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Eucalyptol: A Bio-Based Solvent for the Synthesis of *O*,*S*,*N*-Heterocycles. Application to Hiyama Coupling, Cyanation, and Multicomponent Reactions

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Abstract: We report here the use of eucalyptol as a bio-based solvent for Hiyama coupling, cyanation, and multicomponent reactions on *O*,*S*,*N*-heterocycles. These heterocycles were chosen as targets or as starting materials given their biological potential; they play an important role in therapeutically active compounds. Once again, eucalyptol proved to be a credible and sustainable alternative to common solvents.

Keywords: eucalyptol; sustainable chemistry; *O*,*S*,*N*-Heterocycles; Hiyama coupling; cyanation reaction; multicomponent reaction

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1. Introduction

The solvents used in chemistry are a fundamental element of the environmental performance of processes in industrial and academic laboratories. Their influence on costs, safety, and health cannot be neglected. Even if solvent-free reactions are possible to a certain extent, they are not applicable to a large spectrum of chemical reactions and starting materials, and they may impair overall yield and product purity. Equally important, multiphasic reactions involving solid catalysts and gaseous and/or liquid reagents, which are common practice in the petrochemical and refining industry, are not easily transposable to pharmaceutical active ingredients or fine chemical syntheses.

Solvents are the most abundant constituents of chemical transformations, so acting thereon and replacing standard solvents with safer alternatives can have a great ecological impact. Nitrogen heterocyclic compounds represent an important class of compounds in the pharmaceutical industry. Therefore, it is important to provide new methods and greener approaches for their synthesis [1–7].

Pursuing our objective of developing new practices in the synthesis of heterocycles containing oxygen, sulfur, and nitrogen [8–17], we explored the potential of eucalyptol [15] (Figures 1 and 2) as solvent in Hiyama coupling, cyanation, and multicomponent reactions.

Eucalyptol or 1,8-cineole (Figure 2) is a saturated oxygenated terpene that is widely distributed in some plants and their essential oil fractions, and depending on the species, it is contained in up to 90% in eucalyptus' essential oils isolated from fresh foliage. Its use as a solvent is also very interesting from an environmental point of view, since in addition to the fact that this solvent is recyclable by simple distillation, it comes from the waste (leaves) of the paper and wood industry, which cultivates eucalyptus trees because of their rapid growth (7 to 10 years).

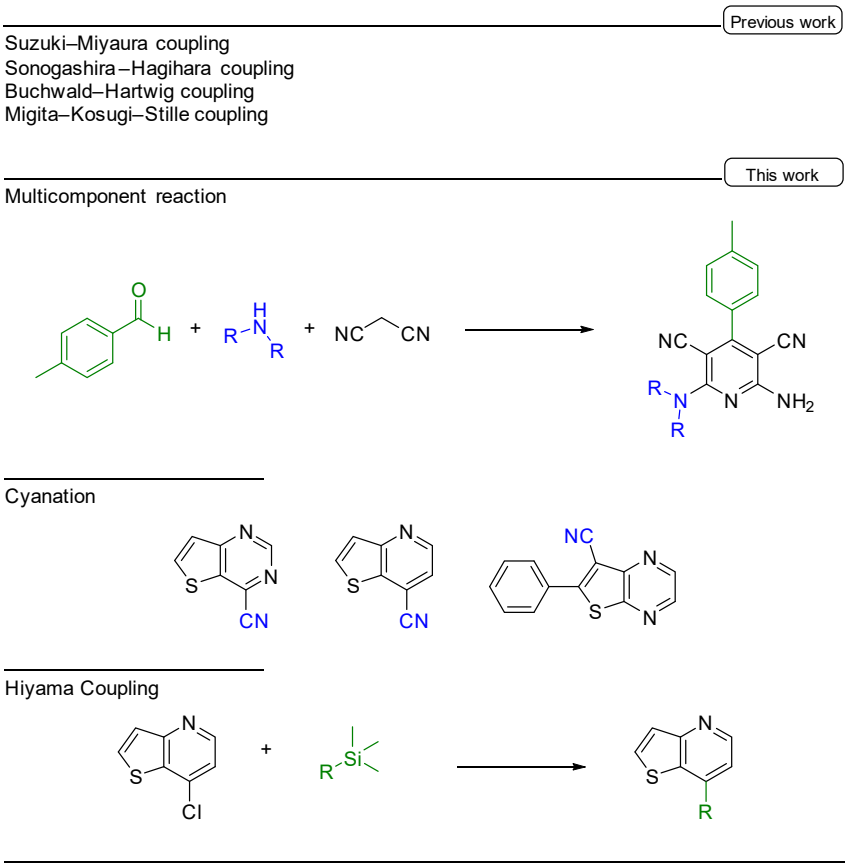
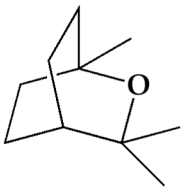


Figure 1. Eucalyptol as bio-based solvent: application to Hiyama coupling, cyanation and multicomponent reactions.



$C_{10}H_{18}0$
bp : 176–177°C
d : 0.921
ε : 4.84
CAS 470-82-6

Eucalyptol

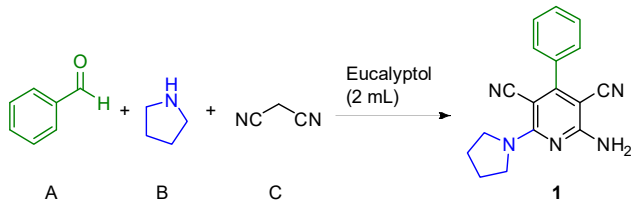
Figure 2. Structure and data of Eucalyptol. Synonyms: 1,8-Cineole, 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane.

2. Results and Discussion

2.1. Multicomponent Reaction

While the chemistry community has made significant efforts toward identifying greener processes that minimize the quantity of catalysts or using multicomponent reactions and one-pot processes, solvents remain a major portion of the environmental performance of a process and have an influence on safety and health [18–21]. One of the goals of the present study was to assess the potential of associating a multicomponent reaction with a more eco-compatible solvent. The class of molecules chosen for synthesis was highly functionalized pyridines [22]. In this specific case, to the best of our knowledge, only three teams have reported their synthesis; however, the reactions were performed using conventional solvents, namely chloroform [23], ethanol [24], and methanol [25]. After ascertaining the most widely used reaction conditions and stoichiometry, we performed the reactions using eucalyptol as solvent (Table 1).

Table 1. Optimization of the multicomponent reaction.



A B C **1**

Entry	A (equiv.)	B (equiv.)	C (equiv.)	Cat (equiv.)	T (°C)	t (h)	Yield [a] (%)
1	1	1	2	-	100	12	39
2	1	2	2	-	100	24	54
3	1	1	2	-	80	24	46
4	1	2	2	-	80	24	49
5	1	1	2	-	r.t.	24	50
6	1	2	2	-	r.t.	24	38
7	1	1	2	DMAP	r.t.	24	28
8	1	2	2	DIPEA	100	24	47
9	1	2	2	Cs_2CO_3	100	24	42
10	1	1	2	-	100	24	46 [b]
11	1	2	2	-	100	24	43 [b]

[a] isolated yield after purification via flash chromatography. [b] reaction performed in MeOH.

The expected compound (**1**) was obtained in 28 to 54% yield. Adding a catalyst to the reaction was always detrimental to the yield when compared to a catalyst-free reaction performed with the same stoichiometry and temperature. The best result was obtained without catalyst using one equivalent of benzaldehyde and two equivalents of pyrrolidine and malonitrile (Table 1, Entry 2). For the synthesis of compound 1, this solvent substitution proved to be advantageous over the above-mentioned studies that used chloroform (32%) [23] and ethanol (52%) [24]. However, our yield was lower when compared to that of the team that performed the reaction in methanol (79%) [25]. Nevertheless, it should be highlighted that the 79% yield was obtained with the addition of DMAP (20 mol%) as catalyst. To test which parameter influenced the yield, we performed the reaction in methanol without catalyst and then verified that the use of eucalyptol resulted in a higher yield when the reaction mixture was catalyst-free. With the best reaction conditions in hand, we proceeded to analyze the scope and limitations of the reaction.

The derivatives (**1**–**6**) were synthesized in 45 to 68% yield (Figure 3). The nature of the aldehyde did not cause major disparities in the yield of the different final compounds. Then, considering the aldehyde that presented the highest yield, the potential of eucalyptol using other sources of amines (piperidine, thiomorpholine, 2,6-dimethylmorpholine, and 1-phenylpiperazine) was evaluated: the final compounds **7**–**10** were synthesized in moderate to good yields (Figure 4).

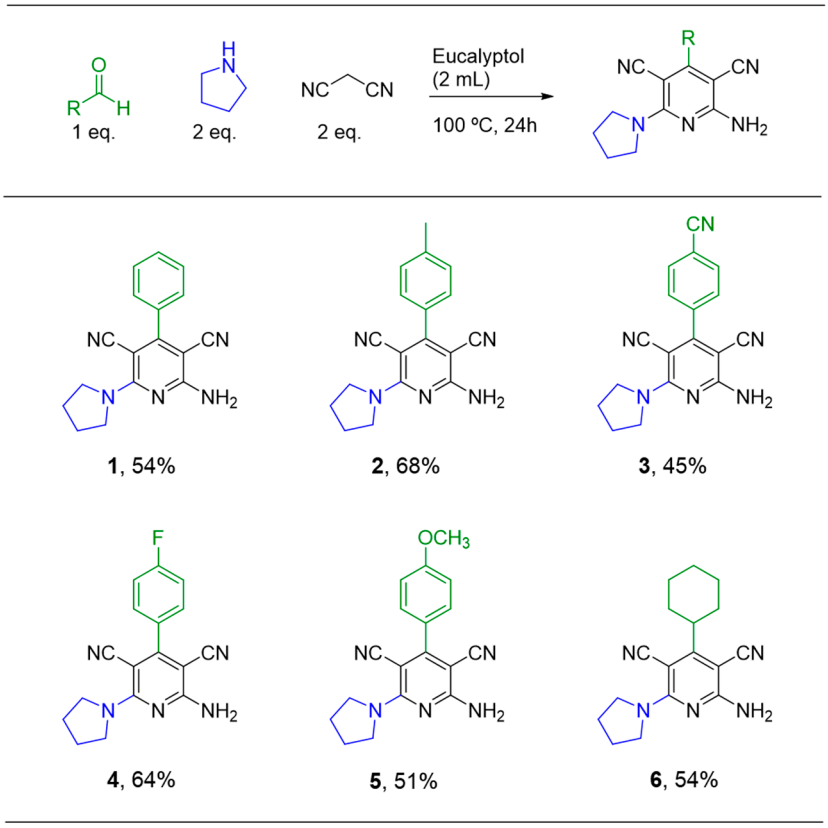


Figure 3. Scope and limitations of multicomponent reaction for the synthesis of highly functionalized pyridines.

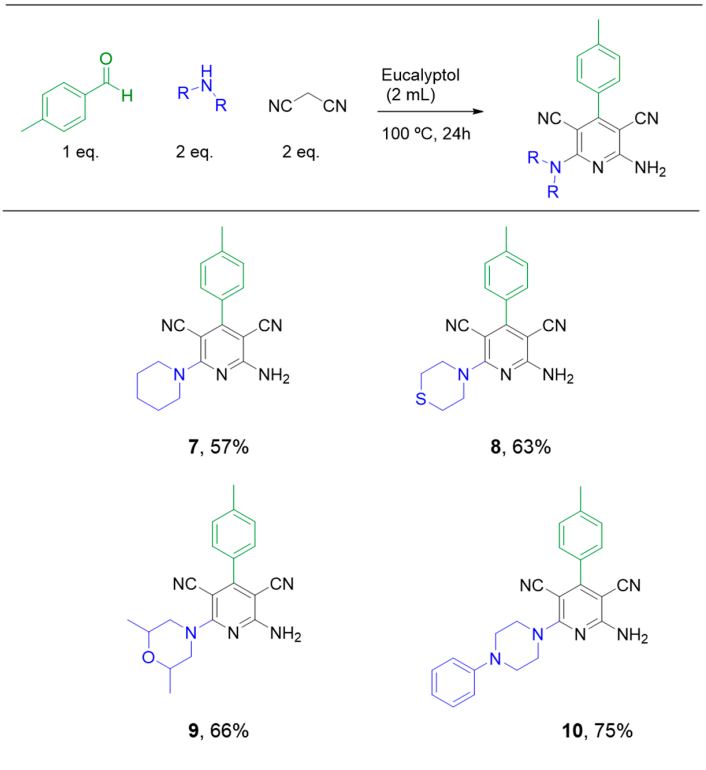


Figure 4. Multicomponent reaction for the synthesis of highly functionalized pyridines.

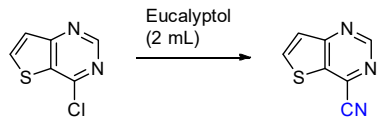
2.2. Palladium Catalyzed Cyanation

The second reaction explored with eucalyptol as solvent was palladium-catalyzed cyanation. This reaction offers an appropriate alternative to the Rosenmund–Von Braun reaction [26–30], which frequently employs severe reaction conditions and sometimes needs an intensive work up. Due to all of these features and properties, efforts were made to find greener conditions. For this study, we used three compounds commonly used in our team to build molecules of interest with biological potential [15,31,32]. Each compound underwent an optimization study in order to find the ideal conditions. To the best of our knowledge, here, we present the first cyanation process of these scaffolds. After reviewing previously reported information [33–39] related to the cyanation of *O*,*S*,*N*-containing heterocycles, we performed the optimization on 4-chlorothieno[3,2-*d*]pyrimidine, 7-chlorothieno[3,2-*b*]pyridine, and 7-bromo-6-phenyl-thieno[2,3-*b*]pyrazine.

In the literature, $Zn(CN)_2$ is often used as cyanide source. The reaction can occur because, as the cyanide nucleophile is a strong σ-donor and can be fatal to the catalytic system, it is essential to keep its concentration low in the reaction. An unfavorable point is its limited solubility in DMF (1.8×10^{-4} g/mL at 80 °C), which is a solvent commonly used in these reactions [40].

Another source of cyanide (non-toxic), $K_4[Fe(CN)_6]$, has also been described and can be used in a mixture with palladium catalysts to obtain aryl nitriles from their corresponding halides [41]. From this background, we tested reaction conditions using eucalyptol as solvent. Compound 11 was obtained in a yield from 7 to 56% (Table 2).

Table 2. Optimization of cyanation.



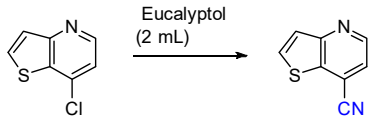
11

Entry	Pd (eq.)	Lig (eq.)	CN (eq.)	T (°C)	t (h)	Yield [a] (%)
1	$Pd(PPh_3)_4$ (0.07)	-	$Zn(CN)_2$ (0.6)	100	96	7
2 [c]	$Pd_2(dba)_3$ (0.05)	dppf (0.05)	$Zn(CN)_2$ (0.6)	100	96	11
3 [c]	$Pd_2(dba)_3$ (0.05)	dppf (0.05)	$Zn(CN)_2$ (0.6)	140	44	55
4	$Pd(PPh_3)_4$ (0.05)	-	KCN (1.5)	140	61	0
5	$PdCl_2(PPh_3)_2$ (0.05)	-	KCN (2)	140	61	0
6 [d]	$Pd(OAc)_2$ (0.05)	dppe (0.1)	KCN (1)	140	61	0
7 [d]	$Pd(OAc)_2$ (0.05)	dppe (0.1)	KCN (1)	140	61	0
8 [d]	$Pd(OAc)_2$ (0.05)	dppe (0.1)	KCN (1)	140	61	0
9 [d]	$Pd(OAc)_2$ (0.05)	dppe (0.1)	KCN (1)	140	61	0
10	$Pd_2(dba)_3$ (0.1)	dppf (0.4)	KCN (2)	140	44	24
11 [e]	$Pd(OAc)_2$ (0.03)	cataCXium (0.09)	$K_4[Fe(CN)_6]$ [b] (0.2)	140	41	traces
12	$Pd_2(dba)_3$ (0.03)	cataCXium (0.09)	$K_4[Fe(CN)_6]$ [b] (0.2)	140	41	traces
13 [e]	$Pd(TFA)_2$ (0.03)	TTBP·HBF_4 (0.09)	$K_4[Fe(CN)_6]$ [b] (0.2)	140	41	traces
14 [e]	$PdCl_2$ (0.03)	TTBP·HBF_4 (0.09)	$K_4[Fe(CN)_6]$ [b] (0.2)	140	41	traces
15 [c]	$Pd_2(dba)_3$ (0.05)	dppf (0.05)	$Zn(CN)_2$ (0.6)	140	96	43
16 [e]	$Pd(OAc)_2$ (0.05)	X-Phos (0.1)	$K_4[Fe(CN)_6]$ [b] (0.25)	140	60	56
17 [c]	$Pd_2(dba)_3$ (0.05)	PCy_3 (0.05)	$Zn(CN)_2$ (0.6)	140	48	48
18 [e]	$Pd(OAc)_2$ (0.05)	dppf (0.1)	$K_4[Fe(CN)_6]$ [b] (0.2)	140	60	43
19 [c]	$Pd_2(dba)_3$ (0.05)	dppf (0.1)	$Zn(CN)_2$ (0.6)	170	26	39
20	-	-	NaCN (5)	rt	26	0
21	-	-	NaCN (5)	170	24	0

[a] isolated yield after purification via flash chromatography. [b] $K_4[Fe(CN)_6]\cdot 3H_2O$. [c] 0.2 equivalent of Zn was added. [d] 0.2 equivalent of amine co-catalyst was added. Entry 6: TMEDA; Entry 7: Sparteine; Entry 8: 2,2-bipyridine; Entry 9: 1-adamantylamine. [e] 0.2 equivalent of base was added. Entry 11, 13, 14 and 18: Na_2CO_3; Entry 16: K_2CO_3.

Starting from 7-chlorothieno[3,2-*b*]pyridine and based on our results with 4-chlorothieno[3,2-*d*]pyrimidine (Table 2), we looked for the conditions that would result in the highest yield. The best outcome was achieved when the reaction was performed using eucalyptol as solvent with $Pd_2(dba)_3$ (5 mol%), dppf (10 mol%), $Zn(CN)_2$ (60 mol%), Zn (20 mol%) at 170 °C for 26 h (Table 3).

Table 3. Optimization of cyanation.



12

Entry	Pd (eq.)	Lig (eq.)	CN (eq.)	T (°C)	t (h)	Yield [a] (%)
1 [c]	$Pd_2(dba)_3$ (0.05)	PCy_3 (0.1)	$Zn(CN)_2$ (0.06)	170	48	9
2 [c,d]	$Pd(OAc)_2$ (0.05)	X-Phos (0.1)	$K_4[Fe(CN)_6]$ [b] (0.2)	170	48	0
3 [c]	$Pd_2(dba)_3$ (0.05)	dppf (0.1)	$Zn(CN)_2$ (0.6)	170	26	61

[a] isolated yield after purification via flash chromatography. [b] $K_4[Fe(CN)_6]\cdot 3H_2O$. [c] 0.2 equivalent of Zn was added. [d] 0.2 equivalent of K_2CO_3 was added.

To test the versatility of conditions over bromine derivatives, we chose a molecule synthesized in a previous study reported by our team [31] (Figure 5).

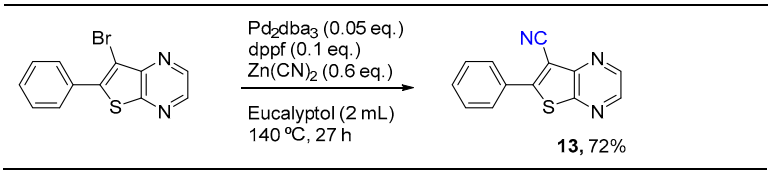


Figure 5. Palladium catalyzed cyanation of 7-bromo-6-phenyl-thieno[2,3-*b*]pyrazine.

The desired product **13** was obtained in good yield using eucalyptol as solvent at 140 °C for 27 h with $Pd_2(dba)_3$/dppf as catalytic system and $Zn(CN)_2$ as cyanide source.

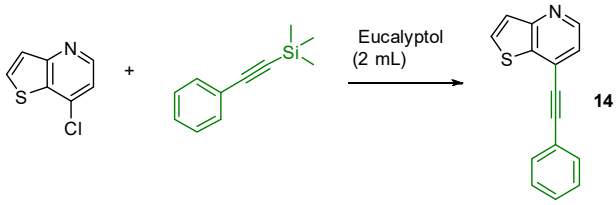
2.3. Hiyama Coupling

Hiyama coupling is a palladium-catalyzed C-C bond formation between aryl, alkenyl, or alkyl halides or pseudohalides and organosilanes. Its particularity lies in the requirement for a fluoride ion or a base as activating agent [42,43]. This coupling was chosen in order to compare it with the results obtained and reported previously by our team [15] on the performance of Sonogashira coupling using eucalyptol as solvent on *O*,*S*,*N*-heterocycles.

As with the previous two reactions reported above, this work started with a literature review [43–47] to test the conditions for our scaffold and identify the best coupling conditions.

Optimization was achieved starting from 7-chlorothieno[3,2-*b*]pyridine and 1-phenyl-2-trimethylsilylacetylene and by varying the amount and type of Pd source with or without ligand as well as the type and amount of activating agent (fluoride ion or a base). Reactions with eucalyptol were conducted at 100 °C for durations summarized in Table 4.

Table 4. Optimization of Hiyama coupling.



Entry	Pd (eq.)	Lig (eq.)	CN (eq.)	T (°C)	t (h)	Yield [a] (%)
1	$Pd(OAc)_2$ (0.025)	X-Phos (0.05)	TBAF·$3H_2O$ (2.5)	100	72	67
2	$PdCl_2(PPh_3)_2$ (0.1)	Ph_3As (0.4)	-	100	48	0
3	$Pd(OAc)_2$ (0.1)	$P(Cy_3)$ (0.4)	CsF (1.5)	100	30	42
4	$Pd(OAc)_2$ (0.1)	DABCO (0.2)	TBAF·$3H_2O$ (2.5)	100	48	0
5	$Pd(PPh_3)_4$ (0.1)	-	CsF (4)	100	30	30
6	$[PdCl(allyl)]_2$ (0.05)	$P(Cy_3)$ (0.1)	TBAF in THF (3)	100	96	0
7	$[PdCl(allyl)]_2$ (0.05)	X-Phos (0.2)	TBAF·$3H_2O$ (5)	100	48	51
8	$PdCl_2(PPh_3)_2$ (0.1)	-	KF (5)	100	96	43
9	$Pd_2(dba)_3$ (0.05)	X-Phos (0.1)	TBAF·$3H_2O$ (5)	100	48	56
10	$Pd(CH_3CN)_2Cl_2$ (0.05)	X-Phos (0.1)	TBAF·$3H_2O$ (5)	100	48	65
11	$Pd(CH_3CN)_2Cl_2$ (0.05)	PPh_3 (0.15)	Cs_2CO_3 (2)	100	48	80

[a] isolated yield after purification via flash chromatography.

Process optimization led to the isolation of compound 14 in a yield ranging from 30 to 80%. The best reaction conditions using eucalyptol as solvent were achieved at 100 °C for 48 h with $Pd(CH_3CN)_2Cl_2/PPh_3$ as a catalytic system and Cs_2CO_3 as a base.

Based on our results (Table 4, Entry 11), the scope and limitations of the Hiyama coupling on 7-chlorothieno[3,2-*b*]pyridine were assessed using several silylacetylenes (Table 4).

Compounds **14**–**19** substituted in position 7 were synthesized in moderate to good yield, demonstrating the generalizability of this method using eucalyptol as solvent (Figure 6).

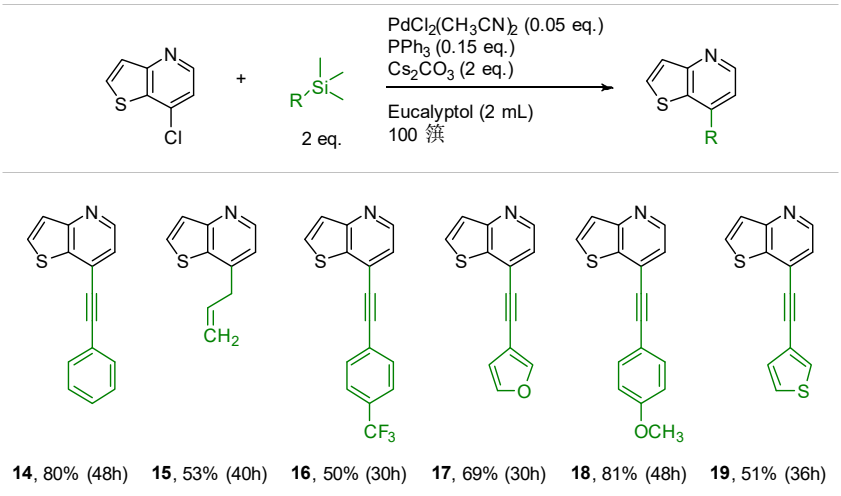


Figure 6. Scope and limitations of the Hiyama coupling from 7-chlorothieno[3,2-*b*]pyridine.

From these results, we explored the same conditions on 4-chlorofuro[3,2-*c*]pyridine.

Two examples (**20**–**21**) were synthesized in low yield by Hiyama coupling (Figure 7). This scaffold showed lower reactivity. This aspect had already been observed when we synthesized the same products by Sonogashira coupling using eucalyptol [15].

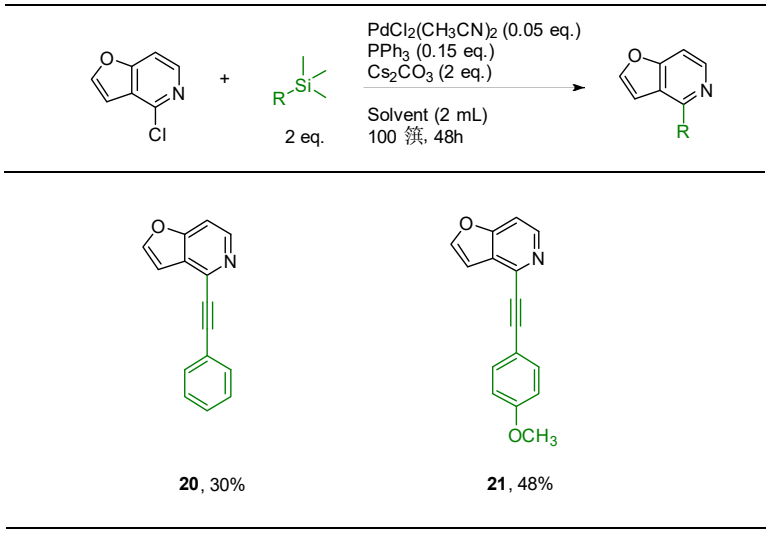


Figure 7. Scope and limitations of the Hiyama coupling from 4-chlorofuro[3,2-*c*]pyridine.

2.4. Recyclability of the Solvent

As the reusability of the solvent is essential from an economic and environmental perspective, we have already shown its feasibility in Pd-mediated cross-coupling reactions in our previous work [15–17], wherein an average 70% solvent recovery (using a rotary evaporator system) was observed for each reaction series without noticeable loss of properties. Although the boiling point of eucalyptol is relatively high, it is possible to evaporate it, in a few minutes, with a normal pump and recirculating chiller in a classical rotary evaporator system.

3. Materials and Methods

3.1. General Methods

All reagents used herein were purchased from commercial suppliers Sigma Aldrich, St Quentin Fallavier Cedex, France; Fluorochem, Derbyshire, SK131QH, UK. All the reactions were monitored by thin-layer chromatography (TLC) using silica gel (60 F254) plates. Flash column chromatographies were performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker avance II spectrometer (Bruker, Wissembourg, France) at 250 MHz (13C, 62.9 MHz) and on a Bruker avance III HD nanobay (Bruker, Wissembourg, France) 400 MHz (13C 100.62 MHz). The following abbreviations: b: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet are used for the proton spectra multiplicities. Coupling constants (J) are reported in Hertz (Hz). Multiplicities were determined by the DEPT 135 sequence and chemical shifts are given from tetramethylsilane (TMS) or deuterated solvent (MeOH-d4, Chloroform-d) as internal standard. High-resolution mass spectra (HRMS) were carried out on a Maxis UHR-q-TOF mass spectrometer (Bruker, Wissembourg, France) Bruker 4G in electrospray ionization (ESI) mode (Bruker, Wissembourg, France). Melting points (mp [°C]) were determined in open capillary tubes and are uncorrected.

3.2. Multicomponent Reaction: General Procedure for Synthesis of Compounds **1–10**

A mixture of aldehyde (50 mg; 1 eq.), amino derivative (2 eq.), malonitrile (2 eq.) in Eucalyptol (2 mL) was stirred at 100 °C for 24 h. The reaction was followed by TLC. After completion, the reaction was cooled to room temperature and the mixture was concentrated under vacuum. The solid obtained was purified by flash chromatography using a mixture of AcOEt/petroleum ether.

2-amino-4-phenyl-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (**1**). Yellow solid (74 mg, 54%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (t, *J* = 6.7 Hz, 4H), 3.81 (s, 4H), 5.31 (d, *J* = 17.5 Hz, 2H), 7.49 (dtt, *J* = 10.0, 6.3, 2.9 Hz, 5H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.4 (2xCH),

49.6 (2xCH), 81.1 (C), 82.0 (C), 116.8 (C), 118.2 (C), 128.5 (2xCH), 128.7 (2xCH), 130.2 (CH), 135.0 (C), 157.5 (C), 159.3 (C), 162.1 (C) ppm. [CAS: 77034-27-6].

2-amino-6-(pyrrolidin-1-yl)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (**2**). Yellow solid (86 mg, 68%), m.p. 234 –236 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (t, *J* = 6.4 Hz, 4H), 2.41 (s, 3H), 3.80 (s, 4H), 5.31 (d, *J* = 11.2 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.5 (CH), 25.4 (2xCH), 49.6 (2xCH), 81.0 (C), 82.0 (C), 117.0 (C), 118.4 (C), 128.4 (2xCH), 129.4 (2xCH), 132.0 (C), 140.4 (C), 157.6 (C), 159.4 (C), 162.2 (C) ppm. HRMS: calcd for $C_{18}H_{18}N_5S$ $[M + H]^+$ 336.1277, found 336.1280.

2-amino-4-(4-cyanophenyl)-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (**3**). Yellow solid (54 mg, 45%), m.p. 258–260 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 4H), 3.81 (s, 4H), 5.37 (s, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.3 (2xCH), 49.6 (2xCH), 80.6 (C), 81.6 (C), 114.2 (C), 116.1 (C), 117.7 (C), 118.0 (C), 129.4 (2xCH), 132.6 (2xCH), 139.4 (C), 157.1 (C), 159.1 (C), 159.9 (C) ppm. HRMS: calcd for $C_{18}H_{15}N_6$ $[M + H]^+$ 315.1353, found 315.1352.

2-amino-4-(4-fluorophenyl)-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (**4**). Yellow solid (79 mg, 64%), m.p. 253–255 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (t, *J* = 6.4 Hz, 4H), 3.80 (s, 4H), 5.35 (s, 2H), 7.19 (t, *J* = 8.6 Hz, 2H), 7.47 (dd, *J* = 8.4, 5.3 Hz, 2H), ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.4 (2xCH), 49.6 (2xCH), 81.5 (d, J = 94 Hz, C), 115.9 (CH), 116.7 (C), 116.1 (CH), 118.1 (C), 130.6 (CH), 130.7 (CH), 131.0 (C), 157.5 (C), 159.3 (C), 161.0 (C), 163.8 (d, *J* = 250Hz, C), ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.05 ppm. HRMS: calcd for $C_{17}H_{15}FN_5$ $[M + H]^+$ 308.1306, found 308.1309.

2-amino-4-(4-methoxyphenyl)-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (**5**). Yellow solid (60 mg, 51%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 5.31 (s, 2H), 3.83 (d, *J* = 21.4 Hz, 7H), 1.97 (t, *J* = 6.4 Hz, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.4 (2xCH), 49.6 (2xCH), 55.3 (CH), 81.0 (C), 81.9 (C), 114.1 (2xCH), 117.1 (C), 118.5 (C), 127.0 (C), 130.2 (2xCH), 157.8 (C), 159.43 (C), 161.1 (C), 161.8 (C) ppm. [CAS: 77034-28-7].

2-amino-4-cyclohexyl-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (**6**). Yellow solid (71 mg, 54%), m.p. 199–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (q, *J* = 13.2 Hz, 3H), 1.71 (d, *J* = 12.2 Hz, 3H), 1.95–1.85 (m, 5H), 2.10 (q, *J* = 12.2 Hz, 2H), 3.07 (t, *J* = 12.4 Hz, 1H), 3.73 (s, 4H), 5.29 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (C), 160.2 (C), 158.2 (C), 118.2 (C), 117.6 (C), 81.5 (C), 79.2 (C), 60.4 (C), 49.6 (2xCH), 44.3 (CH), 29.7 (2xCH), 26.5 (2xCH), 25.4 (CH), 25.3 (CH) ppm. HRMS: calcd for $C_{17}H_{22}N_5$ $[M + H]^+$ 296.1870, found 296.1871.

2-amino-6-(piperidin-1-yl)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (**7**). Yellow solid (75 mg, 57%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 5.36 (s, 2H), 3.79 (s, 4H), 2.41 (s, 3H), 1.70 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (C), 161.3 (C), 159.5 (C), 140.7 (C), 131.9 (C), 129.5 (CH), 129.0 (CH), 128.6 (CH), 117.9 (C), 116.7 (C), 83.6 (C), 81.6 (C), 49.2 (2xCH), 26.0 (2xCH), 24.4 (2xCH), 21.5 (CH) ppm. [CAS: 1268160-67-3].

2-amino-6-thiomorpholino-4-(p-tolyl)pyridine-3,5-dicarbonitrile (**8**). Yellow solid (88 mg, 63%), m.p. 223–225 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.46 (s, 2H), 4.11–4.06 (m, 4H), 2.76 (dd, *J* = 7.4, 2.8 Hz, 4H), 2.41 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 (C), 161.7 (C), 159.5 (C), 140.9 (C), 131.6 (C), 129.6 (2xCH), 128.6 (2xCH), 117.6 (C), 116.3 (C), 84.2 (C), 82.6 (C), 50.8 (2xCH), 27.4 (2xCH), 21.5 (CH) ppm. HRMS: calcd for $C_{18}H_{18}N_5S$ $[M + H]^+$ 336.1277, found 336.1280.

2-amino-6-(2,6-dimethylmorpholino)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (**9**). Yellow solid (95 mg, 66%), m.p. 238–240 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.46 (s, 2H), 4.41 (d, *J* = 13.3 Hz, 2H), 2.78 (dd, *J* = 13.3, 10.5 Hz, 2H), 2.41 (s, 3H), 1.23 (d, *J* = 6.3 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (C), 161.1 (C), 159.5 (2xC), 140.9 (2xC), 131.6 (C), 129.5 (2xCH), 128.6 (2xCH), 117.7 (C), 116.4 (C), 83.9 (C), 82.4 (C), 71.7 (CH), 53.2 (CH), 21.5 (CH), 18.7 (2xCH) ppm. HRMS: calcd for $C_{20}H_{22}N_5O$ $[M + H]^+$ 348.1819, found 348.1818.

2-amino-6-(4-phenylpiperazin-1-yl)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (**10**). Yellow solid (109 mg, 75%), m.p. 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H),

7.35–7.28 (m, 4H), 6.97–6.89 (m, 3H), 5.46 (s, 2H), 4.05–3.98 (m, 4H), 3.35–3.30 (m, 4H), 2.43 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (C), 161.3 (C), 159.5 (C), 150.8 (C), 140.9 (C), 131.6 (C), 129.6 (2xCH), 129.3 (2xCH), 128.6 (2xCH), 120.4 (CH), 117.7 (C), 116.4 (C), 116.3 (2xCH), 84.0 (C), 82.5 (C), 49.2 (2xCH), 47.7 (2xCH), 21.5 (CH) ppm. HRMS: calcd for $C_{24}H_{23}N_6$ $[M + H]^+$ 395.1979, found 395.1978.

3.3. Palladium Catalyzed Cyanation: General Procedure for Synthesis of Compounds **11–13**

A mixture of halo derivative (50 mg; 1 eq.), $Pd_2(dba)_3$ (0.05 eq.), dppf (0.1 eq.), $Zn(CN)_2$ (0.6 eq.), Zn (0.2 eq.) in eucalyptol (2 mL) was stirred at 140–170 °C for 26–44 h. The reaction was followed by TLC. After completion, the reaction was cooled to room temperature, and the mixture was concentrated under vacuum. The solid obtained was purified by flash chromatography using a mixture of AcOEt/petroleum ether.

Thieno[3,2-d]pyrimidine-4-carbonitrile (**11**). White solid (26 mg, 56%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 5.5 Hz, 1H), 8.23 (d, *J* = 5.5 Hz, 1H), 9.34 (s, 1H) ppm. 13C NMR (101 MHz, CDCl3) δ 114.3 (C), 125.0 (CH), 133.5 (C), 135.6 (C), 138.8 (CH), 154.6 (CH), 162.5 (C) ppm. [CAS: 1057249-33-8].

Thieno[3,2-b]pyridine-7-carbonitrile (**12**). White solid (29 mg, 61%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.7 Hz, 1H), 7.93 (d, *J* = 5.5 Hz, 1H), 7.67 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 4.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (C), 147.3 (CH), 133.9 (C), 132.5 (CH), 125.7 (CH), 121.0 (CH), 115.2 (C), 114.8 (C) ppm. [CAS: 1239505-20-4].

6-phenylthieno[2,3-b]pyrazine-7-carbonitrile (**13**). Brown solid (29 mg, 72%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.4 Hz, 1H), 8.60 (d, *J* = 2.4 Hz, 1H), 8.01–7.96 (m, 2H), 7.62–7.57 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 153.5 (C), 149.4 (C), 143.4 (CH), 142.0 (CH), 131.8 (CH), 130.8 (C), 129.7 (2xCH), 128.4 (2xCH), 113.5 (C), 101.8 (C) ppm. [CAS: 1369884-57-0].

3.4. Hiyama Coupling: General Procedure for Synthesis of Compounds **14–21**

A mixture of halo derivative (50 mg; 1 eq.), $Pd(CH_3CN)_2Cl_2$ (0.05 eq.), PPh_3 (0.15 eq.), Cs_2CO_3 (2 eq.) in eucalyptol (2 mL) was stirred at 100 °C for 30–48 h. The reaction was followed by TLC. After completion, the reaction was cooled to room temperature, and the mixture was concentrated under vacuum. The solid obtained was purified by flash chromatography using a mixture of AcOEt/petroleum ether.

7-(phenylethynyl)thieno[3,2-b]pyridine (**14**). Yellow solid (55 mg, 80%), m.p. 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.8 Hz, 1H), 7.79 (d, *J* = 5.5 Hz, 1H), 7.64 (dd, *J* = 6.3, 2.7 Hz, 2H), 7.59 (d, *J* = 5.5 Hz, 1H), 7.44–7.39 (m, 3H), 7.36 (d, *J* = 4.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C), 147.3 (CH), 134.9 (C), 132.0 (2xCH), 130.9 (CH), 129.5 (CH), 128.6 (2xCH), 126.1 (C), 125.6 (CH), 121.9 (C), 120.3 (CH), 97.9 (C), 84.8 (C) ppm. HRMS: calcd for $C_{15}H_{10}NS$ $[M + H]^+$ 236.0528, found 236.0528.

7-allylthieno[3,2-b]pyridine (**15**). Yellow solid (27 mg, 53%), m.p. 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.9 Hz, 1H), 7.73 (d, *J* = 5.6 Hz, 1H), 7.58 (d, *J* = 5.6 Hz, 1H), 7.20 (d, *J* = 4.9 Hz, 1H), 6.77–6.59 (m, 2H), 2.05–2.03 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (C), 147.6 (CH), 140.1 (C), 133.5 (CH), 130.4 (C), 129.8 (CH), 127.7 (CH), 125.6 (CH), 115.3 (CH), 19.0 (CH) ppm. HRMS: calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176.0528, found 176.0530.

7-((4-(trifluoromethyl)phenyl)ethynyl)thieno[3,2-b]pyridine (**16**). Yellow solid (45 mg, 50%), m.p. 161–163 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 5.6 Hz, 1H), 7.38 (d, *J* = 4.8 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C), 147.3 (CH), 134.9 (C), 132.3 (3xCH), 131.3 (C), 131.0 (CH), 125.7 (2xCH), 125.5 (CH), 125.3 (C), 122.4 (C), 120.4 (C), 95.9 (C), 86.8 (C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.95 ppm. HRMS: calcd for $C_{16}H_9F_3NS$ $[M + H]^+$ 304.0402, found 304.0403.

7-(furan-3-ylethynyl)thieno[3,2-b]pyridine (**17**). White solid (46 mg, 69%), m.p. 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.8 Hz, 1H), 7.83–7.76 (m, 2H), 7.59 (d, *J* = 5.5 Hz,

1H), 7.46 (t, *J* = 1.7 Hz, 1H), 7.32 (d, *J* = 4.8 Hz, 1H), 6.61 (d, *J* = 1.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C), 147.2 (CH), 146.8 (CH), 143.3 (CH), 134.6 (C), 130.9 (CH), 126.1 (C), 125.5 (CH), 120.2 (CH), 112.5 (CH), 106.7 (C), 89.3 (C), 86.7 (C) ppm. HRMS: calcd for $C_{13}H_8NOS$ $[M + H]^+$ 226.0321, found 226.0322.

7-((4-methoxyphenyl)ethynyl)thieno[3,2-b]pyridine (**18**). White solid (63 mg, 81%), m.p. 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.8 Hz, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.60–7.53 (m, 3H), 7.31 (d, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (C), 156.0 (C), 147.2 (CH), 134.8 (C), 133.7 (2xCH), 130.7 (CH), 126.5 (C), 125.6 (CH), 120.0 (CH), 114.2 (2xCH), 113.9 (C), 98.3 (C), 83.9 (C), 55.4 (CH) ppm. HRMS: calcd for $C_{16}H_{12}NOS$ $[M + H]^+$ 266.0634, found 266.0638.

7-(thiophen-3-ylethynyl)thieno[3,2-b]pyridine (**19**). White solid (36 mg, 51%), m.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.8 Hz, 1H), 7.77 (d, *J* = 5.5 Hz, 1H), 7.68 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.58 (d, *J* = 5.5 Hz, 1H), 7.37–7.31 (m, 2H), 7.28 (dd, *J* = 5.0, 1.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C), 147.2(CH), 134.8 (C), 130.8 (CH), 130.6 (CH), 129.9 (CH), 126.1 (C), 125.9 (CH), 125.6 (CH), 121.0 (C), 120.2 (CH), 93.0 (C), 84.5 (C) ppm. HRMS: calcd for $C_{13}H_8NS_2$ $[M + H]^+$ 242.0093, found 242.0094.

4-(phenylethynyl)furo[3,2-c]pyridine (**20**). White solid (21 mg, 30%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 5.7 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.66 (dd, *J* = 6.2, 2.7 Hz, 2H), 7.43–7.38 (m, 4H), 7.03 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C), 146.0 (CH), 144.9 (CH), 137.5 (C), 132.1 (2xCH), 129.2 (CH), 128.5 (2xCH), 127.0 (C), 122.2 (C), 106.9 (CH), 105.5 (CH), 92.7 (C), 86.5 (C) ppm. [CAS: 2098141-91-2].

4-((4-methoxyphenyl)ethynyl)furo[3,2-c]pyridine (**21**). Yellow solid (39 mg, 48%) ^{1}H NMR (400 MHz, CDCl3) δ 8.49 (d, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 2.2 Hz, 1H), 7.61–7.57 (m, 2H), 7.40 (d, *J* = 6.6 Hz, 1H), 7.01 (dd, *J* = 2.2, 0.9 Hz, 1H), 6.93–6.89 (m, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4 (C), 159.2 (C), 145.8 (CH), 144.8 (CH), 137.9 (C), 133.7 (2xCH), 126.7 (C), 114.2 (C), 114.1 (2xCH), 106.6 (CH), 105.6 (CH), 93.1 (C), 85.5 (C), 55.3 (CH) ppm.

4. Conclusions

Simple conditions to generate several *O*,*S*,*N*-Heterocycles by Hiyama coupling, cyanation and multicomponent reactions, which may show interesting biological properties, have been presented in this paper. Methods of preparation were optimized using eucalyptol as a biobased solvent.

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