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Article

Sabinene a New Green Solvent: Use in the Synthesis of Thiazolo[5,4-*b*]pyridines by Thermal or Microwave Activation

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Abstract: Following on from work already carried out in our laboratory on a new biomass-derived green solvent, eucalyptol, we are now turning our attention to sabinene as a new green solvent. Sabinene is also derived from biomass. We have shown that it can be used as such or distilled to synthesize thiazolo[5,4-b]pyridine heterocycles by thermal or microwave activation. This new solvent was compared with various conventional and green solvents. The conditions were optimized to enable us to carry out the syntheses in good yields, and we were able to show that sabinene, a natural bicyclic monoterpene, could be used effectively as a solvent.

Keywords: sustainable chemistry; bicyclic *N,S*-heterocycles; biomass-based green solvents; sabinene

1. Introduction

Organic chemistry is mostly using petroleum-based products or solvents which have an important environmental impact. Nowadays, it is important to preserve our non-renewable resources by using new types of solvents made from biomass and to think about atom economy. In 2019, we were able to highlight a new solvent derived from biomass, Eucalyptol [1]. The latter has been compared to conventional known green solvents and has shown an undeniable interest for the organic synthesis of many nitrogenous and sulfur oxygenated heterocyclic compounds via, in particular, nucleophilic substitution, cyclisation, various metallo-catalyzed coupling [2–6] and multicomponent reactions. [2,6]. Although we are still applying this new solvent in various synthetic processes, we are continuing, within the team, our efforts to limit our environmental impact and therefore we are interested in other solvents from biomass. The sabinene is a compound of the family of unsaturated monoterpene hydrocarbons of molecular formula $C_{10}H_{16}$. Sabinene is its trivial name, its IUPAC name is the 4-methylidene-1-(propan-2-yl)bicyclo[3.1.0]hexane. It is classified as food additive and flavoring agent in perfumes industry and found to itself have anti-inflammatory, antioxidant, antifungal [7,8], antiseptic, antimicrobial [9], and bactericidal activities [10].

Sabinene is either extracted from various plants or biosynthesized by enzymatic reaction [11]. It is naturally present in Juniper (*Juniperus Sabina*) [12], Marjoram (*Origanum majorana L.*) [13], Holm oak (*Quercus ilex*) [14], Norway spruce (*Picea abies*), Douglas fir (*Pseudotsuga menziesii*) [15], Spearmint (*Mentha spicata L.*) [16], Angelica (*Angelica archangelica, Apiaceae*) [17], Carrots (*Daucus Carota*) [18], Black pepper (*Piperaceae*) [19], Clausena anisata (Wild) Hook.f. ex Benth (*Rutacea*) [20] or Citrus family [8] and others. Sabinene, which is present in some citrus fruits, could therefore be obtained from the waste products of the fruit juice industry. It was therefore interesting to test it for the organic synthesis of compounds for biological purposes, as its use as a solvent would contribute to the recycling of industrial waste.

Sabinene (Figure 1) has also been reported as a starting material for advanced biofuels [21,22]. Here, it is used as a green solvent for synthesis of various thiazolo[5,4-*b*]pyridines compared to eucalyptol or cyclopentyl methyl ether (CPME), limonene and citral.

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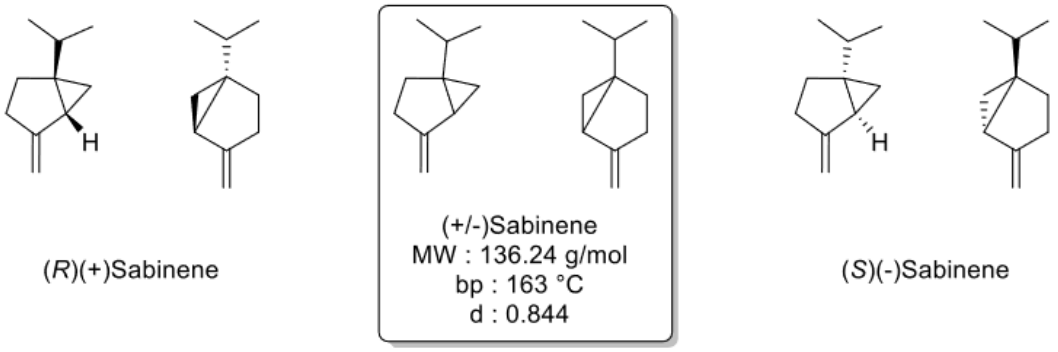

Figure 1. Sabinene structure.

On one hand, heterocycles are widely present in many agrochemicals or pharmaceuticals [23–27]. To date, the number of pharmaceutical products containing a heterocyclic part in their skeleton, and in particular bicyclic heterocycles, is estimated at around 70%, hence the importance of mastering synthesis protocols and carrying them out under the safest possible conditions, for the development and elaboration of new environmentally-friendly drugs or agrochemicals compounds [26,28–30]. On the other hand, thiazolo[5,4-*b*]pyridine analogues are known to have promising properties and are therefore the subject of various developments [31–35], notably in oncology, as some analogues show very good inhibition (nanomolar order) of phosphoinositide 3-kinase (PI3K) [36]. It is an important target for survival, proliferation and differentiation and therefore for tumor-targeted therapy [37]. These compounds can be synthesized in a number of ways, depending on the functionalities envisaged, in particular on the 6-membered ring. They can also be synthesized in a single step from a chloronitropyridine and a suitably substituted thioamide or thiourea [38]. We chose to use the one-step method starting from a 3-amino-2-chloropyridine derivative and an isothiocyanate, a synthetic method already used when we investigated laser irradiation as a new activation method in organic synthesis [39]. This reaction was chosen because of the interest of this type of heterocycle, but also because while the reactants are soluble, the product precipitates in the medium, making it easy to visualize its production.

2. Results and Discussion

2.1. Thiazolo-pyridine synthesis in various standard and green solvents :

On the basis of the results obtained in a previous study [39], the synthesis was first carried out in various conventional solvents before being performed in green solvents. To study ranges and limits, the temperature was maintained at a set point of 110°C for an internal temperature of 100°C in a sealed tube for each experiment by conventional heating using a stirring plate. It was found that 4 hours were required at this temperature, in conventional solvents and that increasing the reaction time did not bring any significant improvement. It should be noted that the product obtained is the HCl salt product as already described by [40], which shows a characteristic NMR spectrum. We tried to carry out the reaction in the presence of a base equivalent such as K_2CO_3, but the reaction was ineffective under these conditions. The solution is to proceed in two stages, forming the product in salt form and then neutralizing it in the presence of a base. We therefore continued our study without a base and formed the products as salts.

As the yields obtained were moderate in both conventional and green solvents, we concentrated on the latter to optimize reaction time using 1 equivalent of each reagent. While citral only led to a disappointing yield of 21% in 16 hours, increasing the reaction time was beneficial for the others green solvents, enabling us to achieve good yields of 58 to 75% (Table 1, entries 7,9,11 and 13). Above 16 hours, we saw no improvement in performance. We used sabinene as a new solvent and obtained encouraging results (Table 1, entries 10 and 11), however, remaining less good than in eucalyptol or CPME (entries 6 to 9). Citral is a compound that doesn't behave very well at this temperature: the

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medium blackens as soon as the reaction temperature reaches 95°C, whereas its boiling point is 229°C. Given this degradation of the medium, we have not studied this solvent in depth, concentrating instead on sabinene and its comparison with eucalyptol, CPME and limonene.

Table 1. Optimisation time of reaction in various solvents.

Entry	Solvent	T (°C)	Time (h)	Yield (%)
1	Acétone	100	4	60
2	DCM	100	4	43
3	Toluène	100	4	44
4	Dioxane	100	4	44
5	THF	100	4	43
6	Eucalyptol	100	4	59
7	Eucalyptol	100	16	75
8	CPME	100	4	63
9	CPME	100	16	71
10	Sabinene	100	4	36
11	Sabinène	100	16	58
12	Limonene	100	4	65
13	Limonene	100	16	70
14	Citral	100	16	21

We therefore continued our optimization, in the previous green solvents, before applying this new solvent (sabinene) to the synthesis of various compounds. The starting 2-chloro-3-aminopyridine (1.5 mmol) was heated in 1 ml of solvent in the presence of phenyl isothiocyanate (Table 2). The yield was improved by increasing the amount of pyridine reagent (Table 2, entries 5, 9 and 12).

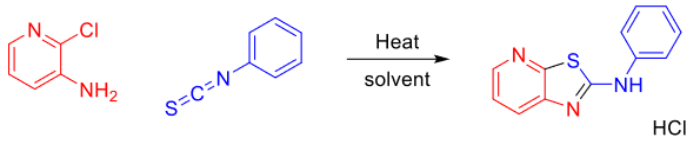

Table 2. Optimization of reaction in green solvents.

Entry	2-chloro-3-amino-pyridine (equiv.)	Isothiocyanate (equiv.)	Reaction time	TP (°C)	Solvent	Yields
1	1	1	4	100	Eucalyptol	59%
2	1	1	16	100	Eucalyptol	75%
3	1	1	4	100	CPME	63%
4	1	1	16	100	CPME	71%
5	1.1	1	16	100	CPME	79%
6	1	1	4	100	Limonene	65%
7	1	1	16	100	Limonene	70%
8	1	1	4	100	Sabinene	36%
9	1.1	1	4	100	Sabinene	38%
10	1	1.1	4	100	Sabinene	33%
11	1	1	16	100	Sabinene	68%
12	**1.1**	**1**	**16**	**100**	**Sabinene**	**76%**
13	1.1	1	16	100	Sabinene	61%
14	1.1	1	16	100	Distilled Sabinene	62%
15	1	1	16	100	Distilled Sabinene	58%

Sabinene being commercially available at 75% purity, we distilled it under reduced pressure with a membrane pump at 12 mbar, at 40°C. However, we found that the reactions carried out in

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distilled or undistilled sabinene were not impacted and yields were equivalent, so we continued our study with commercially available undistilled sabinene.

To visualize the progress of the reaction, the different phases, using chloro-3-aminopyridine heated in 1 ml of sabinene in the presence of benzoyl isothiocyanate, were photographed at different reaction times, starting with the control after mixing the compounds, then during the heating period at 60°C, after 5 min at 100°C, 30 min at 100°C, then after 4h, and finally after 24h of reaction at 100°C, where complete precipitation of the product can be seen (Figure 2).

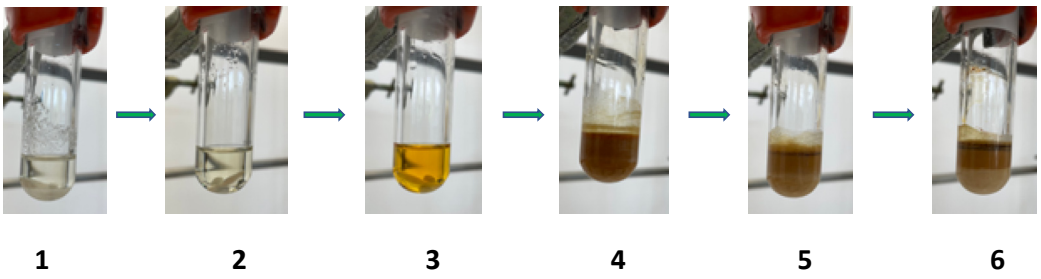

Figure 2. Visual evolution of a manipulation from time T=0 at r.t. to time T= 24h at 100°C. **1**: T=O, reaction medium. **2**: T=60°C during heating period. **3**: after 5 min at 100°C. **4**: after 30 min at 100°C. **5**: after 4 h at 100°C. **6**: after 24 h at 100°C.

2.2. Optimization of thiazolo-pyridine synthesis in sabinene under microwaves irradiation

Based on these initial results, the reaction was performed under conditions described Table 2, entry 12 to obtain the optimum yield. Then, we tried to reduce time reaction by a microwave activation. The temperature has also been adapted. After completion, the product have been filtered and washed with ethyl acetate and diethyl ether and no further purification was required (Table 3).

Table 3. optimization of the reaction conditions under microwaves.

Entry	Reaction time	Temperature (°C)	Yield (%)	Solvant
1	1 h	160	67	Sabinene
2	2 h	150	59	
3	2 h	130	55	
4	4 h	130	62	
5	2 h	130	44	75 :25 Sabinene/Ethanol
6	**2 h**	**130**	**64**	**75 :25 Sabinene/ACN**

Under microwave irradiation, the best results are obtained in 1 hour at 160 degrees, i.e. close to the boiling point of sabinene. However, as this temperature is not compatible with all isothiocyanates, we have tried to reduce the reaction temperature and note that at 130 degrees the time required is 2 hours. As sabinene is not a polar solvent and therefore not the most interesting for microwave reactions, we used 25% of a co-solvent that increases this polarity and chose ethanol or acetonitrile, which proved very interesting as a co-solvent in previous work under microwave irradiation [41]. It turns out that while ethanol doesn't bring any improvement, acetonitrile does halve the reaction time at 130°C, while very slightly increasing the yield (Table 3, entries 4 and 6).

We applied these optimized conditions to some isothiocyanates with, in first, 3-amino-2-chloropyridine in thermal or microwave activation. The results are summarized in Scheme 1.

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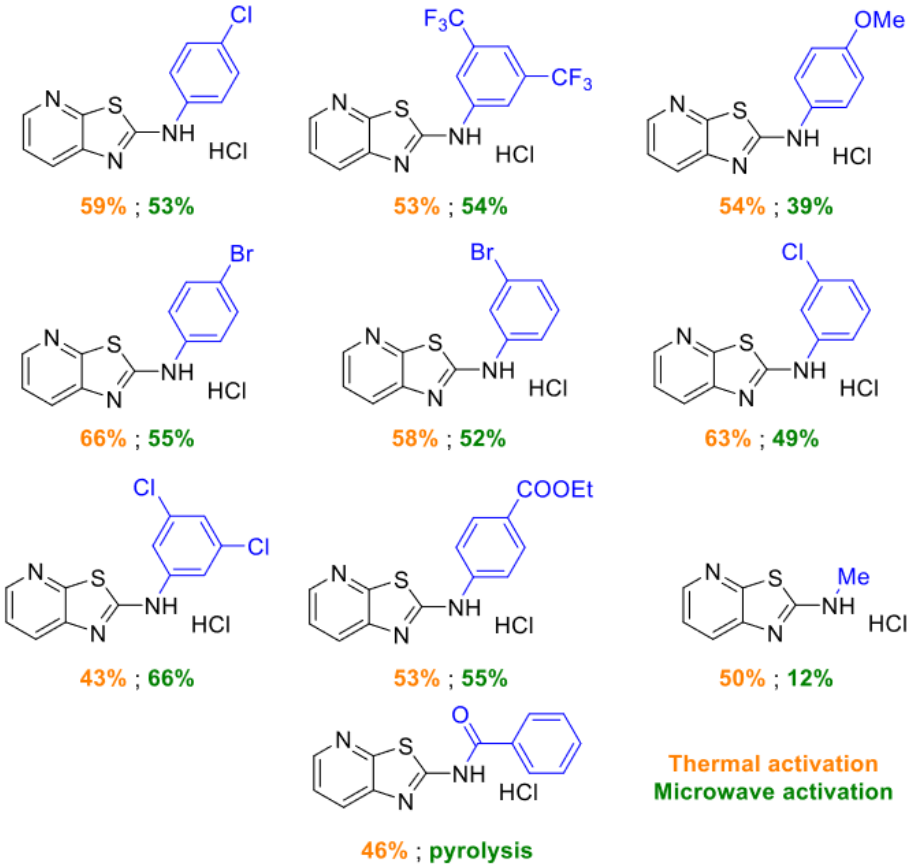

Scheme 1. Thiazolo-pyridine synthesis in Sabinene under thermal or microwaves activation.

Six new structures were synthesized and obtained in great yields and pure by thermal and microwave activation, the four others have already been obtained in a previous study [39]. In a second step, we were interested in the use of other pyridine substituted in particular with an electron donor group of the alkyl type.

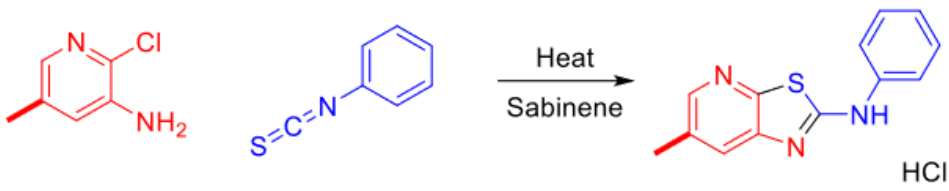

Table 4. Optimization under thermal conditions.

Entry	Reaction time	Pyridine (equiv.)	Isothiocyante (equiv.)	Rinsing solvent	Yield	NMR observation
1	**5 h**	1	1	Diethyl ether	46 %	Clear
2	5 h	**1.1**	1	Diethyl ether	55 %	Parasite peak
3	5 h	1	**1.1**	Diethyl ether	53 %	Parasite peak
4	**16 h**	1.1	1	Diethyl ether	75 %	Parasite peak
5	16 h	1.1	1	**Ethyl acetate**	66 %	Clear

Using 3-amino-2-chloro-5-methylpyridine and isothiocyanate in a sealed tube with 1mL sabinene required heating to 160°C under thermal conditions and took 16 hours to lead to a satisfactory result. After the reaction, the mixture was filtered with ethyl acetate and the desired compound was synthesized in 66% yield (Table 4, entry 5). In this case too, we obtained the product in salt form and the reaction temperature was increased due to the donor effect of methyl in para to

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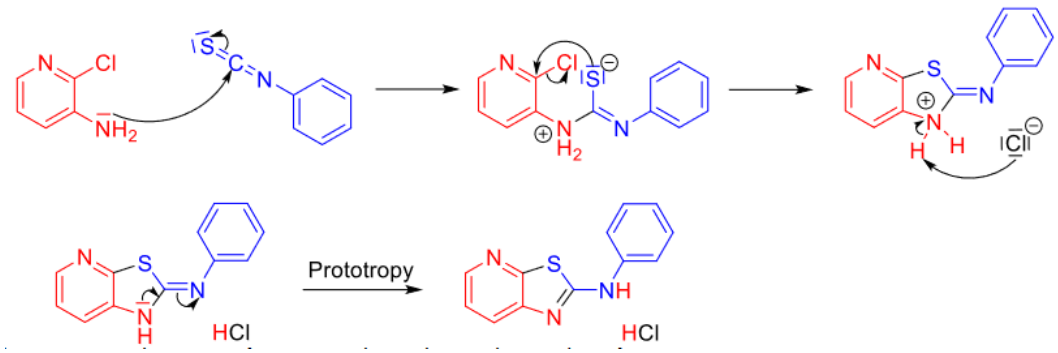
chlorine atom, which could explain the lower reactivity of the latter given the mechanism of 2-aminothiazolo[5,4-*b*]pyridine formation (Scheme 2).



Scheme 2. Mechanism of 2-amino thiazolo[5,4-*b*]pyridine formation.

This mechanism was validated by Atland and Molander [40] with the formation of thiourea, in which the tautomeric thione or thiol displaced the chlorine atom.

Under microwave irradiation, the best results were obtained using 1.1 equiv. of methylpyridine and 1 equiv. of isothiocyanate, in a sealed tube with 1mL of sabinene. The reaction was carried out at 130 degrees for 2 hours to give a yield of 64% (Table 5, entry 7). Again, at the end of the reaction, the mixture was filtered and rinsed with ethyl acetate.

Table 5. Optimization under thermal conditions.

Entry	Reaction time	Temperature	Yield
1	30 mn	150 °C	40 %
2	1 h	150 °C	61%
3	1 h	160 °C	57 %
4	2 h	150 °C	63 %
6	2 h	110 °C	37 %
7	**2 h**	**130 °C**	**64 %**
8	1 h	130°C	50 %

We applied these optimized conditions to some isothiocyanates with, 3-amino-2-chloro-5-methylpyridine in thermal or microwave activation. The results are summarized in Scheme 3.

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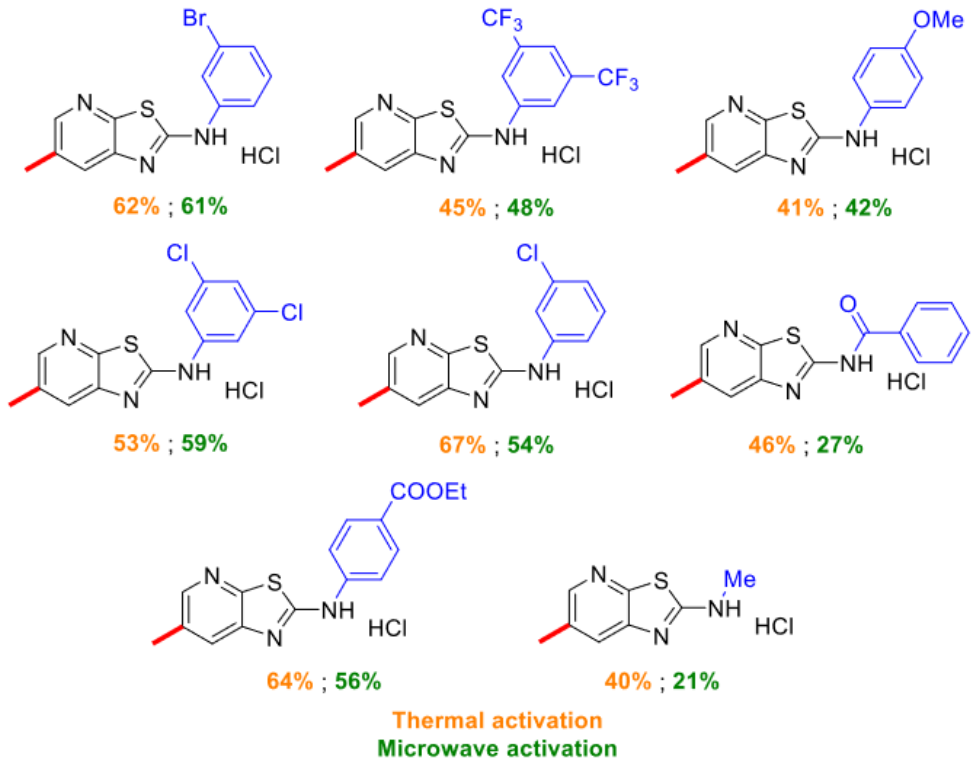
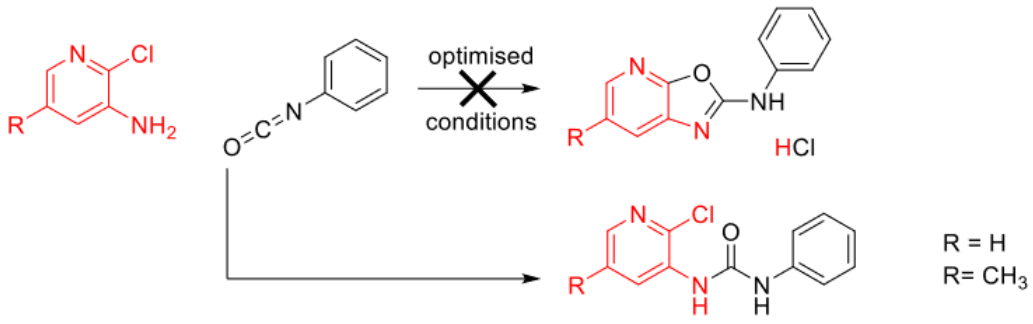


Scheme 3. 6-methyl-thiazolo-pyridine synthesis in sabinene under thermal or microwaves activation.

The use of 3-amino-2-chloro-5-methylpyridine gives good yields when activated by conventional heating. The results remain lower under microwave irradiation, but enable the desired products to be generated more rapidly. We were able to overcome the deactivating effect of methyl in this reaction by adjusting the conditions.

In parallel, we tested these conditions using phenylisocyanate to obtain the corresponding oxazolopyridines. However, as indicated by Sun and co-workers [42] in this case and under our conditions, we also stopped short of urea (Scheme 4).



Scheme 4. Synthesis of corresponding urea instead of desired oxazolopyridine.

3. Materials and Methods

3.1. General Information

All reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 250 (^{13}C, 62.9 MHz) (Bruker, Wissembourg, France), Bruker Avance II 250.13 (^{13}C, 63 MHz), Bruker Avance 400.13 (^{13}C, 101 MHz) (Bruker, Wissembourg, France), or on a Bruker Avance III HD nanobay 400.13 (^{13}C, 101 MHz) (Bruker,

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Wissembourg, France). Chemical shifts are expressed in parts per million (ppm) and were calibrated on deuterated or residual non-deuterated solvent peaks for ^{1}H and ^{13}C spectra. The following abbreviations are used for proton spectra multiplicities: b: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet. Microwave-assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument and temperatures were measured by an IR sensor (Biotage, Uppsala, Sweden). Melting points (p.m. [°C]) were taken on samples placed in open capillary tubes on a Thermo Fisher Melting Point Instrument Digital 9000 Series IA9200X6 and were not corrected. High-resolution mass spectra (HRMS) were performed on a Bruker 4G Maxis UHR-q-TOF mass spectrometer (Bruker, Wissembourg, France), with an electrospray ionization (ESI) mode. The numbering of the atoms on the molecules has been chosen arbitrarily and is indicated on the drawings of the molecules for a better understanding of the NMR spectra.

3.2. General procedure (1)

Substituted 3-amino-2-chloropyridine (1.65 mmol; 1.1 equiv.) and substituted isothiocyanate (1.5 mmol; 1 equiv.) were dissolved in 1mL sabinene and stirred at 100°C for 16 h. The mixture was allowed to cool to room temperature. The mixture was then filtered and washed with ethyl acetate followed by diethyl ether. The product was isolated without further purification.

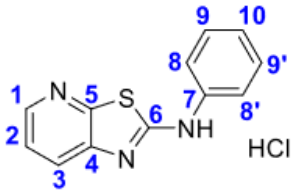
3.3. General procedure (2)

In a sealed tube, substitued 3-amino-2-chloropyridine (1,65 mmol ; 1,1 equiv.) and substituted isothiocyanate (1,5 mmol ; 1 equiv.) were dissolved in 1.0 mL of sabinene. The mixture is placed under microwave irradiation during 2 h at 130 °C. The mixture was allowed to cool to room temperature. Then, the reaction was filtered and washed with ethyl acetate followed by diethyl ether. The product was isolated without further purification.

3.4. General procedure (3)

In a sealed tube, substituted 3-amino-2-chloropyridine (1.65 mmol; 1.1 equiv.) and substituted isothiocyanate (1.5 mmol; 1 equiv.) were dissolved in the solvent consisting of 0.75 ml sabinene and 0.25 ml acetonitrile. The mixture was placed under microwave irradiation for 2 h at 130°C. After cooling to room temperature, the reaction mixture was filtered and washed with ethyl acetate followed by diethyl ether. The product was isolated without further purification.

N-phenylthiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (1) applied to phenyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 65%. Beige solid, m.p. 273 °C. (Lit. 284-285 °C) [40]. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.07 (tt, J = 7.3, 1.2 Hz, 1H, $^{10}H_{Ar}$), 7.32-7.41 (m, 2H, $^{9}H_{Ar}$ and $^{9'}H_{Ar}$), 7.42 (dd, J = 8.1, 5.0 Hz, 1H, $^{2}H_{Ar}$), 7.81 (dd, J = 7.5, 1.3 Hz, 2H, $^{8}H_{Ar}$ and $^{8'}H_{Ar}$), 7.97 (dd, J = 8.2, 1.5 Hz, 1H, $^{3}H_{Ar}$), 8.29 (dd, J = 5.0, 1.5 Hz, 1H, $^{1}H_{Ar}$), 10.94 (bs, 1H, N-H). ^{13}C NMR (101 MHz, DMSO-d6) δ 118.4 ($^{8}CH_{Ar}$ and $^{8'}CH_{Ar}$), 121.7 ($^{2}CH_{Ar}$), 122.8 ($^{10}CH_{Ar}$), 126.2 ($^{3}CH_{Ar}$), 129.0 ($^{9}CH_{Ar}$ and $^{9'}CH_{Ar}$), 140.0 ($^{7}C^{IV}$), 141.8 ($^{1}CH_{Ar}$), 146.5 ($^{4}C^{IV}$), 153.2 ($^{5}C^{IV}$) and 161.1 ($^{6}C^{IV}$).HR-MS (m/z) (ESI+): calcd for m/z $C_{12}H_{10}N_3S$ [M + H+] = 228.0590; found = 228.0588.

N-(4-chlorophenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride

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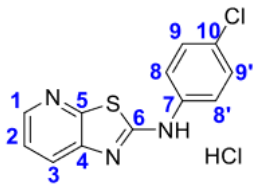
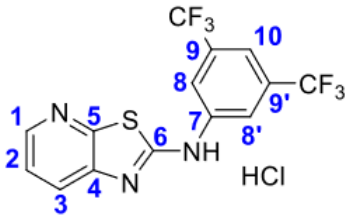


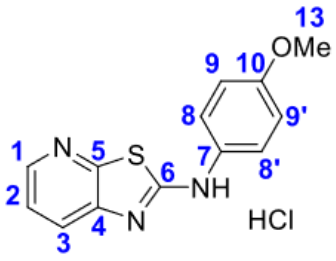
Using general procedure (1) applied to 4-chlorophenyl isothiocyanate and 3-amino-2-chloropyridine. Yied: 59%. Beige solid, m.p. 258 °C. ^{1}H NMR (DMSO-d6, 400 MHz) : δH = 7.39-7.46 (m, 3H, ^{2}H$_{Ar}$ + ^{8}H$_{Ar}$ + $^{8'}$H$_{Ar}$), 7.86 (d, J = 8.0 Hz, 2H, ^{9}H$_{Ar}$ and $^{9'}$H$_{Ar}$), 7.98 (d, J = 8.2 Hz, 1H, ^{3}H$_{Ar}$), 8.31 (d, J = 5.2 Hz, 1H, ^{1}H$_{Ar}$), 11.23 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 119.8 (^{9}CH$_{Ar}$ and $^{9'}$CH$_{Ar}$), 121.8 (^{2}CH$_{Ar}$), 126.2 (^{10}C^{IV}), 126.3 (^{3}CH$_{Ar}$), 128.9 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 139.0 (^{7}C^{IV}), 142.2 (^{1}CH$_{Ar}$), 146.3 (^{4}C^{IV}), 153.4 (^{5}C^{IV}) and 160.8 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_{12}H_9ClN_3S$ [M + H+] = 262.0200; found = 262.0198.

N-(3,5-bis(trifluoromethyl)phenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (3) applied to 3,5-Bis(trifluoromethyl)phenylisothiocyanate and 3-amino-2-chloropyridine. Yield:54%. Colorless solid, m.p. 231°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 7.43 (dd, J = 8.2, 4.9 Hz, 1H, ^{2}H$_{Ar}$), 7.69 (s, 1H, ^{10}H$_{Ar}$), 8.03 (d, J = 8.1 Hz, 1H, ^{3}H$_{Ar}$), 8.34 (d, J = 4.9 Hz, 1H, ^{1}H$_{Ar}$), 8.51 (s, 2H, ^{8}H$_{Ar}$ and $^{8'}$H$_{Ar}$), 11.89 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 114.8 (^{10}CH$_{Ar}$), 117.6 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 121.8 (^{2}CH$_{Ar}$), 123.3 (q, ^{1}J = 274 Hz, ^{11}CF$_3$ and $^{11'}$CF$_3$), 126.7 (^{3}CH$_{Ar}$), 130.9 (q, ^{2}J = 32 Hz, ^{9}C^{IV} and $^{9'}$C^{IV}), 141.8 (^{7}C^{IV}), 143.6 (^{1}CH$_{Ar}$), 145.3 (^{4}C^{IV}), 153.8 (^{5}C^{IV}) and 160.4 (^{6}C^{IV}). ^{19}F NMR (DMSO-*d6*, 376 MHz) **:** δ 61.66. HRMS (m/z) (ESI+): calcd for m/z $C_{14}H_8F_6N_3S$ [M + H$^+$] = 364.0338; found = 364.0341.

N-(4-methoxyphenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (1) applied to 4-methoxyphenyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 54%. Yellow solid, m.p. 241°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 3.74 (s, 3H, ^{11}CH$_3$-O), 6.96 (d, J = 7.0 Hz, 2H, ^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 7.41 (dd, J = 8.1, 5.0 Hz, 1H, ^{2}CH$_{Ar}$), 7.69 (d, J = 7.0 Hz, 2H, ^{9}CH$_{Ar}$ and $^{9'}$CH$_{Ar}$), 7.93 (d, J = 8.1 Hz, 1H, ^{3}CH$_{Ar}$), 8.27 (d, J = 5.1 Hz, 1H, ^{1}CH$_{Ar}$), 10.93 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 55.3 (^{11}CH$_3$-O), 114.3 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 120.5 (^{9}CH$_{Ar}$ and $^{9'}$CH$_{Ar}$), 121.8 (^{2}CH$_{Ar}$), 125.8 (^{3}CH$_{Ar}$), 133.1 (^{7}C^{IV}), 141.1 (^{1}CH$_{Ar}$), 146.7 (^{4}C^{IV}), 152.8 (^{5}C^{IV}), 155.3 (^{10}C^{IV}) and 161.6 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_{13}H_{12}N_3OS$ [M + H$^+$] = 258.0695; found = 258.0693.

N-(4-bromophenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride

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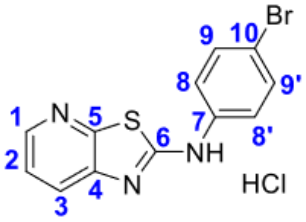
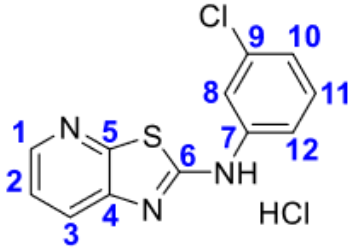


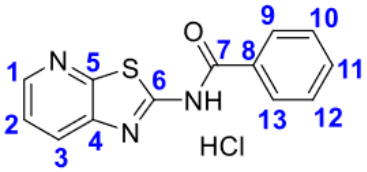
Using general procedure (1) applied to 4-bromophenyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 66%. Beige solid, m.p. 264°C (decomposition). ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 7.41 (dd, J = 8.1, 4.9 Hz, 1H, $^{2}H_{Ar}$), 7.55 (d, J = 8.8 Hz, 2H, $^{8}H_{Ar}$ and $^{8'}H_{Ar}$), 7.80 (d, J = 8.9 Hz, 2H, $^{9}H_{Ar}$ and $^{9'}H_{Ar}$), 7.97 (dd, J = 8.2, 1.6 Hz, 1H, $^{3}H_{Ar}$), 8.30 (dd, J = 4.9, 1.6 Hz, 1H, $^{1}H_{Ar}$), 11.16 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 114.1 ($^{10}C^{IV}$), 120.2 ($^{9}CH_{Ar}$ and $^{9'}CH_{Ar}$), 121.7 ($^{2}CH_{Ar}$), 126.1 ($^{3}CH_{Ar}$), 131.8 ($^{8}CH_{Ar}$ and $^{8'}CH_{Ar}$), 139.4 ($^{7}C^{IV}$), 142.5 ($^{1}CH_{Ar}$), 146.1 ($^{4}C^{IV}$), 153.6 ($^{5}C^{IV}$) and 160.6 ($^{6}C^{IV}$). HRMS (m/z) (ESI+): calcd for m/z $C_{12}H_9BrN_3S$ [M + H+] = 305.9695; found = 305.9698.

N-(3-chlorophenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (1) applied to 3-chlorophenyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 63%. Beige solid, m.p. 205°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 7.10 (dd, J = 7.8, 2.4 Hz, 1H, $^{12}H_{Ar}$), 7.39 (t, J = 8.2 Hz, 1H, $^{11}H_{Ar}$), 7.44 (dd, J = 8.0, 4.9 Hz, 1H, $^{2}H_{Ar}$), 7.67 (dd, J = 8.2, 2.6 Hz, 1H, $^{10}H_{Ar}$), 8.03 (dd, J = 8.2, 1.6 Hz, 1H, $^{3}H_{Ar}$), 8.07 (m, 1H, $^{8}H_{Ar}$), 8.32 (dd, J = 4.9, 1.6 Hz, 1H, $^{1}H_{Ar}$), 11.32 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 116.7 ($^{10}CH_{Ar}$), 117.6 ($^{8}CH_{Ar}$), 121.8 ($^{2}CH_{Ar}$), 122.3 ($^{12}CH_{Ar}$), 126.5 ($^{3}CH_{Ar}$), 130.6 ($^{11}CH_{Ar}$), 133.3 ($^{9}C^{IV}$), 141.4 ($^{7}C^{IV}$), 142.4 ($^{1}CH_{Ar}$), 146.1 ($^{4}C^{IV}$), 153.4 ($^{5}C^{IV}$) and 160.7 ($^{6}C^{IV}$). HRMS (m/z) (ESI+): calcd for m/z $C_{12}H_9ClN_3S$ [M + H^+] = 262.0200; found = 262.0202.

N-benzamidethiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (1) applied to benzoyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 46%. Beige solid, m.p. 183°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 7.54 (dd, J = 8.2, 4.6 Hz, 1H, $^{2}H_{Ar}$), 7.58 (t, J = 7.6 Hz, 2H, $^{10}H_{Ar}$ and $^{10'}H_{Ar}$), 7.67-7.71 (m, 1H, H_{Ar}), 8.11-8.20 (m, 3H, $^{9}H_{Ar}$ + $^{9'}H_{Ar}$ + $^{3}H_{Ar}$), 8.52 (dd, J = 4.8, 1.4 Hz, 1.0H, $^{1}H_{Ar}$), 12.95 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 121.8 ($^{2}CH_{Ar}$), 127.6 ($^{3}CH_{Ar}$), 128.4 ($^{9}CH_{Ar}$ and $^{9'}CH_{Ar}$), 128.7 ($^{10}CH_{Ar}$ and $^{10'}CH_{Ar}$), 131.6 ($^{8}C^{IV}$), 133.1 ($^{11}CH_{Ar}$), 141.8 ($^{4}C^{IV}$), 145.4 ($^{1}CH_{Ar}$), 154.7 ($^{5}C^{IV}$), 158.4 ($^{6}C^{IV}$) and 166.3 ($^{7}C^{IV}$=O). HRMS (m/z) (ESI+): calcd for m/z $C_{13}H_{10}N_3OS$ [M + H^+] = 256.0539; found = 256.0541.

N-(3,5-dichlorophenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride

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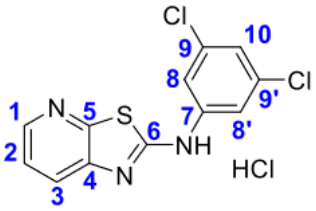
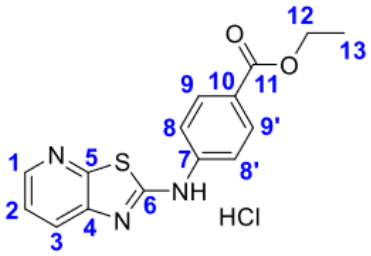


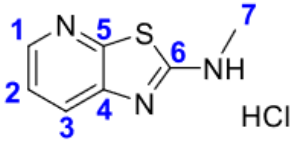
Using general procedure (3) applied to 3,5-dichlorophenyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 66%. Beige solid, m.p. 265°C (decomposition). ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 7.22 (t, J = 1.8 Hz, 1H, ^{10}H$_{Ar}$), 7.43 (dd, J = 8.2, 4.9 Hz, 1H, ^{2}H$_{Ar}$), 7.91 (d, J = 1.8 Hz, 2H, ^{8}H$_{Ar}$ and $^{8'}$H$_{Ar}$), 8.05 (dd, J = 8.2, 1.6 Hz, 1H, ^{3}H$_{Ar}$), 8.33 (dd, J = 4.9, 1.6 Hz, 1H, ^{1}H$_{Ar}$), 11.54 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 116.2 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 121.5 (^{10}CH$_{Ar}$), 121.8 (^{2}CH$_{Ar}$), 126.6 (^{3}CH$_{Ar}$), 134.3 (^{9}C^{IV} and $^{9'}$C^{IV}), 142.2 (^{7}C^{IV}), 143.2 (^{1}CH$_{Ar}$), 145.6 (^{4}C^{IV}), 153.7 (^{5}C^{IV}) and 160.3 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_{12}H_8Cl_2N_3S$ [M + H$^+$] = 295.9811 ; found = 295.9810.

N-(ethyl 4-aminobenzoate)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (3) applied to ethyl 4-isothiocyanatobenzoate and 3-amino-2-chloropyridine. Yield: 55%. Beige solid, m.p. 230°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 1.31 (t, J = 7.1 Hz, 3H, ^{13}CH$_3$), 4.28 (q, J = 7.1 Hz, 2H, ^{12}CH$_2$), 7.45 (dd, J = 8.1, 4.9 Hz, 1H, ^{2}H$_{Ar}$), 7.96 (s, 4H, H$_{Ar}$), 8.04 (d, J = 8.3 Hz, 1H, ^{3}H$_{Ar}$), 8.34 (d, J = 4.9 Hz, 1H, ^{1}H$_{Ar}$), 11.48 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 14.3 (^{13}CH$_3$), 60.4 (^{12}CH$_2$), 117.6 (2xCH$_{Ar}$), 121.8 (^{2}CH), 123.5 (^{10}C^{IV}), 126.8 (^{3}CH), 130.5 (2xCH$_{Ar}$), 142.6 (^{1}CH), 144.2 (^{7}C^{IV}), 146.1 (^{4}C^{IV}), 153.5 (^{5}C^{IV}), 160.5 (^{6}C^{IV}) and 165.3 (^{11}C^{IV}=O). HRMS (m/z) (ESI+): calcd for m/z $C_{15}H_{14}N_3O_2S$ [M + H$^+$] = 300.0801 ; found = 300.0801.

N-methylthiazolo[5,4-*b*]pyridin-2-amine hydrochloride



Using general procedure (1) applied to methyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 50%. Beige solid, m.p. 239°C (lit. 264-265) [40]. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 3.06 (s, 3H, ^{7}CH$_3$), 7.43 (dd, J = 8.1, 5.0 Hz, 1H, ^{2}H$_{Ar}$), 7.88 (d, J = 8.1 Hz, ^{3}H$_{Ar}$), 8.27 (d, J = 5.0 Hz, 1H, ^{1}H$_{Ar}$), 9.69 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 30.9 (^{7}CH$_3$), 122.0 (^{2}CH$_{Ar}$), 123.7 (^{3}CH$_{Ar}$), 141.6 (^{1}CH$_{Ar}$), 142.4 (^{4}C^{IV}), 150.6 (^{5}C^{IV}) and 165.9 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_7H_8N_3S$ [M + H$^+$] = 166.0433 ; found = 166.0438.

N-(3-bromophenyl)thiazolo[5,4-*b*]pyridin-2-amine hydrochloride

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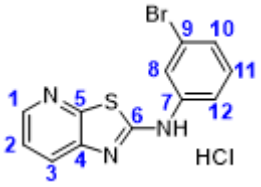
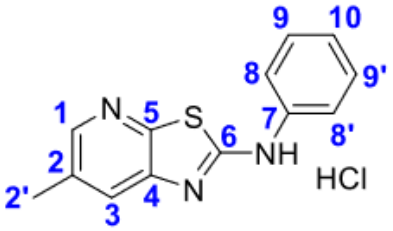


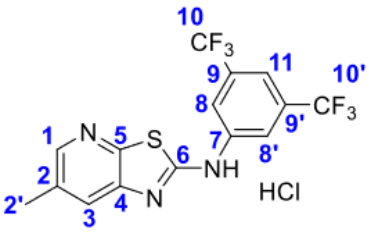
Using general procedure (1) applied to 3-bromophenyl isothiocyanate and 3-amino-2-chloropyridine. Yield: 58%. Yellowish solid, m.p. 231°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 7.23 (d, J = 8.1 Hz, 1H, ^{12}H$_{Ar}$), 7.33 (t, J = 8.1 Hz, 1H, ^{11}H$_{Ar}$), 7.41 (dd, J = 8.4, 5.2 Hz, 1H, ^{2}H$_{Ar}$), 7.71 (d, J = 8.2 Hz, 1H, ^{10}H$_{Ar}$), 7.99 (d, J = 8.1 Hz, 1H, ^{3}H$_{Ar}$), 8.18 (s, 1H, ^{8}H$_{Ar}$), 8.29 (d, J = 5.3 Hz, 1H, ^{1}H$_{Ar}$), 11.12 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 117.2 (^{10}CH$_{Ar}$), 120.5 (^{8}CH$_{Ar}$), 121.8 (^{2}CH$_{Ar}$), 121.9 (^{9}C^{IV}), 125.2 (^{12}CH$_{Ar}$), 127.0 (^{3}CH$_{Ar}$), 130.9 (^{11}CH$_{Ar}$), 141.5 (^{1}CH$_{Ar}$), 141.6 (^{7}C^{IV}), 146.5 (^{4}C^{IV}), 152.7 (^{5}C^{IV}) and 160.8 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_{12}H_9BrN_3S$ [M + H$^+$] = 305.9695 ; found = 305.9689.

N-phenylthiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride



Using general procedure (2) applied to phenyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 64%. Beige solid, m.p. 228°C (decomposition). ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 2.38 (s, 3H, $^{2'}$CH$_3$), 7.06 (t, J = 7.4 Hz, 1H, ^{10}H$_{Ar}$), 7.38 (t, J = 7.6 Hz, 2H, ^{9}H$_{Ar}$ and $^{9'}$H$_{Ar}$), 7.80 (d, J = 8.3 Hz, 2H, ^{8}H$_{Ar}$ and $^{8'}$H$_{Ar}$), 7.88 (s, 1H, ^{3}H$_{Ar}$), 8.20 (s, 1H, ^{1}H$_{Ar}$), 10.93 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.8 ($^{2'}$CH$_3$), 118.5 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 122.9 (^{10}CH$_{Ar}$), 127.4 (^{3}CH$_{Ar}$), 129.1 (^{9}CH$_{Ar}$ and $^{9'}$CH$_{Ar}$), 131.7 (^{2}C^{IV}), 140.0 (^{7}C^{IV}), 141.2 (^{1}CH$_{Ar}$), 146.9 (^{4}C^{IV}), 149.4 (^{5}C^{IV}) and 161.5 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_{13}H_{12}N_3S$ [M + H$^+$] = 242.0746 ; found = 242.0749.

N-(3,5-bis(trifluoromethyl)phenyl)thiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride



Using general procedure (2) applied to 3,5-Bis(trifluoromethyl)phenyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 48%. Beige solid, m.p. 242°C (decomposition). ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 2.37 (s, 3H, $^{2'}$CH$_3$), 7.67 (s, 1H, ^{11}H$_{Ar}$), 7.89 (s, 1H, ^{3}H$_{Ar}$), 8.19 (s, 1H, ^{1}H$_{Ar}$), 8.49 (s, 2H, ^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 11.83 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.7 ($^{2'}$CH$_3$), 114.8 (^{11}CH$_{Ar}$), 117.6 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 123.3 (q, ^{1}J = 274 Hz, ^{10}CF$_3$ and $^{10'}$CF$_3$), 127.3 (^{3}CH$_{Ar}$), 130.9 (q, ^{2}J = 33 Hz, ^{9}C^{IV} and $^{9'}$C^{IV}), 131.6 (^{2}C^{IV}), 141.8 (^{7}C^{IV}), 143.9 (^{1}CH$_{Ar}$), 145.3 (^{4}C^{IV}), 150.6 (^{5}C^{IV}) and 160.6 (^{6}C^{IV}). ^{19}F NMR (DMSO-*d6*, 376 MHz) : δ -61.68. HRMS (m/z) (ESI+): calcd for m/z $C_{15}H_{10}F_6N_3S$ [M + H$^+$] = 378.0494 ; found = 378.0491.

N-(4-methoxyphenyl)thiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride

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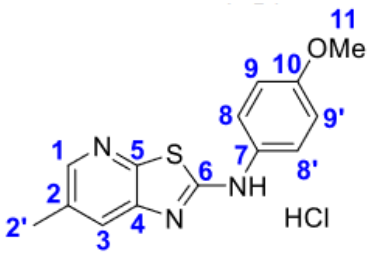
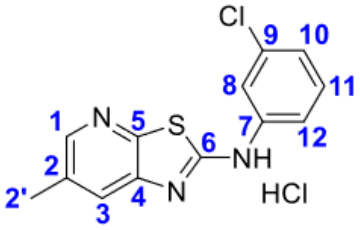


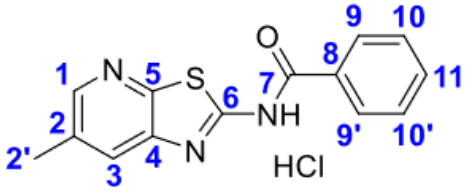
Using general procedure (2) applied to 4-methoxyphenyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 42%. Yellow solid, m.p. 212°C (decomposition). ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 2.37 (s, 3H, $^{2'}$CH$_3$), 3.75 (s, 3H, ^{11}CH$_3$-O), 6.96 (d, J = 9.0 Hz, 2H, ^{8}H$_{Ar}$ and $^{8'}$H$_{Ar}$), 7.67 (d, J = 9.0 Hz, 2H, ^{9}H$_{Ar}$ and $^{9'}$H$_{Ar}$), 7.84 (s, 1H, ^{3}H$_{Ar}$), 8.17 (s, 1H, ^{1}H$_{Ar}$), 10.80 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.8 ($^{2'}$CH$_3$), 55.3 (^{11}CH$_3$-O), 114.3 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 120.6 (^{9}CH$_{Ar}$ and $^{9'}$CH$_{Ar}$), 127.0 (^{3}CH$_{Ar}$), 131.8 (^{2}C^{IV}), 133.1 (^{7}C^{IV}), 140.5 (^{1}CH$_{Ar}$), 147.0 (^{4}C^{IV}), 149.1 (^{5}C^{IV}), 155.4 (^{10}C^{IV}) and 162.1 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z C$_{14}$H$_{14}$N$_3$OS [M + H$^+$] = 272.0852 ; found = 272.0856.

N-(3-chlorophenyl)thiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride



Using general procedure (1) applied to 3-chlorophenyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 67%. Colourless solid, m.p. 214°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 2.38 (s, 3H, $^{2'}$CH$_3$), 7.09 (dd, J = 8.0, 2.3 Hz, 1H, ^{10}H$_{Ar}$), 7.38 (t, J = 8.0 Hz, 1H, ^{11}H$_{Ar}$), 7.64 (dd, J = 8.2, 2.3 Hz, 1H, ^{12}H$_{Ar}$), 7.93 (s, 1H, ^{3}H$_{Ar}$), 8.08 (s, 1H, ^{8}H$_{Ar}$), 8.21 (s, 1H, ^{1}H$_{Ar}$), 11.34 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.8 ($^{2'}$CH$_3$), 116.7 (^{12}CH$_{Ar}$), 117.6 (^{8}CH$_{Ar}$), 122.2 (^{10}CH$_{Ar}$), 127.6 (^{3}CH$_{Ar}$), 130.6 (^{11}CH$_{Ar}$), 131.7 (^{2}C^{IV}), 133.3 (^{9}C^{IV}), 141.4 (^{7}C^{IV}), 141.9 (^{1}CH$_{Ar}$), 146.4 (^{4}C^{IV}), 149.7 (^{5}C^{IV}) and 161.0 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z C$_{13}$H$_{11}$ClN$_3$S [M + H$^+$] = 276.0357 ; found = 267.0360.

N-benzamidethiazolo[5,4-*b*]-6-methyl-2-amine hydrochloride



Using general procedure (1) applied to benzoyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 46%. Colourless solid, m.p. 222°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 2.43 (s, 3H, $^{2'}$CH$_3$), 7.57 (t, J = 7.7 Hz, 2H, ^{10}H$_{Ar}$ and $^{10'}$H$_{Ar}$), 7.67 (t, J = 7.3 Hz, 1H, ^{11}H$_{Ar}$), 7.97 (s, 1H, ^{3}H$_{Ar}$), 8.13 (d, J = 7.8 Hz, 2H, ^{9}H$_{Ar}$ and $^{9'}$H$_{Ar}$), 8.35 (s, 1H, ^{1}H$_{Ar}$), 12.91 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.9 ($^{2'}$CH$_3$), 127.7 (^{3}CH$_{Ar}$), 128.4 (^{9}CH$_{Ar}$ and $^{9'}$CH$_{Ar}$), 128.7 (^{10}CH$_{Ar}$ and $^{10'}$CH$_{Ar}$), 131.5 (^{2}C^{IV}), 131.7 (^{8}C^{IV}), 133.1 (^{11}CH$_{Ar}$), 141.7 (^{4}C^{IV}), 146.2 (^{1}CH$_{Ar}$), 151.8 (^{5}C^{IV}), 158.6 (^{6}C^{IV}) and 166.2 (^{7}C^{IV}=O). HRMS (m/z) (ESI+): calcd for m/z C$_{14}$H$_{12}$N$_3$OS [M + H$^+$] = 270.0696 ; found = 270.0698.

N-(3,5-dichlorophenyl)thiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride

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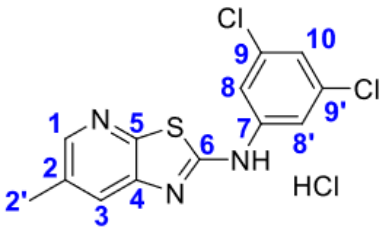
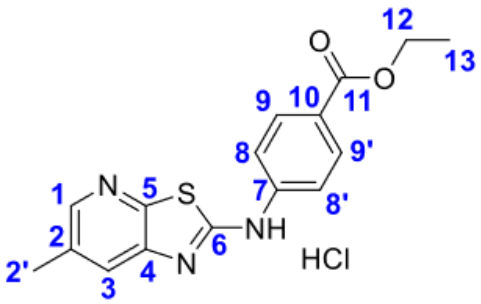


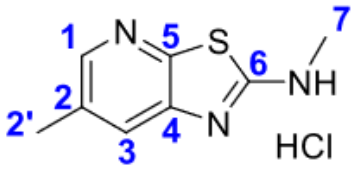
Using general procedure (2) applied to 3,5-dichlorophenyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 59%. Pinkish solid, m.p. 251°C. ^{1}H NMR (DMSO-*d6*, 250 MHz) : δ 2.37 (s, 3H, $^{2'}$CH$_3$), 7.21 (t, J = 1.9 Hz, 1H, ^{10}H$_{Ar}$), 7.89 (d, J = 1.9 Hz, 2H, ^{8}H$_{Ar}$ and $^{8'}$H$_{Ar}$), 7.93 (d, J = 1.0 Hz, 1H, ^{3}H$_{Ar}$), 8.20 (d, J = 1.2 Hz, 1H, ^{1}H$_{Ar}$), 11.51 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.7 ($^{2'}$CH$_3$), 116.1 (^{8}CH$_{Ar}$ and $^{8'}$CH$_{Ar}$), 121.4 (^{10}CH$_{Ar}$), 127.4 (^{3}CH$_{Ar}$), 131.6 (^{2}C^{IV}), 134.2 (^{9}C^{IV} and $^{9'}$C^{IV}), 142.2 (^{7}C^{IV}), 143.2 (^{1}CH$_{Ar}$), 145.7 (^{4}C^{IV}), 150.3 (^{5}C^{IV}) and 160.6 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z C$_{13}$H$_{10}$Cl$_2$N$_3$S [M + H$^+$] = 309.9967 ; found = 309.9973

N-(ethyl 4-aminobenzoate)thiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride



Using general procedure (1) applied to ethyl 4-isothiocyanatobenzoate and 3-amino-2-chloro-5-methylpyridine. Yield: 64%. Beige solid, m.p. 210°C (decomposition). ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 1.31 (t, J = 7.0 Hz, 3H, ^{13}CH$_3$), 2.38 (s, 3H, $^{2'}$CH$_3$), 4.28 (q, J = 7.0 Hz, 2H, ^{12}CH$_2$), 7.89 (s, 1H, ^{3}H$_{Ar}$), 7.89-7.98 (m, 4H, H$_{Ar}$), 8.20 (s, 1H, ^{1}H$_{Ar}$), 11.41 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 14.2 (^{13}CH$_3$), 17.8 ($^{2'}$CH$_3$), 60.4 (^{12}CH$_2$), 117.5 (2 x CH$_{Ar}$), 123.4 (^{10}C^{IV}), 127.4 (^{3}CH$_{Ar}$), 130.5 (2 x CH$_{Ar}$), 131.6 (^{2}C^{IV}), 142.7 (^{1}CH), 144.2 (^{7}C^{IV}), 146.1 (^{4}C^{IV}), 150.2 (^{5}C^{IV}), 160.8 (^{6}C^{IV}) and 165.3 (^{11}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z C$_{16}$H$_{16}$N$_3$O$_2$S [M + H$^+$] = 314.0958 ; found = 314.0956.

N-methylthiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride



Using general procedure (1) applied to methyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 40%. Colourless solid, m.p. 186°C (decomposition). ^{1}H NMR (D$_2$O, 400 MHz) : δ 2.39 (s, 3H, $^{2'}$CH$_3$), 3.13 (s, 3H, ^{7}CH$_3$), 7.60 (s, 1H, ^{3}H$_{Ar}$), 8.12 (s, 1H, ^{1}H$_{Ar}$). ^{13}C NMR (D$_2$O, 101 MHz) : δ 17.5 ($^{2'}$CH$_3$), 31.4 (^{7}CH$_3$), 124.3 (^{3}CH$_{Ar}$), 134.2 (^{2}C^{IV}), 138.1 (C^{IV}), 142.8 (^{1}CH$_{Ar}$), 143.3 (C^{IV}) and 167.7 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z C$_8$H$_{10}$N$_3$S [M + H$^+$] = 180.0590 ; found = 180.0587.

N-(3-bromophenyl)thiazolo[5,4-*b*]-6-methylpyridin-2-amine hydrochloride

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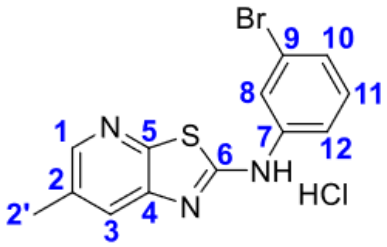

Using general procedure (1) applied to 3-bromophenyl isothiocyanate and 3-amino-2-chloro-5-methylpyridine. Yield: 62%. Beige solid, m.p. 247-248°C. ^{1}H NMR (DMSO-*d6*, 400 MHz) : δ 2.38 (s, 3H, $^{2'}$CH$_3$), 7.23 (d, J = 7.8 Hz, 1H, ^{12}H$_{Ar}$), 7.32 (t, J = 7.9 Hz, 1H, ^{11}H$_{Ar}$), 7.69 (d, J = 8.1 Hz, 1H, ^{10}H$_{Ar}$), 7.91 (s, 1H, ^{3}H$_{Ar}$), 8.20 (s, 2H, ^{1}H$_{Ar}$ and ^{8}H$_{Ar}$), 11.26 (bs, 1H, N-H). ^{13}C NMR (DMSO-*d6*, 101 MHz) : δ 17.8 ($^{2'}$CH$_3$), 117.0 (^{10}CH$_{Ar}$), 120.4 (^{8}CH$_{Ar}$), 121.8 (^{9}C^{IV}), 125.1 (^{12}CH$_{Ar}$), 127.3 (^{3}CH$_{Ar}$), 130.9 (^{11}CH$_{Ar}$), 131.6 (^{2}C^{IV}), 141.5 (^{7}C^{IV}), 142.5 (^{1}CH$_{Ar}$), 146.2 (^{4}C^{IV}), 150.1 (^{5}C^{IV}) and 160.9 (^{6}C^{IV}). HRMS (m/z) (ESI+): calcd for m/z $C_{13}H_{11}BrN_3S$ [M + H$^+$] = 319.9852 ; found = 319.9847.

4. Conclusions

Following our work on eucalyptol as a new green solvent, we show in this article that sabinene is also potentially usable as a new biomass-derived green solvent.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Characterization data for obtained products and copies of 1H, 13C NMR and HRMS spectra. References [40] are cited in the supplementary materials.

Author Contributions: Conceptualization, G.M. and S.B-R.; methodology, G.M., V.F., E.C., L.B., A.A. and S.B-R.; validation, G.M. and S.B-R.; formal analysis, G.M., V.F., E.C., L.B., A.A. and S.B-R.; investigation, G.M., V.F., E.C., L.B., A.A. and S.B-R.; resources, G.M., V.F., E.C., L.B., A.A. and S.B-R.; data curation, G.M., V.F., E.C., L.B., A.A. and S.B-R.; writing—original draft preparation, G.M. and S.B-R.; writing—review and editing, G.M. and S.B-R.; visualization, G.M., V.F., E.C., L.B., A.A. and S.B-R.; supervision, G.M. and S.B-R.; project administration, G.M. and S.B-R.; funding acquisition, S.B-R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

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