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ARTICLE

Eucalyptol : New solvent for the synthesis of heterocycles containing oxygen, sulfur and nitrogen

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Abstract: We reported here a first investigation of the use of eucalyptol as the new solvent for organic transformations. Heterocycles containing oxygen, sulfur and nitrogen were chosen as targets or as starting materials for widely used palladium-catalysed cross-coupling reactions, i.e. Suzuki-Miyaura and Sonogashira-Hagihara reactions. Eucalyptol turned out to be a viable sustainable alternative to common solvents.

Introduction

In a context of sustainable development, the need to find alternatives to compounds from non-renewable resources is a priority. In the field of organic synthesis, solvents often constitute the major part of the reaction medium. This amount was evaluated for active pharmaceutical ingredients syntheses: it reaches 52% by mass, taking into account only organic solvents, and more than 80% including water.[1] As a result of the high environmental impact caused by the solvents, many studies have been devoted to the search for greener and sustainable alternatives[2] and solvent selection guides were published,[3] that included bio-derived solvents.[4] Among the solvents derived from biomass,[5] those produced from food waste represents an interesting approach since their use could participate to a more circular economy. One of those bio-solvents is limonene (Fig 1), a monoterpene unsaturated hydrocarbon with low polarity and weak hydrogen bond basicity (Table 1), making it an alternative to non-polar petroleum-based solvents used in extraction processes or cleaning applications[6,7] but rarely for organic transformations.[8] In this paper, we decided to compare limonene and Eucalyptol or 1,8-cineole (Fig. 1) that we wanted to use as new solvent. The latter is a saturated oxygenated terpene widely distributed in many plants and their essential oil fractions. Its use as green solvent is also related to its safety and pharmacological profiles: Eucalyptol is considered to be a safe chemical when taken in normal doses.

Eucalyptol or 1,8-cineole is often described as contained up to 90% in Eucalyptus' essential oils, depending on the species. For example, the chemical composition determined by GCMS analysis of *E. cinerea's* oil isolated from fresh foliage has showed three major constituents, Eucalyptol (84.39%), Limonene (5.92%) and α-Terpineol (5.55%) with 17 other different compounds occurring in less than 0.5% each.[9]
That is a very interesting proportion because the Eucalyptus forests have been developed strongly, during the last decades, for their use in the paper industry because of their rapid growth (7 to 10 years). The producers of eucalyptus essential oils are mainly: Australia, China, Portugal, Spain and South Africa without problems of supply since Eucalyptus are very big trees with fast growth during which the leaves can produce eucalyptol. The world production of eucalyptus essential oils from *Eucalyptus globulus and Eucalyptus radiata* was estimated, in 2015 at 4 000 tons per year by FranceAgrimer.

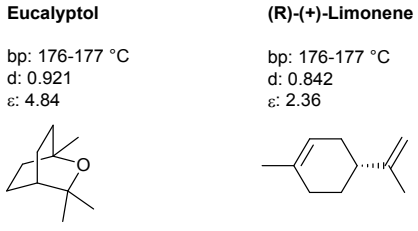

Figure 1. Structures of eucalyptol and limonene

Compared to limonene, this bicyclic ether exhibits higher polarity and hydrogen bond basicity (Table 1). It is insoluble in water but miscible with ether, ethanol and chloroform. Eucalyptol could also be compared to the 2-Methyltetrahydrofuran which has E_T^N = 0.179, acidity (α) = 0, Basicity (β) = 0,58, and Polarity (Π*) = 0,53.[10] The 2-MeTHF is mainly used as solvent to replace THF because of its higher

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boiling point 78-80°C. Nevertheless it can, like THF, generate peroxides and require the addition of inhibitor such as butylated hydroxytoluene (BHT), a powerful antioxidant. In addition Eucalyptol is cheaper than 2 Methyltetrahydrofuran.

Table 1. Solvatochromic parameters of limonene and eucalyptol

	Limonene	Ref.	Eucalyptol	Ref.
E_T^N			0.102	[11]
Acidity (α)	0	[10]	0	[10]
Basicity (β)			0.61	[12]
Polarity (π*)	0.24	[10]	0.36	[12]

To the best of our knowledge, there is no report in the literature to date on the use of Eucalyptol in organic synthesis. In this context, our project aimed at evaluating limonene and eucalyptol as solvents for some of the most prevalent transformations at both process development and manufacturing scale, i.e. the synthesis of heterocycles and cross-coupling reactions.[13]

Based on our previous work in the development of new methodologies and greener approaches in the synthesis of heterocycles,[14-19] we focussed on heterocycles containing oxygen, sulfur or nitrogen.

Results and discussion

A. Synthesis of Imidazo[1,2-*a*]pyridines

Imidazo[1,2-*a*]pyridine is one of the most potential bicyclic 5–6 heterocyclic rings that is recognized as a "drug prejudice" scaffold due to its broad range of applications in medicinal chemistry such as anticancer, antimycobacterial, antileishmanial, anticonvulsant, antimicrobial, antiviral, antidiabetic, proton pump inhibitor, insecticidal activities. This scaffold has also been represented in various marketed preparations such as zolimidine, zolpidem, alpidem. Therefore, many works have been done to propose syntheses[20] and structural modifications of this scaffold with the aim to discover and develop novel therapeutic agents.[21] Greener approaches involving one pot condensation and C-H activation were also proposed by us [22] and others.[23] (Fig.2)

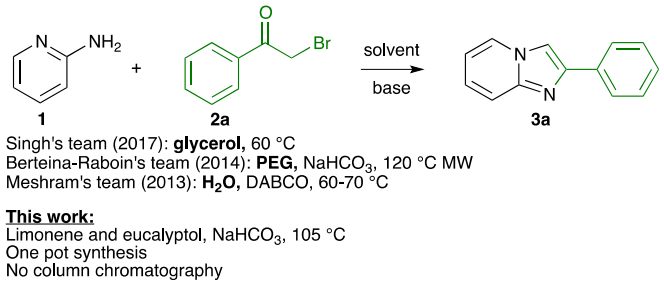


Figure 2. Greener approach for the synthesis of Imidazo[1,2-*a*]pyridine[22,23]

This work started with an optimization of condensation using 2-aminopyridine **1** and 2-bromoacetophenone **2a** (1 equiv.) in presence of several bases in limonene or eucalyptol as the solvents (Table 2).

Table 2. Optimization of the condensation from 2-aminopyridine **1** and bromoacetophenone **2** in limonene or eucalyptol at 105 °C.

Entry	Base (2 equiv.)	Solvent	Time (h)	Yield (%)
1	K_2CO_3	Eucalyptol	24	64
2	KOAc	Eucalyptol	24	71
3	Cs_2CO_3	Eucalyptol	24	75
4	$NaHCO_3$	Eucalyptol	22	83
5	CsOAc	Eucalyptol	24	53
6	KOH	Eucalyptol	48	13
7	K_2CO_3	Limonene	24	85
8	KOAc	Limonene	24	64
9	Cs_2CO_3	Limonene	24	66
10	$NaHCO_3$	Limonene	22	84
11	CsOAc	Limonene	24	50
12	KOH	Limonene	48	33

2-phenylimidazo[1,2-*a*]pyridine **3a** was obtained in good yield after 22 h at 105°C in the presence of $NaHCO_3$ (Table 1, Entries 4 and 10) both in limonene and eucalyptol whereas the use of K_2CO_3 gave better results with limonene as solvent (Table 1, Entries 1 and 7).

As the C-H activation at position C-3 of 2-phenylimidazo[1,2-*a*]pyridine was more effective in eucalyptol (see below), and in order to carry out a one pot procedure, we chose this solvent to study the scope of the reaction with various 2-bromo acetophenones **3b-c** (Fig.3).

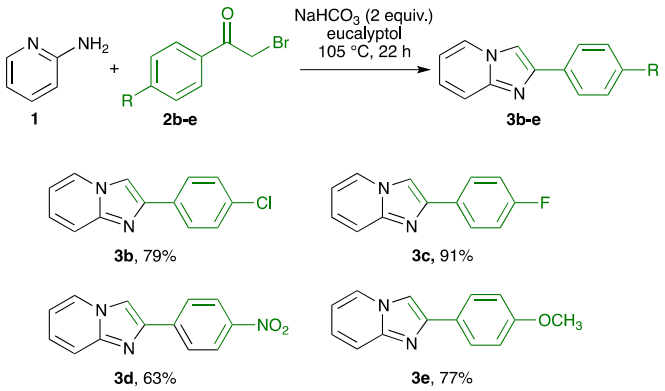
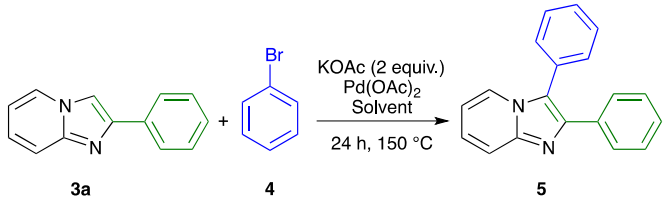


Figure 3. Condensation of 2-amino pyridine with a various 2-bromo acetophenones **2b-e.**

The various groups in position 4 on the aromatic ring had no influence and the expected products were obtained in moderate to excellent yields (Fig. 3).

We then studied the C-H activation at position C-3 of 2-phenylimidazo[1,2-*a*]pyridine **3a** using bromobenzene **4** (1.5 equiv.) and by varying the amount of $Pd(OAc)_2$ in limonene or eucalyptol (Table 3).

Table 3. Optimization of C-H activation of **3a** in eucalyptol and limonene as solvents



3a **4** **5**

Entry	$Pd(OAc)_2$ (mol %)	Solvent	Yield (%)
1	2.5	Eucalyptol	42
2	5	Eucalyptol	60
3	10	Eucalyptol	61
4	2.5	Limonene	Traces
5	5	Limonene	Traces

Compound **5** was obtained in moderate yield in eucalyptol (Table 3, Entries 2 and 3). When the reaction was performed in limonene the results were poor (Table 2, Entries 4 and 5). The amount of $Pd(OAc)_2$ was studied, and the improvement was not sufficient to justify the use of 10 mol% in the last phase.

The one pot procedure was then performed with 2-bromo-4-fluoroacetophenone **2c**, aryl bromides and 2-aminopyridine **1** using eucalyptol as solvent (Fig. 4).

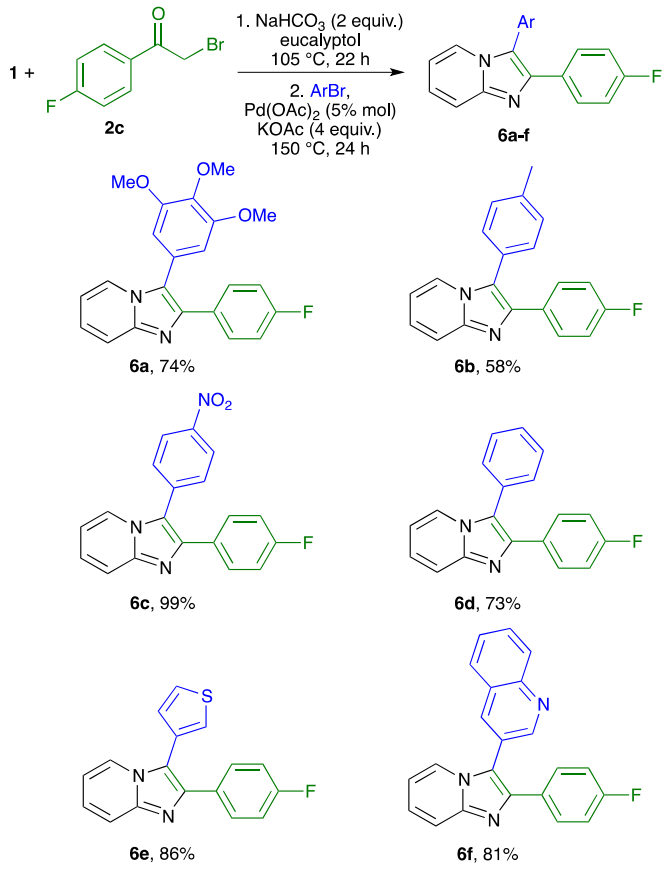
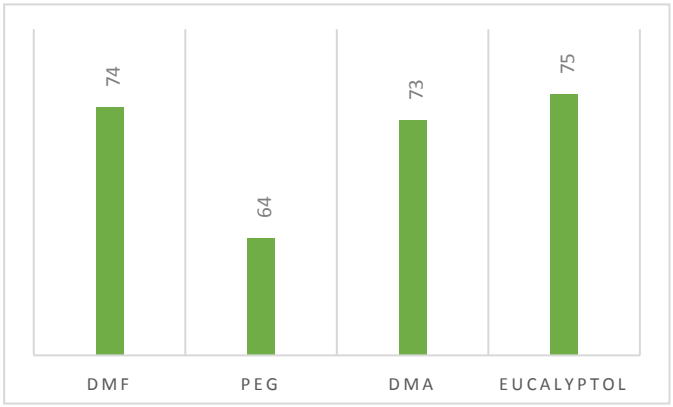


Figure 4. one pot procedure

The 2,3-diarylimidazol[1,2-*a*]pyridines **6a-f** were obtained in moderate to excellent yield, demonstrating the generality of this method. Yields shown at Fig. 4 correspond to tests carried out on a scale of 1 mmol of 2 aminopyridine **1**. We verified that the results were equivalent on a larger scale. Indeed, from 10.6 mmol of **1** (1.0 g), 2-(4-fluorophenyl)-3-(4-nitrophenyl)imidazol[1,2-*a*]pyridine **6c** was isolated in 98% yield (3.47 g). Analysing the mean values obtained by the various teams in the development of the one-pot approach for the synthesis of imidazo[1,2-*a*]pyridines, we can conclude that Eucalyptol is a valid option (Graph 1)[22,24,25]. The average yields were made, depending on published examples, on 18 reactions in DMF, 20 reactions in PEG, 16 reactions in DMA and on the 7 reactions in Eucalyptol described herein.

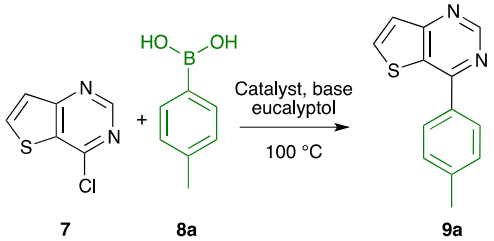


Graph 1. Average yield (%) reported for the synthesis of 2,3-diarylimidazol[1,2-*a*]pyridines in different solvents

Encouraged by the good results obtained previously with eucalyptol as solvent, we decided to use this solvent for palladium catalyzed coupling reactions such as Suzuki-Miyaura and Sonogashira-Hagihara reactions.

B. Suzuki-Miyaura coupling reaction

The Suzuki-Miyaura reaction belongs to the most powerful and most applicable group of reactions for formation of C-C bonds. Its use is effective for a wide range of substrates, which makes this cross coupling reaction a versatile tool. Due to all of these features and properties, efforts were done to find greener conditions.[26]



7 **8a** **9a**

Scheme 1. Suzuki-Miyaura reaction

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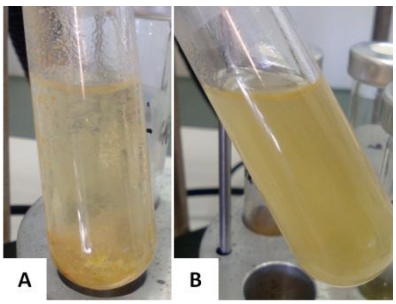


Figure 5. A: Reaction medium at temperature below 100 °C; B: reaction mixture at 100 °C.

Optimization of the Suzuki reaction was achieved starting from 4-chlorothieno[3,2-*d*]pyrimidine **7** using 4-methylphenyl boronic acid **8a** and by varying the catalytic system and the base (Scheme 1). After several attempts, we observed that the complete dissolution of all the reactants and consequently the reaction progress was achieved when the temperature was set at 100 °C. (Fig. 5)Results are summarized in Table 1. Compound **9a** was obtained in moderate (Table 1, Entry 2) to excellent yield (Table 1, Entries 1, 3 and 4). When the reaction was performed in the presence of $Pd(PPh_3)_4$, yields were higher. The base had a pronounced effect: when the reaction was carried out using $Pd(PPh_3)_4$ and Na_2CO_3 as base, quantitative yield was obtained.

Table 4. Optimization of the Suzuki-Miyaura reaction (Scheme 1)

Entry	Catalyst (0.1 eq.)	Ligand (0.2 eq.)	Base (2 eq.)	Time (h)	Yield[a] (%)
1	$Pd(PPh_3)_4$		Na_2CO_3	14	99
2	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	20	65
3	$Pd(PPh_3)_4$		K_2CO_3	14	97
4	$Pd(PPh_3)_2Cl_2$		K_2CO_3	20	90

[a]isolated yields after purification by flash chromatography.

Based on our results (Table 4) the scope and limitations of the Suzuki-Miyaura coupling reaction on 4-chlorothieno[3,2-*d*]pyrimidine **7**, were assessed using various boronic acids **8b-e** (Fig. 6).

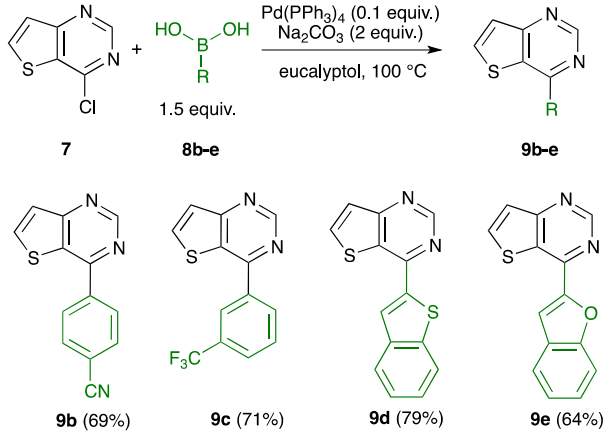
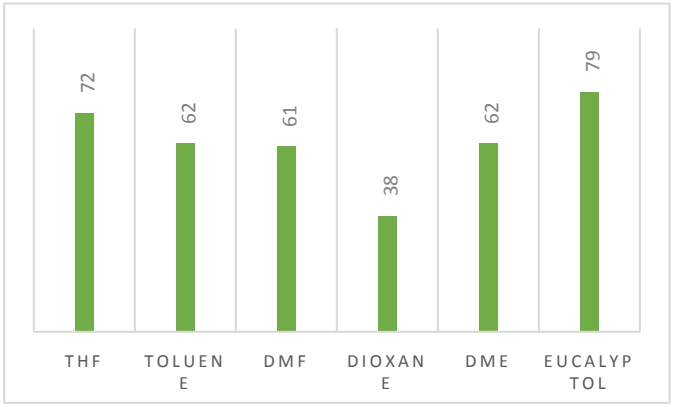


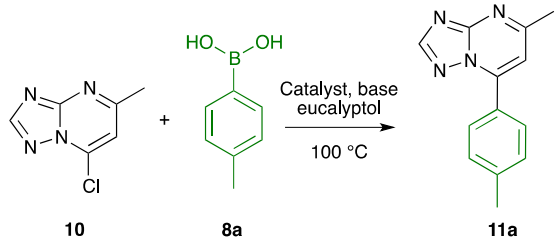
Figure 6. Scope and limitations of the Suzuki-Miyaura coupling reaction on **7**

In comparison with yields obtained for the same reaction of chlorothieno[3,2-*d*]pyrimidine in the most commonly used solvents, eucalyptol proved to be a good alternative (Graph 2).[27-30] The average yields were made on 4 reactions in THF, 15 reactions in Toluene, 5 reactions in DMF, 17 reactions in Dioxane, 4 reactions in DME and on the 5 reactions in Eucalyptol described herein.



Graph 2. Average yield (%) reported for Suzuki-Miyaura coupling reaction of chlorothieno[3,2-*d*]pyrimidine

Optimization of the Suzuki reaction with 7-chloro-5-methyl [1,2,4]triazolo[1,5-*a*]pyrimidine **10** was performed using 4-methylphenyl boronic acid **8a** as a model substrate.



Scheme 2.

The use of different palladium sources as catalyst and sodium bicarbonate, potassium carbonate or cesium carbonate as base were examined. Best conditions were found using $Pd(PPh_3)_4$ and K_2CO_3 (Table 5, entry 3).

Table 5. Optimization of the Suzuki-Miyaura reaction (Scheme 2)

Entry	Catalyst (0.1 eq.)	Ligand (0.2 eq.)	Base (2 eq.)	Time (h)	Yield[a] (%)
1	$Pd(PPh_3)_4$		Na_2CO_3	14	49
2	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	14	71
3	$Pd(PPh_3)_4$		K_2CO_3	14	73
4	$Pd(PPh_3)_2Cl_2$		K_2CO_3	14	66

[a]isolated yield after purification by flash chromatography.

Different boronic acids **8b-e** were then used to evaluate the reaction scope. Several 5-methyl-7-(aryl)-[1,2,4]triazolo[1,5-*a*]pyrimidines **11b-e** were obtained in moderate yield. (Fig. 7)

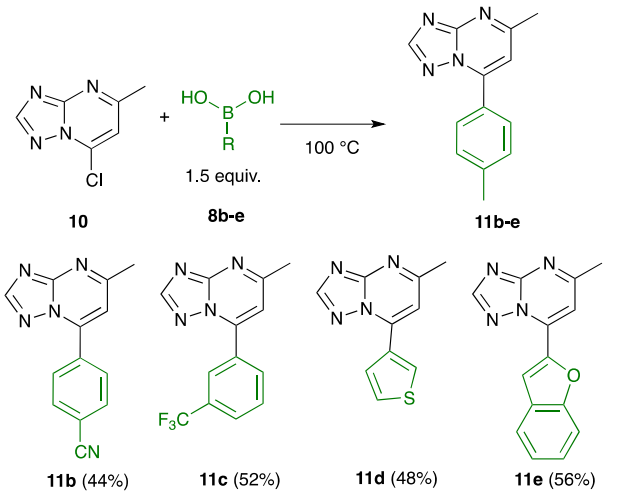
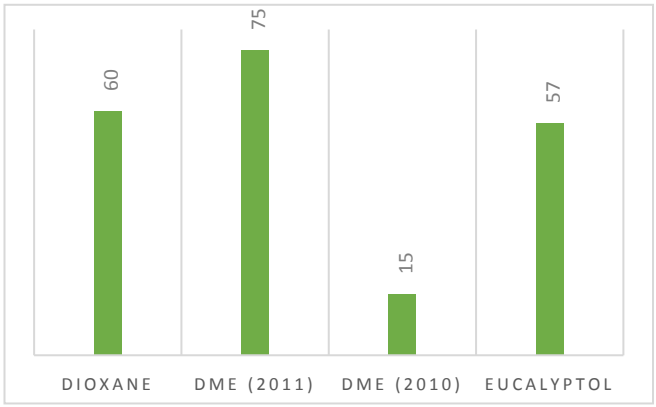


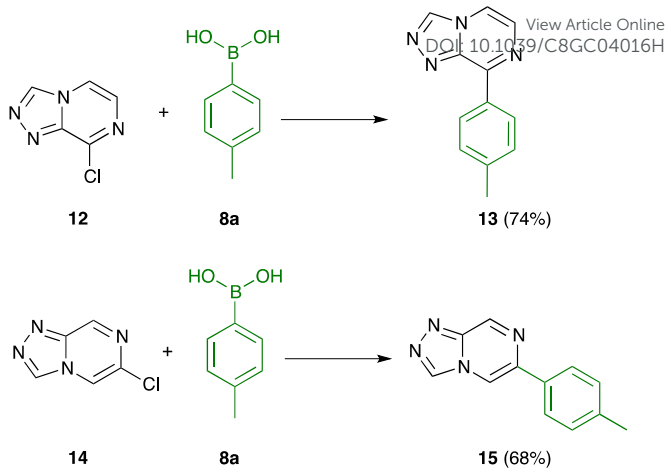
Figure 7. Suzuki-Miyaura coupling reaction on **10**

In comparison with the yields described for this reaction with the same substrate in dioxane or DME,[31-33] those obtained using eucalyptol were generally lower (Graph 3). The average yields were made on 8 reactions in Dioxane, 30 reactions in DME (2011), 2 reactions in DME (2010) and on the 5 reactions in Eucalyptol described herein. However, since dioxane and DME are classified as hazardous,[34] eucalyptol remains a good alternative for this transformation.



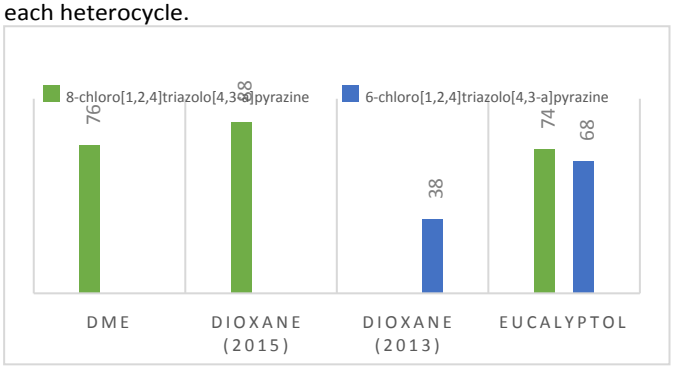
Graph 3. Average yield (%) reported for Suzuki-Miyaura coupling reaction of chloro[1,2,4]triazolo[1,5-*a*]pyrimidine

The 8-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **12** and 6-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **14** were submitted to the same reaction conditions (Scheme 3) affording **13** or **15** in good yield. The yield obtained with **12** in eucalyptol as solvent was similar to those obtained in dioxane or DME,[35,36] whereas with **14**, a significant yield increase was obtained compared to dioxane (Graph 4).



Scheme 3. Conditions: **8a**, 1.5 equiv., $Pd(PPh_3)_4$ 0.1 equiv., Na_2CO_3 2 equiv., eucalyptol 100 °C, 20 h.

In this case the average yields were made on 3 reactions in DME, 2 reactions in Dioxane (2015), 2 reactions in Dioxane (2013) and in Eucalyptol on the reaction described herein for each heterocycle.



Graph 4. Average yield (%) reported for Suzuki-Miyaura coupling reaction on 8-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **12** and 6-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **14**.

Starting from 4-chlorofuro[3,2-*c*]pyridine **16** we obtained, under the same conditions, compounds **17a-e** with moderate to excellent yield (Fig. 8).

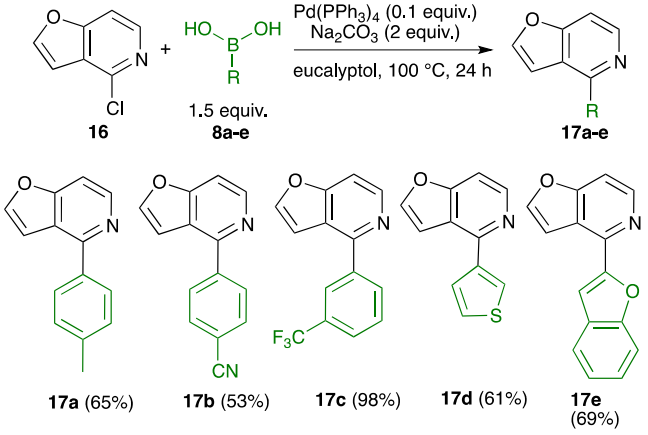


Figure 8. Suzuki-Miyaura coupling reaction on **16**

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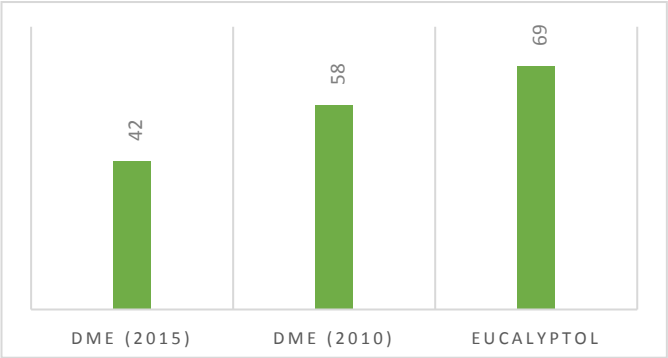
Also in this case, eucalyptol gave better results compared to DME (Graph 5).[37,38] The average yields were made on 18 reactions in DME (2015), 4 reactions in DME (2010) and on the 5 reactions in Eucalyptol described herein.

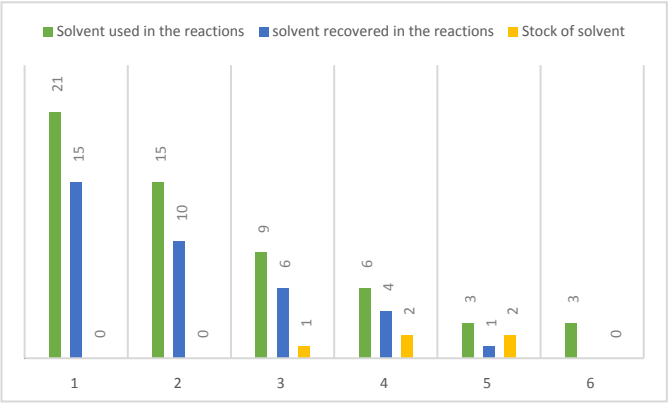


Graph 5. Average yield (%) reported for Suzuki-Miyaura coupling reaction of 4-chlorofuro[3,2-*c*]pyridine **16**.

Recyclability of the solvent

Reusability of the solvent being essential from the economic and environmental point of view, we were incited to implement it during the reactions described above. To illustrate solvent reusability, we present in graph 6 an example of one of the periods of time in which we had relayed a series of 7 reactions, each being carried out in 3 mL eucalyptol/mmol of substrate.

After the reactions, eucalyptol was recovered by distillation under reduced pressure, and then reused immediately for the next run. We started with 21 mL of eucalyptol for 7 reactions, 15 mL were recovered by distillation and used to perform 5 reactions from which we could distillate 10 mL of solvent. These operations were continued so that 21 mL of eucalyptol were used to perform 19 reactions on 1 mmol scale without noticeable loss of properties. The boiling point of Eucalyptol is high but it is possible to evaporate it, in few minutes, with a normal pump and cooling liquid like monoethyleneglycol into a classical rotary evaporator system.



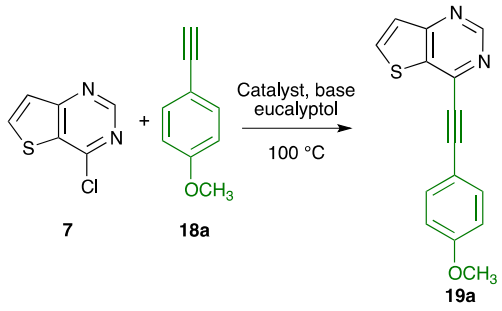
Graph 6. Recyclability of Solvent

Sonogashira-Hagihara coupling reaction

The coupling of aryl or vinyl halides with terminal acetylenes catalysed by palladium and other transition metals, commonly termed as Sonogashira cross-coupling reaction, is another example of the most important and widely used sp2–sp carbon–carbon bond formation reactions in organic synthesis, frequently employed in the synthesis of natural products, biologically active molecules and heterocyclic compounds.[39,40] Optimization of the Sonogashira reaction in eucalyptol was achieved starting from 4-chlorothieno[3,2-*d*]pyrimidine **7** using 4-methoxyphenyl acetylene **18a** and by varying the catalytic system and the base. The results obtained are summarized in Table 8. In this case the conditions previously reported by us[31] (i.e. $Pd(PPh_3)_2Cl_2$ (5 % mol), CuI (10 % mol) in a mixture of solvent and Et_3N) were not the best option with eucalyptol. Compound **19a** was obtained in moderate (Table 8, Entries 1 and 2) to good yield (Table 8, Entry 3). When the reaction was performed in the presence of $Pd(PhCN)_2Cl_2$ and $P(Cy_3)$, yield was increased.

Furthermore, the optimized conditions are in line with other reported conditions in which the use of CuI with aryl chlorides was not necessary.[41-44] It was a curiosity, as it is well known that normally this coupling of terminal alkynes is performed with a palladium catalyst, a copper(I) co catalyst and an amine base.

Table 6. Optimization of the Sonogashira-Hagihara coupling reaction



7 **18a** **19a**

Entry	Catalyst		Base	Time (h)	Yield (%[a])
1	$Pd(PPh_3)_2Cl_2$ (0.01 eq.)	CuI (0.02 eq.)	Et_3N (used as co-solvent in 1/3 ratio)	20	57
2	$Pd(PPh_3)_2Cl_2$ (0.05 eq.)	CuI (0.1 eq.)	Et_3N (used as co-solvent in 1/2 ratio)	16	64
3	$Pd(PhCN)_2Cl_2$ (0.1 eq.)	$P(Cy_3)$ (0.2 eq.)	Cs_2CO_3 (2 eq.)	24	75

[a]isolated yields after purification by flash chromatography.

Based on our results (Table 6) the scope and limitations of the Sonogashira coupling reaction on 4-chlorothieno[3,2-*d*]pyrimidine **7**, were assessed using several acetylenes **18b-e** (Fig. 9).

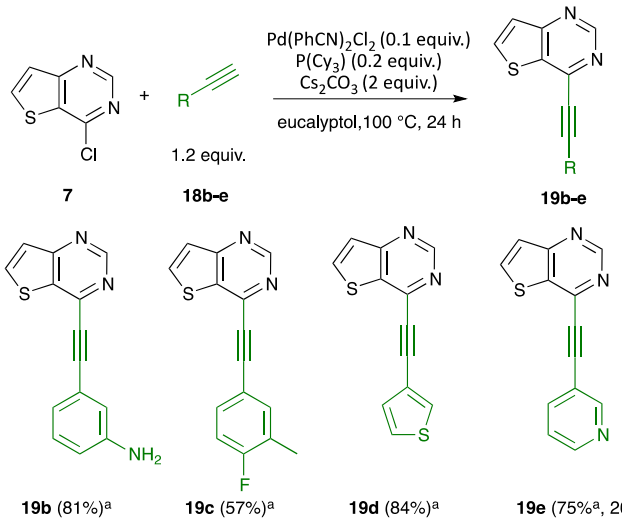
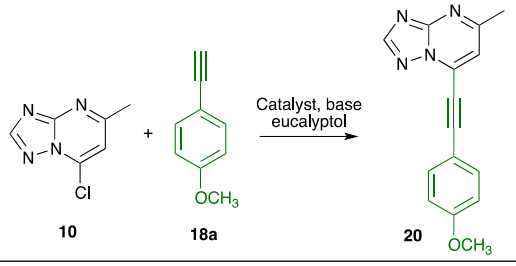


Figure 9. [a]isolated yield after purification by flash chromatography. [b]Limonene as solvent (28 h)

To the best of our knowledge, up to this day there is only one reported case of Sonogashira applied to the thieno[3,2-*d*]pyrimidine[45] skeleton: Zhang's team reported the preparation of 7-phenyl-4-(phenylethynyl)thieno[3,2-*d*]pyrimidine in 51% yield using 4-chloro-7-phenylthieno[3,2-*d*]pyrimidine, $PdCl_2(PPh_3)_2$, CuI, Et_3N and phenylacetylene at reflux for 21 h. The use of eucalyptol as solvent allowed to improve the yield and to work under Cu-free conditions.

The Sonogashira reaction was also tested in eucalyptol from 7-chloro-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine **10** but poor results were obtained (Table 7).

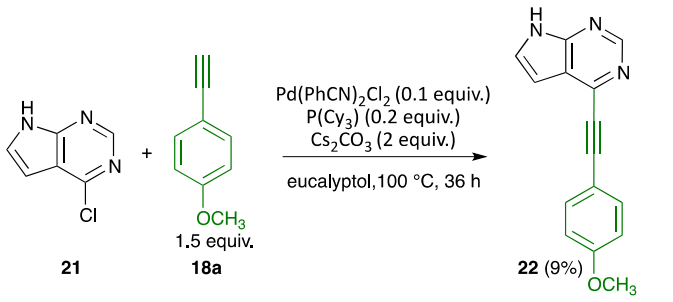
Table 7. Sonogashira reaction in eucalyptol starting from 7-chloro-5-methyl [1,2,4]triazolo[1,5-*a*]pyrimidine **10**



Entry	Catalyst		Base	Time (h)	Yield[c] (%)
1	$Pd(PPh_3)_2Cl_2$ (0.01 eq.)	CuI (0.02 eq.)	Et_3N (used as co-solvent in 1/3 ratio)	24[a]	-
2	$Pd(PPh_3)_2Cl_2$ (0.05 eq.)	CuI (0.1 eq.)	Et_3N (used as co-solvent in 1/2 ratio)	24[b]	-
3	$Pd(PhCN)_2Cl_2$ (0.1 eq.)	$P(Cy_3)$ (0.2 eq.)	Cs_2CO_3 (2 eq.)	16[a]	27

[a] 100 °C; [b] 70 °C; [c] isolated yield after purification by flash chromatography.

Similarly, using 4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine **21** gave very poor yield (Scheme 4) showing that eucalyptol is not a good solvent for Sonogashira-Hagihara coupling reaction with starting material containing nitrogen on the 5-membered ring.



Scheme 4. Sonogashira-Hagihara coupling reaction on 4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine **21**

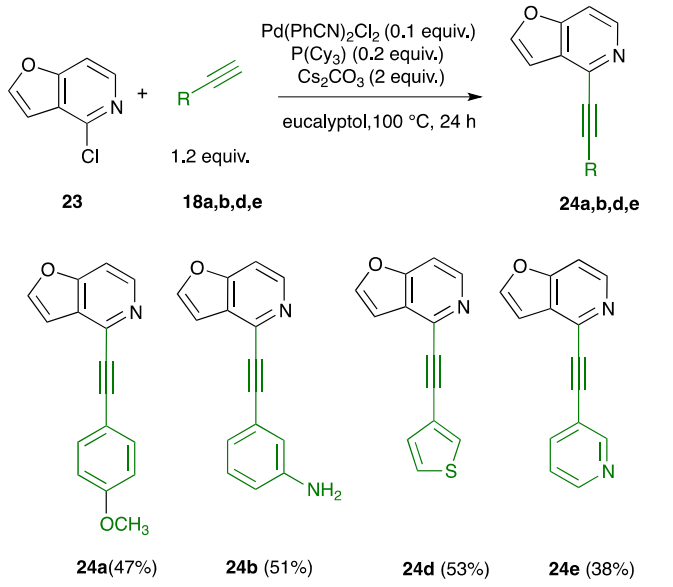


Figure 10. Sonogashira-Hagihara coupling reaction on **23**

Starting from 4-chlorofuro[3,2-*c*]pyridine **23** we obtained better results, since compounds **24a,b,d,e** were synthesized in moderate yield (38% to 53%) under the same conditions (Fig. 10).

Conclusion

We demonstrated, for the first time, that eucalyptol could be used as solvent for organic synthesis. Experiment results described herein and dielectric constant of eucalyptol allow us to think that it can advantageously replace a large number of solvents in which: Anisole, Bromobenzene, chlorobenzene, Chloroform, Diethyl ether, DMF, DMA, DME, 1,4-Dioxane, Ethyl acetate, Ethyl benzoate, THF, Toluene. We have shown that it could be an interesting alternative to conventional solvents for the one-pot synthesis of 2,3-diarylimidazol[1,2-*a*]pyridines involving a condensation between 2-aminopyridine

and bromoacetophenones, followed by a C-H activation at C-3. This solvent, derived from biomass, was also effective for various transformations of heteroatom-containing heterocycles such as oxygen, sulfur or nitrogen. A limitation was found for the Sonogashira-Hagihara coupling reaction with starting material containing nitrogen on the 5-membered ring. However, it should be noted that, the use of eucalyptol as solvent in Sonogashira coupling applied to the thieno[3,2-*d*]pyrimidine allowed to improve the yield and work under Cu-free conditions. Furthermore, we have shown that it was possible to recover this solvent from the reaction media by simple distillation, using a standard equipment, which is very important from the environmental and also economic aspects. As mentioned above, its use as green solvent is also related to its safety and pharmacological profiles: Eucalyptol is considered to be a safe chemical when taken in normal doses. It becomes hazardous via ingestion, skin contact or inhalation at higher doses and does not show genotoxicity or carcinogenicity.[46]

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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