since the nucleophilicity of the exocyclic nitrogen is higher. Benzyl derivatives should also favor more *N*-ex alkylation. Instead, an astonishing increase in favor of *N*-en isomer **2w** with a ratio of 87:13 was achieved, proving that steric hindrance of the imine substituent might after all be important in the alkylation of imino-thiazolidinones. Notably, a substrate bearing an unsubstituted imine led only to the formation of a comp

lex mixture demonstrating that a substituent on the exocyclic nitrogen is mandatory for a clean and complete reaction.

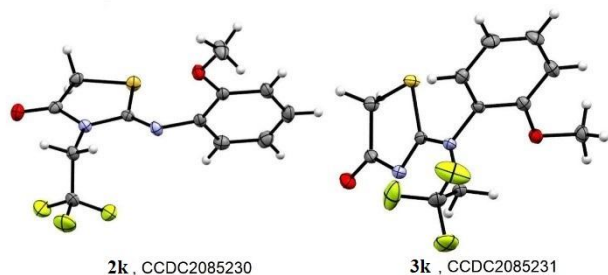
As imino-thiazolidinones are ambident reagents, two regioisomers **2** and **3** were always obtained. The elucidation of their structures was achieved *via* spectroscopy and X-Ray analysis for purified *ortho*-methoxy derivatives **2k** and **3k** (Figure 1). In ¹³C NMR spectroscopy, the first eluted and isolated regioisomer by column chromatography showed a peak at 171 ppm for the carbonyl, and a peak at 154 ppm for the carbon atom surrounded by both nitrogen atoms (Figure 1, a). The second regioisomer possessed signals at 187 ppm and

186 ppm (Figure 1, b). The carbonyl of the amide group and the carbon bearing both nitrogen atoms are expected to be deshielded for the *N*-ex form **3**. We could therefore hypothesize that the first regioisomer was the *N*-en form **2k** and the other one the *N*-ex form **3k**. For infrared spectroscopy, anti-thetical publications were found for the determination of *N*-en and *N*-ex regioisomers. In our case, strong bands at 1638 and 1511 cm⁻¹ were found for speculated **2k** and **3k** respectively. Lesyk *et al.* investigated all the tautomeric forms of free NH imino-thiazolidinone. In conclusion of these studies, a characteristic and very strong band for an endocyclic C=N bond was identified at the absorption of 1640 cm⁻¹,³⁹ indicating that the regioisomer that we obtained with the major band at 1638 cm⁻¹ could be the *N*-ex form. *A contrario*, in a previous manuscript, Lesyk *et al.* were working on the synthesis and anti-inflammatory activity of thiazolidinones.⁴⁰ Their characterization highlighted the presence of 3 tautomers. According to ¹H NMR and infrared spectroscopy, the *N*-en form had higher wavenumbers compared to the *N*-ex form, meaning that the regioisomer with a band at 1638 cm⁻¹ could, this time, be the *N*-en regioisomer. As an unquestionable clue, we performed ¹⁵N-¹H HMBC, which revealed for the *N*-ex regioisomer that the exocyclic nitrogen can undergo a Nuclear Overhauser Effect (NOE) with an aromatic proton as well as with the CH₂ from the trifluoroethyl chain (Figure 1, c). As a last and irrefutable proof, crystals of both regioisomers were obtained and analyzed by X-Ray diffraction (Figure 1, d).

Figure 1. Elucidation of *ortho*-Methoxy Regioisomers^a



d)



^aa and b) ¹³C NMR spectra of both regioisomers **2k** and **3k**. c) ¹⁵N-¹H HMBC of *N*-ex form **3k**. d) ORTEP structures of **2k** and **3k**, ellipsoids at the 50% probability level.

The first isolated regioisomer is thus the *N*-en form **2k** and the second one the *N*-ex form **3k**. The *Z* diastereomer was observed by X-Ray diffraction crystallography for compounds **2k** and **2h** with substituents in *ortho* and *para* position. The absence of NOE between the -CH₂ from the trifluoroalkyl chain and aromatic protons was a first clue to generalize the *Z* configuration of all alkylated imino-thiazolidinones of this work. Furthermore, according to literature and crystallographic data, endocyclic *N*-alkylated species systematically show *Z* configuration.^{3,11,16} Without substituents in *ortho* position on the phenyl group, H-bonding has already been observed between one aromatic -H and the sulfur atom.¹² In addition, we performed DFT calculations on representative products (*i.e.* **2j**, **2k**, **2n** and **2v**) and they support the highly preferential formation of the *Z* isomer in all cases (the energy difference between the *Z* and the *E* isomer was consistently between 5 and 10 kcal/mol, see Supporting Information, Table S1).

CONCLUSIONS

In conclusion, we developed a versatile methodology for the *N*-alkylation of imino-thiazolidinones from commercially available, non-toxic, and economic alcohols in a one-pot procedure. SO₂F₂ is used as an inexpensive and atom economic reagent for the formation of alkyl fluorosulfonates. The purpose was to extend the alkylation to longer chains than methyl and to perform for the first time the direct polyfluoroalkylation of iminothiazolidinones with easily accessible fluorinated surrogates. As the ambident reactivity of imino-thiazolidinones gives rise to regioselectivity issues, we showed that the ratio of *N*-en and *N*-ex regioisomers can be modulated *via* the substituents on the exocyclic nitrogen. Electron withdrawing groups together with polar solvents were required for regioselective alkylation of the endocyclic nitrogen. Furthermore, the electrophilic alkyl fluorosulfonate also plays a role, as we could show that less sterically hindered alcohols or difluoromethyl surrogates can afford excellent regioselectivity. This late stage alkylation allows to produce in a simple way a library of compounds for further biological trials.

EXPERIMENTAL PROCEDURE

General information

All reactions were carried out under argon atmosphere. Warning: Sulfuryl fluoride is a toxic gas and must always be handled with care in a well-ventilated fume hood. Excess sulfuryl fluoride was quenched by passing it through a basic

aqueous medium. All reagents and solvents were purchased commercially and used without further purification unless otherwise stated. Diisopropylethylamine (DIPEA) was distilled and stored over KOH under argon. SO₂F₂ gas bottle was purchased from ABCR. Analytical thin-layer chromatography (TLC) was performed using aluminum plates coated with silica (0.25 mm, Merck silica gel 60-F₂₅₄). Flash column chromatography was performed on VWR silica gel (40–63 μm) using the indicated solvents. ¹H NMR (400 or 600 MHz), ¹⁹F NMR (376 or 565 MHz) and ¹³C NMR (101 or 151 MHz) spectra were recorded on Bruker Avance III HD 400 and 600 MHz instruments respectively. Chemical shifts are reported as δ-values in parts per million (ppm). The spectra were processed with MestreNova (Mestrelab) or ACD/Spectrum Processor. If not otherwise noted, the coupling constants given are either H-H or H-F coupling constants for proton signals, and C-F coupling constants for carbon signals. High resolution mass spectrometry (HRMS) analyses were performed with a Bruker MicroTOF mass analyzer under ESI in positive ionization mode detection (measurement accuracy ≤ 15 ppm) by the analytical facility at the University of Strasbourg. The X-ray crystallographic structure analyses were performed by the radio-crystallographic facility at the University of Strasbourg. The analysis was carried out on a Bruker PHOTON III DUO CPAD diffractometer equipped with an Oxford Cryosystem liquid N₂ device, using Mo-Kα radiation (λ = 0.71073 Å)

General Procedure for the Synthesis of Substrates **1a-l** and **1w**

Rhodanine (1 eq., 3.0 g, 22.5 mmol) was dissolved in a solution of NaOH (2.2 eq., 2.0 g, 50.0 mmol) in water (50 mL) at 22 °C. MeI (1.1 eq., 1.54 mL, 24.8 mmol) was added dropwise to this solution and the reaction mixture was stirred at rt for 17 h. The yellow reaction mixture was diluted with dichloromethane and washed with cold saturated aq. NaHCO₃ and water. The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography from 0 to 60 % of EtOAc in CyH yielding 2-(methylsulfanyl)-4,5-dihydro-1,3-thiazol-4-one as a yellow solid (2.15 g, 14.6 mmol, 65%).

2-(Methylsulfanyl)-4,5-dihydro-1,3-thiazol-4-one (1 eq., 0.50 g, 3.4 mmol) and the desired substituted aniline (1.1 eq., 3.74 mmol) were dissolved in acetic acid (20 mL) and refluxed for 9 h. The reaction mixture was then allowed to cool to room temperature and the formed precipitate was filtered off. Recrystallization from AcOH or EtOH yielded pure aromatic imino-thiazolidinones **1** as powders (yields from 62 to 88%).

Procedure for the synthesis of substrate **1m**

Ammonium thiocyanate (1.1 eq., 1.8 g, 23.3 mmol) was placed in 20 mL of dry acetone. Benzoyl chloride (1 eq., 2.52 mL, 21.6 mmol) was added dropwise by maintaining temperature between 20 and 25 °C. The reaction mixture was refluxed for 30 min and then cooled to rt. 2-Aminopyridine (1eq., 2.0 g, 21.2 mmol) was added gradually to the solution at rt. The reaction mixture was stirred again at reflux for further 30 min. The obtained precipitate was filtered, washed with cold water and dried, yielding **4** as a white powder (4.8 g, 18.4 mmol, 87%). M.p. 128–132 °C.

4 (1 eq., 4.0 g, 15.5 mmol) was added to a solution of NaOH (4 eq., 2.5 g, 62.1 mmol) in 25 mL of water. The reaction mixture was stirred at reflux for 1 h. The solution was filtered

yielding **5** as a yellow powder (1.8 g, 11.6 mmol, 75%). M.p. 145-146 °C.

5 (1 eq., 1.4 g, 9.1 mmol) was placed in 23 mL of acetonitrile and ethyl bromoacetate (1.1 eq., 1.12 mL, 10.0 mmol) was added dropwise. Then, anhydrous sodium acetate (1.3 eq., 1.0 g, 11.8 mmol) was added and the white slurry was stirred at rt for 17 h. The white solid was filtered, washed with water, and dried under vacuum. **1m** was obtained as a white powder (1.5 g, 7.8 mmol, 85%). M.p. 258-259 °C.

Procedure for the synthesis of substrate **1n**

2-Aminothiazole (1 eq., 2.0 g, 20.0 mmol) and triethylamine (1.2 eq., 3.35 mL, 24.0 mmol) were placed in 40 mL of anhydrous DMF. Chloroacetyl chloride (1.0 eq., 1.59 mL, 20.0 mmol) in 10 mL of anh. DMF was added dropwise. The reaction mixture was stirred at rt for 2 h. The solution was taken up in water and filtered, yielding **7** as a white solid (2.5 g, 14.2 mmol, 71%). M.p. 158-160 °C.

7 (1 eq., 2.4 g, 13.5 mmol) and ammonium thiocyanate (2 eq., 2.1 g, 27.1 mmol) were refluxed in acetone for 3 h. The mixture was cooled, and the beige precipitate was collected by filtration, washed with water, and dried under vacuum. **1n** was obtained as a beige solid (2.0 g, 10.0 mmol, 74%). M.p. 187-190 °C.

Procedure for the synthesis of substrate **1v**

N-Methylthiourea (1 eq., 2.0 g, 22.2 mmol), anhydrous sodium acetate (2 eq., 3.6 g, 44.4 mmol) and monochloroacetic acid (1 eq., 1.33 mL, 22.2 mmol) were dissolved in 7 mL of water. The reaction mixture was refluxed for 45 min. The yellow precipitate obtained upon cooling was filtered, washed with cold water and dried under vacuum. **1v** was obtained as a yellow solid (2.0 g, 15.8 mmol, 71%).

General procedure for the synthesis of **2a-2w**

Imino-thiazolidinone **1** (1 eq.), diisopropylethylamine (4 eq.) and alkyl alcohol (2.5 eq.) were placed in 15 mL of DMAc. SO₂F₂, placed in a balloon, was gently bubbled through the reaction mixture for 1 h at rt. The solution was stirred for 17 h at rt. After completion of the reaction, argon was bubbled through to remove SO₂F₂ gas. The solution was concentrated under pressure. The obtained brown oil was diluted with *t*-butyl methyl ether and washed with water. The organic layer was dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography with a gradient of cyclohexane:EtOAc was used when needed.

(*Z*)-2-(2-Chlorophenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2a**) According to the general procedure, **1a** (500 mg, 2.2 mmol), DIPEA (1.54 mL, 8.8 mmol) and TFE (0.40 mL, 5.5 mmol) were used affording the pure mixture of regioisomers **2a** and **3a** (quantitative yield, 690 mg, ratio 92:8). ¹H NMR (600 MHz, ACN-d₃) δ = 7.50 (dd, *J* = 1.3, 8.1 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 1.5, 7.9 Hz, 1H), 4.57 (q, *J* = 9.0 Hz, 2H), 3.98 (s, 2H). ¹³C{¹H} NMR (151 MHz, ACN-d₃) δ = 172.8, 157.7, 146.1, 131.4, 129.3, 127.3, 127.2, 123.2, 125.1 (q, *J* = 279.8 Hz), 44.2 (q, *J* = 35.8 Hz), 34.1. ¹⁹F NMR (565 MHz, ACN-d₃) δ = -69.67 (t, *J* = 9.1 Hz, 3F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₁H₉N₂OF₃SCl, 309.0076; found, 309.0077.

(*Z*)-2-Phenylimino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2b**) According to the general procedure, **1b** (500 mg, 2.6 mmol), DIPEA (1.81 mL, 10.4 mmol) and TFE (0.47 mL, 6.5 mmol) were used affording the pure mixture of regioisomers

2b and **3b** (86% yield, 615 mg, ratio 85:15). ¹H NMR (600 MHz, CDCl₃) δ = 7.38 - 7.35 (m, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.97 (dd, *J* = 8.3 Hz, 2H), 4.55 (q, *J* = 8.5 Hz, 2H), 3.91 (s, 2H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 170.8, 152.3, 147.0, 129.3, 125.0, 120.8, 123.2 (q, *J* = 280.7 Hz), 42.9 (q, *J* = 36.1 Hz, 1C), 32.4. ¹⁹F NMR (565 MHz, CDCl₃) δ = -67.83 (t, *J* = 9.1 Hz, 3F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₁H₁₀N₂OF₃S, 275.0466; found, 275.0466.

(*Z*)-2-(2-Bromophenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2c**) According to the general procedure, **1c** (220 mg, 0.8 mmol), DIPEA (0.54 mL, 3.25 mmol) and TFE (0.15 mL, 2.0 mmol) were used affording the pure mixture of regioisomers **2c** and **3c** (quantitative yield, 290 mg, ratio 88:12). ¹H NMR (400 MHz, CDCl₃) δ = 7.62 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.29 (td, *J* = 7.6, 1.4 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 6.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.58 (q, *J* = 8.4 Hz, 2H), 3.93 (s, 2H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ = 170.5, 154.5, 145.5, 133.0, 128.0, 125.9, 123.0 (q, *J* = 280.6 Hz), 121.2, 115.9, 42.8 (q, *J* = 36.3 Hz, 3F), 32.4. ¹⁹F NMR (377 MHz, CDCl₃) δ = -69.04 (t, *J* = 8.5 Hz). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₁H₉BrN₂OF₃S, 352.9566; found, 352.9589.

(*Z*)-2-(*o*-Tolylimino)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2d**) According to the general procedure, **1d** (500 mg, 2.6 mmol), DIPEA (1.81 mL, 10.4 mmol) and TFE (0.47 mL, 6.5 mmol) were used affording the pure mixture of regioisomers **2d** and **3d** (88% yield, 615 mg, ratio 85:15). ¹H NMR (400 MHz, CDCl₃) δ = 7.13 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.10 - 7.03 (m, 1H), 6.97 (td, *J* = 7.5, 1.4 Hz, 1H), 6.73 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.47 (q, *J* = 8.6 Hz, 2H), 3.83 (s, 2H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 170.8, 151.9, 145.7, 130.8, 129.9, 126.5, 125.0, 123.2 (q, *J* = 280.7 Hz), 119.3, 42.9 (q, *J* = 36.4 Hz), 32.4, 17.5. ¹⁹F NMR (377 MHz, CDCl₃) δ = -69.21 (t, *J* = 8.5 Hz, 3F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₂H₁₂N₂OF₃S, 289.0617; found, 289.0637.

(*Z*)-2-(4-Chlorophenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2e**) According to the general procedure, **1e** (400 mg, 1.8 mmol), DIPEA (1.23 mL, 7.1 mmol) and TFE (0.32 mL, 4.4 mmol) were used affording the pure mixture of regioisomers **2e** and **3e** (78% yield, 426 mg, ratio 91:9). ¹H NMR (600 MHz, CDCl₃) δ = 7.34 - 7.32 (m, 2H), 6.93 - 6.89 (m, 2H), 4.53 (q, *J* = 8.4 Hz, 2H), 3.92 (s, 2H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 170.7, 156.9, 151.8, 139.9, 121.8, 123.2 (q, *J* = 280.7 Hz), 114.4, 55.3, 42.8 (q, *J* = 36.1 Hz), 32.2. NMR (151 MHz, CDCl₃) δ = 170.6, 153.1, 145.5, 130.3, 129.4, 122.2, 123.2 (q, *J* = 280.7 Hz), 43.0 (q, *J* = 36.1 Hz), 32.4. ¹⁹F NMR (565 MHz, CDCl₃) δ = -67.83 (t, *J* = 9.1 Hz, 3F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₁H₉ClN₂OF₃S, 309.0076; found, 309.0067.

(*Z*)-2-(2-Fluorophenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2f**) According to the general procedure, **1f** (480 mg, 2.3 mmol), DIPEA (1.67 mL, 9.6 mmol) and TFE (0.43 mL, 5.9 mmol) were used. Flash column chromatography from 0 to 30 % EtOAc in CyH afforded the pure mixture of regioisomers **2f** and **3f** (94% yield, 626 mg, ratio 85:15). ¹H NMR (600 MHz, CDCl₃) δ = 7.16 - 7.10 (m, 3H), 7.01 - 6.96 (m, 1H), 4.56 (q, *J* = 8.3 Hz, 2H), 3.93 (s, 2H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 170.6, 154.8, 153.4 (d, *J* = 247.0 Hz), 134.7 (d, *J* = 12.3 Hz), 126.0 (d, *J* = 7.5 Hz), 124.5 (d, *J* = 3.6 Hz), 122.5 (d, *J* = 1.5 Hz), 123.2 (q, *J* = 280.7 Hz), 116.4 (d, *J* = 19.6 Hz), 42.9 (q, *J* = 36.3 Hz), 32.5. ¹⁹F NMR (565 MHz, CDCl₃) δ = -67.87 (t, *J* = 9.1 Hz,

3F), -125.7 (m, 1F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{11}H_9N_2OF_4S$, 293.0372; found, 293.0364.

(2Z)-3-(2,2,2-Trifluoroethyl)-2-[2-(trifluoromethyl)phenyl]imino-thiazolidin-4-one (**2g**) According to the general procedure, **1g** (400 mg, 1.8 mmol), DIPEA (1.23 mL, 7.1 mmol) and TFE (0.32 mL, 4.4 mmol) were used affording the pure mixture of regioisomers **2g** and **3g** (96% yield, 426 mg, ratio 96:4). 1H NMR (400 MHz, $CDCl_3$) δ = 7.71 – 7.64 (m, 1H), 7.51 (tdd, J = 8.0, 1.5, 0.7 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.01 (ddd, J = 7.9, 1.3, 0.7 Hz, 1H), 4.53 (q, J = 8.5 Hz, 2H), 3.94 (s, 2H). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -61.96 (3F), -69.27 (t, J = 8.5 Hz, 3F). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$) δ = 170.7, 154.4, 145.3, 132.8, 126.9 (q, J = 5.0 Hz), 124.7, 124.7, 123.2 (q, J = 280.7 Hz), 122.3 (q, J = 30.4 Hz), 121.2, 43.0 (q, J = 36.5 Hz), 32.5. HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{12}H_9N_2OF_6S$, 343.0334; found, 343.0337.

(2Z)-3-(2,2,2-Trifluoroethyl)-2-[4-(trifluoromethyl)phenyl]imino-thiazolidin-4-one (**2h**) According to the general procedure, **1h** (400 mg, 1.5 mmol), DIPEA (1.07 mL, 6.1 mmol) and TFE (0.28 mL, 3.8 mmol) were used. Flash column chromatography from 0 to 30 % EtOAc in CyH afforded the pure mixture of regioisomers **2h** and **3h** (96% yield, 503 mg, ratio 95:5). 1H NMR (600 MHz, $CDCl_3$) δ = 7.63 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 4.55 (q, J = 8.5 Hz, 2H), 3.95 (s, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ = 170.5, 153.6, 150.1, 127.1 (q, J = 32.6 Hz), 126.6 (q, J = 3.6 Hz), 124.1 (q, J = 271.6 Hz), 123.1 (q, J = 280.7 Hz), 121.1, 43.0 (q, J = 36.3 Hz), 32.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -62.09 (s, 3F), -69.18 (t, J = 8.2 Hz, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{12}H_9N_2OF_6S$, 343.0340; found, 343.0334.

(2Z)-2-(4-Nitrophenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2i**) According to the general procedure, **1i** (400 mg, 1.7 mmol), DIPEA (1.17 mL, 6.7 mmol) and TFE (0.31 mL, 4.2 mmol) were used affording pure regioisomers **2i** (86% yield, 465 mg). 1H NMR (600 MHz, $CDCl_3$) δ = 8.26 – 8.22 (m, 2H), 7.10 – 7.05 (m, 2H), 4.54 (q, J = 8.4 Hz, 2H), 3.98 (s, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ = 170.3, 154.3, 152.9, 144.8, 125.2, 121.5, 123.0 (q, J = 280.7 Hz), 43.0 (q, J = 36.4 Hz), 32.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -67.85 (m, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{11}H_9N_3O_3F_3S$, 320.0317; found, 320.0306.

(2Z)-2-(4-Methoxyphenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2j**) According to the general procedure, **1j** (500 mg, 2.2 mmol), DIPEA (1.57 mL, 5.6 mmol) and TFE (0.41 mL, 5.6 mmol) were used affording the pure mixture of regioisomers **2j** and **3j** (77% yield, 524 mg, ratio 76:24). 1H NMR (600 MHz, $CDCl_3$) δ = 6.94 (q, J = 8.3 Hz, 4H), 4.56 (q, J = 8.3 Hz, 2H), 3.92 (s, 2H), 3.83 (s, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $DMSO-d_6$) δ = 171.4, 156.3, 153.4, 121.8, 123.7 (q, J = 280.8 Hz), 114.5, 55.1, 42.5 (q, J = 34.9 Hz), 32.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -69.68 (t, J = 8.7 Hz, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{12}H_{12}N_2O_2F_3S$, 305.0572; found, 305.0560.

(2Z)-2-(2-Methoxyphenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2k**) According to the general procedure, **1k** (400 mg, 1.8 mmol), DIPEA (1.23 mL, 7.1 mmol) and TFE (0.32 mL, 4.4 mmol) were used affording the pure mixture of regioisomers **2k** and **3k** (90% yield, 426 mg, ratio 36:64). 1H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.11 (m, 1H), 6.98 – 6.91 (m, 2H), 6.90 – 6.84 (m, 1H), 4.57 (q, J = 8.5 Hz, 2H), 3.88 (s, 2H), 3.81 (s, 3H). $^{13}C\{1H\}$ NMR (101 MHz,

$CDCl_3$) δ = 171.0, 153.5, 150.6, 136.2, 125.9, 123.3 (q, J = 281.7 Hz), 121.4, 121.0, 112.2, 55.8, 42.9 (q, J = 36.1 Hz), 32.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -69.24 (t, J = 17.0 Hz, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{12}H_{12}N_2O_2F_3S$, 305.0566; found, 305.0583.

(2Z)-2-(2,4-Di(methoxy)phenyl)imino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**3l**) According to the general procedure, **1l** (200 mg, 0.8 mmol), DIPEA (0.55 mL, 3.2 mmol) and TFE (0.14 mL, 2.0 mmol) were used. DMAc afforded the pure mixture of regioisomers **2l** and **3l** with 74% yield (198 mg, ratio 25:75). Toluene afforded the pure mixture of regioisomers **2l** and **3l** with 42% yield (112 mg, ratio 7:93). 1H NMR (600 MHz, $CDCl_3$) δ = 7.23 (d, J = 8.7 Hz, 1H), 6.56 (d, J = 2.6 Hz, 1H), 6.53 (dd, J = 2.6, 8.7 Hz, 1H), 5.24 – 5.17 (m, 1H), 4.00 – 3.94 (m, 1H), 3.91 (q, J = 15.7 Hz, 2H), 3.86 (s, 3H), 3.86 (s, 3H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ = 188.3, 187.5, 162.3, 155.9, 131.2, 123.6 (q, J = 280.3 Hz), 120.6, 104.6, 99.7, 55.8, 55.6, 52.5 (q, J = 34.1 Hz), 41.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -69.45 (t, J = 8.7 Hz, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{13}H_{14}N_2O_3F_3S$, 335.0677; found, 335.0673.

(2Z)-2-(2-Pyridylimino)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2m**) According to the general procedure, **1m** (500 mg, 2.6 mmol), DIPEA (1.80 mL, 10.3 mmol) and TFE (0.47 mL, 6.5 mmol) were used affording pure regioisomer **2m** (78% yield, 555 mg, beige solid, m.p. 110–113 °C). 1H NMR (600 MHz, $DMSO-d_6$) δ = 8.46 – 8.38 (m, 1H), 7.88 – 7.79 (m, 1H), 7.21 – 7.12 (m, 2H), 4.64 (q, J = 9.1 Hz, 2H), 4.04 (s, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $DMSO-d_6$) δ = 171.8, 157.6, 157.2, 146.7, 138.6, 123.7 (q, J = 280.7 Hz), 120.7, 120.3, 42.6 (q, J = 34.9 Hz), 32.6. ^{19}F NMR (565 MHz, $DMSO-d_6$) δ = -67.71 (t, J = 9.1 Hz, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{10}H_9N_3OF_3S$, 276.0418; found, 276.0410.

(2Z)-2-Thiazol-2-ylimino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2n**) According to the general procedure, **1n** (500 mg, 2.5 mmol), DIPEA (1.75 mL, 10.0 mmol) and TFE (0.45 mL, 6.3 mmol) were used. Flash column chromatography from 0 to 45 % EtOAc in CyH afforded the pure mixture of regioisomers **2n** and **3n** (quantitative yield, 745 mg, ratio 59:41, yellow solid, m.p. 133–139 °C). 1H NMR (600 MHz, $DMSO-d_6$) δ = 7.66 (d, J = 3.7 Hz, 1H), 7.50 (d, J = 3.7 Hz, 1H), 4.58 (q, J = 9.2 Hz, 2H), 4.17 (s, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $DMSO-d_6$) δ = 171.8, 168.3, 160.1, 140.0, 123.5 (q, J = 280.5 Hz), 117.7, 42.6 (q, J = 34.9 Hz), 33.2. ^{19}F NMR (565 MHz, $DMSO-d_6$) δ = -67.75 (t, J = 9.1 Hz, 3F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_8H_7N_3OF_3S_2$, 281.9953; found, 281.9977.

(2Z)-3-(2,2,3,3,3-Pentafluoropropyl)-2-phenylimino-thiazolidin-4-one (**2o**) According to the general procedure, **1o** (400 mg, 2.1 mmol), DIPEA (1.45 mL, 8.3 mmol) and 2,2,3,3,3-pentafluoropropanol (0.52 mL, 5.2 mmol) were used. Flash column chromatography from 0 to 30 % EtOAc in CyH afforded the pure mixture of regioisomers **2o** and **3o** (55% yield, 370 mg, ratio 81:19). 1H NMR (600 MHz, $DMSO-d_6$) δ = 7.39 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 7.7 Hz, 2H), 4.59 (t, J = 15.1 Hz, 2H), 4.19 (s, 2H). $^{13}C\{1H\}$ NMR (151 MHz, $DMSO-d_6$) δ = 171.5, 154.1, 147.2, 129.4, 124.6, 120.6, 118.4 (q, J = 273.5 Hz), 112.6 (dt, J = 37.5, 256.7 Hz), 40.6 (t, J = 24.1 Hz), 32.3. ^{19}F NMR (565 MHz, $DMSO-d_6$) δ = -83.83 (s, 3F), -117.95 (t, J = 15.2 Hz, 2F). HRMS (ESI+) m/z : $[M+H]^+$ calcd for $C_{12}H_{10}N_2OF_5S$, 325.0434; found, 325.0432.

(2Z)-3-Ethyl-2-phenylimino-thiazolidin-4-one (**2p**) According to the general procedure, **1p** (300 mg, 1.6 mmol), DIPEA (1.09 mL, 6.2 mmol) and ethanol (0.23 mL, 3.9 mmol) were used affording the pure mixture of regioisomers **2p** and **3p** (58% yield, 200 mg, ratio 96:4). ¹H NMR (600 MHz, DMSO-d₆) δ = 7.36 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 2H), 4.01 (s, 2H), 3.78 - 3.74 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆) δ = 171.6, 154.8, 148.1, 129.2, 124.2, 120.8, 37.3, 32.4, 12.2. HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₁H₁₃N₂OS, 221.0749; found, 221.0736. These data are in accordance with previously reported results.⁴¹

(2Z)-3-(2,2-Difluoroethyl)-2-phenylimino-thiazolidin-4-one (**2q**) According to the general procedure, **1q** (500 mg, 2.6 mmol), DIPEA (1.81 mL, 10.4 mmol) and 2,2-difluoroethanol (0.41 mL, 6.5 mmol) were used affording the pure mixture of regioisomers **2q** and **3q** (77% yield, 510 mg, ratio 93:7). ¹H NMR (600 MHz, CDCl₃) δ = 7.39 - 7.35 (m, 2H), 7.20 - 7.14 (m, 1H), 6.99 - 6.95 (m, 2H), 6.21 (tt, *J* = 5.0, 55.8 Hz, 1H), 4.24 (dt, *J* = 4.7, 13.2 Hz, 2H), 3.88 (s, 2H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 171.1, 153.5, 147.1, 129.3, 124.9, 120.8, 111.9 (t, *J* = 243.2 Hz), 44.2 (t, *J* = 30.3 Hz), 32.6. ¹⁹F NMR (565 MHz, DMSO-d₆) δ = -121.30 (td, *J* = 14.4, 55.7 Hz, 2F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₁H₁₁N₂O₂F₂S, 257.0560; found, 257.0561.

(2Z)-2-Phenylimino-3-(2,2,3,3-tetrafluoropropyl)thiazolidin-4-one (**2r**) According to the general procedure, **1r** (500 mg, 2.6 mmol), DIPEA (2.26 mL, 12.9 mmol) and tetrafluoro-1-propanol (0.70 mL, 7.8 mmol) were used affording the pure mixture of regioisomers **2r** and **3r** (quantitative yield, 830 mg, ratio 95:5). ¹H NMR (600 MHz, DMSO-d₆) δ = 7.38 (t, *J* = 7.6 Hz, 2H), 7.15 (tt, *J* = 1.3, 7.4 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 2H), 6.60 (tt, *J* = 5.7, 51.3 Hz, 1H), 4.41 (t, *J* = 14.7 Hz, 2H), 4.14 (s, 2H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆) δ = 171.7, 154.5, 147.4, 129.3, 124.5, 120.7, 114.9 (tt, *J* = 25.9, 252.2 Hz), 109.4 (tt, *J* = 32.7, 248.3 Hz), 41.1 (t, *J* = 25.4 Hz), 32.3. ¹⁹F NMR (565 MHz, DMSO-d₆) δ = -120.05 - -120.15 (m, 2F), -138.26 (td, *J* = 6.1, 52.0 Hz, 2F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₂H₁₁N₂O₄F₄S, 307.0528; found, 307.0523.

(2Z)-3-iso-Butyl-2-phenylimino-thiazolidin-4-one (**2s**) According to the general procedure, **1s** (500 mg, 2.6 mmol), DIPEA (1.81 mL, 10.4 mmol) and isobutanol (0.60 mL, 6.5 mmol) were used affording the pure mixture of regioisomers **2s** and **3s** (85% yield, 546 mg, ratio 88:12). ¹H NMR (600 MHz, DMSO-d₆) δ = 7.35 (t, *J* = 7.6 Hz, 2H), 7.12 (tt, *J* = 1.2, 7.4 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 2H), 4.05 (s, 2H), 3.57 (d, *J* = 7.5 Hz, 2H), 2.20 - 2.13 (m, *J* = 6.9, 6.9, 13.8 Hz, 1H), 0.92 - 0.88 (m, 7H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆) δ = 172.1, 155.4, 148.2, 129.2, 124.1, 120.7, 49.2, 32.3, 26.2, 19.9. HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₃H₁₇N₂OS, 249.1062; found, 249.1056. These data are in accordance with previously reported results.⁴¹

(2Z)-2-Phenylimino-3-prop-2-ynyl-thiazolidin-4-one (**2t**) According to the general procedure, **1t** (500 mg, 2.6 mmol), DIPEA (1.81 mL, 10.4 mmol) and propargyl alcohol (0.38 mL, 6.5 mmol) were used affording the pure mixture of regioisomers **2t** and **3t** (94% yield, 563 mg, ratio 48:52). ¹H NMR (600 MHz, CDCl₃) δ = 7.31 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 1.0, 8.3 Hz, 2H), 4.57 (d, *J* = 2.5 Hz, 2H), 3.80 (s, 2H), 2.22 (t, *J* = 2.5 Hz, 1H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 170.5, 152.5, 147.3, 129.0, 124.5,

120.8, 76.9, 71.2, 32.4, 31.8. HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₂H₁₁N₂OS, 231.0592; found, 231.0585.

(2Z)-3-Methyl-2-phenylimino-thiazolidin-4-one (**2u**) According to the general procedure, **1u** (100 mg, 0.5 mmol), DIPEA (0.36 mL, 2.1 mmol) and methanol (0.05 mL, 1.3 mmol) were used affording pure regioisomer **2u** (93% yield, 100 mg). ¹H NMR (600 MHz, CDCl₃) δ = 7.35 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 2H), 3.81 (s, 2H), 3.32 (s, 3H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 171.7, 154.8, 147.9, 129.2, 124.6, 120.9, 32.7, 29.5. HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₀H₁₁N₂OS, 207.0592; found, 207.0587. These data are in accordance with previously reported results.⁴²

(2Z)-2-Methylimino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2v**) According to the general procedure, **1v** (84 mg, 0.64 mmol), DIPEA (0.45 mL, 2.58 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.19 mL, 1.3 mmol) and TFE (0.12 mL, 1.6 mmol) were used affording the pure mixture of regioisomers **2v** and **3v** (29% yield, 40 mg, ratio 81:19). ¹H NMR (600 MHz, ACN-d₃) δ = 4.42 (q, *J* = 9.0 Hz, 2H), 3.98 (s, 2H), 3.23 (s, 3H). ¹³C{¹H} NMR (151 MHz, ACN-d₃) δ = 177.0, 155.7, 125.7 (q, *J* = 280.4 Hz), 53.7 (q, *J* = 33.7 Hz), 42.5, 39.4. ¹⁹F NMR (565 MHz, ACN-d₃) δ = -70.37 (t, *J* = 9.1 Hz, 3F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₆H₈N₂O₃F₃S, 212.0309; found, 212.0297.

(2Z)-2-Benzylimino-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**2w**) According to the general procedure, **1w** (100 mg, 0.5 mmol), DIPEA (0.34 mL, 1.9 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.15 mL, 1.0 mmol) and TFE (0.09 mL, 1.2 mmol) were used affording the pure mixture of regioisomers **2w** and **3w** (68% yield, 95 mg, ratio 87:13). ¹H NMR (600 MHz, DMSO-d₆) δ = 7.37 - 7.28 (m, 5H), 4.49 (s, 2H), 4.48 (q, *J* = 9.2 Hz, 2H), 4.19 (s, 2H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆) δ = 171.3, 152.6, 139.0, 128.2, 127.1, 126.7, 123.7 (q, *J* = 280.9 Hz), 54.1, 42.3 (q, *J* = 34.8 Hz), 32.2. ¹⁹F NMR (565 MHz, DMSO-d₆) δ = -67.82 (t, *J* = 9.5 Hz, 3F). HRMS (ESI+) *m/z*: [M+H]⁺ calcd for C₁₂H₁₂N₂O₃F₃S, 289.0622; found, 289.0612.

(NZ)-N-[(2-Pyridylamino)-(2,2,2-trifluoroethylsulfanyl)methylene]benzamide (**8**) According to the general procedure, **4** (300 mg, 1.2 mmol), DIPEA (0.81 mL, 4.7 mmol) and TFE (0.21 mL, 2.9 mmol) were used affording pure compound **8** (quantitative yield, 428 mg, yellow solid, m.p. 92-119 °C). ¹H NMR (600 MHz, CDCl₃) δ = 8.43 (dd, *J* = 1.4, 4.9 Hz, 1H), 8.06 (d, *J* = 7.3 Hz, 2H), 7.79 (dt, *J* = 1.9, 7.7 Hz, 1H), 7.66 - 7.60 (m, 1H), 7.57 - 7.54 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.13 (ddd, *J* = 1.0, 5.0, 7.3 Hz, 1H), 4.07 (q, *J* = 10.2 Hz, 2H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ = 165.5, 158.8, 154.8, 145.4, 139.0, 133.7, 133.0, 128.9, 128.0, 123.3, 125.4 (q, *J* = 276.6 Hz), 120.0, 31.9 (q, *J* = 32.5 Hz). ¹⁹F NMR (565 MHz, CDCl₃) δ = -64.00 (br t, *J* = 10.4 Hz, 3F). HRMS (ESI+) *m/z*: calcd for C₁₅H₁₃N₃F₃O₃S, 340.0731; found, 340.0719.

1-(2-Pyridyl)-2-(2,2,2-trifluoroethyl)isothiourea (**9**) According to the general procedure, **5** (221 mg, 1.4 mmol), DIPEA (1.01 mL, 5.8 mmol) and TFE (0.26 mL, 3.6 mmol) were used affording a mixture of **9** and unreacted **5** (56%, 190 mg, ratio 23:77). ¹H NMR (600 MHz, DMSO-d₆) δ = 8.27 (dd, *J* = 2.1, 5.8 Hz, 1H), 7.72 (dt, *J* = 2.0, 7.7 Hz, 1H), 7.02 - 6.98 (m, 2H), 4.21 (q, *J* = 10.3 Hz, 2H). ¹³C{¹H} NMR (151 MHz, DMSO-d₆) δ = 160.1 (br s), 156.8 (br s), 146.3, 138.5, 125.9 (q, *J* = 275.6 Hz), 120.2, 118.2, 31.0 (q, *J* = 32.3 Hz). ¹⁹F NMR (565 MHz, DMSO-d₆) δ = -65.13 (t, *J* = 10.8 Hz, 3F).

HRMS (ESI+) m/z : calcd for $C_8H_9N_3F_3S$, 236.0469; found, 236.0459.

2-Chloro-N-thiazol-2-yl-N-(2,2,2-trifluoroethyl)acetamide (**10**) According to the general procedure, **7** (500 mg, 2.8 mmol), DIPEA (1.46 mL, 11.3 mmol) and TFE (0.52 mL, 7.1 mmol) were used affording a mixture of regioisomers **10** and unreacted **7** (28%, 510 mg, ratio 79:21). 1H NMR (600 MHz, $CDCl_3$) δ = 7.08 - 7.05 (m, 1H), 6.77 (d, J = 4.8 Hz, 1H), 4.87 (q, J = 8.5 Hz, 2H), 4.30 (s, 2H). ^{13}C {1H} NMR (151 MHz, $ACN-d_3$) δ = 175.8, 170.5, 138.3, 124.4 (q, J = 278.6 Hz), 116.9, 48.3 (q, J = 35.2 Hz), 47.2. ^{19}F NMR (565 MHz, $ACN-d_3$) δ = -71.13 (t, J = 8.7 Hz, 3F). HRMS (ESI+) m/z : calcd for $C_7H_7N_2F_3SOCl$, 258.9841; found, 258.9908.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

DFT calculations, X-ray data, experimental procedures, and characterization data (PDF)

ACCESSION CODES

CCDC2085230, CCDC2085231 and CCDC2097481 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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Notes

The authors declare no competing financial interest.

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