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Nenitzescu Synthesis of 5-Hydroxyindoles with Zinc, Iron and Magnesium Salts in Cyclopentyl Methyl Ether

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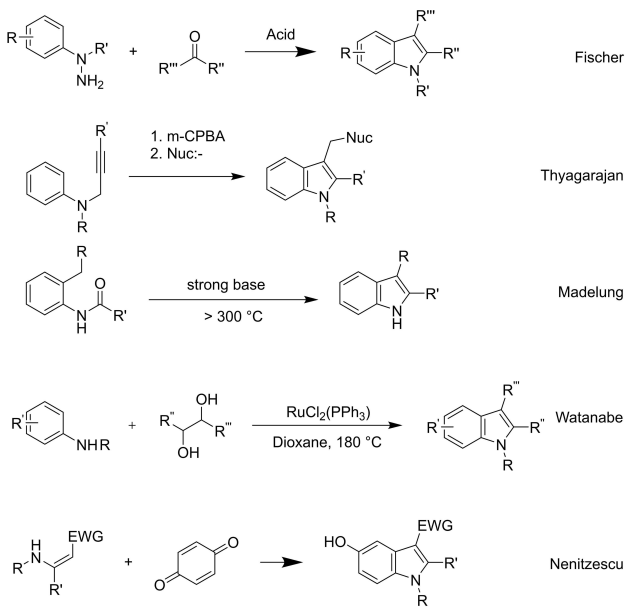
In this work, mild Lewis acids and low environmental impact solvents were investigated for Nenitzescu synthesis. Cyclopentyl methyl ether can be used at room temperature in substitution of halogenated solvents with zinc, iron and magnesium salts as homogeneous catalysts to give 5-hydroxyindoles in fair to good yields. The reaction features a straightforward workup and excellent solvent recycle.

Introduction

Indole ring is present in a great variety of biologically relevant compounds, from the amino acid tryptophan to the hormone melatonin and the neurotransmitter serotonin as well as complex plant secondary metabolites such as vincristine and reserpine, used as chemotherapeutic agents[1] and in hypertension management.[2] Furthermore, the indole ring has attracted considerable attention as scaffold for the development of a great variety of drugs, such as sumatriptan,[3] tadalafil,[4] sertindole,[5] bazedoxifene,[6] just to cite a few, and many others are still under investigation.[7] A large variety of indole synthesis have been established (a selection is reported in Scheme 1). One of the most common methods is the Fischer synthesis, based on a sigmatropic rearrangement of phenyl hydrazones in presence of an acid catalyst.[8] It should be noted that phenyl hydrazones are obtained by condensation of aldehydes or ketones with toxic and mutagenic phenylhydrazines.[9] The indole synthesis proposed by Thyagarajan in 1974[10] proceeds through the oxidation of an *N*-propargylaniline with a stoichiometric amount of *m*-chloroperoxybenzoic acid (*m*-CPBA). The use of stoichiometric amounts of *m*-CPBA and the *N*-propargylanilines synthesis,[11] reduce the greenness of the overall process. The synthesis developed by Madelung[12] works through treatment of o-alkyl-N-acylanilines with strong bases (e.g. 2-methylformanilide with potassium *tert*-butoxide[13]). This method is afflicted by harsh reaction conditions such as high reaction temperatures and strong bases. The Watanabe synthesis between substituted *N*-alkylanilines and 1,2-diols develops through an oxidative cyclization but requires the use of expensive ruthenium-based metal catalysts, dioxane as a solvent and fairly high temperatures (180 °C).[14] When N-methylaniline was reacted with 1,2-propanediol an equimolar mixture of 1,2- and 1,3-dimethyl indole was obtained,[15] showing a limited selectivity and reducing the usefulness of the approach. The Nenitzescu synthesis, named after its discoverer,[16] permits to obtain substituted 5-hydroxyindoles starting from 1,4-benzoquinone and an enamine



Scheme 1. Selected named synthesis of indoles.

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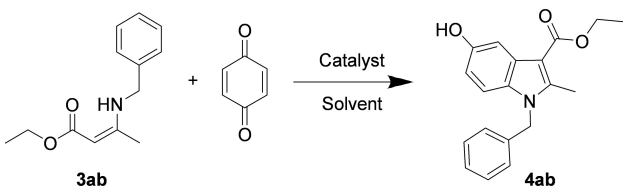
(typically 3-aminocrotonates) by the reaction at reflux. From the sustainability perspective, when applicable, the Nenitzescu synthesis is somewhat favorable because it doesn't require anilines or phenylhydrazines, notorious pollutants and carcinogens, as starting materials and entails a high atom economy, although, the reaction is often plagued by low yields.[17] Many studies have been carried out to investigate the solvent effect on the reactivity: when nitromethane was used as reaction medium, the 5-hydroxyindoles formed readily at room temperature and very often crystallized straight from the reaction mixture with high yield.[18] Nevertheless nitromethane is a suspect carcinogen and potentially explosive,[19] and the yield dropped consistently with the steric hindrance of the reactants. The substitution of nitromethane with other solvents possessing high dielectric constants (dimethylsulfoxide (DMSO), dimethylformamide, nitrobenzene and pyridine) in a multivariate study[20] for the un-catalyzed synthesis of 2-methyl-3-methoxycarbonyl-5-hydroxyindole gave at best 50% yield (HPLC) in DMSO at 90 °C. Mild Lewis acids as catalysts, on the other hand, like $ZnCl_2$ in dichloromethane (DCM)[21,22] or $(NH_4)_2[Ce(NO_3)_6]$ in ethanol (EtOH)[23] gave good yields in the Nenitzescu reaction. Acidic clay in refluxing 1,2-dichloroethane has been used as well with good results.[24] Interestingly BF_3-diethyl etherate, with an excess of urea, has been applied to a modified version of Nenitzescu synthesis assisted by microwaves.[25] These methods have some drawback on the environmental impact side, because all of them use solvents at reflux and some of them require the use of chlorinated solvents,[21,22,24] chromatographic purification[23,24] and for some substrate stoichiometric amounts of Lewis acids[22] or additives.[25]

Results and Discussion

Continuing our recent interest for substitution of aromatic[26,27] and chlorinated[28] solvents, we decided to study alternative reaction media in the Lewis acid catalyzed Nenitzescu synthesis. Reaction of Scheme 2 was chosen to test the substitution of DCM with six solvents that demonstrated low environmental impact and are finding growing application: EtOH, ethyl lactate (EtL),[29,30] γ-valerolactone[31] (GVL), butyl acetate (BuAc),[32,33] 2-methyltetrahydrofuran (2-MeTHF)[34–37] and cyclopentyl methyl ether (CPME).[38,39] A notable result with four of the tested solvents is that compound **4ab** precipitated as a pure crystalline product from the reaction mixture. The isolated yields with BuAc and 2-MeTHF (run 5 and 6 in Table 1) were



Scheme 2. Model reaction.

Table 1. Evaluation of solvents on reaction of Scheme 2.[a]

Entry	Solvent	T [°C]	Isolated Yield [%][b]
1	DCM	20	52
2	EtOH	20	–
3	EtL	20	–
4	GVL	20	–
5	BuAc	20	17
6	2-MeTHF	20	14
7	CPME	20	50
8	DCM	35	51
9	DCM	reflux	62
10	CPME	40	44
11	CPME	50	23

[a] 1 mmol each of reactants, 5 mL of solvent, catalyst $ZnCl_2$ (8 mol%) reaction time 40 minutes; [b] The product was isolated by simple filtration.

low, while CPME gave results comparable with DCM. A first observation is that, as already pointed out by some authors for this reaction,[40] there is no simple correlation between dielectric constant and yields. Furthermore, a difference between DCM and CPME was that an increase in reaction temperature helped to raise the yield in the former (runs 1, 8 and 9 in Table 1) but had the opposite effect in the latter (runs 7, 10 and 11 in Table 1). Efficient homogeneous catalysts were then searched on the basis of the solubility of salts in CPME, as shown in Table 2. Due to the low polarity of the ethereal solvent nine salts among tested dissolved. With Lewis acids with a sufficient solubility in CPME Nenitzescu synthesis was investigated (some of them for the first time).

It is noteworthy that the reaction occurred with $Mg(CF_3SO_3)_2$ and $FeCl_3$, since Mg and Fe are much more abundant elements and less pollutant than Zn (Table 3). The counterion influenced the catalyst efficiency. The most striking example was Zn naphthenate, where, probably, the strong coordination of carboxylate reduced the cation activity of Lewis acid. Nevertheless, a general trend is not obvious; for instance, chloride and iodide determined an opposite effect on Zn and In. Finally, it is worth noting that ZnI_2 gave the best yield, but it should be bear in mind its higher cost, lower Atom Economy and stability. Following Scheme 3, a variety of enamines (**3aa**–**be**) were synthesized and used to exploit the reaction scope in CPME at

Table 2. Salts solubility in CPME.[a]

Soluble	Insoluble
$ZnCl_2$	$Zn(CF_3SO_3)_2$
ZnI_2	$Mn(CH_3CO_2)_3 \cdot 2H_2O$
Zn-naphthenate	CuCl
$FeCl_3$	$CuCl_2$
InI_3	$ZrCl_4$
$InCl_3$	$FeCl_2$
$MgBr_2 \cdot Et_2O$	$AlCl_3$
$Mg(CF_3SO_3)_2$	$MgCl_2$
$LiClO_4$	$AgNO_3$
	$Ce(SO_4)_2$
	$Ce(SO_4)_2 \cdot 2H_2O$
	$(NH_4)_2[Ce(NO_3)_6]$
	$Yb(CF_3SO_3)_3$

[a] 8×10^{-5} mol of salt in 5 mL of CPME.

Table 3. Evaluation of catalysts on reaction of Scheme 2.[a]

Entry	Catalyst [mol%]	Isolated Yield [%][b]
1	$ZnCl_2$ (4)	42
2	$ZnCl_2$ (8)	50
3	$ZnCl_2$ (16)	23
4	ZnI_2 (8)	61
5	Zn-naphthenate (8)	<1
6	$FeCl_3$ (8)	47
7	InI_3 (8)	17
8	$InCl_3$ (8)	34
9	$MgBr_2 \cdot Et_2O$ (8)	23
10	$Mg(CF_3SO_3)_2 \cdot$(8)	36
11	$LiClO_4$ (8)	<1

[a] 1 mmol each of reactants, 5 mL of CPME, temperature 20 °C, reaction time 40 minutes; [b] The product was isolated by simple filtration.

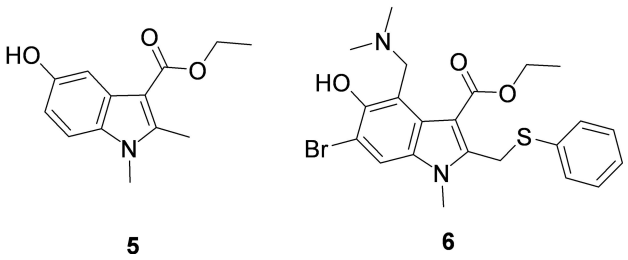
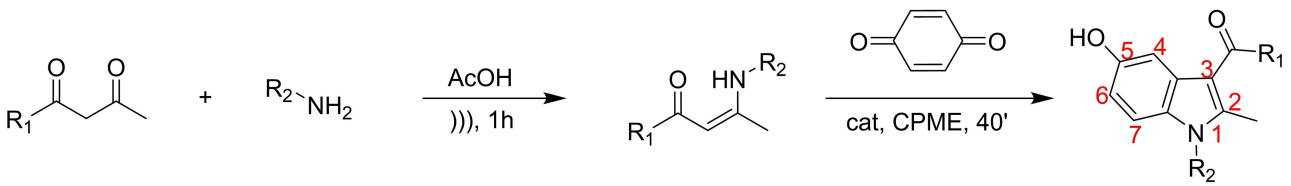


Figure 1. Dimecarbine (**5**) and Arbidol (**6**) structures.

room temperature with the four best catalysts selected so far. The results are summarized in Table 4. Zn salts were superior to $FeCl_3$ and $Mg(CF_3SO_3)_2$ with all tested substrates. The effect of substituents at N1 and C3 was not obvious but it can be thought that they imposed steric hindrance, as already noted by some authors.[41] The yields were probably affected by the solubility of the catalyst in CPME and the ability to coordinate to the substrates and intermediates. Interestingly compound **4ad** was obtained with a considerably higher yield (50%) compared to literature (15%).[7] The reaction was run on a gram scale to give dimecarbine (mecarbinate, **5**) an antihypertensive drug[42] and an intermediate in the synthesis of antiviral Arbidol, (**6**)[43] with an isolated yield of 65% (Figure 1).

The use of CPME have some additional advantages over other solvents, for instance the possibility to telescope the reactions shown in Scheme 4. The reaction between benzylamine (**2b**) and ethyl acetoacetate (**1a**) catalyzed by $ZnCl_2$ was run in CPME at reflux with azeotropic removal of by-product water to obtain the formation of enamine **3ab**. After the crude solution of **3ab** was cooled to room temperature, the addition of benzoquinone dissolved in CPME without any additional catalyst was performed to obtain the indole **4ab** with an isolated yield of 42%. The telescopic reaction was repeated in the same fashion with **1a**+**2a** and **1b**+**2e** to obtain **4aa** and **4be** in 20% and 70% isolated yields respectively. The recycle of CPME[44] and catalyst over two runs of Nenitzescu synthesis was assessed as depicted in Figure 2. A first synthesis was run on 10 mmol scale to obtain **4ab** with 54% isolated yield by filtration. The mother liquor was extracted with acidic water to separate the catalyst from the organic phase. The organic phase was distilled to recover CPME. Recovered CPME and the catalyst solution in water were mixed, and water removed by azeotropic distillation. The solution of the catalyst in CPME was treated



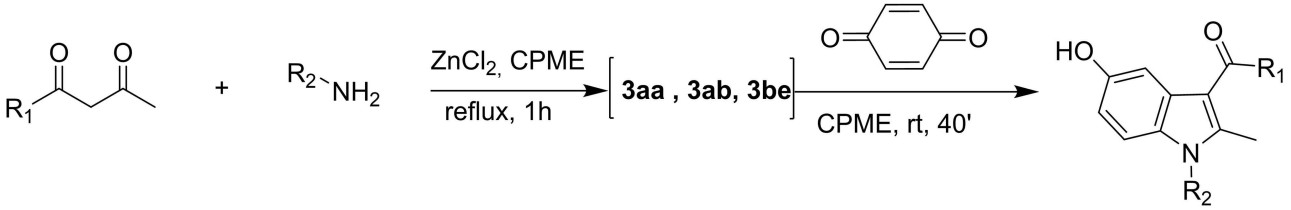
1 a-b
R_1 = EtO **1a**;
Me **1b**

2 a-e
R_2 = C_5H_{11} **2a**;
Bn **2b**;
CH_2CH_2OH **2c**;
4F-Bn **2d**;
4Cl-Bn **2e**.

3 aa-be

4 aa-be

Scheme 3. Reaction scope.



1 a-b **2 a,b,e** **4 aa, 4ab, 4be**

Scheme 4. Telescopic reaction.

Table 4. Isolated yields for Nenitzescu reaction in CPME.[a]

Catalyst	**4aa**	**4ba**	**4ab**	**4bb**	**4ac**
$ZnCl_2$	22	49	55	38	54
ZnI_2	35	55	61	47	54
$Mg(CF_3SO_3)_2$	17	34	36	25	51
$FeCl_3$	–	–	47	28	19

Catalyst	**4bc**	**4ad**	**4bd**	**4ae**	**4be**
$ZnCl_2$	10	49	70	50	74
ZnI_2	21	50	60	51	80
$Mg(CF_3SO_3)_2$	<1	31	27	38	10
$FeCl_3$	–	29	31	20	43

[a] Reaction conditions: enamine 1 mmol, benzoquinone 1 mmol, catalyst 0.08 mmol, CPME 5 mL, room temperature for 40 minutes.

Table 5. Green metrics comparison for the synthesis of selected indoles.

Product	Procedure	RME[a]	PMI[b]	E factor[c]	CO_2 emission[d]
4ab	Suryavanshi[23]	65%	171	–	3.04
4ab	This work	49%	64	7.3	1.45
4ab	This work[e]	38%	36	5.0	1.04
4ac	Velezheva[22]	60%	29	9.8	0.79
4ac	This work	51%	32	4.1	0.56
4aa	This work[e]	18%	80	12	2.25
4be	This work	72%	19	2.3	0.34
4be	This work[e]	60%	22	2.7	0.39

[a] Reaction Mass Efficiency;[45] [b] Process Mass Intensity;[45,46] [c] Environmental Factor;[45] [d] kg of CO_2 per kg of product, from energy consumption;[47] [e] Telescopic reaction. See experimental section and Supporting Information for calculation details.

with enamine **3ab** and benzoquinone to obtain **4ab** with 37% isolated yield. This recovery experiment was not further optimized but showed that CPME could be efficiently recycled and to some extent the catalyst as well. To evaluate the sustainability of our procedure, we calculated some green metrics and compared with the data obtainable from literature,[21–23] the results are reported in Table 5.

The advantages due to the straightforward work-up and efficient recovery of CPME used as a solvent are highlighted by E factor and Process Mass Intensity (PMI).[45,46] Compound **4ab** has been synthesized in a one-pot procedure by Suryavanshi et al.[23] with 73% yield, which gives a favorable Reaction Mass Efficiency (RME) value.[45] The easier work-up of our procedure gave a better E factor[45] with a lower value for the telescopic

Table 6. Isolated yields for Nenitzescu reaction with different quinones.[a]

Catalyst	**4ab**	**4abB + 4abB′**	**4abC**
$ZnCl_2$	55	<1	56
ZnI_2	61	<1	73
$Mg(CF_3SO_3)_2$	36	<1	<1
$FeCl_3$	47	13 (9:1)[b]	30

[a] Reaction conditions: enamine 1 mmol, benzoquinone 1 mmol, catalyst 0.08 mmol, CPME 5 mL, room temperature for 40 minutes. [b] isomer ratio as determined by ^{1}H-NMR.

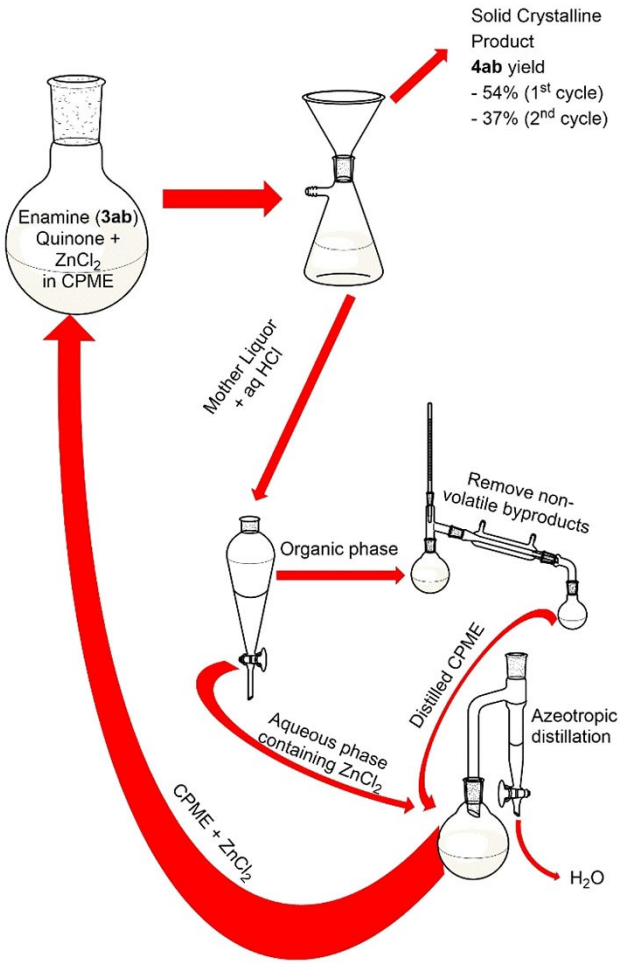


Figure 2. Recycle experiment workflow.

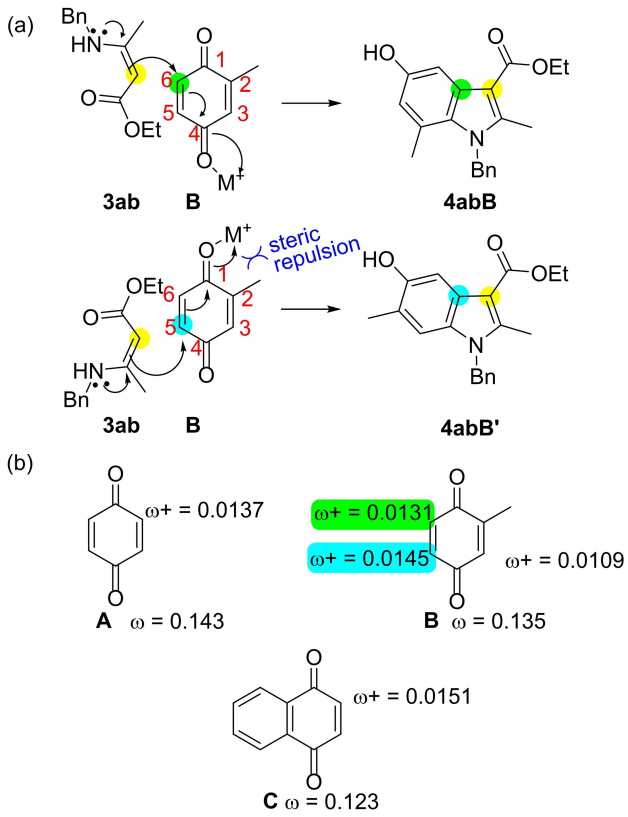
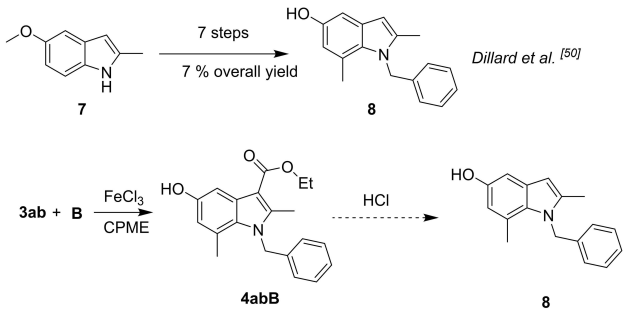


Figure 3. (a) First step of the reaction catalyzed by a generic Lewis acid M+. (b) Quinones global electrophilicity indexes (ω) and local electrophilicity indexes (ω+), the values are directly proportional to the electrophilicity of the molecule or the labelled atom.

reaction as compared to two step procedure. Compound **4ac** has been synthesized by Velezheva and coauthors[22] in 83% yield using 50% mol/mol of catalyst, this affected RME value. The values of PMI reflect the absence of chromatographic purification in Velezheva procedure and this work. The waste was calculated considering recovery of the solvents and the better performances of CPME are highlighted by E factor and CO_2 emission (heating the solvent is the main source of energy consumption[47]). Calculations for newly synthesized compounds **4aa** and **4be** were included in Table 5 to chart the lower and upper limits of green metrics obtained with this work. To further expand the application of the system, two different quinones (**B** and **C** in Figure 3) were used instead of benzoquinone. The enamine (**3ab**) chosen for the experiments was obtained from ethyl acetoacetate (**1a**) and benzylamine (**2b**). The results, reported in Table 6, were compared with the global and local electrophilicity indexes calculated for the different parent quinones by using density functional theory (DFT) (Figure 3). The differences of electrophilicity alone (estimated with calculated electrophilicity indexes) do not correlate with the yields. The presence of methyl group negatively affects the reactivity as compared to unsubstituted benzoquinone and naphthoquinone.

The regioselectivity obtained from 2-methyl-1,4-benzoquinone (**B** in Figure 3) suggests the hypothesis of a reaction influenced by steric repulsion, since enamine **3ab** attacked mainly at C6, that should not be the most electrophilic one, but it was activated by coordination of Lewis acid on the carbonyl farthest from methyl group, giving mostly **4abB** with a methyl group in position 7 of indole ring. The course of the Nenitzescu reaction in the absence of Lewis acid catalysis for substituted quinones was reported to give mainly indoles with electron-donating substituents at position 6,[17] a result that fits with the local electrophilicity calculated by considering the Fukui Function for toluquinone (**B**), i.e. attack of enamine on C5. To the best of our knowledge, this is the first synthesis of indole **4abB** and one of the few Nenitzescu synthesis giving a 7-alkyl-5-hydroxyindole, with the exception of compounds obtained, in low yields, from enamines with small substituents at the nitrogen, such as hydrogen,[48] methyl[17] and a fused pyrrolidine.[49] Despite the low yield of **4abB** and **4abB′** (13%), the result obtained with $FeCl_3$ is interesting. 1-benzyl-5-hydroxy-2,7-dimethyl-indole (**8** in Scheme 5) was synthesized for medicinal chemistry studies starting from 5-methoxy-2-methyl-indole (**7**) in 7 steps with an overall yield of 7%.[50] Compound **4abB**, obtained in this work in two steps, could be



Scheme 5. Comparative synthesis of compound **8**.

decarboxylated[51–53] in just one more step obtaining compound **8** with a similar yield.

Conclusion

In conclusion, the system composed of $ZnCl_2$ (or ZnI_2) in CPME at room temperature permitted to obtain a variety of target 5-hydroxyindoles with reasonable yields, in pure form with a simple and fast procedure avoiding chlorinated solvents and chromatographic purification. In addition, considering the low toxicity of solvent and catalyst, the use of CPME and $ZnCl_2$ at room temperature represents a sustainable alternative to the literature procedures, especially when mild conditions are wanted. Furthermore, the use of magnesium and iron salts, cheap, nontoxic and abundant elements, demonstrated as a possible alternative to zinc in some cases.

Experimental Section

Materials: acetylacetone (Merck KGaA), acetic acid (Sigma Aldrich, 99.7%) benzylamine (Sigma Aldrich 99%), 4-chlorobenzylamine (Sigma Aldrich 97%), zinc chloride (Sigma Aldrich 97%), zinc iodide (Carlo Erba 98%), cyclopentyl methyl ether (Sigma Aldrich 99.9%), ethyl acetoacetate (Alfa Aesar 99%), ethanolamine (Sigma Aldrich 99%), ethanol (Carlo Erba 99.9%), pentylamine (Sigma Aldrich 99%), sodium sulfate anhydrous (Sigma Aldrich 99%), benzoquinone (Sigma Aldrich 99%), (−)-ethyl L-lactate (Aldrich 98%), γ-valerolactone (TCI >98.0%), butyl acetate (TCI >99.0%), 2-methyltetrahydrofuran (Stabilized with BHT, TCI >98.0%), dichloromethane (Sigma Aldrich >99%), magnesium turnings (purum, for Grignard reactions, Fluka >=99.5%,), trifluoromethanesulfonic acid (Alfa Aesar 98+%). Benzoquinone was purified by sublimation. Magnesium triflate was synthesized from trifluoromethanesulfonic acid and magnesium.

^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded in $CDCl_3$ with a Bruker Ascend 400 spectrometer in $CDCl_3$ or DMSO d_6 solutions, residual solvents peaks were used for calibration at 7.26 ppm and 2.50 ppm respectively. Mass Spectra were acquired with a Thermo Finnigan Q Exactive spectrometer with API-HESI source and a Fourier Transform orbital trap (Orbitrap). Samples were introduced as acetonitrile solutions at 0.1 mg/L concentration.

Synthesis of magnesium triflate. 1.00 g (41.7 mmol) of magnesium metal was dispersed under stirring at room temperature in 3.70 mL (41.8 mmol) of triflic acid in a two necked flask equipped with condenser and dropping funnel under Ar atmosphere. Water was slowly added from a dropping funnel (CAUTION: strong exothermal reaction and hydrogen evolution!) until all the solid dissolved. The mixture was concentrated until a white solid was formed, filtered and kept under high vacuum overnight. Yield 10.0 g, 75.2%, m.p.: >300 °C.

General procedure for synthesis of enamines. The enamines were synthesized following a literature procedure,[54] briefly: ethyl acetoacetate (**1a**) or acetylacetone (**1b**) (12 mmol) was mixed with selected amine (**2a**–**2e**) (12 mmol) and acetic acid (1.2 mmol) and put in an ultrasound bath (Falc Instruments LBS1, 50 kHz, 100 W) for 1 h, afterward ethanol (30 mL) was added, the solution dried with Na_2SO_4 and evaporated under vacuum to obtain the desired enamines (**3aa**–**3be**) mostly as yellow oils that solidified on standing.

General procedure for synthesis of indoles. Solution A: quinone (1 mmol, 1 eq) and catalyst (0,08 mmol, 0,08 eq) were put in a round bottom flask with 3 mL of solvent, and the suspension was stirred until complete solubilization of the two solids. Solution B: in a separate vessel, the enamine (1 mmol, 1 eq) was solubilized in 2 mL of solvent. Solution A was added to B and left under stirring at the chosen temperature for 40 minutes. At the end of this time, flask was left in the fridge overnight. Precipitated solid was filtered under vacuum and washed with few mL of diethyl ether (can be substituted with CPME) to obtain the product as light pink/white crystals. In case of discoloured product, the purity could be improved by crystallization from hot CPME.

Gram scale synthesis of mecarbinate. An aqueous solution of methylamine (40%, 25.6 mL, 300 mmol) was added dropwise to 12.6 mL of ethyl acetoacetate (100 mmol) to a round bottom flask in a water bath with stirring. The reaction was stirred at rt for 3 h, and then diluted with CH_2Cl_2 (50 mL) and H_2O (15 mL). The organic layer was collected, dried over anhydrous calcium chloride, and concentrated to afford (Z)-Ethyl 3-(methylamino)but-2-enoate as a pale-yellow oil in quantitative yield. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.25 (t, J=7.10 Hz, 3 H) 1.92 (s, 3 H) 2.91 (d, J=5.23 Hz, 3 H) 4.09 (q, J=7.08 Hz, 2 H) 4.47 (s, 1 H) 8.49 (br. s., 1 H). Solution A: (Z)-Ethyl 3-(methylamino)but-2-enoate, 1.53 g (10.7 mmol) was dissolved in 20 mL of CPME. Solution B: 1.15 g of benzoquinone (10.7 mmol) and 116 mg of $ZnCl_2$ (0.851 mmol) were dissolved in 30 mL of CPME. Solution B was added to A and left under stirring for 40 minutes at room temperature and in the refrigerator overnight. A white solid was collected by filtration under vacuum to give 1.62 g of mecarbinate (yield 65%). The spectra correspond to the ones for ethyl 1,2-dimethyl-5-hydroxyindole-3-carboxylate reported in literature[55] 1H NMR (400 MHz, DMSO-d6) δ 8.90 (br s, 1H), 7.36 (d, J=2.3 Hz, 1H), 7.27 (d, J=8.7 Hz, 1H), 6.66 (dd, J=8.7, 2.4 Hz, 1H), 4.25 (q, J=7.1 Hz, 2H), 3.64 (s, 3H), 2.66 (s, 3H), 1.35 (t, J=7.1 Hz, 3H). 13 C NMR (101 MHz, DMSO) δ 165.19, 152.67, 145.26, 130.69, 127.12, 111.29, 110.29, 105.50, 101.89, 58.65, 29.57, 14.55, 11.66.

Procedure for telescopic synthesis. In a round-bottomed flask were placed 1.10 mL (10.0 mmol) of benzylamine (**2b**), 1.26 mL (10.0 mmol) of ethyl acetoacetate (**1a**), 110 mg (0.800 mmol) of $ZnCl_2$ and 20 mL of cyclopentyl methyl ether and the mixture was brought to reflux, using the Dean-Stark equipment to remove water. After sixty minutes, the mixture was cooled and a solution of 1.08 g of benzoquinone in 30 mL of CPME was added and left at room temperature under stirring for 40 minutes. The flask was then placed in the fridge and the precipitate was isolated by filtration on a Buchner funnel (1.30 g, yield 42%). The procedure was repeated with pentylamine (**2a**) (1.16 mL, 10.0 mmol) instead of benzylamine to give **4aa** (0.58 g, yield 20%) or 4-chlorobenzylamine (10.0 mmol) and acetylacetone (1.22 mL, 10.0 mmol) to give **4be** (2.18 g, 70%).

Recycle experiment. Benzoquinone (1.08 g, 10.0 mmol, 1 eq) and $ZnCl_2$ (0.109 g, 0.8 mmol, 0.08 eq) were put in a round bottom flask followed by the addition of 30 mL of CPME. The suspension was stirred until complete dissolution of the two solids. Separately, ethyl 3-(benzylamino)but-2-enoate (**3 ab**) (2.19 g, 10.0 mmol, 1 eq) was solubilized in 20 mL of CPME. The solution of enamine was added to the round bottom flask with benzoquinone and catalyst solubilized, and the mixture left under stirring at room temperature for 40 minutes. At the end of this time, flask was left in the fridge overnight. Precipitated solid was filtered under vacuum and washed with 5 mL of CPME to obtain 1.51 g of product (55.3 % yield). Filtrate was extracted with 4×10 mL aqueous HCl 1 M. The organic phase was evaporated under reduced pressure to recover CPME. Distilled CPME was mixed back with aqueous phases and put under reflux with Dean-Stark apparatus to remove water. The resulting organic phase was split in a 30 mL aliquot to dissolve benzoquinone (1.08 g, 10 mmol, 1 eq) and a 20 mL aliquot to dissolve ethyl 3-(benzylamino)but-2-enoate (**3 ab**) (2.19 g, 10.0 mmol, 1 eq). The two solutions were mixed and left under stirring at room temperature for 40 minutes. At the end of this time, flask was left in the fridge overnight. Precipitated solid was filtered under vacuum and washed with 5 mL of CPME to obtain 1.13 g of product (36.5 % yield).

Green metrics calculation. The Green Metrics used for comparing our method to the works of Velezheva et al.[21,22] and Suryavanshi et al.,[23] were calculated with the following equations:

$$\text{Reaction Mass Efficiency (RME)} = (\text{mass of product}/\text{mass of all reactants})^{*}100$$

$$\text{E Factor} = \text{total waste mass}/\text{mass of product}$$

$$\text{Process Mass Intensity (PMI)} = \text{total mass used in the process}/\text{mass of product}$$

To calculate the E Factors we considered a solvent recovery of 90 % for CPME. For other solvents, recovery percentages have been evaluated from GSK's Solvent Selection Guide.[56]

The amount of materials is reported in the Table S1 and Table S2

Computational methods. To estimate electrophilicities, benzoquinone, toluquinone and naphthoquinone structures were optimized and natural bond orbitals (NBO) calculations were performed at the DFT/B3LYP level of theory with 6-31G(d) basis set using Gaussian 09 W package.[57] The global electrophilicity index, ω, as proposed by Parr et al.[58] is given by the equation $\omega = \mu^2/2\eta$ where μ is the electronic chemical potential and η the chemical hardness estimated from the calculated energies for HOMO (ε_H) and LUMO (ε_L) frontier orbitals by considering $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$.[59,60] The local parameters, approximated by a simplification of the Fukui function[61] where calculated using UCA-Fukui package.[62]

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Conflict of Interest

The authors declare no conflict of interest.

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