Regiochemistry of N-substitution of Some 4(5)-Substituted Imidazoles under Solvent-free Conditions

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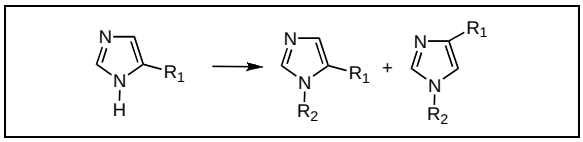

Imidazole-4(5)-carboxaldehyde and 4(5)-cyanoimidazole were N-benzylated and N-methylated using benzyl chloride and methyl iodide on zinc oxide (ZnO), alumina, and KF/alumina under basic conditions without solvent. Triethylamine (Et_3N) or potassium carbonate was added as base in the reactions on ZnO and alumina. Imidazole-4(5)-carboxaldehyde was also benzylated on silica and carbon nanotubes. The effect of bases and solids on the product distribution of 1,4- and 1,5-substituted compounds was investigated. In some cases, the product ratios were different for imidazole-4(5)-carboxaldehyde and 4(5)-cyanoimidazole. In the reactions on KF/alumina the 1,4-product was favored for both compounds. The combination of Et_3N and ZnO favored the 1,5-product, however for the nitrile effect was not so pronounced. When N-benzylation and methylation of the aldehyde were performed in the presence of catalytic amount of zinc chloride with Et_3N as base, the product distributions were the same as in the reactions on ZnO. Nitrile gave different product ratios on ZnO and in the presence of $ZnCl_2$. In addition, a mixture of N-benzylimidazole and 1,3-dibenzylimidazolium was produced when imidazole was benzylated on KF/alumina. Only the latter product was afforded when two equivalents of benzyl chloride were used.

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INTRODUCTION

Imidazole nitrogen can be substituted by applying an alkyl halide as electrophile under basic conditions. Alkylations have also been carried out in neutral conditions, but since the imidazolate anion is a far more effective nucleophile, most alkylations are done in basic conditions. For 2-substituted and symmetrically substituted compounds the reaction is straightforward, although quaternization may occasionally be a problem. Typically N-substitutions in basic conditions are made in one pot, using a strong base, such as sodium hydride, to deprotonate the imidazole before the introduction of the alkylating agent. However, Begtrup and Larsen achieved excellent yields by dividing the reaction into two steps, allowing the use of optimal conditions for both steps [1]. In the same study, so called alkylation potentials were defined for different alkylating agents and solvents. When alkylation potentials are considered together with the pKa values of the starting material and the product, the alkylation conditions can be optimized while still avoiding the production of the quaternized product [1].

When 4(5)-substituted imidazoles are N-alkylated the product is usually a mixture of 1,4- and 1,5-substituted compounds (Figure 1). Various factors influence the product distribution. When electrophile or the substituent at 4(5)-position is bulky, 1,4-isomer dominates, and in some cases it is afforded exclusively. The steric effect of the electrophile has been utilized in the preparation of 1,5-substituted compounds. First, nitrogen is substituted with a group, which can be easily removed and which is bulky enough to produce only 1,4-substituted compound; trityl group is commonly used for this purpose [2-5]. The product is then quaternized at N3 with the group desired as the N-substituent in the final product. The removal of the group attached to N1 produces 1,5-substituted imidazole. In addition to steric effects, mesomeric effect and electron withdrawing/donating character of the substituent may affect the product ratio. Electron withdrawing substituents tend to deactivate the nearest nitrogen by inductive effect, favoring the 1,4 product. The product ratio is also dependent on whether the reacting species is imidazolate anion or neutral imidazole. When the reacting species is neutral imidazole, tautomerism may affect the product distribution; however the product distribution does not always reflect the position of the tautomeric equilibrium. The minor tautomer may be more reactive than the major tautomer [6,7]. The reaction temperature may be relevant in some cases. Alkylations that produced a mixture of the two regioisomers at room temperature produced 1,4-substituted compounds exclusively at elevated temperatures, or the 1,5-products could be isomerized to the 1,4-products by heating in the presence of alkylating agent [8]. In sum, many factors affect the product distribution of regioisomers, making it

difficult to predict the product ratio except where the steric factors are clearly dominating.

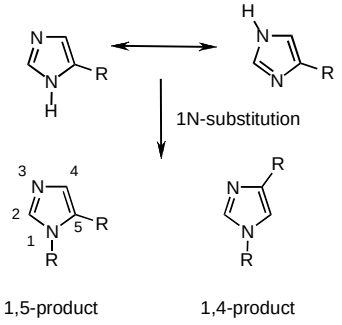


Figure 1. Imidazole tautomerism of 4(5)-substituted compounds and product regioisomers of N-substitution reactions.

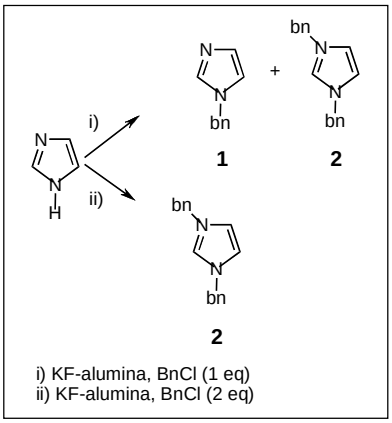
Organic reactions in solvent-free conditions have been studied actively in recent years [9,10]. More selective reactions, better yields, and even completely new reaction paths have been achieved, especially where solid supports such as alumina and silica are employed. Often these reactions are more environmentally friendly than their solution counterparts in reducing the amount of solvent waste. Alumina is frequently used as a catalyst in solvent-free or heterogeneous conditions, owing to its versatile surface characteristics. The surface of alumina provides sites of different chemical character, acidic and basic, situated side by side[11]. KF/alumina is strongly basic, modified alumina, prepared by absorbing KF on the alumina surface [11,12]. Zinc oxide (ZnO) is more rarely used in organic syntheses, although, in recent years it has been used as a catalyst in reactions like Friedel-Crafts acylations and O-acylations[13,14].

Our interest in N-substitutions under solvent-free conditions originates from our previous studies on 1,5-substituted imidazoles [15,16]. Some studies of alkylations exist, such as Michael additions on basic clays in microwave [17], benzylation of imidazole using CsF-Celite in heterogeneous conditions [18] and ultrasound promoted substitution using alkali-metal doped carbons [19]. However, to our knowledge no studies on the regiochemistry of alkylations of 4(5)-substituted compounds have been published, the subject in which we were most interested. In present work we investigated the regiochemistry of the benzylation and methylation of imidazole-4(5)-carboxaldehyde and 4(5)-cyanoimidazole on different solids in the presence of base. The compounds for the study were chosen not only because we had used them as intermediates in our previous work [15,16], but also because they are representative of 4(5)-substituted compounds bearing electron withdrawing substituent, not bulky enough to cause significant steric effects. Additionally, in solution in basic conditions, benzylation and methylation of imidazole-4(5)-carboxaldehyde with benzyl chloride and methyl iodide produce 1:1 mixtures of 1,5- and 1,4-substituted compounds [20-22].

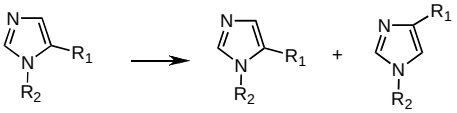
RESULTS AND DISCUSSION

We began our study by examining solvent free-benzylation of imidazole on KF/alumina (Scheme I). Various conditions were tested, but the product was always a mixture of 1-benzylimidazole **1** and the quarternized product 1,3-dibenzylimidazolium chloride **2**. Compound **2** was afforded as sole product when two equivalents of benzyl chloride were used. In solution, 1-benzylimidazole is typically prepared in DMF solution using sodium hydride as a base [23].

Scheme I



Scheme II



	R1	R2
3	CHO	H
4	CN	H
5a-b	CHO	Bn
6a-b	CN	Bn
7a-b	CHO	Me
8a-b	CN	Me

Benzylation of imidazole-4(5)-carboxaldehyde **3** (Scheme 2) was performed using benzyl chloride in basic conditions, on alumina, ZnO, KF/alumina, silica and carbon nanotubes (Table 1). Triethylamine or K_2CO_3 was used as a base, except in reactions on KF/alumina where base was not needed since KF/alumina itself is basic. Other tertiary amines besides Et_3N were tested as a base on ZnO. And as a comparison, a reaction with Et_3N was performed without solid and a reaction on ZnO without a

Table 1

The product ratios of 1,5-products **5a**, **6a** and 1,4-products **5b**, **6b** upon benzylation of **3** and **4**.

Entry	Compd.	Solid support/ base	Product ratio (%)	
			a	***b***
1	**3**	KF-alumina	30	70
2	**3**	KF-alumina[a]	26	74
3	**3**	ZnO/K_2CO_3	45	55
4	**3**	alumina/K_2CO_3	37	63
5	**3**	ZnO/Et_3N	69	31
6	**3**	ZnO/Et_3N[a]	68	32
7	**3**	alumina[b]/Et_3N	52	48
8	**3**	alumina/Et_3N	53	47
9	**3**	alumina[e]/Et_3N[c]	54	46
10	**3**	silica/Et_3N[c]	53	47
11	**3**	carbon nanotubes/Et_3N[c,d]	49	51
12	**3**	no solid support/Et_3N[c,d]	45	55
13	**3**	ZnO/ no base[c]	-	-
14	**3**	ZnO/Pr_3N[c]	77	23
15	**3**	ZnO/pyridine[c]	68	32
16	**3**	ZnO/N,N-dimethylpropyl amine[c]	67	33
17	**4**	KF-alumina/BnCl	24	76
18	**4**	ZnO/Et_3N/BnCl	50	50
19	**4**	alumina/Et_3N/BnCl	29	71

Amounts of the reagents: imidazole compound 0.25 g, base K_2CO_3 1.5 eq.; Et_3N 2 eq., solid support: KF-alumina 0.8 g, others 0.5 g a) Heated at 50 °C. b) Dried at 300 °C in vacuum for 20 h. c) Small-scale preparations (1/4 amounts of reagents). d) Product distributions from partly reacted mixtures. e) Acidic alumina.

base. A test of benzyl bromide in place of benzyl chloride, showed it to be much more effective, but the product was contaminated with a side product, even at short reaction times. The side product was assumed to be a quaternized 1,3-dibenzylimidazolium bromide and the assumption was verified by ms. Since our main interest was to study the effect of different factors on the product ratio, part of the syntheses were made in small scale, and yields are not reported for these syntheses. Reactions were monitored by nmr taking small samples of the reaction mixture and mixing the sample with deuterated DMSO. The product distributions were calculated from the integrals of ^{1}H nmr spectra. In all cases the product was a mixture of 1-benzylimidazole-5-carboxaldehyde **5a** and 1-benzylimidazole-4-carboxaldehyde **5b**.

When triethylamine was used as a base, a competing reaction occurred and benzyltriethylammonium chloride was afforded as a side product. For this reason, 1.5 equivalents of benzyl chloride was used in the reactions with triethylamine. The side product was identified by allowing triethylamine and benzyl chloride to react on zinc oxide. After a few days, crystals formed in the reaction flask, and the structure could be verified by X-ray crystallography [24]. Another practical difficulty was encountered with the reactions on ZnO with Et_3N as base: the reaction mixture turned to a sticky material, which made the isolation of the products more difficult.

Taking into account both reaction times and overall yields, the most efficient solid is KF-alumina. At room temperature the reaction required 27 h, and heating at 50 °C shortened the reaction time to 5 h. Even though the reaction times on alumina, ZnO, and silica were long, it is clear that these solids catalyze the reaction too, since the reaction was really slow when solid support was not used. In an nmr spectrum measured from the sample taken from the reaction mixture after standing two weeks at room temperature, the product peaks were only half those of the starting material **3**. The effect of the drying of alumina was tested in the reaction with Et_3N, and drying had no effect on the product distribution, nor on the reaction time and yield. Acidic alumina was tested, and the reaction proceeded similarly to that on neutral alumina. Yields were quite modest in all reactions.

Close examination of the product ratios of aldehyde **3** (Table 1) revealed a number of trends. The 1,4-product **5b** (70%) was favored on KF/alumina and the 1,5-product **5a** (69%) on ZnO with Et_3N as base. Changing the triethylamine to another tertiary base (Table 1, entries 14-16) did not significantly influence the product ratio. When bulky tripropylamine was used, the reaction was extremely slow, and was not completed before 17 days at room temperature. In an comparison of Et_3N and K_2CO_3, reactions where Et_3N was used as base produced the 1,5-product **5a** in proportion 69% on ZnO and 52% on alumina, while reactions with K_2CO_3 produced **5a** in proportion 45% on ZnO and 37% on alumina. Thus Et_3N favored the 1,5-product **5a** more than K_2CO_3 did. If the intrinsic effects of aldehyde **3** on product distribution are

considered, steric effects and electron withdrawing character of the formyl group should favor the 1,4-product. When tautomeric effects are concerned, 4-tautomer is usually favored by electron withdrawing substituents, so if the major tautomer is reacting in neutral form, the 1,5-product is produced. Thus the only evident intrinsic effect of imidazole compound favoring the 1,5-product is that the reacting species is neutral. There is also a difference between the product ratios of reactions on KF/alumina and reactions with K_2CO_3. The basicity of KF/alumina derives from the KOH produced in its preparation or from active fluoride and Al-O^- anions on the surface [11,12]. The reactions were also more efficient on KF/alumina. It is not possible to say whether these effects are just a result of high basicity of the KF/alumina or of a more specific interaction between the surface components and the starting materials.

With both Et_3N and K_2CO_3 the 1,5-product **5a** was more favored on ZnO than on alumina. More reactions on other solids and without solid were carried out with use of Et_3N as base. The proportion of the 1,5-product **5a** was the 69% on ZnO, 52 % on alumina, 53 % on silica, 49 % on carbon nanotubes, and 45% without any solid. Surface characteristics of the used solids were different. Lewis acidic sites Al^{3+}, basic O^{2-} sites, and OH-groups may be present on the surface of alumina with the concentration dependent on the activation temperature [11]. There are mainly hydroxyl groups on the surface of silica while ZnO resembles alumina. Carbon nanotubes can be considered to be quite inert surface and this solid had only a weak effect on the product ratio as compared with the reaction made without any solid. Since the product distribution was the same on alumina and silica and clearly different on ZnO, eventhough the surface properties of ZnO resemble those of alumina, the reason for the different product ratios has to originate from some more specific effect than the general surface properties.

KF-alumina favored 1,4-substituted compound in reaction of both aldehyde **3** and nitrile **4**, but otherwise **3** and **4** behaved differently. Benzylations of nitrile **4** were made on KF/alumina and, with Et_3N as base, on ZnO and alumina. KF/alumina favored the 1,4-product **6b** (76%) as did the combination of alumina and Et_3N (**6b** 71%). The ZnO support had a distinct effect on the product ratio, producing a 1:1 mixture of **6a** and **6b**.

Friedel-Crafts acylations have been reported to proceed in excellent yields in the presence of catalytic amount of ZnO [13]. It was suggested that, in these reactions, traditionally catalyzed by Lewis acids, the true catalyst would be $ZnCl_2$ generated in situ through reaction of ZnO with acid chloride and hydrogen chloride. This suggestion was based on the failure of acid anhydrides to react in Friedel-Crafts acylations on ZnO. To test the hypothesis, we carried out benzylation in the presence of zinc chloride. When aldehyde **3** was benzylated in the presence of catalytic amount of $ZnCl_2$ with Et_3N as a base (Table 2), products were afforded in the same distribution as in reactions on ZnO (Table 1, entry 5). Again when K_2CO_3 was used as base the ratio of **5a** to **5b** was the same as on ZnO: 45% and 55%. If one equivalent of $ZnCl_2$ was used, only small amounts of products were seen in the nmr spectrum after a week. Whether the reaction was performed on alumina or without solid support did not have any effect on the product distribution, but reaction times were longer on solid supports. When the Lewis acid was changed from $ZnCl_2$ to aluminum chloride, the product ratio changed and a mixture of 55% of **5a** and 45% of **5b** were produced. Nitrile **4** behaved differently: the product ratio was different on ZnO and in the presence of $ZnCl_2$. Instead of the 1:1 mixture on ZnO, the 1,4-product **6b** (70%) was favored in the presence of $ZnCl_2$.

Table 2. The product ratios of 1,5-products **5a**, **6a** and 1,4-products **5b**, **6b** upon benzylation of **3** and **4** in the presence of Lewis acid.

	Lewis acid/solid support/ base	Product ratio (%)	
		a	**b**
3	$ZnCl_2$/alumina/K_2CO_3	45	55
3	$ZnCl_2$ 1 eq /alumina/Et_3N	-	-
3	$ZnCl_2$ 0.2 eq/alumina/Et_3N	69	31
3	$ZnCl_2$ 0.2 eq /no solid support/Et_3N	68	32
3	$AlCl_3$ 0.2 eq/alumina/Et_3N	55	45
4	$ZnCl_2$/no solid support/Et_3N	30	70

The finding of the same product distribution was afforded in the case of aldehyde **3** on ZnO and in the presence of $ZnCl_2$ might be interpreted to suggest that $ZnCl_2$ is formed during the reaction, but the different product ratio for nitrile **4** does not support this conclusion. It needs to be pointed out that ZnO, too, may function as a Lewis acid, that in the case of Friedel-Crafts acylations the unreactivity of acid anhydrides may simply be due to the inability of ZnO to activate them. However, some evidence does exist in the literature that chloride ions have an activating effect on ZnO. In a study of catalytic activities of Pt/ZnO catalyst for the hydrogenation of crotonaldehyde, the catalyst was prepared from two different platinum precursors, H_2PtCl_6 and $Pt(NH_3)_4(NO_3)_2$. The catalyst prepared from H_2PtCl_6 was more efficient and selective and showed stronger Lewis acidity compared to the catalyst prepared from $Pt(NH_3)_4(NO_3)_2$ [25,26]. In our study, irrespective of whether $ZnCl_2$ is produced, the results of the substitution of **3** suggest, that the reason for the different product distribution on ZnO as compared with that on alumina or to other solids could be that aldehyde **3** is interacting with Zn in a specific manner.

Many kinds of interaction are possible on the surface of alumina and ZnO, like hydrogen bonding of imidazoles through N3 with surface hydroxyl groups, and through N1

hydrogen with surface acidic O^-; additionally carbonate anion and Et_3N may interact with the solids. However, these interactions may be expected to be similar on alumina and ZnO. In addition, the same product distributions were afforded on metal oxides and metal chlorides, and since the latter compounds lack the OH and O^- groups, the differences in product distribution most likely originate from metal-imidazole interaction, which is less specific for aluminum than for zinc. Differences in the product ratios of regioisomers in the presence of different Lewis acids have also been reported for pyrazole. The difference was most pronounced between $ZnCl_2$ and $AlCl_3$; regioisomers were produced in ratios 10:1 and 1:99, respectively [28].

In the case of nitrile **4**, 1,4-product **6b** was favored not only on KF/alumina but also on alumina with Et_3N. On ZnO the product ratio was 1:1. Since the product distribution on ZnO and in the presence of $ZnCl_2$ was different, another factor must be operating besides the interaction with Zn^{2+}. Nitrile **4** is not likely to interact with Zn in the same manner as aldehyde **3**, but it could be expected, that if coordination were the dominating factor, it would also operate in the presence of $ZnCl_2$.

In addition to benzylations, some methylations of aldehyde **3** and nitrile **4** were performed to see whether the same effects would apply. Syntheses were made with methyl iodide on KF alumina and on ZnO using triethylamine as a base and using catalytic amount of $ZnCl_2$ (Table 3). Product ratios were the same as in benzylations, but methylations on ZnO with Et_3N were inefficient, reaction times were quite long and significant amounts of side products were afforded, probably also in this case via reaction of the electrophile with amine.

Table 3. The product ratios of 1,5-products **7a**, **8a** and 1,4-products **7b**, **8b** upon methylation of **3** and **4**.

Compd	Solid support/ base	Products (%)	
		a	**b**
3	KF-alumina	26	74
3	ZnO/Et_3N	66	34
3	$ZnCl_2$/Et_3N	64	36
4	KF-alumina	30	70
4	ZnO/Et_3N	50	50
4	$ZnCl_2$/Et_3N	38	62

In all conditions studied the product of reactions with imidazole-4(5)-carboxaldehyde and with 4(5)-cyanoimidazole was a mixture of regioisomers, but the choice solid and base influenced on the product distribution. KF/alumina favored the 1,4-product in all cases. A clear preference for the 1,5-substituted compound was achieved when aldehyde was benzylated or methylated on zinc oxide with use of triethylamine as base. Reaction in the presence of $ZnCl_2$ on alumina or without any solid support, gave the same product distribution, suggesting that it was controlled by the interaction of aldehyde with Zn^{2+}. When $AlCl_3$ was used instead of $ZnCl_2$, the regioisomers were afforded in ratio 1:1. Nitrile behaved somewhat differently; the 1,4-product was favored (70%) on KF/alumina, on alumina with Et_3N, and in the presence of $ZnCl_2$, but a 1:1 mixture was produced in the reaction on ZnO.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were obtained from commercial suppliers and were used without further purification. Details of the solid supports are as follows: Aluminum oxide, neutral activity I, 0.063-0.200 mm; Silica gel 60, 70-230 ASTM; Multiwall carbon nanotubes OD=3-10 mm, ID=1-3 nm, length 0.1-10μm >90%. 4(5)-Cyanoimidazole **4** was prepared according to a literature procedure [28]. ^1H and ^{13}C nmr spectra were recorded on a Bruker Avance 250 and 400 nmr spectrometer. Reactions were monitored by taking samples of the reaction mixture and mixing the samples with DMSO. Product ratios were calculated from integrals of the ^1H nmr spectra. Overall yields are raported for isomer mixtures which did not contain any nmr active impurities or starting materials. Small-scale preparations were made according to the general procedures but using reagents in only ¼ amounts.

General procedure for substitution reactions on solid supports.

Imidazole compound (0.25 g) and solid support (see Table 4) were ground in a mortar to achieve a homogeneous mixture. The mixture was transferred to a flask and halide and base were added (excluding the reactions of KF-alumina, where no added base was needed). The mixture was left standing at room temperature (unless otherwise indicated). After a sufficient reaction time, acetone was added and the mixture was stirred for a few minutes. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in ethyl acetate and washed with two portions of water. The organic phase was dried on $MgSO_4$, filtered and evaporated.

Table 4.

Method	Solid support	Base[a]
A	KF-alumina 0.8 g	-
B	Alumina 0.5 g	K_2CO_3 1.5 eq
C	Alumina 0.5 g	Et_3N 2 eq
D	ZnO 0.5 g	K_2CO_3 1.5 eq
E	ZnO 0.5 g	Et_3N 2 eq

a) Amount of base is reported in relation to imidazole compound.

General procedure for substitution reactions in the presence of Lewis acid, Method LA.

Imidazole compound (0.25 g), solid support (if used), and Lewis acid (1 eq or 0.2 eq) were mixed. Halide (1.2 eq) and triethylamine (1.5 eq) were added. The mixture was left standing at room temperature. After a sufficient time 2 mL of water and 50 mL EtOAc were added to the reaction mixture. The suspension was stirred for a few minutes, and filtered if solid support was present. Phases were separated and the organic phase was washed with 5 mL water, dried on $MgSO_4$, filtered and evaporated.

1,3-Dibenzylimidazolium chloride 2.

Method A: Benzyl chloride 2 eq, reaction time 24h at RT, chloroform was used instead of acetone to wash the product from KF-alumina, yield 50%. ^{1}H nmr ($CDCl_3$) □δ=5.55 (s,4H); 7.24-7.34 (m, 12 H); 10.66 (s, 1H) in agreement with literature [29].

1-Benzyl imidazole-5-carbaldehyde 5a and 1-benzyl-imidazole-4-carbaldehyde 5b.

Method A: Benzyl chloride 1 eq, reaction time 27 h at RT, yield 68%, products **5a** 30%, **5b** 70%; benzylchloride 1 eq, reaction time 5 h at 50 ºC, yield 50%, products **5a** 26%, **5b** 74% **Method B**: Benzyl chloride 1 eq, reaction time 94 h at RT, yield 50% products **5a** 37%, **5b** 63%. **Method C** but with alumina dried at 300 ºC in vacuum for 20 h. Benzyl chloride 1.5 eq, reaction time 94 h at RT, yield 60%, products **5a** 52%, **5b** 48%. **Method C**: Benzyl chloride 1.5 eq, reaction time 94 h at RT, yield 54%, products **5a** 53%, **5b** 47%. **Method D**: Benzyl chloride 1 eq, reaction time 96 h at RT, yield 44%, products **5a** 45%, **5b** 55%. **Method E**: Benzyl chloride 1.5 eq, reaction time 48 h at RT, yield 50%. Products **5a** 69%, **5b** 31%. Benzyl chloride 1.5 eq, reaction time 22h at 50ºC, yield 38%. Products **5a** 68%, **5b** 32%.

Small scale preparations: Benzyl chloride 1.5 eq, silica 0.5 g, Et_3N 2 eq, reaction time 96h at RT. Products **5a** 53%, **5b** 47%. No solid support, benzyl chloride1.5 eq, Et_3N 2 eq Products **5a** 45%, **5b** 55%. Product ratio is from partly reacting mixture, according to nmr spectra measured after two weeks in RT. Benzyl chloride 1.5 eq, carbon nanotubes 0.1 g, Et_3N 2 eq, products **5a** 49%, **5b** 51%. Product ratio is from partly reacting mixture, according to nmr spectra measured after 10 days in RT. Benzyl chloride 1eq, Pr_3N 2 eq, ZnO 0.5g, reaction time 17 days at RT . Products **5a** 77%, **5b** 23%. Benzyl chloride 1.5 eq, ZnO 0.5g, pyridine 2 eq, reaction time 48h at RT. Products **5a** 68%, **5b** 32%. Benzyl chloride 1.5 eq, acidic alumina 0.5g, Et_3N 2 eq, reaction time 96h at RT. Products **5a** 54%, **5b** 46%. Benzyl chloride1.5 eq, N,N-dimethylpropyl amine 2 eq, ZnO 0.5 g, reaction time 48h at RT. Products **5a** 67%, **5b** 33%.

Method LA: 1 eq $ZnCl_2$, alumina, after a 7 days no products were seen in nmr spectra. 0.2 eq $ZnCl_2$, alumina, reaction time 96 h at RT, yield 44%, products **5a** 69%, **5b** 31%; 0.2 eq $ZnCl_2$, no solid support, reaction time 48 h at RT, yield 48%, products **5a** 68%, **5b** 32%; 0.2 eq $ZnCl_2$, K_2CO_3 was used instead of Et_3N, alumina, reaction time 96 h at RT, the reaction was made in small scale, using ¼ amounts of the starting materials, products **5a** 45 %, **5b** 55%; 0.2 eq $AlCl_3$, reaction time 96 h at RT, the reaction was made in small scale, using ¼ amounts of the starting materials, products **5a** 55%, **5b** 45%.

^{1}H nmr (DMSO-d_6): δ= **5a**: 5.52 (s, 2H); 7.20-7.41 (m); 7.94 (s, 1H); 8.27 (s, 1H); 9.71 (s, 1H), in agreement with literature [30]. **5b** ^{1}H nmr (DMSO-d_6): δ= 5.29 (s, 2H); 7.20-7.41 (m); 8.02 (s, 1H); 8.14 (s, 1H); 9.69 (s, 1H).

1-Benzyl-5-cyano-imidazole 6a and 1-benzyl-4-cyano-imidazole 6b

Method A: Benzyl chloride 1 eq, reaction time 48 h at RT, yield 49%, products **6a** 24%, **6b** 76 % **Method C**: Benzyl chloride 1.5 eq, reaction time 72 h at RT, yield 60%, products **6a** 29%, **6b** 71%. **Method E**: Benzyl chloride 1.5 eq, reaction time 72 h at RT, yield 41 %, products **6a** 50%, **6b** 50 %.**Method LA**: Benzyl chloride 1.5 eq, reaction time 24h at RT, yield 43%, products **6a** 30%, **6b** 70%. ^{1}H nmr (DMSO-d_6): δ=**6a** 5.39 (s, 2H); 7.25-7.46 (m); 7.88 (s, 1H); 8.28 (s, 1H) in agreement with literature [16], **6b** 5.29 (s, 2H); 7.25-7.46 (m); 8.07 (s, 1H); 8.23 (s, 1H).

1-Methyl imidazole-5-carbaldehyde 7a and 1-methyl imidazole-4-carbaldehyde 7b.

Method A: Methyl iodide 1 eq, reaction time 24 h at RT, yield 50%, products **7a** 26%, **7b** 74%. **Method E**: Methyl iodide 1.5 eq, reaction time 96 h at RT, yield 35%, products **7a** 66%, **7b** 34%.**Method LA**: Methyl iodide 1.5eq, reaction time 96 h at RT, yield 39%, products **7a** 64%, **7b** 36%. ^{1}H nmr ($CDCl_3$): **7a** δ=3.95 (s, 3H); 7.62 (s, 1H); 7.79 (s, 1H) in agreement with literature [22], **7b** δ= 3.78 (s, 3H); 7.54 (s, 1H); 7.53 (s, 1H) in agreement with literature [22].

1-Methyl-5-cyano-imidazole 8a and 1-methyl-4-cyano-imidazole 8b.

Method A: Methyl iodide 1 eq, reaction time 24 h at RT, yield 48%, products **8a** 30%, **8b** 70%. **Method E**: Methyl iodide 1.5 eq, reaction time 96 h at RT, yield 34%, products **8a** 50%, **8b** 50%. **Method LA**: Methyl iodide 1.5 eq, reaction time 96 h at RT, yield 60%, products **8a** 39%, **8b** 61%. ^{1}H nmr ($CDCl_3$): **8a** δ=3.83 (s, 3H); 7.62 (s, 1H); 7.66 (s, 1H) in agreement with literature [31], **8b** δ=3.78 (s, 3H); 7.48 (s, 1H); 7.50 (s, 1H) in agreement with literature [31].

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