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Benzoin condensation of aromatic aldehydes catalyzed by *N*-heterocyclic carbenes under mild conditions

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ABSTRACT

The benzoin condensation was used to evaluate the catalytic activity of different *N*-heterocyclic carbenes as a function of their structure and *N*-substituents. There is a correlation between the length of an *N*-alkyl substituent and its performance as an organocatalyst. Heteroaromatic aldehydes were found to be the most reactive, among the screened substrates, finishing the reaction in 30 minutes, with almost quantitative yields. On the other hand, *p*-nitrobenzaldehyde, a strongly electrophilic aldehyde, was the least reactive. Electronic effects have little influence on the reaction yield but steric effects can dramatically reduce it. The preformed organocatalyst reacts faster than the generated in situ, with minimum solvent.

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1. Introduction

N-Heterocyclic carbenes (NHCs) are widely used as organocatalysts to promote known or new reactions, due to their umpolung mode of action [1-3]. They are now useful tools in the synthetic chemist arsenal [4-7], they have been used for the synthesis of molecules of interest in medicinal chemistry [8], domino reactions [9-11], polymerization reactions [12-15]. Recent research emphasizes the use of NHCs as organocatalysts in highly enantioselective reactions with great success [6,9,16-18]. However, non-asymmetric reactions are attracting interest on their own, because they can accomplish organic transformations with advantages over other catalysts [1-3,12-15,19].

The benzoin condensation forms α-hydroxyketones from aldehydes and can be catalyzed by NHCs in an umpolung fashion. Ugai *et al.* used thiamine as a catalyst for it and this was the first report of an NHC catalyzing the reaction, but he did not know the nature of the catalyst at the molecular level [20]. However, it was until Breslow demonstrated the mode of reaction and proposed a mechanism for the benzoin condensation that the mechanism was understood [21]. Since then, it has attracted considerable interest because their numerous applications: it is used as a model reaction to study the properties of new NHCs [1,7,22,23], preparation of intermediates for the synthesis of anti-neoplastic agents [24], and in the synthesis of natural products [25]. Benzoin products can also be transformed into 1,2-diketones [26-28], key intermediates for the synthesis of compounds with biological activity [29-33].

Thiazolium salts were the first NHCs precursors used in the benzoin condensation but later, other heteroazolium derivatives, including imidazoliums, imidazoliniums, benzimidazoliums, and triazoliums were developed and used [19,34,35]. Benzimidazolium NHC precursors have been used as organocatalysts for the benzoin condensation under different conditions, using water or organic solvents [36].

We are interested in the chemistry of NHCs [37,38] and sought to develop a protocol to catalyze the benzoin condensation with NHCs, using the minimum amount of solvent and a catalytic amount of 5 mol%. Our previous experience with the transesterification of glycerol and dimethyl carbonate, catalyzed by NHCs under mild conditions in short time, encouraged us to evaluate some of our previously used catalysts, and others, to explore their catalytic efficiency on the benzoin condensation. In our previous work [37], we used imidazolium salts, with an *N*-xylyl and an *N*-alkyl substituent, as NHC precursors and found out a correlation between the

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length of the alkyl chain and the catalytic activity. Our best organocatalyst bears an alkyl chain with sixteen carbons. This sparked our interest in investigating the scope of our best catalyst, for other organocatalyzed reactions, previously developed for the transesterification reaction [37], using the minimum amount of solvent. One of our goals was to compare the performance of the preformed catalyst against the generated in situ.

2. Experimental

All chemicals were purchased from Aldrich or Fisher and used as received, at least otherwise indicated; deuterated solvents were purchased from Cambridge Isotope Laboratories. The imidazolium salts precursor, 1-(2,6-dimethyl phenyl)-1*H*-imidazole, was synthesized by a reported literature procedure [39]. THF was distilled from sodium/ benzophenone under nitrogen previous to use. All aldehydes were distilled in a Kugelrohr and used immediately. A brief screening of bases showed that the best combination, catalyst precursor/base, was the imidazolium salt and potassium *tert*-butoxide, Table 1, entry 1.

All glassware was oven or flame dried. Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR was recorded on a Bruker Ultra-Shield-300 (300 MHz) or 400 MHz. Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ as an internal standard (δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) and integration.

2.1. Imidazolium salts

1-(2,6-Dimethylphenyl)-3-hexadecyl-1H-imidazol-3-ium bromide, (Table 2, entry 1) [37]: A glass vial provided with a stirring bar was charged with 1-(2,6-dimethylphenyl)-1*H*-imidazole (2.00 g, 1 equivalent) and hexadecyl bromide (3.55 g, 1 equivalent). The vial was capped and heated at 100-110 °C overnight. The imidazolium salt was obtained in quantitative yield and used without further purification [37]. Color: Pale yellow. Yield: 100.0 %. M.p.: 130.9-131.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 10.34 (s, 1H, Imidazolium proton), 7.90 (s, 1H, H-imidazolium), 7.30-7.11 (m, 4H, Ar-H), 4.64 (t, 2H, CH_2, J = 7.2 Hz), 2.05 (s, 6H, CH_3), 1.95-1.83 (m, 2H, CH_2), 1.28-1.17 (m, 26H, CH_2), 0.810 (t, 3H, CH_3, J = 6 Hz).

1-(2,6-Dimethylphenyl)-3-methyl-1H-imidazol-3-ium iodide, (Table 2, entry 2) [37]: To a 10 mL vial 1-(2,6-dimethyl phenyl)-1*H*-imidazole (1.50 g, 1 equivalent) and methyl iodide (1.63 mL, 3 equivalents) were added and the mixture allowed to react for four hours at room temperature. The volatiles were removed under vacuum leaving a yellow solid [37]. Color: Yellow. Yield: 100.0 %. M.p.: 194.5-196.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.86 (s, 1H, H-imidazolium), 9.86 (s, 1H, H-imidazole), 7.33-7.14 (m, 4H, Ar-H), 4.31 (s, 3H, CH_3), 2.09 (s, 6H, CH_3).

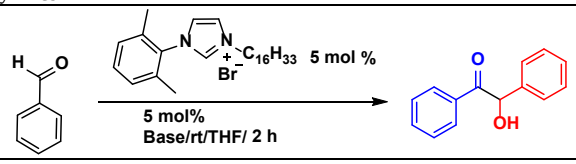
1,3-bis(2,6-Dimethylphenyl)-1H-imidazol-3-ium chloride, (Table 2, entry 3) [40]: In a 250 mL round-bottomed flask provided with a stirring bar ethyl acetate (140 mL) was added and warmed up to 70 °C using an oil bath. (*N*,*N*'*E*,*N*,*N*'*E*)-*N*,*N*'-(ethane-1,2-diylidene)*bis*(2,6-dimethylaniline) (5.02 g, 19 mmol) and paraformaldehyde (0.576 g, 19.19 mmol) were added and the walls washed with EtOAc (10 mL). A solution of chlorotrimethylsilane (2.428 mL, 19.00 mmol) in EtOAc (25 mL) was added dropwise over 45 min with vigorous stirring, and the resulting yellow suspension stirred for 2 h at 70 °C. After cooling to 10 °C (ice bath) with vigorous stirring, the suspension was filtered and the solid washed with EtOAc and *t*-BuOMe. The solid was dried to constant weight in an oven [40]. Color: Dark yellow. Yield: 85.0 %. M.p.: >300 °C (Dec.). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.11 (s, 1H, H-imidazolium), 7.65-7.65 (m, 2H, Ar-H), 7.36-7.32 (m, 2H, Ar-H), 7.22- 7.20 (m, 4H, Ar-H), 2.22 (s, 12H, CH_3).

1,3-Dimethyl-1H-benzo[d]imidazol-3-ium iodide, (Table 2, entry 4) [41]: The synthesis was carried out with a slight modification from a reported procedure [41]. A flame dried 10 mL vial provided with a stirring bar was charged with 1-methylbenzimidazole (15.13 mmol, 2 g) and 2.83 mL of iodomethane (45.4 mmol, 3 equivalent) and then capped and stirred for 12 h. Afterwards, the excess of iodomethane was removed by evaporation in vacuo and the product used without any further purification. This compound had spectral properties identical with those reported in the literature. Color: Yellow. Yield: 100.0 %. M.p.: 197.9-199.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.05 (s, 1H, H-imidazolium), 7.74-7.68 (m, 4H, Ar-H), 4.28 (s, 6H, CH_3).

3-Hexadecyl-1-methyl-1H-benzo[d]imidazol-3-ium iodide, (Table 2, entry 5) [42]: The synthesis was carried out with a slight modification from a reported procedure [42]. A 100 mL flame dried round-bottom flask with a stirring bar provided with a stirring bar was charged sodium hydride (0.528 g, 22 mmol), THF (15 mL) and a solution of H-benzo[d]imidazole (2 g, 16.93 mmol) in THF (15 mL) was added dropwise. The suspension was stirred for 1 hour and then a solution of 1-bromohexadecane (5.17 g, 16.93 mmol) was added dropwise. The reaction mixture continued to stir for 24 h at 60 °C. The mixture was cooled down at room temperature and then quenched with methanol. Water was added, then the aqueous extracted with EtOAc 3×30 mL, dried over $MgSO_4$, concentrated and then filtered through a pad of celite and silica gel and eluted under vacuum with EtOAc:hexanes (8:2, *v*:*v*), concentrated in the rotavap and dried under high vacuum. 1-*n*-hexadecylbenzoimidazole was obtained as a pale-yellow solid. Afterwards, a 10 mL vial, provided with a stirring bar was charged with dry powdered 1-hexadecyl-1*H*-benzo[d] imidazole (2 g, 5.84 mmol) and then iodomethane (1.09 mL, 17.51 mmol) was added. The vial was capped, and the mixture allowed to stay overnight at room temperature. The excess of iodomethane was evaporated under the vacuum, leaving the pure imidazolium salt as a yellow solid. The product used without any further purification. This compound had spectral properties identical with those reported in the literature [42]. Color: White. Yield: 93.5 %. M.p.: 109.6-111.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.03 (s, 1H, H-imidazolium), 7.76-7.66 (m, 4H, Ar-H), 4.56 (t, m2H, CH_2, J = 7.6 Hz), 4.30 (s, 3H, NCH_3), 2.11-2.03 (m, 2H, CH_2), 1.46-1.31 (m, 4H, CH_2), 1.29-1.22 (m, 22H, CH_2), 0.80 (t, 3H, CH_3, J = 6.7 Hz).

2-(Perfluorophenyl)-6, 7-dihydro-5H-pyrrolo[2, 1-c][1, 2, 4] triazol-2-ium tetrafluoroborate, (Table 2, entry 6) [43]: In a glove box, a flame-dried round bottom flask provided with a stir bar was charged with pirrolidinone (3 g, 35.25 mmol), DCM (150 mL), then trimethyloxonium tetrafluoroborate (5.21 g, 35.25 mmol) was added, the mixture was stirred at rt for 1.5 h. Then, pentafluorophenylhydrazine (6.98 g, 35.25 mmol) was added. The mixture was stirred 4 h. The magnetic stir bar is removed followed by removal of the solvent in vacuo. The flask is then placed in an oil bath heated to 100 °C for 1 h under vacuum (2 mmHg). A magnetic stirring bar, chlorobenzene (150 mL) and triethyl orthoformate (10.45 g, 11.73 mL, 70.5 mmol, 2.0 equiv) are then added via syringe and the flask is fitted with a reflux condenser, placed in an oil bath heated to 130 °C and stirred for 24 h open to the atmosphere. After removal of the reaction vessel from the oil bath and cooling to room temperature, the reaction mixture is added to a 250 mL round-bottomed flask containing toluene (150 mL) that is agitated with a magnetic stir bar for 1 h. The reaction flask is then rinsed with toluene (30 mL) followed by addition of the heterogeneous mixture to the 1 L round-bottomed flask containing the crude product. The slurry is stirred for 10 min followed by vacuum filtration.

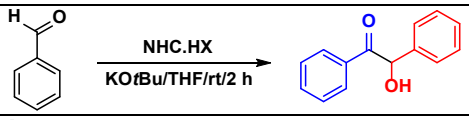
Table 1. Benzoin condensation promoted by NHCs.

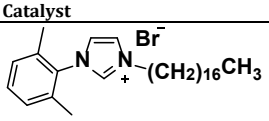
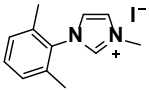
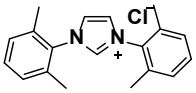
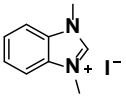
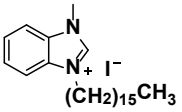
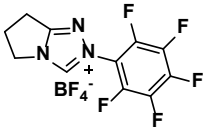


Entry	Base	Yield (%) [a,b]
1	KO*t*Bu	87.0
2	*i*-Pr$_2$NEt	0.0
3	1,8-Diazabicyclo[5.4.0]undec-7-ene	26.5
4	K_2CO_3	0.0
5 [c]	KO*t*Bu	17.7
6 [d]	KO*t*Bu	98.5

[a] Isolated yields.
[b] An average of two experiments.
[c] NHC generated in situ.
[d] The reaction was run for 3 h.

Table 2. Screening of NHC catalyst precursors.



Entry	Catalyst	Yield (%) [a,b]
1		87.0
2		20.0
3		85.0
4		56.4
5		100.0
6		97.0

[a] Isolated yields.
[b] An average of two experiments.

The filtrate is rinsed with toluene (120 mL) and hexanes (120 mL). The crude brown solid is then transferred to a 125 mL Erlenmeyer flask containing a magnetic stir bar by means of a powder funnel. The solid is triturated with ethyl acetate (12 mL) and methanol (1.8 mL) and stirred vigorously for 30 min. The heterogeneous mixture is then filtered through a medium fritted funnel under vacuum (120 mmHg). The filter cake is then washed with cold ethyl acetate (9 mL) via a glass pipette to yield an off-white powder. The off-white solid is transferred to a 100-mL round-bottomed flask by means of a powder funnel, placed in an oil bath heated to 100 °C and subjected to vacuum (2 mmHg) for 1 h, affording 5.80 g (45.3%) of the imidazolium salt [43]. Color: White. Yield: 67.0 %. M.p.: 248.2-249.4 °C. ^{1}H NMR (400 MHz, Acetone-d_6, δ, ppm): 10.24 (s, 1H, H-imidazolium), 4.81 (t, 2H, CH_2, J = 6.8 Hz), 3.43 (t, 2H, CH_2, J = 6.8 Hz), 3.05-2.97 (m, 2H, CH_2).

2.2. General procedure for the benzoin condensation

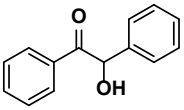
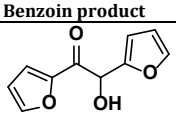
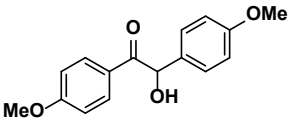
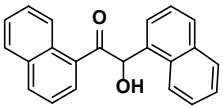
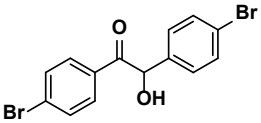
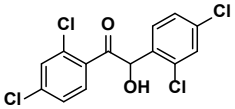
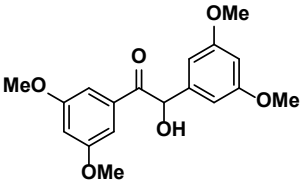
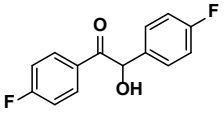
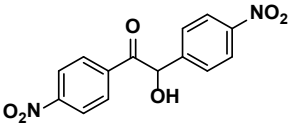
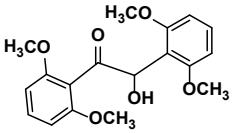
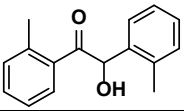
In a glove box a 2 mL vial, dried with a flame and provided with a stirring bar, was charged with potassium *tert*-butoxide (11.22 mg, 0.104 mmol), the NHC catalyst precursor (0.104 mmol), and 0.2 mL of anhydrous THF. The mixture was stirred for 30 min at rt, capped with a septum and then the aldehyde (2 mmol) was added quickly. The vial was capped and taken out of the glove box. The mixture was stirred for 2 h at room temperature, quenched with NH_4Cl/HCl, extracted with CH_2Cl_2 and purified by column chromatography.

2-Hydroxy-1,2-diphenylethan-1-one (Table 3, entry 1) [44]: Color: White. Yield: 98.5 %. M.p.: 134.2-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.87 (d, 2H, J = 7.3 Hz, Ar-H), 7.43 (s, 1H, Ar-H), 7.35 (dd, 2H, J_1 = 7.3 Hz, J_2 = 7.5 Hz, Ar-H), 7.39-7.22 (m, 5H, Ar-H), 5.92 (s, 1H, C-H), 4.59 (s, 1H, OH).

2-Hydroxy-1,2-bis(4-methoxyphenyl)ethan-1-one (Table 3, entry 2) [45]: Color: Yellow. Yield: 91.0 %. M.p.: 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.92-7.88 (m, 2H, Ar-H), 7.26-7.27 (d, 2H, Ar-H), 6.88-6.82 (m, 4H, Ar-H), 5.85 (d, 1H, J = 6.0 Hz, C-H), 4.59 (d, 1H, J = 6.0 Hz, O-H), 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3).

1,2-bis(4-Bromophenyl)-2-hydroxyethan-1-one (Table 3, entry 3) [45]: Color: Pale yellow. Yield: 88.5 %. M.p.: 102-103

Table 3. Substrate scope for the benzoin condensation catalyzed by an NHC.

Entry	Benzoin product	Yield (%) [a,b]	Entry	Benzoin product	Yield (%) [a,b]
1		98.5	7		94.0
2		91.0	8		36.0
3		88.5	9		43.0
4		93.0	10		51.0
5 [c]		0.0	11		0.0
6		54.0			

[a] Reactions were carried out at 200 mg scale of the aldehyde, 5 mol % of the imidazolium salt, 5 mol% of KO*t*Bu, 2 hours of reaction time, and room temperature.
[b] An average of two experiments.
[c] The diketone was isolated [36].

°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.74 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.55 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.46 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.18 (d, 2H, *J* = 8.2 Hz, Ar-H), 5.85 (d, 1H, *J* = 5.7 Hz, C-H), 4.49 (d, 1H, *J* = 5.9 Hz, OH).

1,2-bis(3,5-Dimethoxyphenyl)-2-hydroxyethan-1-one (Table 3, entry 4) [46]: Color: Yellow. Yield: 93.0 %. M.p.: 66.9-68.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.52 (d, 2H, *J* = 9.5 Hz, Ar-H), 6.90 (d, 1H, *J* = 8.4 Hz, Ar-H), 6.80-6.78 (m, 2H, Ar-H), 5.84 (d, 1H, *J* = 5.3 Hz, C-H), 4.58 (d, 1H, *J* = 5.6 Hz, OH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3).

2-Hydroxy-1,2-di-o-tolylethan-1-one (Table 3, entry 6) [47]: Color: Yellow. Yield: 54.0 %. M.p.: 72.5-74.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.39 (d, 1H, *J* = 7.7 Hz, Ar-H), 7.33-7.28 (m, 1H, Ar-H), 7.19-7.12 (m, 6H, Ar-H), 6.04 (s, 1H, C-H), 4.53 (s, 1H, OH), 2.38 (s, 3H, CH_3), 2.35 (s, 3H, CH_3).

1,2-Di(furan-2-yl)-2-hydroxyethan-1-one (Table 3, entry 7) [47]: Color: Yellow. Yield: 94.0 %. M.p.: 133.1-134.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.60 (s, 1H, Het-H), 7.36 (d, 1H, *J* = 0.5 Hz Het-H), 7.24 (d, 1H, *J* = 3.4 *Hz*, Het-H), 6.53 (dd, 1H, *J* = 3.7, 1.5 Hz, Het-H), 6.39 (d, 1H, *J* = 2.9 Hz, Het-H), 6.34-6.33 (m, 1H, Het-H), 5.79 (s, 1H, C-H), 4.21 (s, br, 1H, OH).

2-Hydroxy-1,2-di(naphthalen-1-yl)ethan-1-one (Table 3, entry 8) [48]: Color: Pale yellow. Yield: 36.0 %. M.p.: 192.5-193.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.80 (d, 1H, *J* = 8.5 Hz, Ar-H), 8.39 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.86-7.64 (m, 6H, Ar-H), 7.68-7.53 (m, 2H, Ar-H), 7.47 (dd, 3H, *J* = 20.5, 6.5 Hz, Ar-H), 7.20 (d, 1H, *J* = 7.5 Hz, Ar-H), 6.78 (d, 1H, *J* = 4.6 Hz, C-H), 4.91 (d, 1H, *J* = 4.7 Hz, OH).

1,2-bis(2,4-Dichlorophenyl)-2-hydroxyethan-1-one (Table 3, entry 9) [49]: Color: White. Yield: 43.0 %. M.p.: 89.9-90.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.37 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.22 (s, 4H, Ar-H), 6.25 (s, 1H, C-H), 4.43 (s, br, 1H, OH).

1,2-bis(4-Fluorophenyl)-2-hydroxyethan-1-one (Table 3, entry 10) [50]: Color: Yellow. Yield: 51.0 %. M.p.: 83.1-85.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.94-7.91 (m, 2H, Ar-H), 7.31-7.28 (m, 2H, Ar-H), 7.08 (dd, 2H, J_1 = 10.2 Hz, J_2 = 8.4 Hz, Ar-H), 7.04-7.00 (m, 2H, Ar-H), 5.90 (s, 1H, C-H), 4.43 (s, br, 1H, OH).

3. Results and discussion

Intrigued by the influence of the hydrocarbon chain length on the catalytic efficiency, of non-symmetrical NHC's, we started exploring the effectiveness of our best catalyst from our previous study [37] on the benzoin condensation. Herein, we report our findings of the benzoin condensation catalyzed by NHCs. A brief screening of bases showed that the best combination, catalyst precursor/base, was the imidazolium salt and potassium *tert*-butoxide, Table 1, entry 1. Other bases and imidazolium salt combinations were not as effective or gave no product at all, under the conditions employed, Table 1, entries 2 to 4.

It is noteworthy to mention that the *in situ* generated NHC works slower than the preformed organocatalyst, Table 1, entries 1 *vs.* 5. However, the reaction requires three hours to go to completion with almost quantitative yield, Table 1, entry 6.

A survey of NHCs precursors with structural variation was carried out and results from the screening helped us to identify 3-hexadecyl-1-methyl-1*H*-benzo[d]imidazol-3-ium iodide as the leading catalyst precursor, Table 2, entry 5. This catalyst is more active than our previously leading catalyst, completing the reaction in 2 hours at room temperature with quantitative yields for the model reaction, using benzaldehyde as model substrate, Table 2, entries 1 *vs.* 5. The difference in reaction

rate between these two catalysts is presumably due to the steric hindrance of the mesityl group in the imidazolidine derivative [51]. In fact, the imidazolidine NHC needs longer time, 3 h, to have similar reaction yield to the benzoimidazoline NHC, Table 1, entry 6 *vs*. Table 2, entry 5. Interestingly, the length of the alkyl chain does play a role in the catalytic activity, where a longer chain enhances the catalytic activity of the NHC generated, Table 2, entry 1 *vs*. entry 2 and entry 4 *vs*. entry 5. As it was mentioned before, we had previously observed this trend for the transesterification reaction between glycerol and dimethyl carbonate [37]. Currently, we do not have an explanation for this behavior. Others researchers have observed the same correlation between the length of the chain and the catalytic activity of alkyl benzoimidazole NHC derivatives in the benzoin condensation but have not an explanation either [36].

For comparison, we used 2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate, an active NHC for several reactions [45-52], but its performance is similar to the leading catalyst in this report, Table 2, entries 5 *vs*. 6. However, the fact that the leading catalyst is slightly superior in performance and easier to prepare, by alkylation of benzoimidazole, encouraged us to continue this study using it.

A survey of substrate scope was carried out with the optimized conditions, Table 3. In general, the catalyst does not seem to be sensitive toward the presence of electron-withdrawing or electron-releasing groups, providing the benzoin product in fairly high yields, Table 3, entries 2 to 3 and 4. However, the steric hindrance has a remarkable effect decreesing the yield, independently of the electronic effect of the aromatic ring, Table 3, entries 6, 8, and 10. The importance of the steric over the electronic affect can be observed when two activated groups are compared. The methyl in the ortho position, entry 6, lowers they yield considerably to 54 and 0% for the more sterically hindered 1,6-dimethoxy substrate, entry 11, while electron-rich groups in para or meta positions does not significantly affect the yield, entries 2 and 4 with yields of 91 and 93% respectively. A deactivating group in the para position provides similar yields, 88.5 %, Table 3, entry 3. These results suggest that the electronic effect plays no an important role but the steric effect it does. Substrates with acidic protons, such as 4-hydroxy-3-methoxybenzaldehyde, did not give any benzoin product, because the acidic protons quench the NHC.

An heteroaromatic ring give excellent yield, the reaction is exothermic and goes to completion faster, ~45 minutes, than in the case of carbocyclic aromatic aldehydes, Table 3, entry 7. A hydrogen bonding with the oxygen could explain the fast shifting of the equilibrium in the Breslow intermediate toward the product.

When *p*-nitrobenzaldehyde was used as substrate no benzoin product was observed, but the diketone was isolated, the benzoin derivative is prone to oxidation as it was observed by others [36].

We were interested in the cross-benzoin of our system and used equimolar amounts of benzaldehyde and isovaleraldehyde but no cross-product was observed. When mixing equimolar amounts of benzaldehyde and furfural an almost statistical amount of product was observed and it was difficult to separate them by column chromatography.

4. Conclusion

In summary, we have developed a milder protocol for the benzoin condensation, which uses a minimum amount of solvent. The leading catalyst, an NHC precursor, is a benzimidazolium salt, bearing *N*-alkyl substituents, is easily prepared from commercially available materials. Interestingly, the preformed NHC reacts faster than the *in situ* formed organocatalyst. This protocol gives high yields for electron-releasing or electron-withdrawing groups in aromatic aldehydes but gives low yields for sterically hindered substrates.

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