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N-Heterocyclic Carbenes as key intermediates in the synthesis of fused mesoionic, tricyclic heterocycles

Idir Benaissa,[‡] Lenka Pallova,[‡] Marie-Emilie Morantin, Thomas Lafitte, Mathieu Huynh, Cécile Barthes, Laure Vendier, Noël Lugan, Stéphanie Bastin,* Vincent César*.^[a]

Abstract: The coupling between 5-bromoimidazo[1,5-*a*]pyridinium salts and malonate or arylacetate esters leads to a facile and straightforward access to the new mesoionic, fused tricyclic system imidazo[2,1,5-*cd*]indolizinium-3-olate. Mechanistic studies show that the reaction pathway consists in a nucleophilic aromatic substitution (S_NAr) on the cationic, bicyclic heterocycle by an enolate-type moiety and in a nucleophilic attack of a transient free N-Heterocyclic Carbene (NHC) species on the ester group, the relative order of those two steps depending on the nature of the starting ester. This work highlights the valuable implementation of free NHC species as key intermediates in synthetic chemistry, beyond their classical use as stabilizing ligands or organocatalysts.

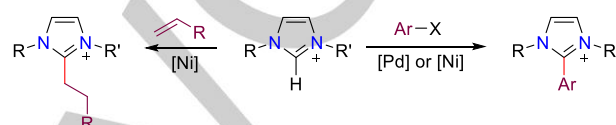
Introduction

Since the seminal discoveries of a stable singlet (phosphino)(silyl)carbene by Bertrand,^[1] and of the first stable imidazol-2-ylidene by Arduengo,^[2] the chemistry of N-Heterocyclic Carbenes (NHCs) has been fascinating chemists and attracted great research interest.^{[3],[4]} Being singlet, nucleophilic carbenes generated from versatile, highly modular nitrogen-heterocycles,^[5] NHCs have been mainly employed as strong donating and sterically protecting ancillary ligands in organometallic chemistry^[6] with important applications in homogeneous catalysis,^[7] materials,^[8] or medicinal chemistry.^[9] In addition, NHCs have shown outstanding aptitudes to coordinate and stabilize main-group element compounds and to form adducts with small molecules,^[10] and they constitute on their own highly efficient nucleophilic organocatalysts.^[11]

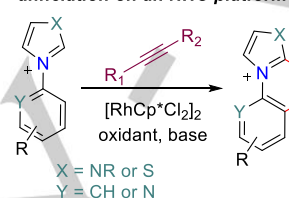
Conversely, besides the use of NHCs as partners for the activation of small molecules,^[12] there are very few examples of synthetic protocols, which occur through the intermediacy of a NHC as one of the key reactive substrates or intermediates. In a seminal contribution, Cavell and co-workers reported on the decomposition of alkyl- and aryl-NHC Pd(II) complexes through reductive elimination to form C2-substituted imidazolium salts and palladium black.^[13] Building on this specific reactivity, the Ni- or

Pd-catalyzed C2-alkylation and arylation of imidazol-2-ylidenes were further developed (Scheme 1A).^{[14],[15]}

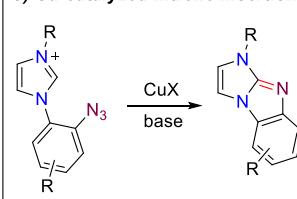
A) Pd- and Ni-catalyzed arylation/alkylation of imidazolium cycles



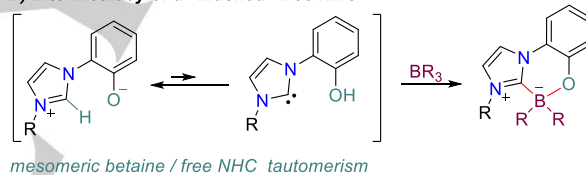
B) Rh(III)-catalyzed annelation on an NHC platform



C) Cu-catalyzed nitrene insertion

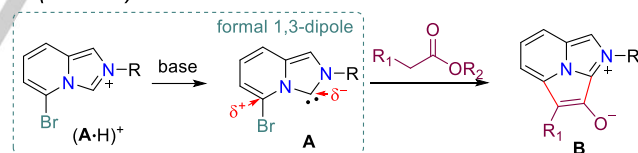


D) Intermediacy of a "masked" free NHC



mesoionic betaine / free NHC tautomerism

E) Formal 1,3-dipole from 5-bromoimidazo[1,5]pyridinium (this work)



Scheme 1. Examples of previously reported synthetic procedures involving a NHC as key reactive intermediate and general depiction of the cyclization strategy developed in this study.

More recently, Choudhury's group reported a versatile protocol for the Rh(III)-catalyzed C-H activation-annelation on a NHC platform from N-(hetero)aryl-azolium salts, in which the *in situ* generated NHC serves as directing group for the C-H activation and as coupling partner in a further reductive elimination step (Scheme 1B).^[16] Analogously to the Staudinger reaction, NHCs rapidly react with organic azides to form 1,3-triazenes, which can further be interconverted into cyclic guanidine or guanidinium salts by loss of dinitrogen upon heating or acidic treatment.^[17] This coupling reaction was recently extended to nitrous oxide^[18] and to nitric oxide.^[19] Fused nitrogen-containing heterocycles were also accessed from N-(2-azidophenyl)azolium salts through a key insertion step of a nitrene/amido ligand into a Cu-NHC bond (Scheme 1C).^[20]

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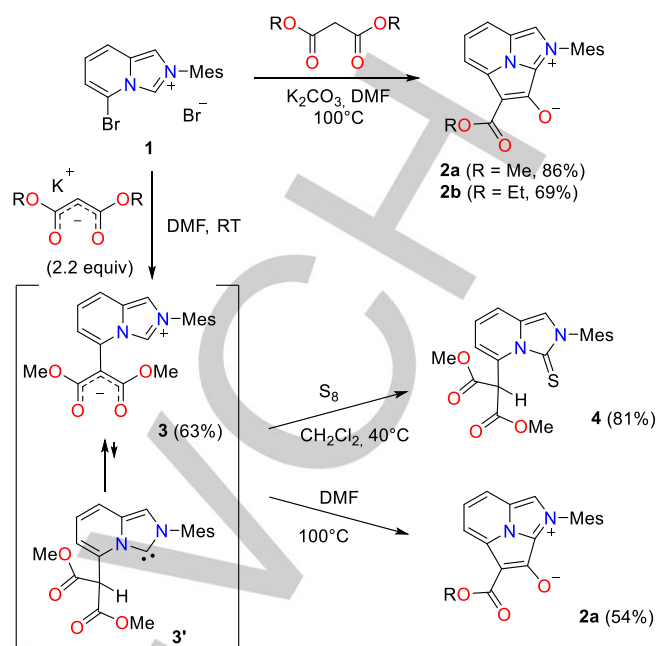
Supporting information for this article is given via a link at the end of the document. ((Please delete this text if not appropriate))

In recent years, mesomeric betaines – defined as conjugated molecules, in which the positive and negative charges are delocalized within a common π -system and that can be exclusively described using a dipolar canonical form^[21] – were shown to be in equilibrium with the corresponding free carbenic form through a proton shift (Scheme 1D).^{[22],[23]} As this equilibrium is strongly shifted toward the more stable mesoionic compounds, the latter can be viewed as “masked” free NHC sources. Nevertheless, addition of a reaction partner usually results in full conversion of the NHC, thanks to its high reactivity.

We recently reported on 5-functionalized imidazo[1,5-*a*]pyridin-3-ylidene (IPy) ligands, whose precursors were efficiently accessed through a key nucleophilic aromatic substitution (S_NAr) on the 5-bromoimidazo[1,5-*a*]pyridinium cation (**A·H**)⁺.^{[24],[25]} While the pre-carbenic imidazolium ring was here unaffected, we speculate on the possibility to access – at least transiently – the corresponding carbene **A** (or an analogue) and thus to generate a *formal* 1,3-dipole composed of the nucleophilic carbenic center and of the electrophilic bromo-substituted pyridinic position. We report herein the efficient annelation of 5-bromoimidazo[1,5-*a*]pyridinium salts (**A·H**)⁺ with 2-substituted acetate esters to yield new mesoionic, fused, tricyclic heterocycles **B**, and demonstrate the intermediacy of NHC species.

Results and Discussion

In the course of our study on the scope of the above-mentioned S_NAr reaction, we focused our attention on malonate esters as coupling partners as they constitute acyclic analogues of the hexapyrimidinetrione, which was successfully grafted onto the IPy scaffold. Thus, heating 5-bromoimidazo[1,5-*a*]pyridinium bromide **1** with dimethyl or diethyl malonate in presence of an excess of potassium carbonate at 100°C led to a highly fluorescent crude mixture, from which the mesoionic heterotricyclic compounds **2a-b** were isolated in good yields (86%, and 69%, respectively). **2a-b** were fully characterized by spectroscopic and analytical techniques, and their molecular formulation was firmly established by an X-Ray diffraction experiment on a single crystal of **2b** (Figure 1).^[26] The main core of **2b** is a novel type of fused mesoionic heterocycle, namely an imidazo[2,1-*cd*]indolizinium-3-olate, which appears to be completely flat. Noteworthy, related neutral and cationic four-ring system benzo[*a*]imidazo[2,1,5-*cd*]indolizine fluorophores were recently developed by Charette and co-workers.^[27] The perfect planarity of the central nitrogen atom environment [$\Sigma N2 = 359.95^\circ$] speaks for a sp² hybridization of that atom, and indicates that the 10-electron aromaticity of the imidazopyridine bicycle is conserved. Moreover, the almost perfect coplanarity of the ester and tricyclic planes [torsion angle (O1-C3-C4-C5) = 2.64°] associated with rather long and identical bond distances for the inner-ring C4-C5 [1.4497(17) Å] and exocyclic C3-C4 [1.4459(17) Å] bonds are testimony of the existence of a mesomeric resonance within the acetylacetate moiety. This resonance behavior suggests negligible 10-electron aromaticity around the three rings, which is confirmed by the very long connecting C4-C12 [1.4367(17) Å] and especially C5-C6 [1.4964(17) Å] bonds.



Scheme 2. Reactivity of 5-bromoimidazo[1,5-*a*]pyridinium bromide **1** with malonic esters. Mes = 2,4,6-trimethylphenyl.

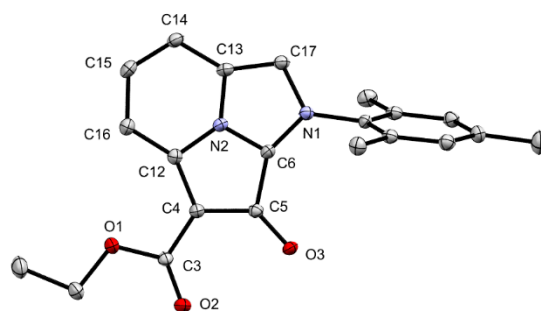
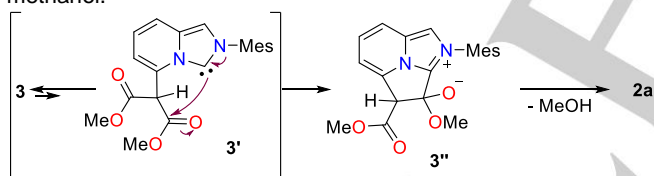


Figure 1. Molecular structure of **2b** (ellipsoids drawn at 30% probability level). Two independent molecules are present in the unit cell, differing only by a 180° rotation of the ester moiety around the C3-C4 bond. Hydrogen atoms and solvent molecule were omitted for clarity. Selected bond lengths (Å) and angles (deg): C6-N1 1.3543(16), C6-N2 1.3330(16), N1-C17 1.3840(15), C13-C17 1.3909(18), C13-C14 1.4180(18), C14-C15 1.3781(19), C15-C16 1.4330(18), C12-C16 1.3761(17), C4-C12 1.4367(17), C4-C5 1.4497(17), C5-C6 1.4964(17), C5-O3 1.2403(15), C3-C4 1.4459(17), C3-O1 1.3646(15), C3-O2 1.2147(15), O1-C3-C4-C5 2.64.

Intrigued by this somewhat unexpected reactivity and final structure, we decided to study in more details the mechanism of this annelation reaction. Reacting the bromo derivative **1** with the potassium salt of the dimethyl malonate anion under milder conditions, *i.e.* at room temperature, allowed isolation of the zwitterionic compound **3**, in which the malonate unit is grafted on the position 5 of the cationic heterobicycle. The C-C bond formation between the two parts occurred through an S_NAr pathway, as we reported previously for related nucleophiles.^{[24],[25]} Two equivalents of the potassium malonate reagent were

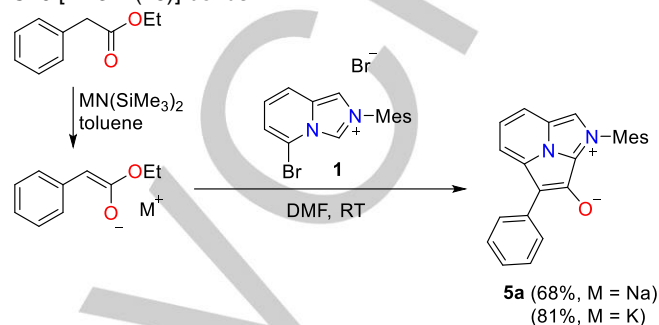
required in this case, since the second equivalent served as a base to trap the acidic proton on the central malonate carbon atom in the intermediate after the S_NAr reaction. The zwitterionic formulation of **3** was in particular inferred from its 1H and ^{13}C NMR spectra at 298K, in which the signals for the imidazolium N_2CH moiety were detected at δ_H 9.06 ppm, and δ_C 129.1 ppm, respectively, and the central sp^2 -hybridized malonate carbon atom was identified at δ_C 72.7 ppm. Upon cooling down to 193 K, the signals of the hydrogen atoms on the IPy bicycle broadened and the N_2CH signal vanished (Figure S1), indicating the occurrence of a fast proton shift between the imidazolyl N_2C carbon atom of the major mesoionic species **3** and the central malonate carbon atom of the elusive free NHC species **3'**. This tautomeric equilibrium was also reflected by the ^{13}C NMR data with the disappearance of the peaks corresponding to the imidazolyl N_2C and carbonyl carbon atoms at 193 K (Figure S2). Further evidence of the tautomeric equilibrium between **3** and **3'** was provided upon reacting **3** with sulfur to yield the thiourea **4** in 81% yield. The imidazolium proton was shifted to the central malonate position, as indicated by the corresponding singlets at δ_H 8.53 ppm and δ_C 52.6 ppm in the 1H and ^{13}C NMR spectra. Likewise, heating a solution of compound **3** in DMF at 100°C led to the formation of the tricyclic mesoionic compound **2a** in 54% isolated yield, evidencing the intermediacy of compound **3** in the annelation reaction between **1** and potassium malonates. A suitable mechanism for the transformation of **3** into **2a** could also be drawn, which highlighted the crucial role of the tautomeric equilibrium between **3** and **3'** (Scheme 3). Indeed, the proximity of the nucleophilic carbene center and one of the two ester moieties in the minor free NHC tautomer **3'** would favor the intramolecular reaction between both entities,^[28] generating the tetrahedral intermediate **3''**, which would interconvert into **2a** by loss of methanol.



Scheme 3. Proposed mechanism for the transformation of **3** into **2a**.

At that point, we turned our attention on the extension of this methodology to other types of substituted acetate esters and we first selected ethyl phenylacetate as coupling partner (Scheme 4). Using the previous one-pot protocol, *i.e.* with an excess of K_2CO_3 at 100°C, an intractable mixture was obtained arising from the decomposition of compound **1**. Decreasing the reaction temperature to room temperature led to no reaction at all, the two reagents being recovered intact. We thus decided to first generate quantitatively the corresponding enolate using a strong base. Hence, ethyl phenylacetate was deprotonated with NaHMDS or KHMDS in toluene to yield the corresponding metallated enolates.^[29] After changing the solvent for DMF, the bromoimidazopyridinium salt **1** was added at room temperature, inducing an immediate color change to dark red. The tricyclic mesoion **5a** was isolated as a red solid and KHMDS was found to

lead to a better yield than NaHMDS. Compound **5a** was fully characterized by spectroscopic and analytical techniques, including by an X-Ray diffraction experiment (Figure 2). The tricyclic skeleton in **5a** is fully planar and displays about the same metrical features as in **2b**, *i.e.* a 10 electron aromatic imidazo[1,5-a]pyridinium bicycle, on which the enolate-type O1-C2-C3 moiety is grafted through the two quite long C2-C12 [1.4847(15)] and C3-C10 [1.4321(15)] bonds.



Scheme 4. Formation of compound **5a** from 5-bromoimidazo[1,5-a]pyridinium bromide **1** and ethyl phenylacetate.

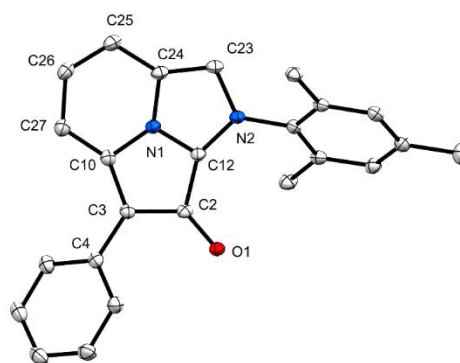
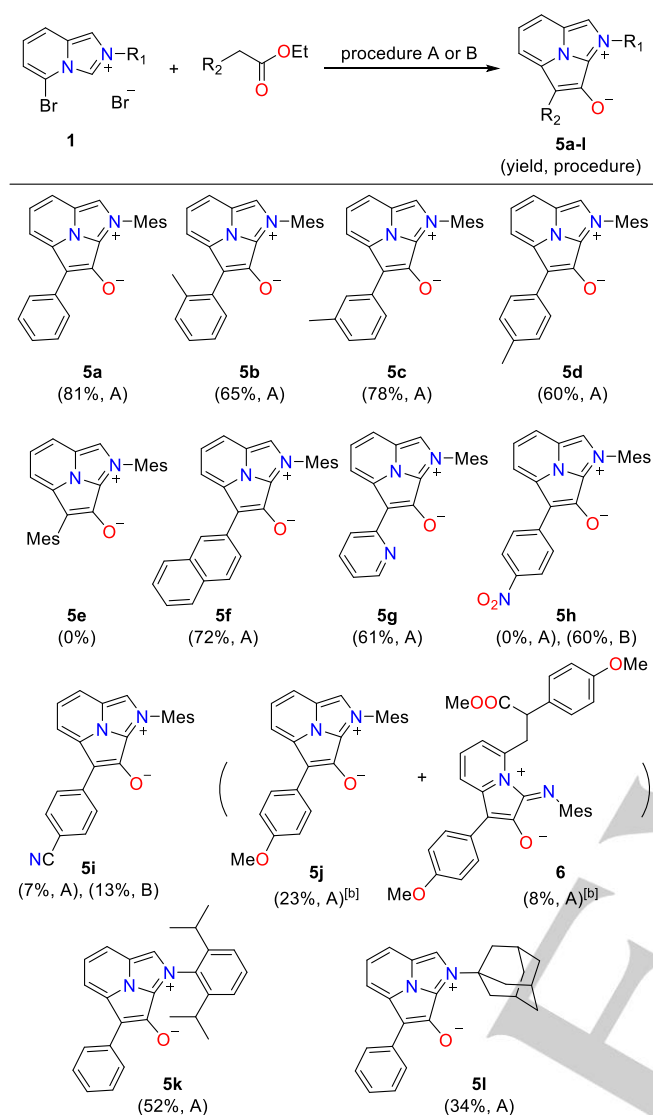


Figure 2. Molecular structure of **5a** (ellipsoids drawn at 30% probability level). Hydrogen atoms and solvent molecule were omitted for clarity. Selected bond lengths (Å) and angles (deg): C12-N2 1.3565(14), C12-N1 1.3288(14), N2-C23 1.3853(14), C23-C24 1.3909(16), C24-C25 1.4130(16), C25-C26 1.3774(17), C26-C27 1.4255(17), C27-C10 1.3792(16), C2-C10 1.4321(15), C2-C3 1.4411(15), C2-C12 1.4847(15), C2-O1 1.2519(12).

The scope of the annelation reaction was then investigated and the results are displayed in scheme 5. Using the previous procedure involving the pre-generation of the ester enolate (procedure A), the ortho-, meta- and para-tolylacetate esters gave the corresponding products **5b-d** in good isolated yields, without any noticeable effect of the methyl position. However, only decomposition products were observed when using the highly hindered ethyl mesitylacetate as coupling partner and the expected product **5e** could not be detected in the crude mixture.



Scheme 5. Scope of the annelation reaction to generate tricyclic, mesoionic compounds **5a-l**. [a] Procedure A:) Ethyl 2-arylacrylate (2.22 equiv.), KHMDS (2.2 equiv.), toluene, RT, 2) **1** (1 equiv.), DMF, RT; Procedure B: **1** (1 equiv.), ethyl 2-arylacrylate (1.1 equiv.), K₂CO₃ (3.5 equiv.), DMF, 100°C 1. [b] Methyl (4-methoxyphenyl)acetate used instead of ethyl (4-methoxyphenyl)acetate.

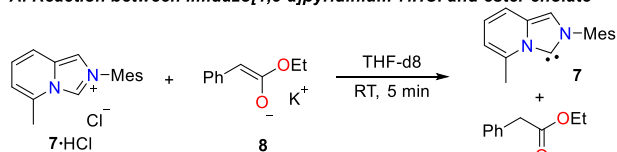
While good yields were also observed with the extended 2-naphthyl group (**5f**) and the 2-pyridinyl heterocycle (**5g**), the electronic effects were shown to play a critical role on the outcome of the reaction (products **5h-j**). The two-step procedure A failed to yield any trace of the desired 4-nitrophenyl-substituted **5h**. Fortunately, when using the previous one-pot procedure involving excess of potassium carbonate at 100°C (procedure B), compound **5h** was smoothly and cleanly produced in 60% yield. 4-Cyanophenylacetate ester appeared to be a much more reluctant substrate, since the best isolated yield in **5i** was 13% using procedure B. Using the electron-rich methyl *p*-anisylacetate as coupling partner, the dark purple, fused tricyclic product **5j** was isolated in 23% yield, along with the dark blue by-product **6** in 8%

yield after column chromatography. While such an intense navy blue band had been previously observed from time to time with some of the previous substrates, the amount was too small to allow isolation and characterization of the compound. Luckily here, the isolated amount of compound **6** was sufficient to allow its complete characterization and structural determination by a thorough multinuclear, multidimensional NMR study.^[30] Compound **6** was obtained through the coupling of compound **1** with two equivalents of *p*-anisylacetate esters and was shown to be composed of a mesoionic 1-iminopyrrolo[1,2-*a*]pyridinium-2-olate core. While its formation involved the opening of the imidazolyl ring of the imidazo[1,5-*a*]pyridinium bicycle, it was shown not to arise from a subsequent attack of an ester enolate on compound **5j**, since no reaction was observed when mixing the two compounds. Eventually, the *N*-substituent in the starting 5-bromoimidazo[1,5-*a*]pyridinium salt **1** was also changed for 2,6-diisopropylphenyl and 1-adamantyl groups and compounds **5k** and **5l** were isolated in 52% and 34% yields respectively.

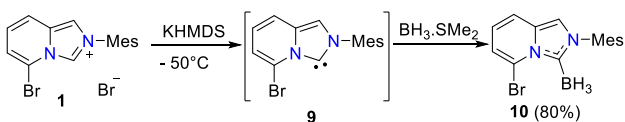
The quite different relative reactivities and conditions between the previous malonate and the 2-arylacrylate esters prompted us to explore in more details the mechanism of the latter annelation reaction, by carrying out some additional experiments. As the reaction between **1** and the potassium enolate of ethyl phenylacetate occurred really quickly and no intermediate could be characterized during the reaction, we decided to block the inherent reactivity of the position 5 of the bicyclic heterocycle by replacing the bromine atom by a methyl group. Thus, the imidazo[1,5-*a*]pyridinium **7**·HCl instantaneously reacted with the ester enolate **8** in THF-*d*₈ at room temperature through an acid-base reaction to yield free NHC **7** and ethyl phenylacetate (Scheme 6A). This result is consistent with the relative pK_a values of the different reagents. Indeed, considering that the acidity of imidazo[1,5-*a*]pyridinium is within the range of those of imidazolium salts [pK_a ~19-24 in DMSO],^[31] a malonate anion is not enough basic [pK_a(malonate) = 16.4 in DMSO] to induce its deprotonation and generation of the free NHC, when the basicity of the ester enolate [pK_a(ethyl phenylacetate) = 22.7 in DMSO] is sufficient to fully deprotonate **1** or **7**·HCl.^[32] The resulting mixture of **7** and ethyl phenylacetate did not evolve further even under heating to 60°C. In a second step, we studied the generation and stability of the free NHC **9** deriving from **1**. While reaction of **1** with potassium bis(trimethylsilyl)amide (KHMDS) at room temperature only led to decomposition products, the free NHC **9** could be cleanly generated at -50°C and trapped with BH₃·SMe₂ to form the borane adduct **10** in 80% yield after purification (Scheme 6B). Noteworthy, the molecular structure of **10** was firmly established by an X-ray diffraction experiment (Figure 3). The C1-B1 bond distance of 1.604(3) Å falls within the standard range of NHC-BH₃ adducts [1.58-1.62 Å].^[33] The *peri* positioning of the bromine and the borane moieties induces a steric repulsion between them, which is reflected by the dihedral angle B1-C1-C7-Br1 of 23.99°. Going back to the reaction conditions, we were prompted to prove that free NHC **9** is effectively produced as first intermediate in the reaction between **1** and potassium enolate **8**. Thus the two latter reagents were mixed under the standard conditions of the annelation reaction (DMF, RT) but in presence of a small excess of sulfur. After 15 min of reaction, no tricyclic product **5a** was

detected and only the thiourea **11** was observed in the crude mixture. Compound **11** was then isolated in 52%, demonstrating our hypothesis that free NHC **9** is the actual first intermediate in the annelation reaction.

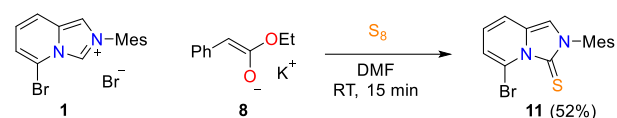
A. Reaction between imidazo[1,5-a]pyridinium 7.HCl and ester enolate



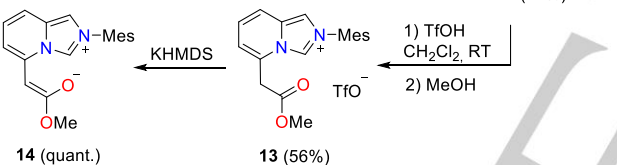
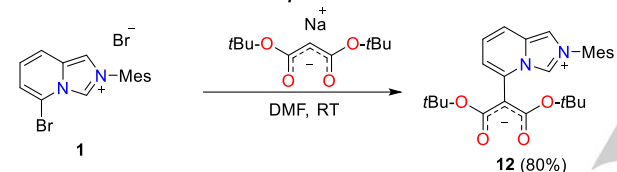
B. Generation and trapping of the free NHC 9 derived from 1



C. Trapping of transient free NHC 9 generated during the annelation reaction



D. Generation of zwitterionic compound 13



Scheme 6. Additional test reactions for establishing the mechanism of the reaction between compound **1** and arylacetate esters.

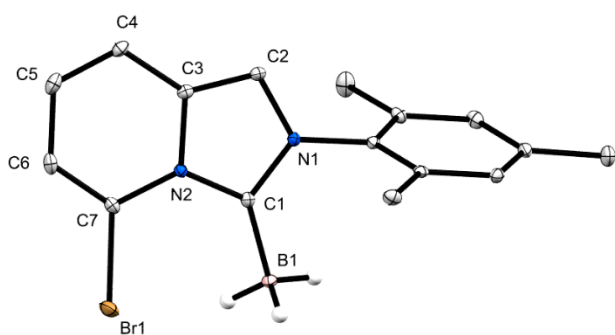
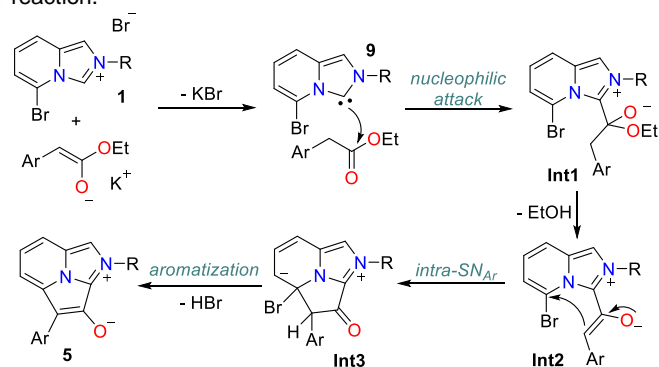


Figure 3. Molecular structure of compound **10** (ellipsoids drawn at 30% probability level). Hydrogen atoms and solvent molecule were omitted for clarity. Selected bond lengths (Å) and angles (deg): C1-B1 1.604(3), C7-Br1 1.874(2), B1-C1-C7-Br1 23.99.

Conversely, if the coupling between **1** and arylacetate esters proceeded through the same S_NAr /cyclization pathway as with the malonate esters, the last cyclization step would occur from the phenylacetate-substituted analogue of mesoion **3** and through a tautomeric equilibrium similar to the one observed for **3**. In order to access this mesoionic compound, we devised to first graft a phenylmalonate moiety on the position 5 of the imidazo[1,5-a]pyridinium skeleton through the S_NAr reaction as developed in the first part followed by a decarboxylation reaction. Unfortunately, no coupling was observed between **1** and di(*tert*-butyl) phenylmalonate even under drastic conditions.^[34] Releasing some steric pressure on the malonate by removing the central phenyl group allowed the clean formation of the zwitterionic compound **12** in 94% yield (Scheme 6C). Acidic treatment of **12** by triflic acid followed by addition of methanol led to a decarboxylation reaction and esterification of the remaining carboxylic acid group to yield the imidazo[1,5-a]pyridinium triflate **13** in average yield. The mesoionic compound **14** was then quantitatively obtained by deprotonation of **12** with 1 equivalent of KHMDS. While no definite conclusion about a tautomeric equilibrium could be drawn from the VT NMR experiment, no tricyclic compound similar to **5** was detected by heating compound **14**, and adding sulfur to **14** led a complexed mixture.^[29] Even if the latter does not possess an aryl group on the α -position of the carboxylate group, it appeared unlikely that the annelation reaction between **1** and arylacetate esters proceeds through such an intermediate.

Altogether, based on the latter experiments, the formation of compounds **5** could be explained by the proposed mechanism described in scheme 7. In a first fast reaction, potassium enolate deprotonates the imidazolium **1** to generate transiently the free carbene **9**, which would attack the ester moiety to form the tetrahedral intermediate **Int1**. Evolution by loss of ethanol would lead to the imidazolium enolate **Int2**,^{[28d],[35]} which would undergo a facile intramolecular S_NAr reaction generating the intermediate **Int3**, and then the final mesoionic tricycle **5** in a final aromatization reaction.



Scheme 7. Proposed mechanism for the formation of the fused mesoionic tricycle **5** from **1** and arylacetate esters enolates.

Conclusions

Beyond their use as outstanding ligands for transition metals and main-group elements or as organocatalysts, NHCs have been only seldom regarded as potential intermediates for synthetic purposes, mainly due to their reputation of too reactive species. While most of the recent implementations of NHCs as synthetic intermediates relied on a transition-metal catalysis, we have now demonstrated that NHCs constitute valuable key intermediates in heterocyclic synthesis. Indeed, new, fused, and mesoionic imidazo[2,1,5-*cd*]indolizinium-3-olate scaffold were obtained in straightforward and efficient manner starting from readily available 5-bromoimidazo[1,5-*a*]pyridinium salts. Depending on the nature of the coupling reagent, the annelation reaction proceeds through two different pathways, characterized by the order of the two key reactions, namely the aromatic nucleophilic substitution by an enolate-type reagent and the nucleophilic attack of a free NHC on an ester moiety. This work also shows that the high reactivity of free NHC intermediates can be controlled and tempered by slow generation of NHCs as elusive intermediates. This paves the way to rethinking disconnections for retrosynthetic analysis in heterocyclic chemistry, and to conceive new mesoionic compounds.

Acknowledgements

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Keywords: carbenes • nitrogen heterocycles • zwitterion • aromatic substitution • tautomerism

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