ChemComm

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Cite this: Chem. Commun., 2012, 48, 6642-6644

www.rsc.org/chemcomm

COMMUNICATION

1,3,5-Triaryl 2-pyridylidene: base-promoted generation and complexation^{†‡}

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Received 3rd May 2012, Accepted 9th May 2012 DOI: 10.1039/c2cc33184e

We herein report a base-promoted generation of sterically hindered 1,3,5-triaryl 2-pyridylidene from the corresponding pyridinium salt. The thus-generated 2-pyridylidene was trapped by S_8 and Me₂SAuCl to form 2-pyridinethione and a 2-pyridylidene–gold(1) complex, respectively. Rearrangement of pyridylidene to pyrido[1,2-*a*]indole indicates high reactivity of the carbene center of 2-pyridylidene.

N-Heterocyclic carbenes (NHCs) have a great role in synthetic organic chemistry. NHCs are recognized as useful ligands for transition metal catalysts and as a new class of nucleophilic organic catalysts.¹ Recently, stable singlet carbenes bearing one bound heteroatom rather than two have attracted attention because of their high HOMO energy levels.² Representative compounds, cyclic amino alkyl carbenes (CAAC) and acyclic amino alkyl carbenes (AAAC), showed unusual properties such as strong σ -donation to transition metals and cleavage of unreactive H–H or N–H bonds.^{3*a*–*i*} Recently, aminoylide carbenes (AYC) were also reported as strong donating ligands.^{3*j*-*l*} Herein we report the generation and trapping reactions of 1,3,5-triaryl 2-pyridylidene.

Pyridylidene is a pyridine-based carbene species bearing one heteroatom. In Fig. 1, pyridine (A) and the isomeric 2-, 3-, and 4-pyridylidenes (B, C, and D) are depicted. According to theoretical studies, 2- and 4-pyridylidene are stable singlet carbenes with higher HOMO energies than those of other NHCs and even CAAC. High nucleophilicity and basicity of



Fig. 1 Pyridine (A) and pyridylidenes (B, C, D) as isomers of pyridine.

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† This article is part of the ChemComm 'Aromaticity' web themed issue.

‡ Electronic supplementary information (ESI) available: Experimental procedures, spectra of new compounds, and details of computational study. CCDC 879859 (1), 879860 (3 toluene), 879861 (5), 879862 (6 toluene), 879863 (7) and 879864 (9). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc33184e

free pyridylidene and strong σ -donation of a pyridylidene ligand were predicted.⁴ Since its first indication of generating 2-pyridylidene (**B**) in 1937 by Hammick *et al.*,^{5*a*} there have been a number of theoretical and experimental studies on the free carbene and transition metal complexes of pyridylidenes.^{4–7} However, the isolation of pyridylidenes has not been achieved yet.^{7,8} Reaction of pyridinium salt with strong bases and ruthenium to form bridged pyridylidene complexes reported by Cabeza *et al.* is the only example describing the generation and reactivity of pyridylidenes.⁷ Thus, the stability and reactivity of pyridylidene toward electrophilic reagents remain unclear.

Our strategy for generating reasonably stable 2-pyridylidene is shown in Fig. 2. We envisaged that (i) three bulky aryl groups introduced at the 1,3,5-positions would help stabilize otherwise reactive 2-pyridylidene, and (ii) the target carbene could be generated by the deprotonation of the corresponding pyridinium salt by a strong base. The formation of pyridylidene should then be confirmed by trapping experiments with S₈ or a gold(1) complex, which are well known as reactive reagents toward free NHCs.

We first synthesize pyridinium salt bearing sterically demanding substituents at 1,3,5-positions (Scheme 1). We chose aryl



Fig. 2 Synthetic strategy of 2-pyridylidene.



Scheme 1 Synthesis of pyridinium 3. $Xyl = 2,6-Me_2C_6H_3$, Mes = 2,4,6-Me_3C_6H_2, Tf = CF₃SO₂.



Scheme 2 Generation of 2-pyridylidene 4 and its reactions. Yields are isolated yields. "NaH was used instead of LiHMDS. HMDS = $N(SiMe_3)_2$

groups with methyl substituents at ortho-positions. Suzuki-Miyaura cross-coupling⁹ of 3,5-dibromopyridine and 2,6-dimethylphenylboronic acid (Xyl-B(OH)₂) in the presence of a Pd(PPh₃)₄ catalyst and Ba(OH)₂ produced 3,5-Xyl₂pyridine (1) in 80% yield. A Zincke salt¹⁰ was then produced by the reaction of 1 with 1-chloro-2,4-dinitrobenzene. The chloride anion was then exchanged with triflate using silver triflate to afford pyridinium 2 OTf. As Zincke salt 2 OTf was slowly decomposed to starting material 1, the following reaction was performed without isolation. Finally the 2,4-dinitrophenyl group was replaced by a mesityl (1.3.5-trimethylphenyl) group by treating 2 OTf with MesNH₂ at 150 °C. The desired sterically hindered 1,3,5-triaryl 2-pyridinium 3 was obtained in 34% yield over three steps from 1. The structures of 3 and synthetic intermediate 1 were confirmed by ¹H, ¹³C NMR, elemental analysis, and X-ray crystallography.¹¹

With the requisite pyridinium **3** in hand, we next examined its reaction with a base. After many attempts we found that lithium hexamethyldisilazide (LiHMDS) produced 2-pyridylidene **4** in THF at room temperature (Scheme 2). The generation of **4** was confirmed by trapping it with S_8 and Me₂SAuCl to yield the corresponding pyridinethione **5** (82% yield) and 2-pyridylidene–gold(i) complex **6** (27% yield), respectively. Other strong bases such as NaH and KH were also able to generate pyridylidene species **4** from **3**.

It should be noted that no 4-pyridylidene product was observed in these reactions. Preferential deprotonation at the 2-position of pyridylidene might be due to the higher acidity of the hydrogen atoms at the 2-position. To estimate the acidity of the hydrogen atoms at the 2- and 4-position, DFT calculation was performed by using B3LYP/6-31+G(d) level of theory.¹² It was found that 2-pyridylidene is 13.3 kcal mol⁻¹ (ΔH) more stable than 4-pyridylidene, which is consistent with the experimental results.

On the other hand, treatment of **3** with *tert*-butyllithium caused nucleophilic attack of the *tert*-butyl group at the 4-position of **3** to form 1,4-dihydropyridine derivative **7** in 39% yield (Scheme 3). Treatment of **3** with NaBH₄ led to the formation of dihydropyridine derivatives **8a** and **8b** (83% yield, **8a/8b** = 1 : 0.6). As the mixture of **8a** and **8b** did not undergo any reaction with S₈ to form **5**, a possibility that 1,2-dihydropyridine **8a** is involved in the reaction of **3**



Scheme 3 Reactions of 3 with t-BuLi and NaBH₄.

with NaH can be excluded. However, a possible involvement of the N(SiMe₃)₂ adduct in the LiHMDS-mediated generation of **4** cannot be completely excluded.^{8b}

The formation of **6** represents the first example of the synthesis of the pyridylidene–gold(1) complex from the reaction of a pyridinium and a base. This method does not require any substituents such as chloro or carboxyl groups on the pyridinium precursor. To the best of our knowledge, this is the most direct way to produce transition metal pyridylidene complexes among previously reported methods.⁶

The X-ray crystal structures of 3 toluene and 6 toluene are shown in Fig. 3. In both structures, Xyl and Mes groups are at about right angles to the pyridine ring to minimize steric hindrance of the methyl groups. Due to the carbene character of 6, the N(1)–C(1)–C(2) angle of 6 (116.0(5)°) is smaller than that of 3 (121.38(13)° and 120.79(15)°). However, there is no other significant structural difference of the pyridine rings between 3 and 6. It should be noted that the Au–Cl bond length of 6 (2.2845(16) Å) indicates the strong *trans* influence of the 2-pyridylidene ligand.¹³

During our attempt to isolate 2-pyridylidene **4**, we identified 7,9-Xyl₂-2,4-Me₂-pyrido[1,2-*a*]indole (**9**), a decomposed product, by NMR spectroscopy and X-ray crystallography.¹⁴ Shown in Scheme 4 is a plausible mechanism for the generation of **9**. Proton transfer from the benzylic position of the mesityl group to the carbene carbon affords zwitterionic compound **10**. Nucleophilic attack of the benzylic anion at the 2-position of pyridinium results in the formation of 9a,10-dihydropyrido-[1,2-*a*]indole **11**, which is oxidized and aromatized to **9**. Similar rearrangement reactions of NHCs were reported.¹⁵ These results clearly indicate the high reactivity (nucleophilicity and basicity) of the carbene center of 2-pyridylidene.



Fig. 3 ORTEP drawings of **3**-toluene (a) and **6**-toluene (b) with 50% thermal ellipsoids. Hydrogen atoms and toluene are omitted for clarity.





Scheme 4 Rearrangement of 4 to pyrido[1,2-*a*]indole 9 and its plausible mechanism. *"*KH was used instead of LiHMDS.

We have established that a sterically hindered 1,3,5-triaryl 2-pyridylidene could be generated by the reaction of the corresponding pyridinium salt with a strong base such as LiHMDS, NaH, and KH. The thus-generated 2-pyridylidene was trapped by S_8 and Me₂SAuCl to form 2-pyridinethione and a 2-pyridylidene–gold(1) complex, respectively. Rearrangement of pyridylidene to pyrido[1,2-*a*]indole indicates a high reactivity of the carbene center of 2-pyridylidene. As 2-pyridylidenes are among the most electron-donating and nucleophilic *N*-heterocyclic carbenes, the present findings should provide tremendous opportunity for using 2-pyridylidenes for various purposes. Further work is in progress to design and synthesize isolable 2-pyridylidenes.

This work was supported by the Funding Program for Next Generation World-Leading Researchers from JSPS (220GR049 to K.I.) and KAKENHI from MEXT (23750038 to Y.S.). K.H. thanks the Integrative Graduate Education and Research Program in Green Natural Sciences for support.

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