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Betaine Adducts of N-Heterocyclic Carbenes: Synthesis, Properties, and Reactivity

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N-Heterocyclic carbenes (NHCs) form stable zwitterionic adducts with a range of heteroallenes, ketenes, and allenes. Although the first representatives of this class of inner salts were first investigated as far back as the 1960s, they have enjoyed a sustained interest from the chemical community over the years. Depending on the nature of their anionic moiety, NHC betaines display a very broad palette of reactivities and have found applications in various fields of organic synthesis and catalysis. In this Microreview, the synthesis, properties, and reactivity of NHC betaines are surveyed. The NHCs under consideration include ylidenes derived from imidazole, benzimidazole, imidazoline, thiazole, or triazole, and the heteroallenes investigated so far are carbon dioxide, carbon disulfide, isocyanates, isothiocyanates, and their selenium analogues. A historical background is provided for each type of adduct under consideration, but emphasis is placed mainly on developments that have appeared in the literature within the past few years.

1. Introduction

N-Heterocyclic carbenes (NHCs) have become ubiquitous in organometallic chemistry and catalysis over the past two decades.[1,2] These divalent carbon species behave as neutral, two-electron ligands with only little π-back-bonding tendency.[3] They serve as phosphane mimics, yet they are better σ-donors and form stronger bonds to metal centers than most phosphanes. Their electronic and steric properties are liable to ample modifications simply by varying the substituents on the heterocyclic ring, and as they are powerful nucleophilic agents, they have also been widely used as reagents[4] and organocatalysts[5] in their own right, sometimes in an asymmetric fashion.[6]

Most NHCs investigated so far are derived from imidazole, triazole, or thiazole (Scheme 1). These five-membered, electron-rich heterocycles provide a suitable framework that stabilizes the carbene center located between two donor atoms.[7] So far, investigations have focused mainly on imidazolin-2-ylidene and imidazolidin-2-ylidene deriva-

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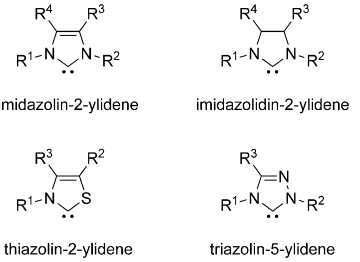
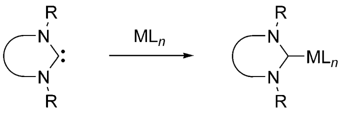
tives. Countless structural variations have been performed on the nitrogen substituents of these two ring systems, in either a symmetric ($R^1 = R^2$) or asymmetric ($R^1 \neq R^2$) fashion.[8] Substitution on the 4- and 5-positions of the heterocycle is also common, although slightly less frequent. Suitable R^3 and R^4 groups include hydrogen, chlorine, bromine, methyl, and phenyl groups, among others.[9] Stable carbenes derived from thiazole or triazole have been less studied than their imidazole-based counterparts, yet they have proven to be valuable intermediates for various organic or organometallic catalytic processes.[10]



Scheme 1. Stable NHCs derived from various ring systems.

Thanks to their remarkable electron-donating properties and structural diversity, NHCs form stable complexes not only with all the transition metals, whether in high or low oxidation state,[2] but also with main group elements,[11] such as lithium or beryllium, as well as lanthanides and actinides[12] [Equation (1)]. Carbenes also form stable, neutral adducts with a variety of organic species, including alcohols,[13] amines,[14] and chloroform.[15] The reaction proceeds via insertion of the carbene into a labile H–Z bond and is thermally reversible [Equation (2)].



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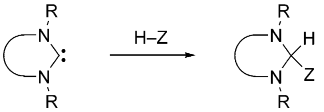
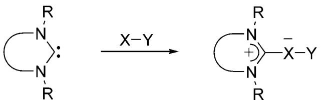


(2)

The formation of zwitterionic adducts via nucleophilic attack of a suitable electrophile is a distinct type of transformation [Equations (3) and (4)]. Reactions with halogens,[16] boranes,[17] silicon tetrachloride,[18] or phosphorus pentafluoride,[19] to name just a few, lead to ylide products [Equation (3)], whereas the use of allenes, ketenes, or heteroallenes of the X=C=Y type affords betaines [Equation (4)].[20]



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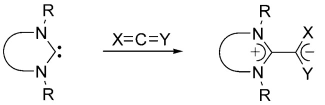


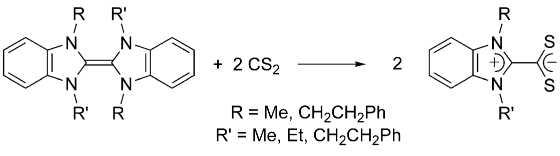
(4)

The various addition compounds of carbenes with nonmetals were reviewed by Kirmse in 2005.[21] The same year, Kuhn and Al-Sheikh published a more specific survey on the chemistry of imidazolin-2-ylidene species and main group elements.[11] In this contribution, we shall focus on the synthesis, properties, and reactivity of zwitterions of the betaine type, in other words neutral molecules having charge-separated forms with an onium atom bearing no hydrogen atoms and which is not adjacent to the anionic atom.[22] Unlike ylides, for which a non-charged ylene resonance form may be written, these compounds cannot be represented without formal charges. Although a historical background will be provided for each type of adduct under discussion, emphasis will be placed mainly on developments that have appeared in the literature within the past few years.

2. Adducts of NHCs with Carbon Disulfide

2.1. Synthesis

Although stable free carbenes were first isolated and characterized by Arduengo in 1991,[23] the chemistry of their formal enetetramine dimers has been under investigation since the 1960s.[24] It was soon recognized that these electron-rich olefins could be cleaved in exothermic reactions by various electrophiles, including carbon disulfide, to afford stable zwitterionic adducts, and initial reports describing the preparation of imidazol(in)ium-2-dithiocarboxylates were based on this approach. The procedure was successfully applied to a range of *N*-alkyl or *N*-aryl bis(imidazolidin-2-ylidene) starting materials (R = Me,[25] Et,[25,26] CH_2Ph,[25] Ph,[25,27,28] p-C_6H_4Cl)[25] (Scheme 2). It was also subsequently extended to symmetrical (R = R′ = Me,[29] CH_2CH_2Ph)[30] or unsymmetrical (R = CH_2CH_2Ph, R′ = Et)[30] benzimidazolidine derivatives [Equation (5)]. Some of these dimers were shown to be in equilibrium with the corresponding NHCs in solution (the so-called "Wanzlick equilibrium").[31] Their prior dissociation into carbenes is not required, however, to account for the formation of $NHC·CS_2$ adducts – a more likely mechanism involves the direct reaction of enetetramines with carbon disulfide, followed by cleavage of the remaining exocyclic C–C bond in a subsequent step (Scheme 2).[25]



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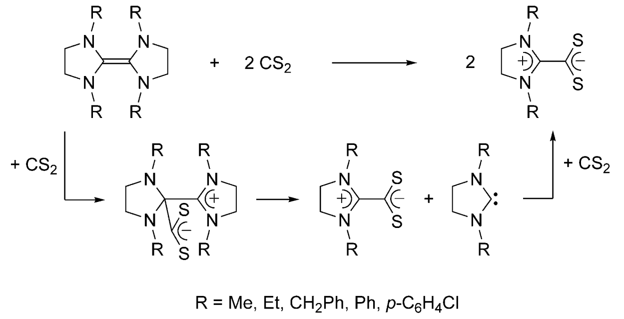
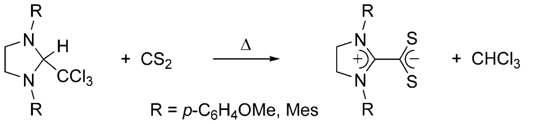


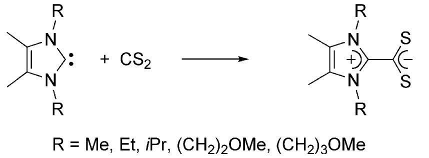
Scheme 2. Reaction of enetetramine dimers with carbon disulfide.

Another less common strategy to obtain NHC·CS_2 betaines from stable NHC precursors involves the displacement of chloroform by carbon disulfide upon thermolysis of NHC·$CHCl_3$ adducts [Equation (6)]. To the best of our knowledge, only two examples of this reaction have been reported in the literature starting from saturated imidazolidine heterocycles bearing either *p*-anisyl[25] or mesityl[32] substituents on their nitrogen atoms.



(6)

In 1993, Kuhn et al. isolated a series of 1,3-dialkyl-4,5-dimethylimidazolin-2-ylidene species by reduction of the corresponding thioketones with potassium in refluxing thf.[33] These free carbenes were treated with a stoichiometric amount of carbon disulfide in thf at 0 °C to afford dithiocarboxylate inner salts in good yields [Equation (7)]. A first report focused on the preparation and characterization of three adducts bearing simple alkyl groups on their nitrogen atoms (R = Me, Et, *i*Pr).[34] The authors later complemented this study by introducing alkoxy-terminated alkyl chains at the heterocycle 1,3-positions [R = $(CH_2)_2OMe$ or $(CH_2)_3OMe$].[35] Their methodology was further exploited by Enders and co-workers in 1996 to prepare the CS_2 adduct of 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene [Equation (8)].[36]



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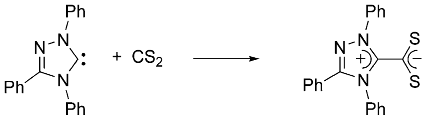
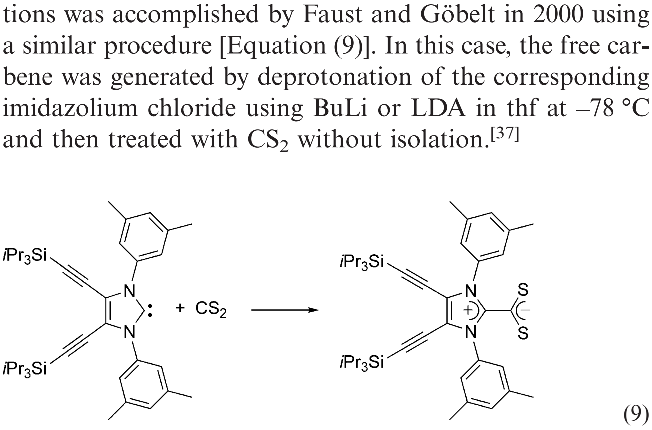


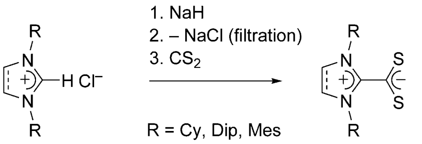
(8)

Synthesis of a 1,3-dixylylimidazolium-2-dithiocarboxylate with silylated alkynyl functional groups on its 4,5-positions was accomplished by Faust and Göbelt in 2000 using a similar procedure [Equation (9)]. In this case, the free carbene was generated by deprotonation of the corresponding imidazolium chloride using BuLi or LDA in thf at –78 °C and then treated with CS_2 without isolation.[37]



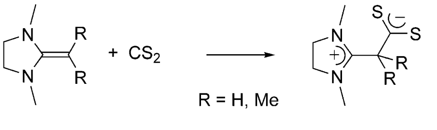
(9)

An in situ protocol was also chosen by Delaude et al. for the synthesis of five representative NHC·CS_2 adducts bearing alkyl or aryl groups on their nitrogen atoms [Equation (10)]. Imidazol(in)ium chlorides served as starting materials and were treated with sodium hydride in thf. Once the deprotonation was complete, the suspensions were allowed to settle and the inorganic by-product (NaCl) was filtered off. Addition of a small excess of carbon disulfide to the free carbene solutions led to an instantaneous color change and the rapid formation of zwitterionic adducts. 1,3-Dimesitylimidazolium-2-dithiocarboxylate (IMes·CS_2) and its saturated heterocycle analogue (SIMes·CS_2) precipitated from the reaction medium, whereas betaines bearing 2,6-diisopropylphenyl (IDip·CS_2 and SIDip·CS_2) or cyclohexyl substituents (ICy·CS_2) on their nitrogen atoms remained soluble in thf.[38]



(10)

Last but not least, the group of Nakayama has reported the formation of 1,3-dimethylimidazolinium-2-dithiocarboxylate from 1,3-dimethyl-2-methyleneimidazolidine and disulfur dichloride in the presence of triethylamine.[39] The reaction most likely proceeds via two consecutive addition–elimination steps (Scheme 3). The same NHC·CS_2 adduct was also obtained upon treatment of 1,3-dimethylimidazolinium-2-diselenocarboxylate with elemental sulfur (see Section 6).[40] Interestingly, when carbon disulfide was employed as the electrophile in the absence of a base, a new type of zwitterion was obtained in which the imidazolinium cation and the dithiocarboxylate anion were separated by an intermediate sp^3 carbon atom [Equation (11)].[41]



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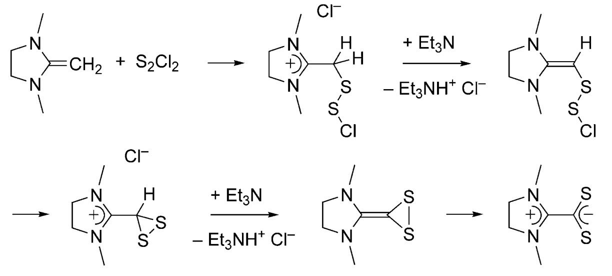


Scheme 3. Reaction of a cyclic enediamine with S_2Cl_2 and Et_3N.

2.2. Properties

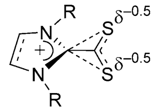
Because NHC·CS_2 betaines are stable, crystalline, ionic compounds, determination of their molecular structures by X-ray diffraction analysis is rather straightforward.[38] Indeed, a wide range of imidazol(in)ium or benzimidazolium derivatives bearing various alkyl or aryl groups on their nitrogen atoms have been characterized by this technique (Scheme 4). In all the compounds investigated so far, the central heterocycle and the dithiocarboxylate unit are nearly orthogonal, with N1–C2–C6–S7 torsion angles varying between 72° and 115° (Table 1). Nearly equivalent distances for both C–S bonds indicate that the negative charge is equally distributed between the two sulfur atoms. The rather long C2–C6 distances (ca. 1.50 Å) confirm the poor electronic communication between the dithiocarboxylate anion and the onium moiety. Similar conformations have also been observed in acyclic amidinium dithiocarboxylates.[42]

According to Nakayama et al., the perpendicular arrangement between the CS_2^- and N_2C^+ parts of 1,3-dimethylimidazolinium dithiocarboxylate and its thioseleno and diseleno analogues is probably retained in solution, as suggested by ^{1}H NMR spectroscopic data and ab initio calculations.[40] Through-space attractive Coulombic interactions between the imidazolium C2 carbon atom and the lone pair of electrons on the sulfur atoms are thought to be responsible for this situation (Scheme 5). In addition, incorporation of bulky aryl substituents, such as 1,3-bis(2,4,6-trimethylphenyl) or 1,3-bis(2,6-diisopropylphenyl) groups, on the nitrogen atoms should further stabilize a perpendicular disposition of the imidazol(in)ium and dithiocarboxylate ions due to steric effects.

Table 1. Selected bond lengths [Å] and angles [°] derived from the crystal structures of various NHC·CS_2 betaines.[a]

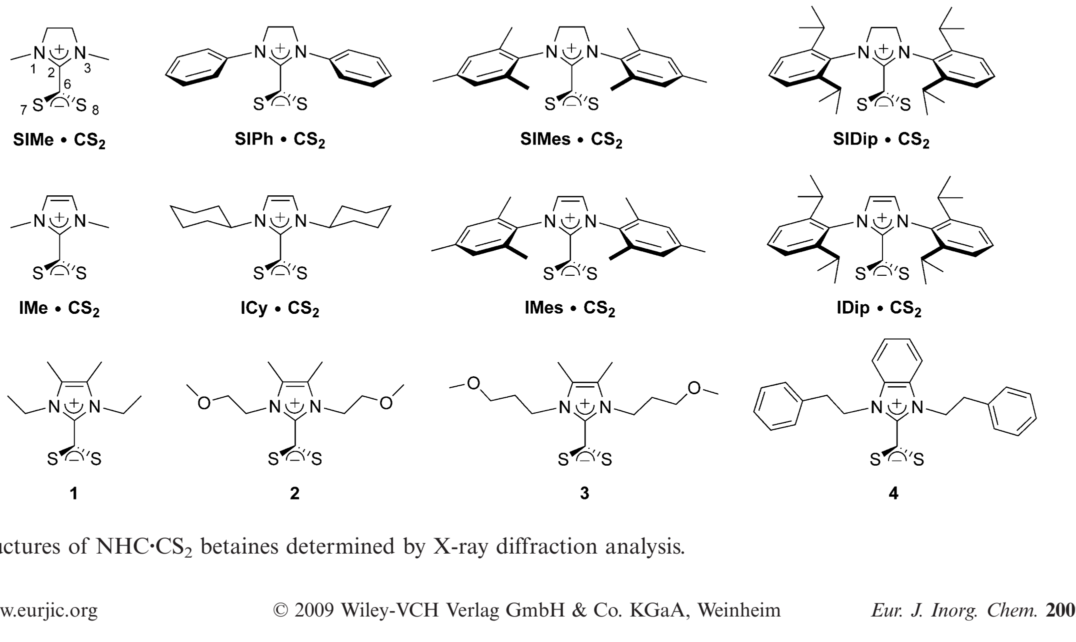
Compound	C2–C6	S7–C6–S8	N1–C2–C6–S7	Ref.
SIMe·CS_2	1.484(2)	131.3(1)	88.1	[40]
SIPh·CS_2	1.497(6)	131.3(3)	79.2	[28]
SIMes·CS_2	1.502(6)	130.3(3)	92.4(2)	[38]
SIDip·CS_2	1.495(2)	131.5(2)	92.0(2)	[38]
IMe·CS_2	1.498(3)	129.4(1)	71.7	[43]
ICy·CS_2[b]	1.483(3)	130.2(1)	87.0(3)	[38]
IMes·CS_2[b]	1.483(8)	129.1(4)	114.7(5)	[38]
IDip·CS_2	1.487(2)	128.5(2)	93.2(2)	[38]
1	1.498(4)	129.0(2)	80.8	[34]
2	1.513(2)	129.95(10)	94.0	[35]
3	1.486(6)	130.1(3)	77.5	[35]
4[b]	1.484(3)	130.24(13)	95.7(2)	[44]

[a] See Scheme 4 for molecular structures and atom numbering system. [b] Data from only one of the two molecules present in the asymmetric unit.



Scheme 5. Coulombic interactions responsible for the orthogonal disposition of the N_2C^+ and CS_2^- units in NHC·CS_2 betaines.

The antifungal and antibacterial properties of benzimidazolium-2-dithiocarboxylate (**4**) and another related NHC·CS_2 adducts have been investigated against standard strains of yeasts and bacteria. Although they display a significant activity against several pathogenic agents in vitro, none of them was found to be effective against *Escherichia coli* and *Pseudomonas aeruginosa* at the concentrations studied.[29,30]

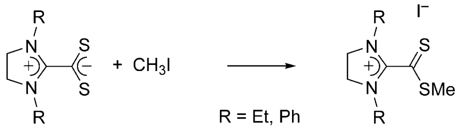


Scheme 4. Structures of NHC·CS_2 betaines determined by X-ray diffraction analysis.

2.3. Reactivity

Various reactions of NHC·CS$_2$ adducts have been reported in the literature, although none of them involve the regeneration of free carbenes. Thus, the reactivity of these inner salts is determined mainly by the presence of a Lewis acid center in the N-heterocyclic ring, while the CS$_2$ group acts as a Lewis or Brønsted base. To the best of our knowledge, this dual behavior has been exploited in a single catalytic application so far, namely the cyanosilylation of aldehydes with imidazolinium-2-dithiocarboxylates as organocatalysts.[45] Stoichiometric reactions with inorganic, organic, or organometallic compounds are better documented, and a few representative examples are listed below.

Upon alkylation with methyl iodide, SIEt·CS$_2$[26] and SIPh·CS$_2$[27] afford the corresponding methyl dithiocarboxylates [Equation (12)]. The same reaction also occurs with an extra spacer inserted between the two zwitterionic groups [Equation (13)].[41]



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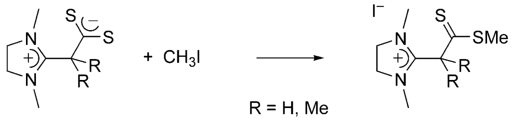
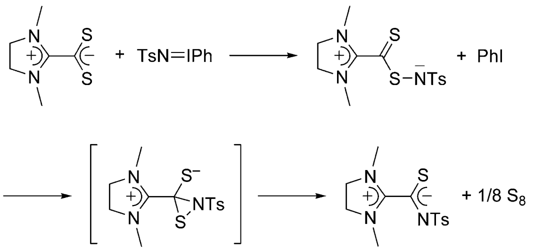


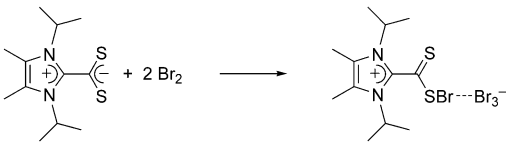
(13)

1,3-Dimethylimidazolidinium-2-dithiocarboxylate has been S-iminated with [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane in dichloromethane at –18 °C. The nitrene inner salt initially obtained is very labile in solution and cannot be isolated in analytically pure form. It decomposes during work-up to afford a tosylisothiocyanate betaine instead (Scheme 6). This adduct can also be obtained directly in higher yield when the reaction is carried out at room temperature.[46]



Scheme 6. Reaction of SIMe·CS$_2$ with TsN=IPh.

The reaction of 1,3-diisopropyl-4,5-dimethylimidazolium-2-dithiocarboxylate with two equivalents of bromine in dichloromethane leads to the formation of a well-defined ion pair whose molecular structure has been determined by X-ray crystallography [Equation (14)]. When a larger proportion of halogen is employed, only uncharacterized decomposition products are obtained, probably due to halogenation of the alkyl side-chains.[34]



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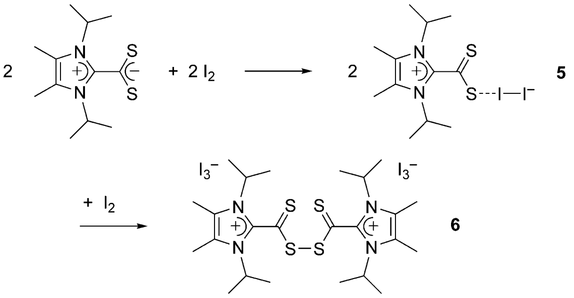
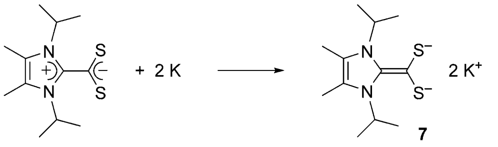
A different reaction path is observed with iodine. In this case, addition of a stoichiometric amount of halogen affords the intermediate charge-transfer complex **5**, whose molecular structure has been established by XRD. In the presence of excess iodine, a clean oxidative coupling occurs to give the dicationic salt **6**, which has been fully characterized [Equation (15)].[34]



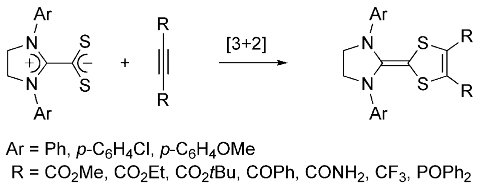
(15)

The reduction of 1,3-diisopropyl-4,5-dimethylimidazolium-2-dithiocarboxylate with potassium in thf gives the potassium 1,1-dithiolate **7** as a yellow, air-sensitive solid [Equation (16)]. The structure of the solvate complex [**7**·(2 thf)·(1/3 K$_2$S$_2$)], which was found to include a K$_{12}$S$_{12}$ cluster, has been determined by single-crystal X-ray diffraction analysis. A detailed examination of the geometry of **7** in this supramolecular assembly revealed that the 1,1-dithiolate unit and the five-membered ring are coplanar, which means that reduction of the carbene adduct significantly alters the distribution of the π electrons and causes a major reorientation of the CS$_2$ moiety.[47] Subsequent electrochemical studies confirmed that the two-electron reduction of 1,3-dialkyl-4,5-dimethylimidazolium-2-dithiocarboxylates is accompanied by considerable structural changes.[48]



(16)

The use of NHC·CS$_2$ adducts as cycloaddition partners has been investigated by Regitz and co-workers. No reaction occurred when a series of imidazolinium-2-dithiocarboxylates bearing alkyl or aryl groups on their nitrogen atoms were treated with electron-rich alkynes, such as phenyl- or diphenylacetylene, or with electron-poor alkenes, such as tetracyanoethylene. When electron-poor alkynes were employed, however, 1,3-diaryl betaines quickly reacted to afford the corresponding [3+2] cycloaddition products in high yields [Equation (17)]. Some of these bicyclic products were further treated with dimethyl acetylenedicarboxylate. Under these conditions, a [2+2] cycloaddition followed by electrocyclic ring-opening was postulated. The overall transformation led to 1,3-butadiene derivatives [Equation (18)]. The intervention of zwitterionic resonance forms was invoked to account for the broadening of some ^{1}H NMR signals, although this hypothesis was not further investigated.[25] Alternatively, a stepwise mechanism may also be operative, as evidenced in related reactions of thione S-methylides.[49] When 1,3-dialkylimidazolinium-2-dithiocarboxylates were used as substrates, no intermediate could be detected and only the final butadiene products were isolated, even when a sub-stoichiometric amount of alkyne was added to the dithiocarboxylate starting materials at low temperature.[25]



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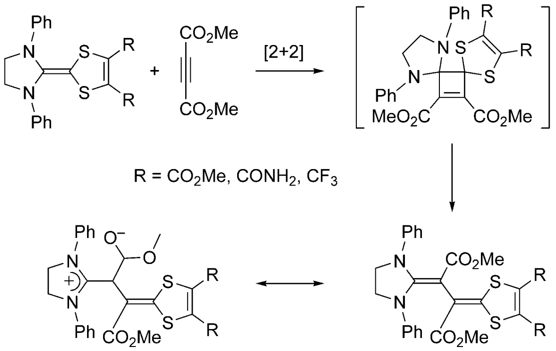
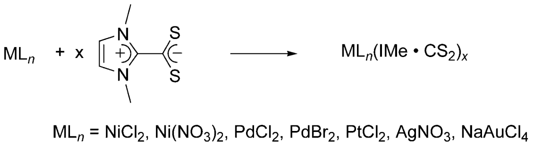


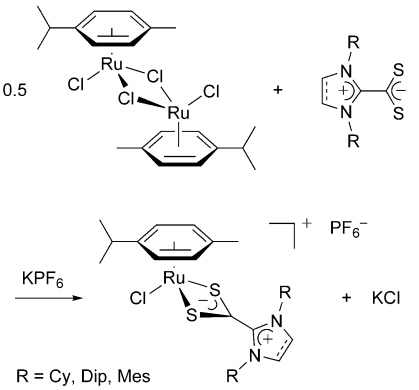
(18)

Whereas phosphane–carbon disulfide adducts have been widely employed as κ^1*S*, κ^2*S,S′*, or κ^3*S,C,S′* ligands for mono- and binuclear metal complexes,[50] the coordination chemistry of NHC·CS$_2$ betaines is still largely uncharted territory. Preliminary experiments in this field were conducted by Borer et al., who showed that 1,3-dimethylimidazolium-2-dithiocarboxylate forms stable complexes with a range of transition metal halides or nitrates [Equation (19)]. The products obtained were characterized by IR and UV/Vis spectroscopy only. Electrical conductivity, magnetic susceptibly, or cyclic voltammetry measurements complemented the analyses in some cases, but no NMR or XRD analyses were reported. Thus, the accurate structure of the products obtained, and the binding mode of the zwitterionic ligand, remains highly speculative.[51]



(19)

A more detailed investigation of the organometallic chemistry of imidazol(in)ium-2-dithiocarboxylates was initiated by Delaude and co-workers. When treated with the dimer [{RuCl$_2$(*p*-cymene)}$_2$] and potassium hexafluorophosphate, the NHC·CS$_2$ betaines retain their zwitterionic nature and lead to cationic complexes of the [RuCl(*p*-cymene)(NHC·CS$_2$)]PF$_6$ type, in which the dithiocarboxylate group acts as a κ^2*S,S′* chelating ligand [Equation (20)]. The molecular structure of the cationic complex bearing the IMes·CS$_2$ ligand has been solved by X-ray crystallography.[52]

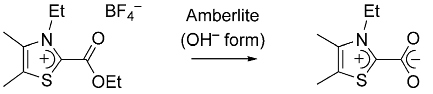


(20)

3. Adducts of NHCs with Carbon Dioxide

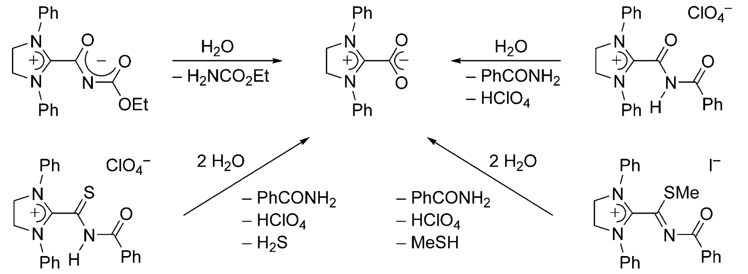
3.1. Synthesis

The first synthesis of an NHC·CO$_2$ adduct dates back to 1974. During the course of their investigations on betaines obtained by treating an imidazolidin-2-ylidene dimer with acyl isocyanates or isothiocyanates (see following Sections), Schössler and Regitz observed the formation of SIPh·CO$_2$ by hydrolysis of more complex zwitterionic adducts under various experimental conditions (Scheme 7).[27] A related indirect method was devised by Castells et al. for the preparation of 3-ethyl-4,5-dimethylthiazolium-2-carboxylate via ester hydrolysis on a basic ion-exchange resin [Equation (21)].[53]



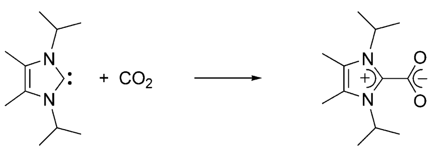
(21)

The preparation of a betaine by direct carboxylation of a free carbene with carbon dioxide was achieved for the first time by Kuhn and co-workers in 1999 using 1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidene as starting material [Equation (22)].[54] The same strategy was adopted by Louie et al. for the synthesis of the adducts IMes·CO$_2$ and IDip·CO$_2$ a few years later.[55] This latter team further streamlined the experimental protocol by performing the



Scheme 7. Formation of SIPh·CO_2 by hydrolysis of more complex zwitterionic adducts.

deprotonation of imidazolium salts with potassium *tert*-butoxide under a CO_2 atmosphere, thereby avoiding the isolation of air- and moisture-sensitive free carbenes. The inorganic by-products (KCl or KBF_4) were removed by selective redissolution of the zwitterionic adducts in dichloromethane and filtration through Celite. Delaude et al. used a slightly modified version of this in situ procedure in which the filtration step is performed prior to the introduction of carbon dioxide [Equation (23)]. The Liège group also further extended the scope of the method by preparing additional saturated or unsaturated NHC·CO_2 betaines bearing cyclohexyl, 2,6-diisopropylphenyl, or mesityl groups on their nitrogen atoms.[56]



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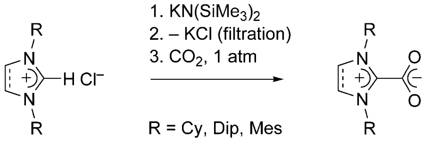

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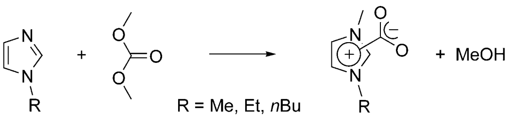
The unexpected formation of 1,3-dimethylimidazolium-2-carboxylate from 1-methylimidazole and dimethyl carbonate was discovered in 2003. This transformation is believed to proceed via initial alkylation of the imidazole 3-position, followed by an acid-base reaction between the methyl carbonate anion and the imidazolium cation. Decomposition of the unstable methyl hydrogen carbonate into methanol and carbon dioxide would then provide the capping group for 1,3-dimethylimidazol-2-ylidene (Scheme 8).[57] This procedure was further extended to 1-ethylimidazole[58] and 1-butylimidazole[59] [Equation (24)]. Prolonged heating at high temperature (70–120 °C) in sealed tubes was required to complete the transformation in all cases. Under these conditions, competitive formation of the thermodynamically more stable 4- and 5-carboxylate isomers was sometimes observed. Careful optimization of the reaction conditions led to the isolation of almost pure 1,3-dimethylimidazolium-2-carboxylate when the alkylation/carboxylation of 1-methylimidazole with dimethyl carbonate was performed below 95 °C, whereas the 4-carboxylate isomer was obtained in pure form when working above 120 °C.[60]



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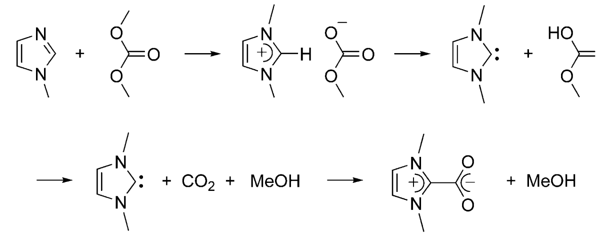
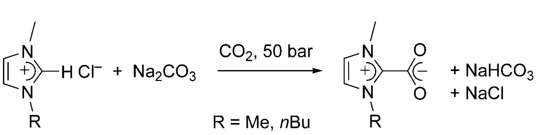


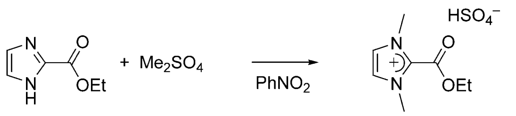
Scheme 8. Reaction of 1-methylimidazole with dimethyl carbonate.

The direct carboxylation of two 1,3-dialkylimidazolium chlorides with Na_2CO_3/CO_2 in dmf was reported by Tommasi and Sorrentino in 2006 [Equation (25)]. High pressure (50 bar CO_2) and high temperature (110 °C) were required to achieve satisfactory conversions. Carrying out the reaction at 135 °C decreased the selectivity in favor of the 1,3-dialkylimidazolium-2-carboxylates by enabling the formation of the 4- and 5-carboxylate isomers in significant proportions.[61]



(25)

To avoid any complication due to isomerization, 1,3-dimethylimidazolium-2-carboxylate was prepared in two steps by methylation of ethyl 1*H*-imidazole-2-carboxylate with dimethyl sulfate in the presence of nitrobenzene, followed by hydrolysis with 50% aqueous sulfuric acid [Equations (26) and (27)]. A closely related procedure starting from imidazole-4-carboxylic acid and using basic conditions for saponification led to the corresponding 4-carboxylate adduct [Equations (28) and (29)].[62]



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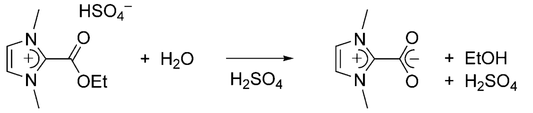

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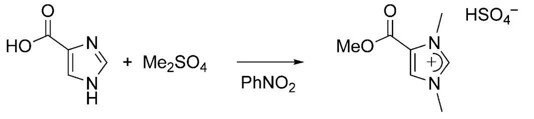

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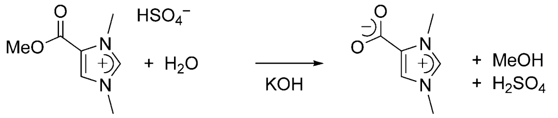
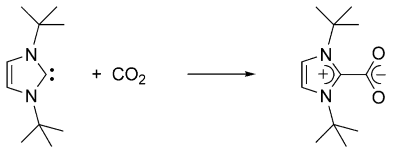


(29)

Although this method has limited preparative value, formation of I*t*Bu·CO_2 was evidenced after UV irradiation of an oxygen-saturated solution of 1,3-di-*tert*-butylimidazolin-2-ylidene and *meso*-tetraphenylporphyrin (TPP) in benzene.[63] Singlet oxygen was held responsible for the formation of an initial carbonyl oxide, which cyclized into an unstable dioxirane intermediate before affording the NHC·CO_2 product and the corresponding diimine (Scheme 9). In the absence of TPP, no consumption of the free carbene was detected, thereby suggesting that oxidation occurred only with $^1O_2$ but not with $^3O_2$. Thus, the spin-selection rule was respected by the singlet carbene. For control purposes, the carboxylate adduct under study was also prepared by bubbling carbon dioxide into a solution of I*t*Bu [Equation (30)]. Its structure was established by ^{1}H NMR spectroscopy.



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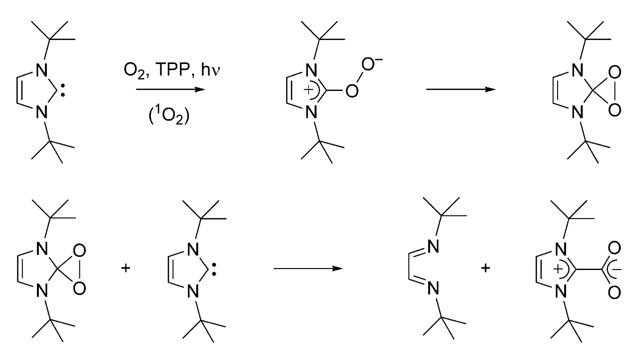


Scheme 9. Reaction of I*t*Bu with singlet oxygen.

3.2. Properties

NHC·CO_2 adducts are more labile in solution and less thermally stable in the solid state than their dithiocarboxylate analogues. This latter point has been evidenced by thermogravimetric analysis (TGA) of several imidazol(in)ium-2-carboxylates[55,56] and dithiocarboxylates.[38] The case of 1,3-dicyclohexylimidazolin-2-ylidene adducts is representative (Figure 1). ICy·CO_2 begins to lose weight at around 80 °C, whereas ICy·CS_2 resists decomposition until about 200 °C. Both NHC adducts are, however, more stable than tricyclohexylphosphonium dithiocarboxylate, which cleanly starts losing its CS_2 fragment at around 60 °C.[38] These observations are in line with the greater nucleophilicity and basicity of NHCs compared to phosphanes.[2a] Indeed, only strongly basic trialkylphosphanes form stable, isolable zwitterions with carbon disulfide.[50] Less basic triarylphosphanes do not afford stable adducts with CS_2 alone, and, to the best of our knowledge, no phosphane whatsoever reacts with CO_2.

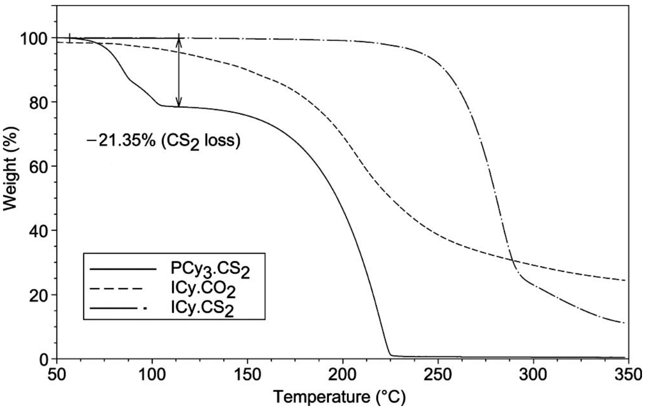


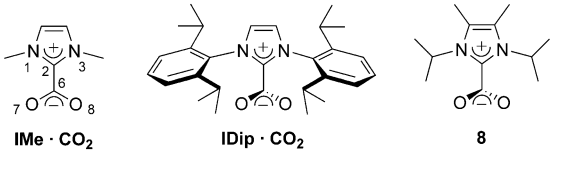
Figure 1. TGA curves of three betaines derived from PCy_3 or ICy.

The relative stabilities of three NHC·CO_2 adducts in solution have been determined by Louie and co-workers from crossover experiments between free carbenes and their betaines. Thus, the addition of 1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidene to either IMes·CO_2 or IDip·CO_2 leads to quantitative formation of carboxylate **8** and IMes or IDip, while the reverse addition of IMes or IDip to adduct **8** gives no reaction. Similarly, the addition of IMes to IDip·CO_2 affords IMes·CO_2 and IDip, whereas the reverse reaction was not observed. The relative order of stability is therefore: **8** > IMes·CO_2 > IDip·CO_2. TGA data corroborated this analysis.[55] Transfer of the CO_2 moiety between 1,3-dimethyl- or 1-butyl-3-methylimidazolium-2-carboxylate and 1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidene has also been observed by Tommasi and Sorrentino by ^{13}C NMR spectroscopy.[59]

Both 1,3-dimethyl- and 1-butyl-3-methylimidazolium-2-carboxylates are very stable toward decarboxylation at room temperature in common organic solvents (acetone, alcohols, dmf). Above 100 °C, however, their behavior depends on the nature of the solvent used. For example, they resist degradation until 140 °C when heated in ethylene glycol under a slow stream of nitrogen, whereas significant decomposition occurs in the presence of oxygen, as evidenced by ^{13}C NMR analysis.[59]

Very recently, Lu et al. further investigated the stability of IDip·CO_2 and SIDip·CO_2 in dichloromethane at various temperatures by in situ FT-IR monitoring of their ν(CO_2) asymmetric stretching vibration bands. The latter adduct is more stable in solution than its aromatic heterocycle counterpart. As expected, temperature was found to have a marked influence on the rate of decomposition. Thus, IDip·CO_2 remains unchanged after 4 h in CH_2Cl_2 at 12 °C but disappears almost completely within 1 h at 100 °C. Degradation was significantly retarded when a high CO_2 pressure was applied to the IR cell (20 bar), thereby suggesting that a dynamic equilibrium exists in solution between the zwitterionic compound and its neutral constituents.[64] A similar conclusion was also reached by Louie et al. based on the enhancement of the carbonyl resonance observed by ^{13}C NMR spectroscopy when a solution of IDip·CO_2 was placed under 1 atm of $^{13}CO_2$.[55] Unrelated experiments from the group of Schmidt showed that H/D-exchange takes place at the C4 and C5 positions of 1,3-dimethylimidazolium-2-carboxylate dissolved in MeOD, but not in [D_6]-DMSO.[62]

The solid-state geometries of three carboxylate inner salts were determined by X-ray diffraction analysis (Scheme 10 and Table 2). The same conclusions that were drawn from the crystal structures of NHC·CS_2 adducts also apply to IDip·CO_2 and compound **8**. As discussed previously in Section 2.2, no delocalization of the electron density from one end of the molecule to the other is possible because the imidazole ring is almost perpendicular to the plane defined by the O–C–O unit. Only in 1,3-dimethylimidazolium-2-carboxylate are the imidazolium and the carboxylate groups almost coplanar, with a twist angle of 29°. In this case, steric requirements from both the nitrogen substituents and the CO_2 moiety are minimized, thus allowing the formation of hydrogen-bonded sheets with a dense columnar π–π stacking in the crystal structure.[57]



Scheme 10. Structures of NHC·CO_2 betaines determined by X-ray diffraction analysis.

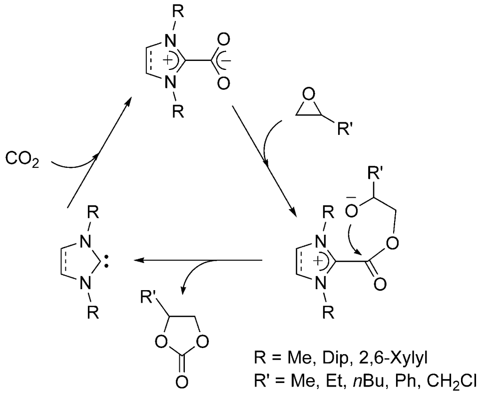
Table 2. Selected bond lengths [Å] and angles [°] derived from the crystal structures of various NHC·CO_2 betaines.[a]

Compound	C2–C6	O7–C6–O8	N1–C2–C6–O7	Ref.
IMe·CO_2	1.523(3)	129.66(18)	29.03	[57]
IDip·CO_2	1.511(4)	129.9(3)	89.75	[55]
8	1.536(5)	131.2(4)	111.0(2)	[54]

[a] See Scheme 10 for molecular structures and atom numbering.

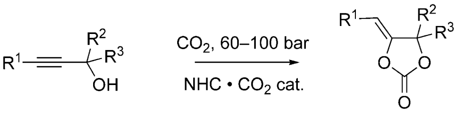
3.3. Reactivity

Following the seminal contribution of Breslow regarding the possible intervention of NHCs in the thiazolium-mediated benzoin condensation,[65] a great deal of effort was put into the development of highly efficient, enantioselective carbene-based catalysts for this reaction.[66] Most systems investigated so far have been generated by deprotonation of azolium salts, although an early example of organocatalysis with a thiazolium-2-carboxylate was reported by Castells et al. in 1985. This NHC precursor cleanly led to the condensation of benzaldehyde or dodecanal in the absence of any base.[53] More recently, the catalytic activity of five imidazol(in)ium-2-carboxylates was probed in the coupling reaction of carbon dioxide and epoxides to afford cyclic carbonates. The mechanism postulated for this transformation involves the intermediacy of a new zwitterionic adduct formed upon nucleophilic addition of the carboxylate anion to the epoxide (Scheme 11). Catalytic tests were performed at 120 °C under CO_2 pressure (20 bar) for 24 h using a 0.2 mol-% loading of zwitterionic adduct. Due to its high solubility and lability, IDip·CO_2 was singled out as the most efficient coupling agent in the series under examination. Addition of an electrophilic co-catalyst such as (Salen)AlEt further enhanced its activity because of intermolecular cooperative effects.[64]



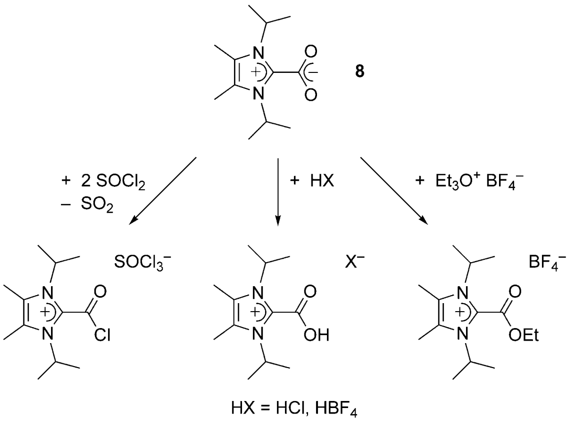
Scheme 11. Possible mechanism for the coupling reaction of CO_2 with epoxides catalyzed by NHC·CO_2 betaines.

The ability of NHC·CO_2 betaines to catalyze the carboxylative cyclization of propargyl alcohols into 4-alkylidene-1,3-dioxolan-2-one derivatives was first disclosed in a 2006 patent by Kayaki and Ikariya [Equation (31)]. The reactions were carried out in autoclaves at high pressure (up to 100 bar) and high temperature (up to 200 °C) with a range of imidazol(in)ium-2-carboxylates bearing isopropyl, *tert*-butyl, or mesityl groups on their nitrogen atoms.[67] Sub-



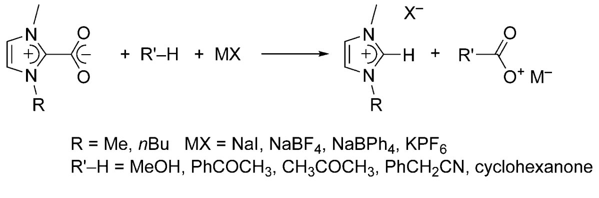
R^1 = H, aryl, alkenyl, alkynyl R^2, R^3 = alkyl, cycloalkyl, phenyl (31) strates with a terminal triple bond (R^1 = H) instead of an internal one (R^1 = aryl, alkenyl, alkynyl) were found to be more reactive and required slightly less forcing conditions.[68]

A few stoichiometric reactions between NHC·CO_2 betaines and inorganic reagents have been carried out by Kuhn and co-workers (Scheme 12). Thus, protonation of 1,3-diisopropyl-4,5-dimethylimidazolium-2-carboxylate (**8**) with hydrogen chloride or tetrafluoroboric acid under anhydrous conditions affords the corresponding imidazoliumcarboxylic acid, whose dissociation constant was determined in aqueous solution. The rather high acidity observed (pK_a = 1.8) reflects the strong electron-attracting effect exerted by the imidazolium substituent on the carboxylic acid function. Other standard functional group interconversions include the formation of an acid chloride upon treatment of the betaine with thionyl chloride or its alkylation with triethyloxonium tetrafluoroborate (Scheme 12).[54]



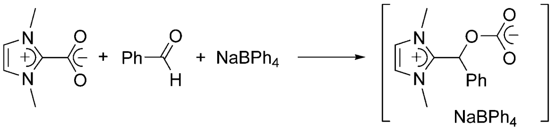
Scheme 12. Functional group interconversion of the carboxylate group of 1,3-diisopropyl-4,5-dimethylimidazolium-2-carboxylate (**8**).

The carboxylation of various activated hydrogen compounds with 1,3-dialkylimidazolium-2-carboxylates in the presence of alkali metal salts has been investigated by Tommasi and Sorrentino [Equation (32)]. Initial experiments focused on the reaction of methanol or acetophenone to afford methylcarbonate or benzoylacetate derivatives.[59] The procedure was subsequently extended to acetone, cyclohexanone, and phenylacetonitrile.[68] In all cases, a quantitative transfer of CO_2 was achieved at room temperature after a variable period of time, depending on the solubility of the ionic starting materials in the reaction mixture. Because the imidazolium salt by-products are ionic liquids, they could be easily separated from the metal carboxylates.



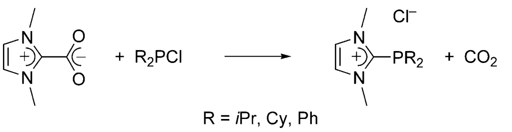
(32)

The reaction of benzaldehyde with 1,3-dimethylimidazolium-2-carboxylate and $NaBPh_4$ under similar conditions affords a single insertion product that still contains the imidazolium and the carboxylate units. This betaine was isolated as a 1:1 complex with the metal salt [Equation (33)].[59]



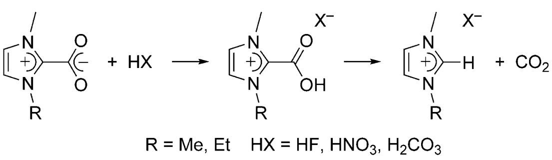
(33)

Three imidazolium-2-phosphane chlorides have been synthesized by electrophilic addition of a suitable chlorophosphane to 1,3-dimethylimidazolium-2-carboxylate [Equation (34)]. Ion metathesis with a small excess of potassium hexafluorophosphate then leads to the corresponding halide-free salts in high yields. The electronic and steric properties of these new phosphane ligands have been thoroughly investigated and their coordination chemistry with nickel and platinum explored.[69]



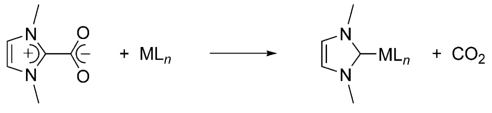
(34)

Currently, the most common synthetic pathways for preparing imidazol(in)ium-based ionic liquids (ILs) with bulky polyatomic anions such as BF_4^-, PF_6^-, $CF_3SO_3^-$ (TfO^-), or $(CF_3SO_2)_2N^-$ (Tf_2N^-) involve metathesis reactions from halide intermediates.[70] The ion exchange is usually achieved via liquid/liquid separation or precipitation of an inorganic halide salt, such as AgCl. Contamination of the final products with water or halide traces is a major concern as these impurities may dramatically alter the physical and chemical properties of the ILs[71] and interfere with their catalytic activities.[72] New, halide-free methodologies that would allow direct access to a wide range of organic and inorganic counterions are therefore eagerly sought.[73] A promising strategy relies on 1,3-dialkylimidazolium-2-carboxylates, whose preparation from 1-alkylimidazoles and dimethyl carbonate circumvents the need for any halide-containing reagent [cf. Equation (24)]. Protonation of IMe·CO_2 to form the corresponding imidazoliumcarboxylic acid, followed by thermal or DMSO-catalyzed decarboxylation, affords pure ILs with nitrate[74] or hydrogen carbonate[75] counterions [Equation (35)]. A solvent-less route to 1-ethyl-3-methylimidazolium fluoride that does not require the intervention of chloride salts has also been devised along the same lines.[58]



(35)

When transition metal species react with NHC•CO_2 betaines they generally behave as convenient, air- and moisture-stable, free carbene surrogates. They have therefore been used to transfer NHC ligands to a variety of metal compounds with concomitant release of carbon dioxide [Equation (36)]. Work in this field was pioneered by Crabtree et al., who successfully isolated a variety of late transition metal–NHC complexes by treating 1,3-dimethylimidazolium-2-carboxylate with suitable metal precursors (Table 3). Experimental observations and DFT calculations ruled out the dissociation of the betaine prior to its reaction with a metal source. Thus, IMe•CO_2 was believed to coordinate via two *cis* vacant sites on the metal, followed by C–C bond cleavage and transfer of the NHC moiety to the metal.[60,76]



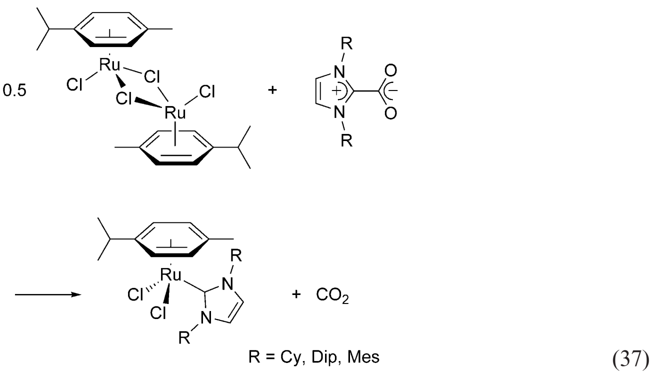
(36)

Table 3. NHC–metal complexes obtained by reaction of suitable metal precursors with IMe•CO_2.

Reactant[a]	Product[a]	Isolated yields (%)
$[\{RuCl_2(p\text{-cymene})\}_2]$	$RuCl_2(p\text{-cymene})(IMe)$	85
$[Rh(COD)Cl]_2$	$Rh(COD)(IMe)Cl$	93
$[Ir(COD)Cl]_2$	$Ir(COD)(IMe)Cl$	82
$[Ir(COD)(PPh_3)_2]PF_6$	$[Ir(COD)(PPh_3)(IMe)]PF_6$	89
$[Ir(COD)(PPh_3)_2]PF_6$	$[Ir(COD)(IMe)_2]PF_6$	84
$[Ir(COD)(py)_2]PF_6$	$[Ir(COD)(py)(IMe)]PF_6$	78
$[Ir(COD)(py)_2]PF_6$	$[Ir(COD)(IMe)_2]PF_6$	76
$IrCl(CO)(PPh_3)_2$	$[Ir(CO)(PPh_3)_2(IMe)]Cl$	79
$Pd(OAc)_2$	$[Pd(IMe)_3(OAc)]OAc$	71
$PdCl_2(MeCN)_2$	$[PdCl(IMe)_3]Cl$	65
K_2PtCl_4	$[PtCl(IMe)_3]Cl$	76

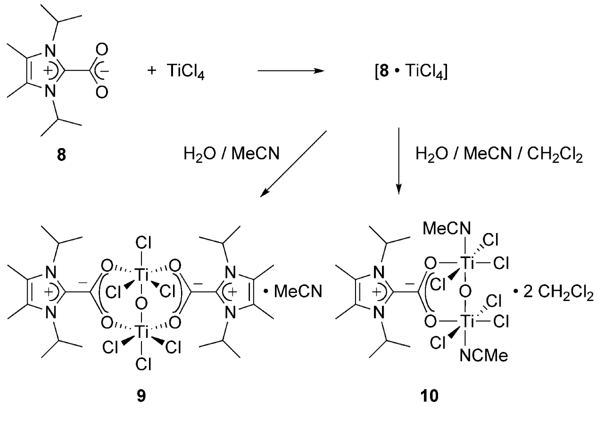
[a] COD = 1,5-cyclooctadiene, *p*-cymene = 4-isopropyltoluene, py = pyridine, IMe = 1,3-dimethyl-imidazolin-2-ylidene.

As an alternative to the deprotonation of imidazol(in)ium salts with a strong base, Delaude and Demonceau have used CO_2 adducts to generate active metal–NHC species in situ for various catalytic processes. Thus, a series of five imidazol(in)ium-2-carboxylates bearing cyclohexyl, 2,6-diisopropylphenyl, or mesityl groups on their nitrogen atoms were probed in ruthenium-promoted olefin metathesis and cyclopropanation reactions. At 60 °C in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$, the use of NHC•$CO_2$ betaines or a mixture of NHC•HX salts (X = Cl, BF_4) and *t*BuOK led to similar results. When metathesis polymerizations were performed at room temperature, the carboxylates proved far superior to the corresponding imidazol(in)ium salts and displayed the same level of activity as the preformed complex $[RuCl_2(p\text{-cymene})(IMes)]$.[56] Active species generated in situ from palladium acetate and a variety of imidazol(in)ium carboxylates and dithiocarboxylates have also been screened in the Suzuki–Miyaura cross-coupling of aryl halides with *trans*-2-phenylvinylboronic acid. The NHC•CO_2 adducts showed excellent activity, comparable to that of the parent imidazol(in)ium chlorides, whereas NHC•CS_2 inner salts were poorly efficient.[77] To account for this dichotomy, the reactivity of NHC•CX_2 adducts (X = O, S) toward the dimer $[\{RuCl_2(p\text{-cymene})\}_2]$ was investigated in detail.[52] The CS_2 betaines led to cationic complexes of the $[RuCl(p\text{-cymene})(NHC•CS_2)]PF_6$ type [cf. Equation (20)], which did not show any significant catalytic activity in the systems under consideration, whereas the CO_2 adducts cleanly afforded ruthenium–arene complexes bearing NHC ligands [Equation (37)], which are well-known catalyst precursors for several ruthenium-mediated organic transformations.[78]



(37)

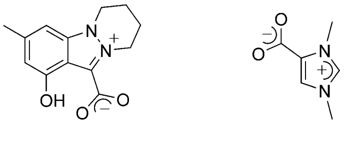
When 1,3-diisopropyl-4,5-dimethylimidazolium-2-carboxylate (**8**) was treated with titanium tetrachloride in dichloromethane, a yellow precipitate of molecular formula [**8**•$TiCl_4$] was initially obtained (Scheme 13). This compound was not further characterized because of solubility issues, but it probably has a polymeric structure. When left in contact with organic solvents containing traces of water, it slowly undergoes hydrolysis into well-defined crystalline adducts **9** or **10**. X-ray diffraction analysis showed that the imidazolium-2-carboxylate zwitterion is preserved in these complexes and acts as a $\kappa^2 O,O'$ bridging ligand.[79] This is in sharp contrast with the loss of CO_2 observed in the examples described above. The higher oxophilicity of titanium(IV) compared to late transition metals is most likely responsible for this difference of behavior.



Scheme 13. Reaction of 1,3-diisopropyl-4,5-dimethylimidazolium-2-carboxylate (**8**) with $TiCl_4$.

3.4. Natural Alkaloid Betaines

There is a close relationship between the NHC·CO_2 betaines described in this section and the family of alkaloid compounds referred to as heterocyclic mesomeric betaines.[80] According to the classification of Ollis, Stanforth, and Ramsden, these natural products may be divided into four main classes, namely heterocyclic *N*-ylides, conjugated mesomeric betaines (CMB), cross-conjugated mesomeric betaines (CCMB), and pseudo-cross-conjugated mesomeric betaines (PCCMB).[81] This latter category encompasses several indazolium, pyrazolium, or quinolinium carboxylates, among others, and includes representatives such as nigellicine [(6,7,8,9-tetrahydropyridazino[1,2-*a*]indazolium-11-carboxylate (**11**)], an alkaloid isolated from the widely distributed herbaceous plant *Nigella sativa* L. (black cummin) (Scheme 14).[82] Imidazol(in)ium-2-carboxylates may be viewed as PCCMBs, whereas their 4-carboxylate isomers would fall into the CCMB category. Indeed, 1,2-dimethylimidazolium-4-carboxylate (**12**) is also known as norzooanemonine and has been identified as the alkaloid in marine sponges such as *Pseudopterogorgia americana*, *Cacospongia scalaris*, and *Astrosclera willeyana* LISTER 1900.[83]



Nigellicin (**11**) Norzooanemonine (**12**)

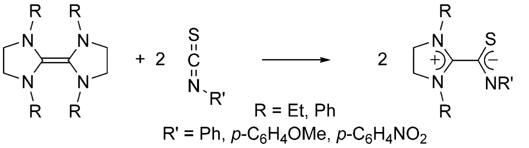
Scheme 14. Structures of the PCCMB alkaloid nigellicine (**11**) and of the CCMB alkaloid norzooanemonine (**12**).

Although natural alkaloid betaines and their derivatives display a very rich chemistry and have been shown to generate new NHCs upon extrusion of CO_2,[62,84] their study is beyond the scope of the present survey. Interested readers are referred to the recent review of Schmidt et al. for the latest advances in the field of indazole-based NHCs and betaines.[85]

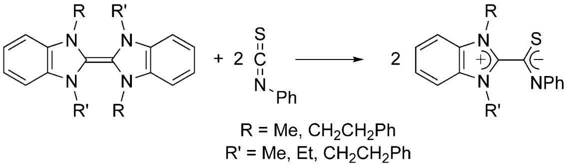
4. Adducts of NHCs with Isothiocyanates

4.1. Synthesis

The cleavage of a 1,1′,3,3′-tetraethylbis(imidazolidin-2-ylidene) dimer with phenyl isothiocyanate was the first example reported in the literature of a reaction leading to an NHC·RNCS zwitterionic adduct.[26] This procedure was subsequently extended to a few other starting materials bearing aryl groups on their nitrogen atoms [Equation (38)],[27,86,87] and to symmetrical (R = R′ = Me)[29] or unsymmetrical (R = CH_2CH_2Ph, R′ = Me, Et)[30] benzimidazole derivatives [Equation (39)].

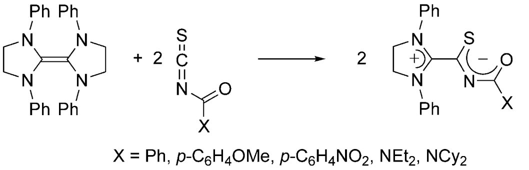


(38)



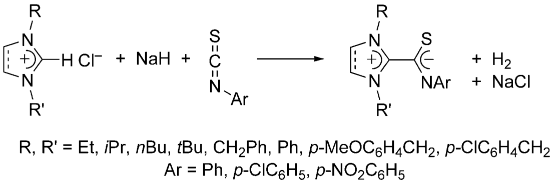
(39)

In many cases, however, the reaction of enetetramines with isothiocyanates bearing electron-donating alkyl or aryl substituents does not afford NHC·RNCS betaines as these adducts react further with the heteroallene via 1,3-cycloaddition (see below). Conversely, introduction of electron-withdrawing acyl[27] or carbamoyl[87] moieties onto the isothiocyanate function effectively stabilizes the corresponding NHC zwitterionic adducts and allows their isolation in satisfactory yields [Equation (40)].



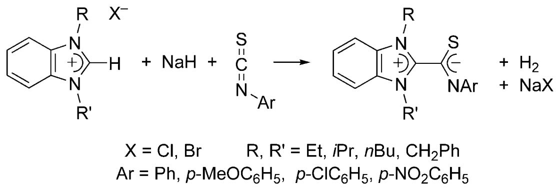
(40)

The deprotonation of azolium salts with a strong base, followed by in situ trapping of the free carbenes with suitable isothiocyanates, has provided a convenient alternative access to NHC·RNCS betaines. Because imidazol(id)in-2-ylidene species are better nucleophiles than enetetramine dimers, their reaction with isothiocyanates can be successfully carried out at lower temperatures, thereby limiting side-reactions. An early application of this strategy was reported by Schönherr and Wanzlick in 1970 for the preparation of IPh·PhNCS from 1,3-diphenylimidazolium perchlorate, potassium *tert*-butoxide, and phenyl isothiocyanate.[88] More recently, the group of Cheng has successfully extended the scope of the procedure to the synthesis of a wide range of imidazol(in)ium-2-arylthiocarbamoyl inner salts using sodium hydride as a base [Equation (41)].[89,90]



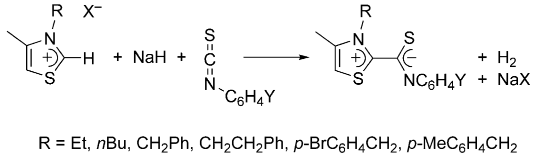
(41)

The generality of the method has been further demonstrated by applying it to benzimidazolium bromides or chlorides bearing identical (R = R′) or different (R ≠ R′) alkyl groups on their nitrogen atoms [Equation (42)].[89,91]


X = Cl, Br R, R' = Et, *i*Pr, *n*Bu, CH_2Ph
Ar = Ph, p-$MeOC_6H_5$, p-ClC_6H_5, p-$NO_2C_6H_5$

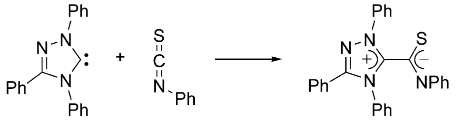
(42)

The deprotonation of thiamine hydrochloride and related thiazolium salts in the presence of aryl isothiocyanates was first carried out with triethylamine in dmf heated from room temperature to 50 °C. Under these conditions, the presence of an electron-attracting substituent on the aryl group favors betaine formation, while an electron-donating substituent leads to a higher proportion of the 1:2 cycloadduct instead (see below). In most cases, however, a complex mixture of both adducts and additional side-products is obtained.[92] A much cleaner reaction occurs when *N*-alkyl thiazolium chlorides or bromides are deprotonated with sodium hydride at –30 °C, followed by dropwise addition of an aryl isothiocyanate. Indeed, with this experimental protocol, Cheng et al. were able to isolate sixteen different thiazolium-2-arylthiocarbamoyl compounds in high yields [Equation (43)].[93]

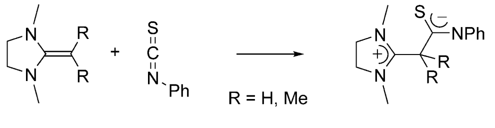

R = Et, *n*Bu, CH_2Ph, CH_2CH_2Ph, p-$BrC_6H_4CH_2$, p-$MeC_6H_4CH_2$
X = Cl, Br Y = H, p-Me, p-F, p-CF_3, p-NO_2, m-NO_2

(43)

During the course of their investigations on a stable triazolin-5-ylidene,[94] Enders and co-workers studied its reaction with phenyl isothiocyanate and isolated the corresponding betaine adduct in a straightforward manner [Equation (44)].[36]


(44)

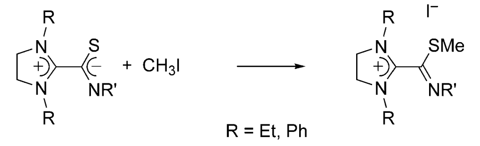
Last but not least, addition of an equimolar amount of phenyl isothiocyanate to two 2-alkylidene-1,3-dimethylimidazolidine compounds in thf at 0 °C has afforded thermally stable, crystalline adducts having a 1,4-dipolar structure [Equation (45)]. Examination of the various bond lengths and angles obtained by X-ray diffraction analysis indicated that the negative charge is mostly located on the sulfur atom and that it interacts with the carbenium carbon atom via through-space Coulombic attraction.[95]


R = H, Me

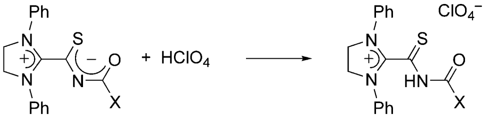
(45)

4.2. Reactivity

Exclusive *S*-methylation rather than *N*-methylation takes place when NHC·RNCS zwitterions bearing aryl or acyl groups on their exocyclic nitrogen atoms are treated with methyl iodide [Equation (46)].[26,27,87] Conversely, protonation occurs on the nitrogen end of the thiocarbamoyl function when imidazolinium-2-acylthiocarbamoyl betaines are treated with perchloric acid diluted in ethanol or *n*-butanol [Equation (47)].[27] Under more forcing hydrolysis conditions, the resulting benzamido moiety is cleaved off and the corresponding NHC·CO_2 adduct ultimately obtained (cf. Scheme 6).

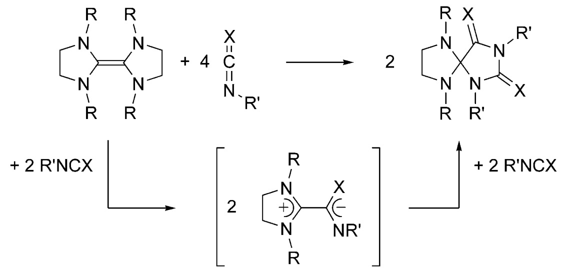

R = Et, Ph
R' = Ph, p-$NO_2C_6H_4$, EtOCO–, PhCO–, p-$MeOC_6H_4CO$–, p-$NO_2C_6H_4CO$–

(46)


X = Ph, p-$MeOC_6H_4$, p-$NO_2C_6H_4$

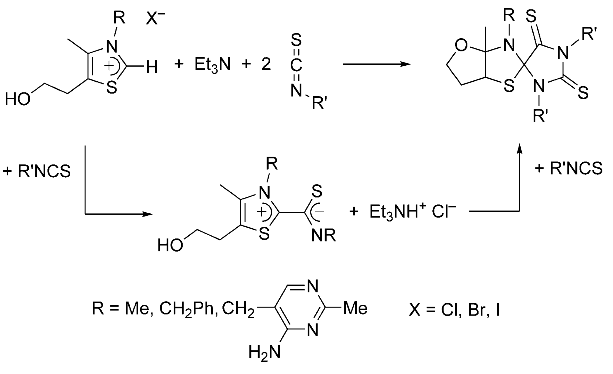
(47)

Because 2-thiocarbamoyl imidazol(in)ium, thiazolium, and benzimidazolium betaines are ambident C^+–C–S^- or C^+–C–N^- 1,3-dipoles, they react very easily via [3+2] cycloaddition with suitable dipolarophiles. This propensity has important practical consequences. Indeed, in many cases, the reaction of enetetramines with isothiocyanates cannot be stopped after formation of the initial NHC·RNCS adducts and the betaines react further with the residual heteroallene, even when this reagent is present in sub-stoichiometric amounts, to finally give spirocyclic products (Scheme 15). The intermediate zwitterionic adducts could only be isolated in the case of isothiocyanate derivatives bearing strongly deactivating substituents on their nitrogen atom, such as *p*-nitrophenyl, acyl, or carbamoyl groups [cf. Equation (40)].[26,27,86,87]


R = Et, Ph R' = alkyl, aryl X = O, S

Scheme 15. Reaction of enetetramine dimers with iso(thio)cyanates.

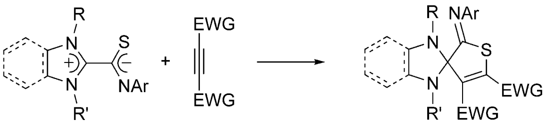
Similarly, a mixture of 1:1 and 1:2 adducts is usually obtained when thiazolin-2-ylidene species generated in situ from thiamine hydrochloride or related thiazolium salts and triethylamine in dmf are treated with isothiocyanates (Scheme 16). Alkyl isothiocyanates favor the formation of cycloadducts, whereas phenyl, *p*-chlorophenyl, or *p*-nitrophenyl derivatives mainly afford zwitterionic compounds. Hence, bolstering the negative charge of the C^+–C–N^- dipole by electron-donating substituents increases its reactivity toward dipolarophiles, whereas extended delocalization of this charge decreases it.[92,96]



R' = Me, Et, CH_2Ph, $CH_2CH{=}CH_2$, Ph, *p*-Cl-C_6H_4, *p*-$NO_2C_6H_4$

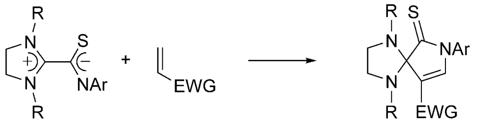
Scheme 16. Reaction of thiamine hydrochloride and related thiazolium salts with isothiocyanates.

Detailed experimental and theoretical studies by Cheng et al. have shown that imidazolinium or benzimidazolium 2-arylcarbamoyl betaines act as C^+–C–S^- 1,3-dipoles toward strongly electrophilic and rather sterically hindered dipolarophiles, such as dimethyl acetylenedicarboxylate or dibenzoylacetylene, to afford spirothiophene derivatives [Equation (48)]. On the other hand, when confronted with weaker electrophilic, less hindered dipolarophiles, such as ethyl propiolate, methyl acrylate, or acrylonitrile, they behave as C^+–C–N^- dipoles and produce imidazole spiropyrrole derivatives in high yields [Equation (49)]. DFT calculations have suggested that an asynchronous concerted mechanism is operative for both types of cycloadditions.[89] An analogous reaction path has also been postulated for the [3+2] cycloaddition of a range of NHC·ArNCS betaines with ketenes generated in situ from acyl chlorides and triethylamine or from α-diazo ketones. Incorporation of the nitrogen atom of the carbamoyl function into a new heterocycle, which leads to imidazolidine, benzimidazolidine, or triazoline spiropyrrolidone adducts in high yields and selectivities, was observed with these dipolarophiles [Equation (50)].[97]



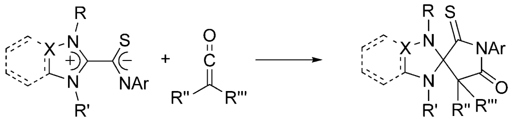
R, R' = Et, *i*Pr, *n*Bu, *t*Bu, CH_2Ph, Ph, *p*-$MeOC_6H_4CH_2$, *p*-$ClC_6H_4CH_2$
Ar = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$
EWG = CO_2Me, COPh

(48)



R = CH_2Ph, *p*-$MeOC_6H_4CH_2$, *p*-$ClC_6H_4CH_2$
Ar = Ph, *p*-ClC_6H_4 EWG = CO_2Me, CN

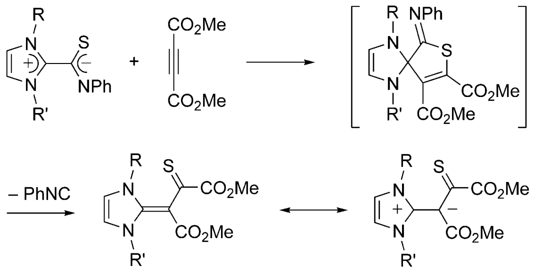
(49)



R, R' = Et, *n*Bu, CH_2Ph, Ph, *p*-$ClC_6H_4CH_2$
R'', R''' = H, Me, *i*Pr, Ph, CH_2Ph, CH_2CH_2Ph
Ar = Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4 X = C, N

(50)

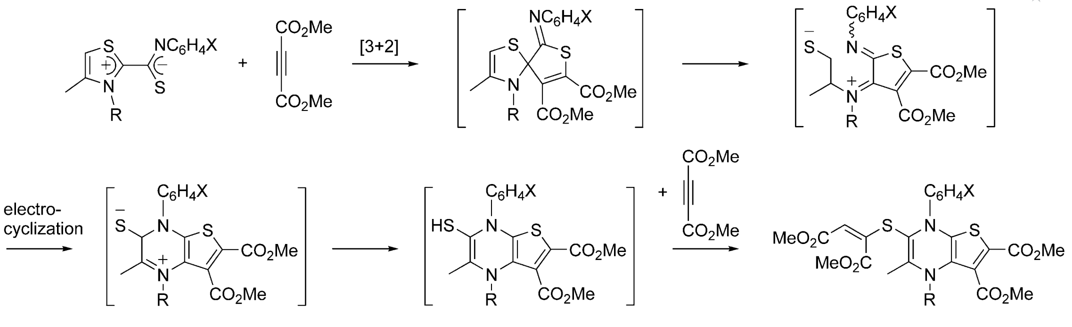
Treatment of 2-phenylthiocarbamoyl imidazolium inner salts with dimethyl acetylenedicarboxylate gives the expected [3+2] cycloaddition of the C^+–C–S^- 1,3-dipoles, followed immediately by cheletropic elimination of phenyl isocyanide to afford 2-(imidazolin-2-ylidene)-3-thioxobutanedioates, a new type of push-pull olefins with potential applications in nonlinear optical materials [Equation (51)].[90] A distinct tandem process was observed when 2-arylthiocarbamoyl thiazolium betaines were used as starting materials. In this case, the initial cycloadducts were transformed into functionalized thieno[2,3-*b*]pyrazine derivatives via a complex ring expansion sequence involving an electrocyclization step, followed by isomerization and addition of a second equivalent of dimethyl acetylenedicarboxylate (Scheme 17).[93]



R, R' = Et, *i*Pr, *n*Bu, CH_2Ph

(51)

Other types of tandem reactions involving cycloadducts derived from NHC·RNCS betaines have also been investigated.[98] These reactions further illustrate the rich chemistry of these ambident C^+–C–S^- or C^+–C–N^- 1,3-dipoles, although yields and/or selectivities are usually inferior to those reported in the above examples. The different behavior of thiazolium and imidazolium zwitterions compared to their benzimidazolium or imidazolinium counterparts has been attributed to differences in the stability of the spirothiophene cycloadducts. Increases of ring strain depending on the exact nature of the N-heterocyclic moiety or formation of aromatic systems have tentatively been invoked as driving forces for the additional steps, but general guidelines to predict the reactivity of thiocarbamoyl betaines with dipolarophiles are still missing.[90,93]

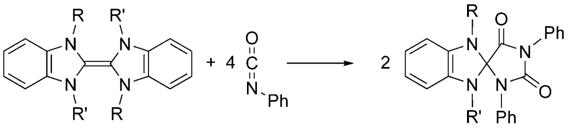


R = Et, *n*Bu, CH_2Ph, *p*-$BrC_6H_4CH_2$, *p*-$MeC_6H_4CH_2$ X = H, *p*-Me, *p*-F, *p*-CF_3, *p*-NO_2, *m*-NO_2

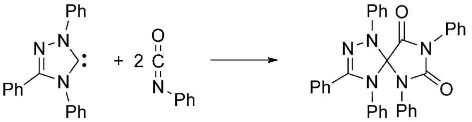
Scheme 17. Possible mechanism for the reaction of 2-arylthiocarbamoyl thiazolium betaines with dimethyl acetylenedicarboxylate.

5. Adducts of NHCs with Isocyanates

When NHCs or immediate precursors thereof are treated with isocyanates instead of isothiocyanates, the transformation does not usually stop at the zwitterion stage. The intermediate NHC·RNCO betaines undergo a further [3+2] dipolar cycloaddition with residual isocyanate species present in the reaction media to afford the corresponding spirocyclic hydantoins. Indeed, a wide range of 1:2 cycloadducts have been isolated starting from bis(imidazolidin-2-ylidene)[86,87] or bis(benzimidazolidin-2-ylidene)[29,30] species [see Scheme 15 and Equation (52), respectively]. A similar clean reaction has been observed between Ender's stable triazolin-5-ylidene and phenyl isocyanate [Equation (53)].[36]

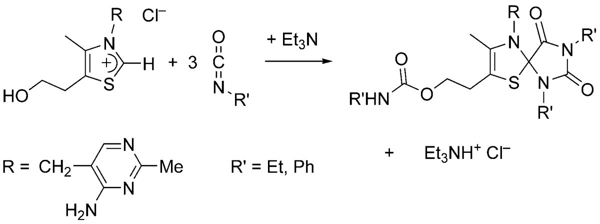


R = R' = Me or R = Et, R' = CH_2CH_2Ph (52)



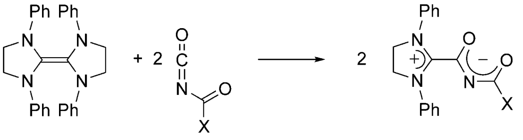
(53)

When thiamine hydrochloride is treated with ethyl or phenyl isocyanate in the presence of triethylamine, two equivalents of the heteroallene are used to build up a spirocyclic ring system [Equation (54)]. In addition, the alcohol and possibly also the primary amino group of the substrate side-chains react via nucleophilic attack of the isocyanate reagent. Ethyl isocyanate affords a mixture of *O*- and *N*-acylated products, whereas the less reactive phenyl isocyanate reacts only with the hydroxy function. When a strong base such as potassium *tert*-butoxide is employed instead of triethylamine, however, *N*-acylation also takes place with PhNCO and up to four equivalents of isocyanate per thiamine are consumed.[99]



(54)

In most cases, isolation of carbamoyl betaines has proved impossible, even at low temperature in the presence of an excess of carbene reagent. To the best of our knowledge, only two examples of stable imidazolinium-2-carbamoyl inner salts have been described so far, both of which were obtained by treating an enetetramine dimer with strongly deactivated acyl isocyanates [Equation (55)].[27]

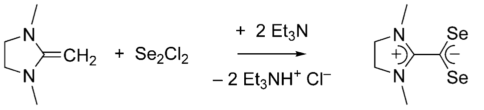


X = Ph, OEt (55)

The difference of reactivity between isocyanates and isothiocyanates is most likely due to the higher activity of RNCO species as dipolarophiles compared to their RNCS counterparts. Thus, the 1,3-dipolar cycloaddition probably occurs much faster than the primary attack of the carbene onto the heteroallene. This assumption may be rationalized based on a stronger polarization of the C=N bond by an oxygen atom compared to the less electronegative sulfur. Moreover, the charge stabilization in the anionic part of NHC·RNCS adducts should be more efficient than in the corresponding NHC·RNCO betaines due to the higher polarizability of sulfur. This would further decrease the reactivity of thiocarbamoyl species toward cycloaddition and permit the isolation of 1:1 adducts.[36]

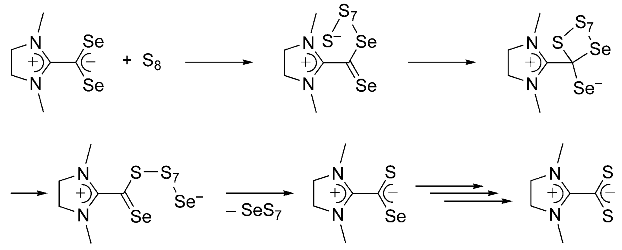
6. Miscellaneous Adducts

In parallel with the synthesis of 1,3-dimethylimidazolinium-2-dithiocarboxylate from 1,3-dimethyl-2-methyleneimidazolidine and disulfur dichloride in the presence of triethylamine, Nakayama et al. obtained the SIMe·CSe$_2$ adduct using diselenium dichloride under similar conditions [Equation (56)]. Full characterization of this compound was achieved using various analytical techniques, including IR and NMR spectroscopy, and XRD. The same mechanism postulated for the reaction with S$_2$Cl$_2$ probably also applies in this case (cf. Scheme 3).[40]



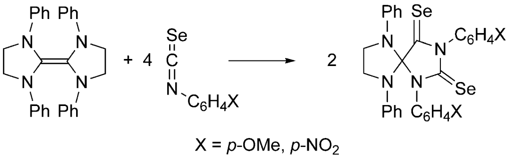
(56)

Treatment of 1,3-dimethylimidazolinium-2-diselenocarboxylate with an excess of elemental sulfur in refluxing chloroform for 4 h affords the corresponding dithiocarboxylate inner salt in 95% yield. An iterative pathway initiated by the nucleophilic attack of the CSe$_2^-$ group onto sulfur and involving the intermediacy of the selenothiocarboxylate adduct has been proposed (Scheme 18). Indeed, when the reaction is performed with only one equivalent of sulfur in dichloromethane at room temperature, a mixture of diseleno-, selenothio-, and dithiocarboxylates is obtained. Separation by column chromatography afforded the mixed zwitterionic adduct SIMe·CSSe in modest yield.[40]



Scheme 18. Reaction of SIMe·CSe$_2$ with elemental sulfur.

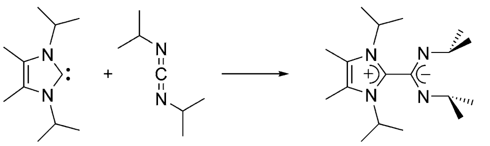
Two examples of 2,4-diselenoxo-1,3,6,9-tetraazaspiro[4.4]nonane cycloadducts, obtained by treating bis(1,3-diphenylimidazolidin-2-ylidene) with aryl isoselenocyanates, have been described by Regitz and co-workers [Equation (57)]. Their formation most likely involves the intermediacy of the corresponding 2-selenocarbamoyl betaines (cf. Scheme 15), although no evidence for the isolation of NHC·RNCSe inner salts was reported.[87]



(57)

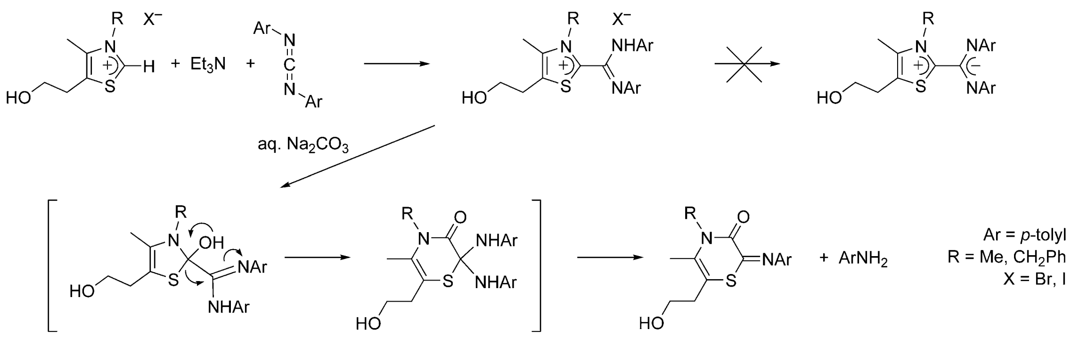
Initial synthetic efforts to isolate NHC·RNCNR betaines by treating thiazolin-2-ylidene species generated in situ with di-*p*-tolylcarbodiimide led to the corresponding hydrogen halides instead (Scheme 19). Various attempts to deprotonate these products failed, and a different reaction path was evidenced when aqueous sodium carbonate was used as a base. Nucleophilic attack by hydroxide anions takes place on the thiazolium C2 carbon atom to afford a tetrahedral intermediate, which rearranges and undergoes ring expansion with extrusion of *p*-toluidine.[100]

The successful preparation of an imidazolium-2-amidinate was reported by Kuhn and co-workers in 1999 using 1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidene and diisopropylcarbodiimide [Equation (58)]. Steric congestion across the C–C zwitterionic link results in a lowered symmetry of the amidinate fragment, as evidenced by NMR and XRD spectroscopy. The dihedral angle between the N$_2$C$^+$ and N$_2$C$^-$ moieties was found to be 85.6° and the molecule displays strongly basic properties toward Brønsted acids.[100]



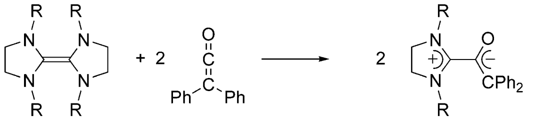
(58)

In addition to heteroallenes of the X=C=Y type (X, Y = NR, O, S, Se), a few ketenes and allenes also afford stable zwitterions when treated with NHC precursors. Two examples of diphenylketene adducts have been reported by Regitz et al. to illustrate the reactivity of electron-rich olefins [Equation (59)]. These betaines are characterized by the ex-



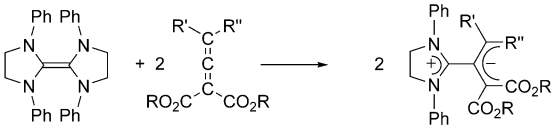
Scheme 19. Possible mechanism for the reaction of thiazolin-2-ylidene species generated in situ with di-*p*-tolylcarbodiimide followed by treatment with aqueous Na$_2$CO$_3$.

treme readiness with which they undergo [3+2] cycloaddition with dipolarophiles, such as phenyl isothiocyanate or dibenzoylacetylene, although no experimental details about these transformations were given.[101]



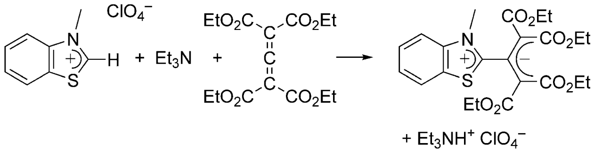
R = Ph, p-C_6H_4OMe (59)

The reaction of allene di-, tri-, or even tetracarboxylic esters with a range of nucleophilic substrates has been investigated by Gompper and Wolf. Besides phosphanes and pyridines, two types of N-heterocyclic carbenes derived from enetetramines [Equation (60)] and thiazolium salts [Equation (61)] were examined, and satisfactory yields of highly colored zwitterionic adducts were obtained in all cases.[102]



R = Me, Et

R', R'' = Me, Ph, CO_2Et (60)



(61)

7. Conclusion

N-Heterocyclic carbenes form stable zwitterionic adducts with a range of heteroallenes, ketenes, and allenes. Although the first representatives of this class of inner salts were first investigated as far back as the 1960s, they have enjoyed sustained interest from the chemical community over the intervening years. Depending on the nature of their anionic moiety, NHC betaines display a very broad palette of reactivities and have found applications in various fields of organic synthesis and catalysis.

The dithiocarboxylate adducts are usually highly stable, crystalline compounds that do not readily dissociate, hence they are convenient derivatives for probing the steric and electronic properties of air- and moisture-sensitive free carbenes. Their chemistry is governed mainly by the reactivity of the CS_2 group and they have been shown to act as bridging $\kappa^2 S,S'$ ligands toward ruthenium–arene complexes. Conversely, the NHC·CO_2 zwitterions are labile in solution and lose their CO_2 moiety upon coordination with late transition metals. They have been successfully employed as CO_2 transfer agents in various carboxylation processes, either in stoichiometric or catalytic amounts.

Isothiocyanate adducts are ambident C^+–C–S^- or C^+–C–N^- 1,3-dipoles which react primarily via [3+2] cycloaddition in the presence of suitable dipolarophiles. Reactions usually proceed with remarkable selectivities. Depending on the exact nature of the reaction partners, a wide range of heterocyclic products are accessible, some of which are not easily available by any other synthetic methods. The isocyanate betaines are even more reactive than their sulfur analogues, hence it is more difficult to control their reaction path as they tend to undergo immediate cycloaddition with residual isocyanate starting materials to afford 1:2 spirocyclic hydantoin adducts.

Additional NHC betaines can be obtained by substitution of sulfur with selenium in heteroallenes, thereby affording NHC·CSe_2, NHC·CSSe, or NHC·RNCSe zwitterions. Examples of adducts prepared from carbon-based allene or ketene derivatives are still scarce in the literature, but preliminary results indicate that they are good candidates for performing cycloaddition reactions.

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