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Aromatic Substitution

N-Heterocyclic Carbenes as Key Intermediates in the Synthesis of Fused, Mesoionic, Tricyclic Heterocycles

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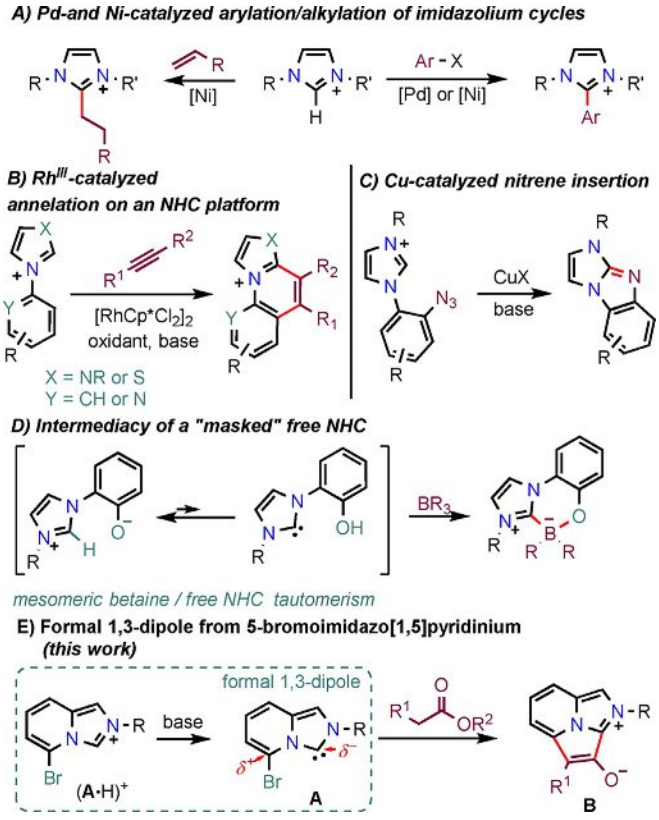
Abstract: Coupling between 5-bromoimidazo[1,5-*a*]pyridinium salts and malonate or arylacetate esters leads to a facile and straightforward access to the new mesoionic, fused, tricyclic system of imidazo[2,1,5-*cd*]indolizinium-3-olate. Mechanistic studies show that the reaction pathway consists of nucleophilic aromatic substitution on the cationic, bicyclic heterocycle by an enolate-type moiety and in the nucleophilic attack of a transient free N-heterocyclic carbene (NHC) species on the ester group; the relative order of these two steps depends 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 et al.[1] and of the first stable imidazol-2-ylidene by Arduengo et al.,[2] the chemistry of N-heterocyclic carbenes (NHCs) has been fascinating chemists and attracted great research interest.[3,4] As 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 science,[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] They are also highly efficient nucleophilic organocatalysts.[11]

Conversely, apart from 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 an 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 1 A).[14,15]



Scheme 1. Examples of previously reported synthetic procedures involving an NHC as a key reactive intermediate and general depiction of the cyclization strategy developed herein. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

More recently, the group of Choudhury reported a versatile protocol for Rh^{III}-catalyzed C–H activation–annulation on an NHC platform from *N*-(hetero)aryl azolium salts, in which the in situ generated NHC serves as a directing group for C–H activation and as a coupling partner in a further reductive elimina-

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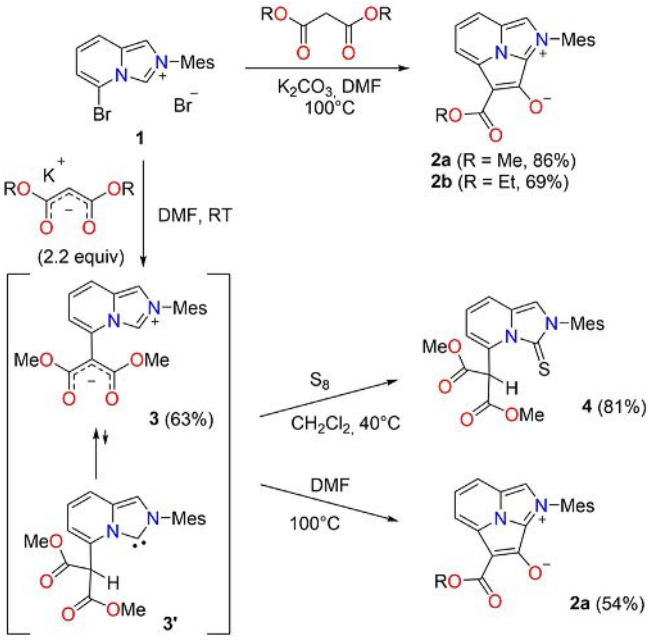
tion step (Scheme 1 B).[16] Analogously to the Staudinger reaction, NHCs rapidly react with organic azides to form 1,3-triazenes, which can further be interconverted into cyclic guanidine or guanidinium salts by loss of dinitrogen upon heating or acidic treatment.[17] This coupling reaction was recently extended to nitrous oxide[18] and 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 1 C).[20]

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 by using a dipolar canonical form[21]—were shown to be in equilibrium with the corresponding free carbenic form through a proton shift (Scheme 1 D).[22,23] Because this equilibrium is strongly shifted toward the more stable mesoionic compounds, the latter can be viewed as "masked" free NHC sources. Nevertheless, the 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, the precursors of which were efficiently accessed through a key nucleophilic aromatic substitution (SN_{Ar}) on the 5-bromoimidazo[1,5-*a*]pyridinium cation (**A**·H)$^+$ (Scheme 1 E).[24,25] Although the pre-carbenic imidazolium ring was unaffected, we speculated 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 the electrophilic bromosubstituted pyridinic position. We report herein on the efficient annulation 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 abovementioned SN_{Ar} reaction, we focused our attention on malonate esters as coupling partners because they constituted acyclic analogues of 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 the 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; Scheme 2). Compounds **2a**,**b** were fully characterized through spectroscopic and analytical techniques, and their molecular formulas were firmly established through an XRD 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[2,1,5-*cd*]indolizinium-3-olate, which appears to be completely flat. Notably, 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 (ΣN2 = 359.95°) speaks for the



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

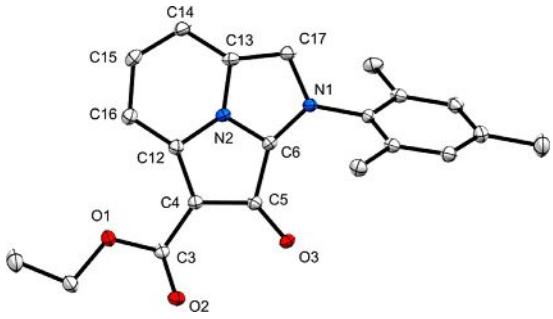


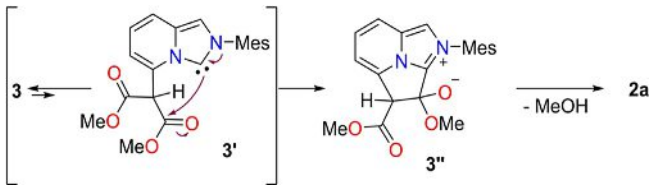
Figure 1. Molecular structure of **2b** (ellipsoids are drawn at the 30% probability level). Two independent molecules are present in the unit cell; these differ only by 180° rotation of the ester moiety around the C3–C4 bond. Hydrogen atoms and solvent molecule were omitted for clarity. Selected bond lengths [Å] and angles [°]: 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.

sp^2 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 lengths 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 C5–C6 (1.4964(17) Å) bonds, in particular.

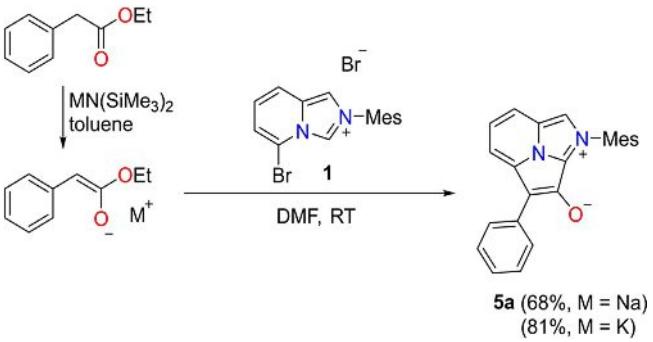
Intrigued by this somewhat unexpected reactivity and final structure, we decided to study in more detail the mechanism

of this annulation reaction. Reacting bromo derivative **1** with the potassium salt of the dimethyl malonate anion under milder conditions, that is, at room temperature, allowed the isolation of zwitterionic compound **3**, in which the malonate unit is grafted onto the 5-position of the cationic heterobicycle. The C–C bond formation between the two parts occurred through an SN_{Ar} pathway, as we reported previously for related nucleophiles.[24,25] Two equivalents of the potassium malonate reagent were required in this case because the second equivalent served as a base to trap the acidic proton on the central malonate carbon atom in the intermediate after the SN_{Ar} reaction. The zwitterionic formulation of **3** was inferred from its ^1H and ^{13}C NMR spectra at 298 K, in which the signals for the imidazolium N_2CH moiety were detected at $\delta_H = 9.06$ ppm and $\delta_C = 129.1$ ppm, respectively, and the central sp^2-hybridized malonate carbon atom was identified at $\delta_C = 72.7$ ppm. Upon cooling to 193 K, the signals of the hydrogen atoms on the IPy bicycle broadened and the N_2CH signal vanished (Figure S1 in the Supporting Information); thus 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 spectroscopy data, with the disappearance of signals corresponding to the imidazolyl N_2C and carbonyl carbon atoms at 193 K (Figure S2 in the Supporting Information). Further evidence of the tautomeric equilibrium between **3** and **3′** was provided upon reacting **3** with sulfur to yield thiourea **4** in 81% yield. The imidazolium proton was shifted to the central malonate position, as indicated by the corresponding singlets at $\delta_H = 8.53$ ppm and $\delta_C = 52.6$ ppm in the ^1H and ^{13}C NMR spectra, respectively. Likewise, heating a solution of compound **3** in DMF at 100 °C led to the isolation of tricyclic mesoionic compound **2a** in 54% yield, which provided evidence of the intermediacy of compound **3** in the annulation 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 minor free NHC tautomer **3′** would favor the intramolecular reaction between both entities,[28] generating the tetrahedral intermediate **3″**, which would interconvert into **2a** through loss of methanol.

At this point, we turned our attention to the extension of this methodology to other types of substituted acetate esters and we first selected ethyl phenylacetate as a coupling partner (Scheme 4). By using the previous one-pot protocol, that is, with an excess of K_2CO_3 at 100 °C, an intractable mixture was



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



Scheme 4. Formation of compound **5a** from **1** and ethyl phenylacetate.

obtained, which arose from the decomposition of **1**. Decreasing the reaction temperature to room temperature led to no reaction at all; the two reagents were recovered intact. We thus decided to first generate quantitatively the corresponding enolate by using a strong base. Hence, ethyl phenylacetate was deprotonated with sodium (NaHMDS) or potassium bis(trimethylsilyl)amide (KHMDS) in toluene to yield the corresponding metalated enolates.[29] After changing the solvent to DMF, salt **1** was added at room temperature; this induced 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 that with NaHMDS. Compound **5a** was fully characterized by means of spectroscopic and analytical techniques, including an XRD experiment (Figure 2). The tricyclic skeleton in **5a** is fully planar and displays similar geometric features to those in **2b**, that is, a 10-electron aromatic imidazo[1,5-a]pyridinium bicycle, upon which the enolate-type O1-C2-C3 moiety is grafted through the two quite long C2–C12 (1.4847(15) Å) and C3–C10 (1.4321(15) Å) bonds.

The scope of the annulation reaction was then investigated and the results are displayed in Scheme 5. By using the previous procedure, which involved the pregeneration of the ester enolate (procedure A), the *ortho*-, *meta*-, and *para*-tolylacetate esters gave the corresponding products **5b–d** in good yields, without any noticeable effect of the methyl position. However,

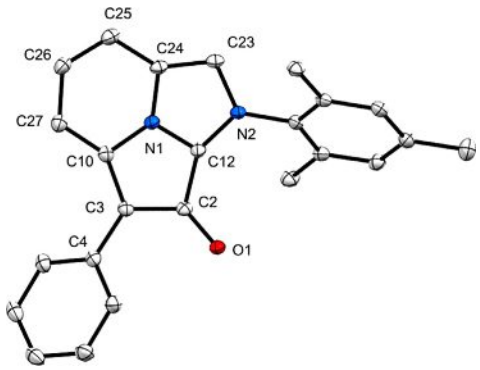
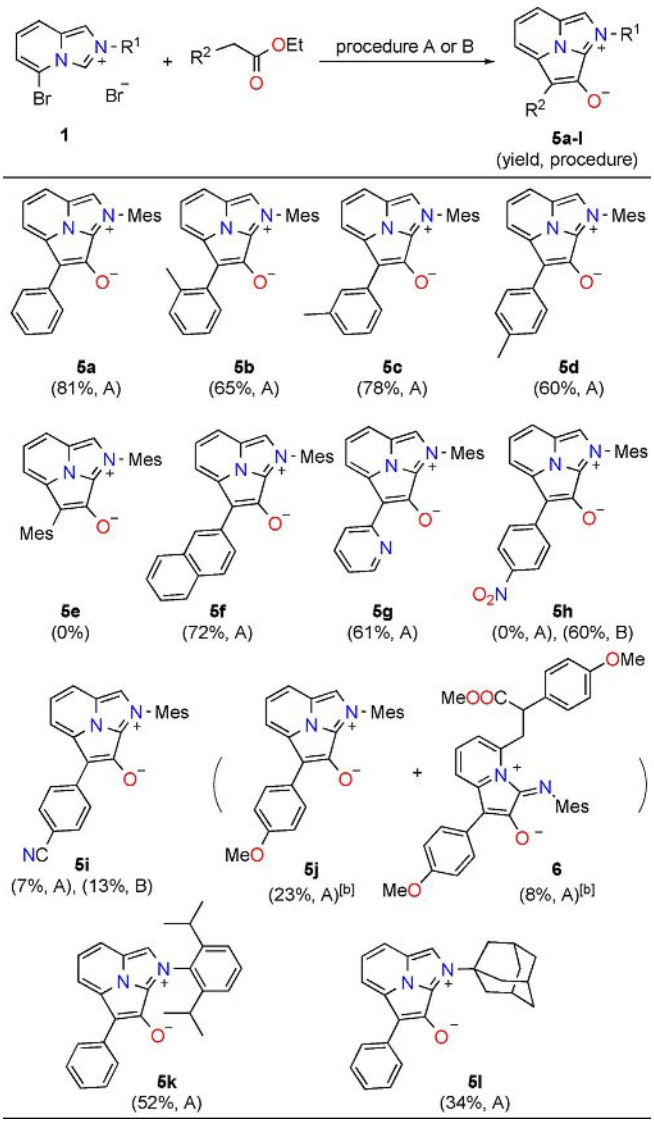


Figure 2. Molecular structure of **5a** (ellipsoids are drawn at the 30% probability level). Hydrogen atoms and solvent molecule were omitted for clarity. Selected bond lengths [Å]: C12–N2 1.3565(14), C12–N1 1.3288(14), N2–C23 1.3853(14), C23–C24 1.3909(16), C24–C25 1.4130(16), C25–C26 1.3774(17), C26–C27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



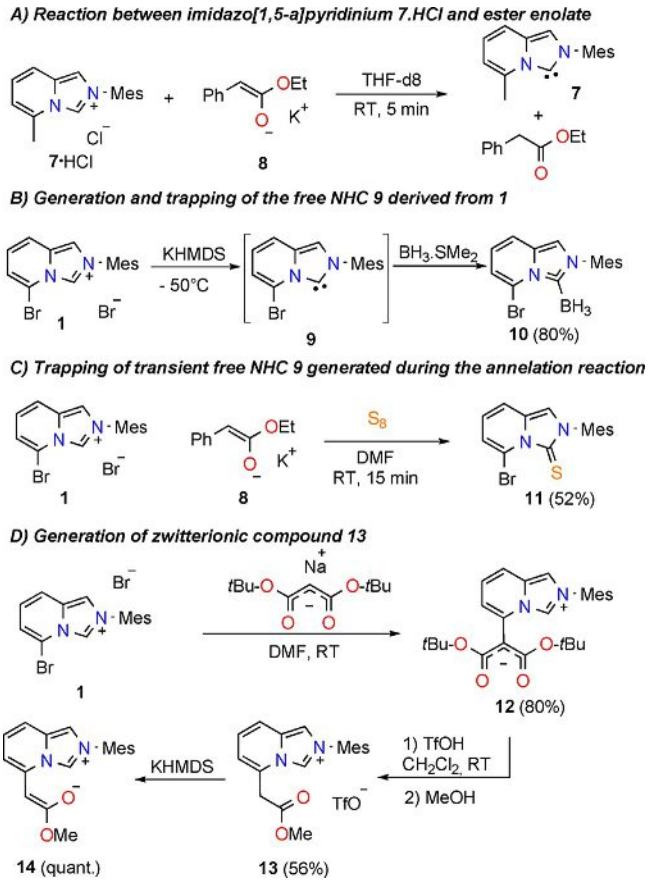
Scheme 5. Scope of the annulation reaction to generate tricyclic, mesoionic compounds **5a**–**l**. Procedure A: 1) Ethyl 2-arylacetate (2.22 equiv), KHMDS (2.2 equiv), toluene, RT; 2) **1** (1 equiv), DMF, RT. Procedure B: **1** (1 equiv), ethyl 2-arylacetate (1.1 equiv), K_2CO_3 (3.5 equiv), DMF, 100 °C. [a] Methyl (4-methoxyphenyl)acetate was used instead of ethyl (4-methoxyphenyl)acetate.

only decomposition products were observed if highly hindered ethyl mesitylacetate was used as a coupling partner and the expected product, **5e**, could not be detected in the crude mixture.

Although 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 in the outcome of the reaction (products **5h**–**j**). Two-step procedure A failed to yield any trace of the desired product 4-nitrophenyl-substituted **5h**. Fortunately, upon using the previously discussed one-pot procedure, involving an 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 yield of **5i** isolated was 13% by using procedure B. With electron-rich methyl *p*-anisylacetate as a coupling partner, the dark purple, fused, tricyclic product **5j** was isolated in 23% yield, along with dark-blue byproduct **6** in 8% yield after column chromatography. Although such an intense navy blue band had previously been observed occasionally with some of the previous substrates, the amount was too small to allow isolation and characterization of the compound. Luckily, here, the amount of compound **6** isolated was sufficient to allow its complete characterization and structural determination in a thorough multinuclear, multidimensional NMR spectroscopy 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. Although its formation involved opening of the imidazolyl ring of the imidazo[1,5-*a*]pyridinium bicycle, it was not shown to arise from the subsequent attack of an ester enolate on compound **5j**, since no reaction was observed upon mixing the two compounds. Eventually, the N-substituent of starting salt **1** was also substituted for 2,6-diisopropylphenyl and 1-adamantyl groups, and compounds **5k** and **5l** were isolated in 52 and 34% yields, respectively.

The different relative reactivities and conditions between the previous malonate and 2-arylacetate esters prompted us to explore in more detail the mechanism of the latter annulation reaction, by carrying out some additional experiments. Because the reaction between **1** and the potassium enolate of ethyl phenylacetate occurred quickly and no intermediate could be characterized during the reaction, we decided to block the inherent reactivity of the 5-position of the bicyclic heterocycle by replacing the bromine atom with a methyl group. Thus, imidazo[1,5-*a*]pyridinium **7**·HCl instantaneously reacted with ester enolate **8** in [D_8]THF 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 (p$K_a \approx 19$–24 in DMSO),[31] a malonate anion is not sufficiently basic (pK_a(malonate) = 16.4 in DMSO) to induce its deprotonation and generation of the free NHC, while 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 free NHC **9**, which was derived from **1**. Whereas the reaction of **1** with KHMDS at room temperature only led to decomposition products, free NHC **9** could be cleanly generated at −50 °C and trapped with BH_3·SMe_2 to form borane adduct **10** in 80% yield after purification (Scheme 6B). Notably, the molecular structure of **10** was firmly established through an XRD experiment (Figure 3). The C1–B1 bond length of 1.604(3) Å falls within the standard range of NHC–BH_3 adducts (1.58–1.62 Å).[33] The *peri* positioning of the bromine and borane moieties induces steric repulsion between them, which is reflected by the dihedral angle for B1-C1-C7-Br1 of 23.99°.

Going back to the reaction conditions, we were prompted to prove that free NHC **9** was effectively produced as the first



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

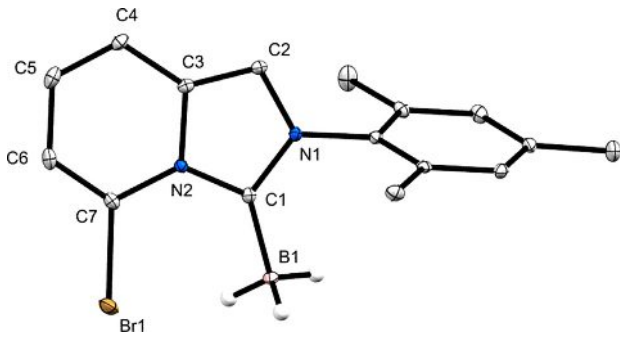
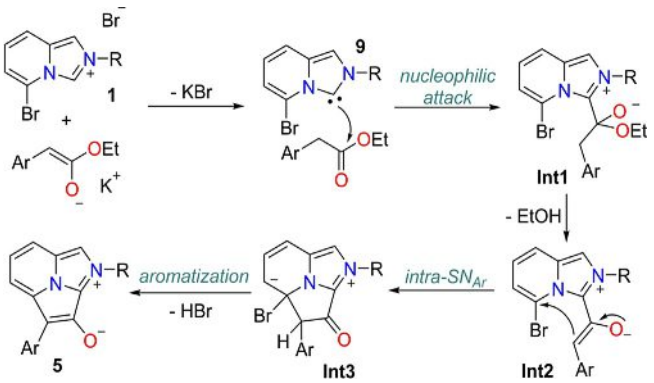


Figure 3. Molecular structure of compound **10** (ellipsoids are drawn at the 30% probability level). Hydrogen atoms and solvent molecule were omitted for clarity. Selected bond lengths [Å] and angles [°]: C1–B1 1.604(3), C7–Br1 1.874(2), B1-C1-C7-Br1 23.99.

intermediate in the reaction between **1** and potassium enolate **8**. Thus, the last two reagents were mixed under standard conditions of the annulation reaction (DMF, RT), but in the presence of a small excess of sulfur. After 15 min of reaction, no tricyclic product **5a** was detected and only thiourea **11** was observed in the crude mixture. Compound **11** was then isolated in 52% yield; this confirmed our hypothesis that free NHC **9** was the actual first intermediate in the annulation reaction.

Conversely, if coupling between **1** and arylacetate esters proceeded through the same SN_{Ar}/cyclization pathway as that with malonate esters, the last cyclization step would occur from the phenylacetate-substituted analogue of mesoion **3** and through a tautomeric equilibrium similar to that observed for **3**. To access this mesoionic compound, we devised to first graft a phenylmalonate moiety onto the 5-position of the imidazo[1,5-*a*]pyridinium skeleton through the SN_{Ar} 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 harsh conditions.[34] Releasing some steric pressure on the malonate by removing the central phenyl group allowed the clean formation of zwitterionic compound **12** in 80% yield (Scheme 6D). Treatment of **12** with triflic acid followed by the addition of methanol led to a decarboxylation reaction and esterification of the remaining carboxylic acid group to yield imidazo[1,5-*a*]pyridinium triflate **13** in moderate yield. Mesoionic compound **14** was then quantitatively obtained by deprotonation of **12** with one equivalent of KHMDS. Although no definitive conclusion of a tautomeric equilibrium could be drawn from the variable-temperature NMR spectroscopy experiment, no tricyclic compound similar to **5** was detected by heating compound **14**, and adding sulfur to **14** led to a complex mixture.[30] Even if **14** does not possess an aryl group on the α position of the carboxylate group, it appears unlikely that the annulation reaction between **1** and arylacetate esters proceeds via such an intermediate.

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



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

Conclusions

Beyond their use as outstanding ligands for transition metals and main-group elements or as organocatalysts, NHCs have only seldom been regarded as potential intermediates for syn-

thetic purposes, mainly due to their reputation of being too reactive. Although most recent implementations of NHCs as synthetic intermediates relied on 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 scaffolds were obtained in a straightforward and efficient manner, starting from readily available 5-bromoimidazo[1,5-*a*]pyridinium salts. Depending on the nature of the coupling reagent, the annulation reaction proceeds through two different pathways, as characterized by the order of the two key reactions, namely, aromatic nucleophilic substitution by an enolate-type reagent and 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 the slow generation of NHCs as elusive intermediates. This paves the way to rethinking disconnections for retrosynthetic analysis in heterocyclic chemistry and to conceiving new mesoionic compounds.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenes · heterocycles · reactive intermediates · tautomerism · zwitterions

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