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Synthesis of New Class of Alkyl Azarene Pyridinium Zwitterions via Iodine Mediated sp^3 C−H Bond Activation

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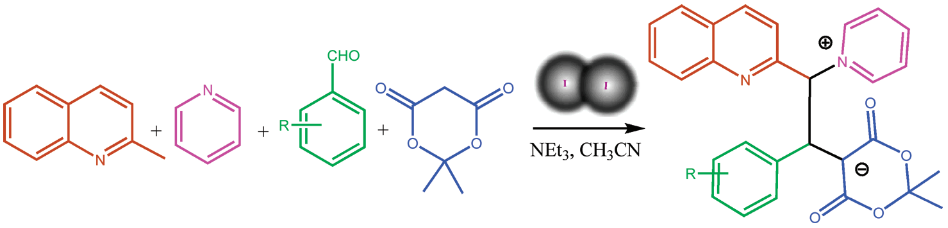
ABSTRACT



An efficient and conceptually different approach toward C−H bond activation by using iodine mediated sp^3 C−H functionalization for the synthesis of alkyl azaarene pyridinium zwitterions is described. This work has the interesting distinction of being the first synthesis of a new class of alkyl azaarene pyridinium zwitterion via transition-metal-free sp^3 C−H bond activation of an alkyl azaarene.

C−H bond activation has revalorized the science of synthesis by its ingenious contribution to synthetic organic chemistry.[1,2] C−H activation generally involves synthetic methodologies that make use of metal catalyzed activation and successive functionalization of sp^2 and sp^3 C−H bonds which directly install important functional groups to build complex structures.[3] With increasing environmental concerns and waste management, especially in the area of pharmaceuticals, identification of methods that do not require transition metal catalysts are very important because the removal of metallic impurities from final pharmaceutical entities increases the cost considerably. The development of an efficient and transition-metal-free protocol will significantly change synthetic applications of direct C−H functionalization. Recently some efficient transition-metal-free sp^2 C−H bond activations have been reported.[2e,4] Inspired by these we describe a remarkable result from our laboratory which demonstrates a new transition-metal-free strategy for achieving sp^3 C−H activation. This first iodine mediated synthesis of an alkyl azaarene pyridinium (AAP) zwitterion is an efficient strategy for sp^3 C−H bond activation in a multicomponent protocol.

A zwitterion is a neutral molecule with a positive and negative electrical charge at different locations within that molecule. Zwitterions are widely used in organic synthesis[5] and can be trapped by a series of electrophiles and proton donors to give a variety of heterocyclic compounds.[6] To the best of our knowledge zwitterions have not yet been formed from an inactivated C−H bond. The direct and simple approach for the synthesis of zwitterions via C−H activation of alkyl azaarene remains a challenging task.

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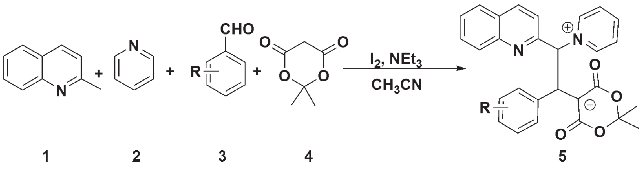
Herein, we demonstrate the first iodine promoted sp^3 C−H bond activation for the efficient and direct synthesis of AAP zwitterions via a new multicomponent reaction in the presence of triethylamine without the use of any transition metal.

Scheme 1. Synthesis of AAP Zwitterions from Quinaldine, Pyridine, Aromatic Aldehydes, and Meldrum Acid



Our strategy for the synthesis of unusual charge separated AAP-meldrum acid zwitterionic salts involve a one-pot multicomponent reaction of quinaldine, pyridine, aromatic aldehydes, and meldrum acid in the presence of iodine and triethylamine. We started our exploration by taking quinaldine as an alkyl azaarene, pyridine, benzaldehyde, and meldrum acid as model substrates for the reaction. Based on precedent in the Lewis acid catalyzed intramolecular C(sp^3)−H functionalization[7] and Lewis acid supported C(sp^2)−H activation of pyridines and/or quinolines,[8] we envisioned the use of different Lewis acids[9] for the functionalization of quinaldine under proton-transfer conditions (Table 1).

To test the feasibility of our hypothesis, we screened various Lewis acids using quinaldine, pyridine, benzaldehyde, and meldrum acid with triethylamine in acetonitrile as solvent. Initial trials using metal triflates Sc(OTf)$_3$, Zn(OTf)$_2$, Fe(OTf)$_3$ and Lewis acids like AlCl$_3$, ScBr$_3$, BF$_3$(OEt)$_2$ did not promote the desired reaction at all. Only Cu(OTf)$_2$ and CuCl$_2$ promoted the reaction in very low yield (10%). To our surprise when iodine was used as a Lewis acid in the reaction for the synthesis of an AAP zwitterion, the results obtained were interesting. The reaction proceeded to form the desired zwitterion in low yield (35%) with 40 mol % iodine. Further we tried to optimize the reaction conditions with iodine to get improved results. The reaction progressed in improved yield (45%) with 70 mol % of iodine. At room temperature with 100 mol % iodine, the reaction was complete after 36 h and we obtained a 55% reaction yield. Encouraged by these results we adopted a sequential addition methodology to form zwitterions with the above-mentioned standardized reaction conditions to further improve the reaction yield. We added quinaldine, pyridine, and iodine and stirred the reaction for 2 h at 100 °C, followed by the addition of benzaldehyde, meldrum acid, and triethylamine at room temperature in acetonitrile as solvent. To our delight the reaction was complete in 24 h and a 70% reaction yield was obtained. However any further increase in the iodine amount (150 mol %) did not improve the yield (Table 1). At higher temperatures (70−80 °C), a complex mixture of products resulted which were difficult to identify. These zwitterions are usually very reactive species, which should be kept at low temperature and in an inert atmosphere.

Table 1. Optimization with Different Lewis Acids

entry	Lewis acid (*x* mol %)	time (h)	yield (%)^c
1^a	Sc(OTf)$_3$ (40 mol %)	36	0
2^a	Zn(OTf)$_2$ (40 mol %)	36	0
3^a	Fe(OTf)$_3$ (40 mol %)	36	0
4^a	Cu(OTf)$_2$ (40 mol %)	36	10
5^a	AlCl$_3$ (40 mol %)	36	0
6^a	ScBr$_3$ (40 mol %)	36	0
7^a	CuCl$_2$ (40 mol %)	36	10
8^a	BF$_3$(OEt)$_2$ (40 mol %)	36	0
9^a	I$_2$ (40 mol %)	36	35
10^a	I$_2$ (70 mol %)	36	45
11^a	I$_2$ (100 mol %)	36	55
12^b	I$_2$ (100 mol %)	24	70
13^b	I$_2$ (150 mol %)	48	70

^{a} Reaction conditions: **1** (1.0 mmol), **2** (2.5 mmol), **3** (benzaldehyde) (1.0 mmol), **4** (1.0 mmol), Lewis acid, NEt$_3$ (1.5 mmol), CH$_3$CN (5.0 mL). ^{b} Reaction conditions: **1** (1.0 mmol), **2** (2.5 mmol), I$_2$ heated at 100 °C for 2 h then added **3** (benzaldehyde) (1.0 mmol), **4** (1.0 mmol), NEt$_3$ (1.5 mmol) at room temperature in CH$_3$CN (5.0 mL). ^{c} Isolated yield after column chromatography.

Thus we developed a one pot multicomponent protocol via reaction of quinaldine, pyridine, aromatic aldehyde and meldrum acid in the presence of iodine as Lewis acid and triethylamine as base resulting in the formation of the 1-(2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-aryl-1-(quinolin-2-yl)ethyl)pyridinium (Scheme 1). The reaction occurs via sp^3 C−H bond activation of methyl of

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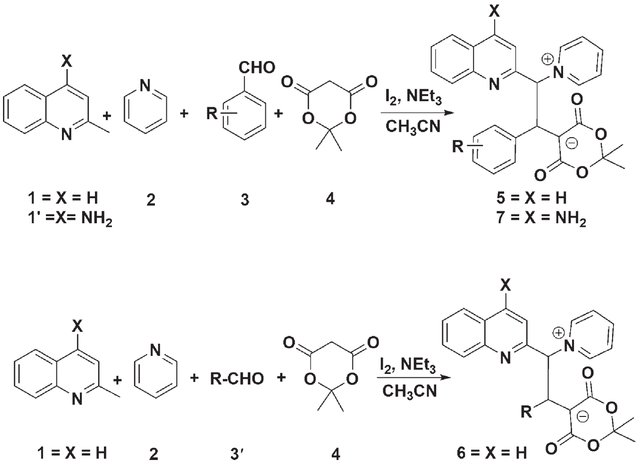
Table 2. Synthesis of Various Zwitterions with Iodine As Lewis Acid



entry	product	X	aldehyde	R	time (h)	yield (%)[c]
1[a]	5a	H	3a	4-CH_3O	24	70
2[a]	5b	H	3b	4-Cl	24	75
3[a]	5c	H	3c	4-NO_2	24	60
4[a]	5d	H	3d	2,4-Cl	24	65
5[a]	5e	H	3e	4-F	24	70
6[a]	5f	H	3f	3,4,5-CH_3O	24	75
7[a]	5g	H	3g	4-$(CH_3)_2N$	24	70
8[a]	5h	H	3h	H	24	70
9[a]	5i	H	3i	3,4-CH_3O	24	75
10[a]	5j	H	3j	4-$PhCH_2O$	24	65
11[a]	5k	H	3k	3-NO_2	24	70
12[a]	5l	H	3l	3-CH_3O	24	70
13[a]	5m	H	3m	2-NO_2	24	65
14[a]	5n	H	3n	2-Cl	24	70
15[a]	5o	H	3o	1-C_4H_4	24	65
16[a]	5p	H	3p	4-HO	24	70
17[a]	5q	H	3q	2,5-CH_3O	24	80
18[b]	6a	H	3'a	H_3C CH H_3C	30	55
19[b]	6b	H	3'b	$CH_3CH_2CH_2$	30	60
20[a]	7a	NH_2	3b	4-Cl	24	35
21[a]	7b	NH_2	3e	4-F	24	40

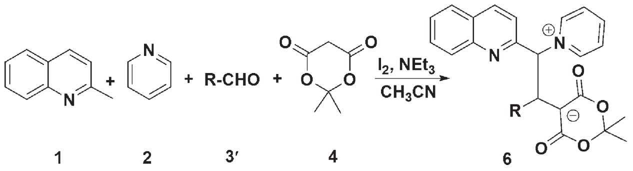
[a] Reaction conditions: **1** or **1'** (1.0 mmol), **2** (2.5 mmol), I_2 (1.0 mmol) heated at 100 °C for 2 h then added **3** (1.0 mmol), **4** (1.0 mmol), and NEt_3 (1.5 mmol) at room temperature in CH_3CN (5.0 mL) and stirred for additional 22 h. [b] Reaction conditions: **1** (1.0 mmol), **2** (2.5 mmol), I_2 (1.0 mmol) heated at 100 °C for 2 h then added **3'** (1.0 mmol), **4** (1.0 mmol), and NEt_3 (1.5 mmol) at room temperature in CH_3CN (5.0 mL) and stirred for additional 28 h. [c] Isolated yield after column chromatography.

quinaldine by the coordination to Lewis acid that would increase the acidity of benzylic C–H bonds.

With the optimized conditions in hand, the scope of the reaction with regard to the structure of various aromatic aldehydes was investigated. The reaction of quinaldine with various aromatic aldehydes bearing electron-donating or -withdrawing aryl substituents proceeded smoothly and provided the desired zwitterionic compounds in moderate to good yields (60–80%) (Table 2, entries 1–17). The structures of the products were fully characterized by mass spectroscopy, ^{1}H, ^{13}C NMR, and elemental analysis. Based on these studies, it is clear that the formed zwitterionic salt came from all four components of the reaction. The pyridyl group and meldrum acid moiety were present on the same side of the molecule which causes the positive and negative charge in the shortest distance. The quinaldine and phenyl group exist on the other side. The methylene carbon atom in the meldrum acid unit adopts an sp^2 hybrid, and the negative charge is delocalized to two carbonyl groups. In ^{1}H NMR spectra the methylene group connected with the unit of meldrum acid usually shows one doublet at about δ 5.00–6.00 ppm with the vicinal coupling constant J = 12.0 Hz. Due to the connection with the strongly electron-withdrawing pyridinium group, the absorption peak of another methylene group greatly shifts to the range of δ 7–8 ppm and overlaps with signals of aromatic protons. ^{1}H–^{1}H COSY, HMBC, and HSQC spectra of **5l** supported the formation of the AAP zwitterion.

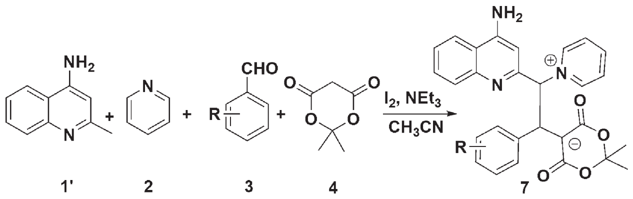
In order to examine the substrate scope and limitation of this multicomponent reaction, aliphatic aldehydes were also tested under the above-mentioned reaction conditions. Aliphatic aldehydes such as butyraldehyde and isobutyraldehyde reacted similarly, and new substituted AAP zwitterions were obtained in moderate yields (Scheme 2) (Table 2, entries 18–19). The structures of zwitterions were fully characterized by ^{1}H, ^{13}C NMR, mass spectroscopy, and elemental analysis performed for **6a** and **6b**. These results demonstrated that this reaction has great generality, and a library of AAP zwitterions could be efficiently synthesized.

Scheme 2. Synthesis of AAP Zwitterions from Quinaldine, Pyridine, Aliphatic Aldehydes, and Meldrum Acid



To further evaluate the scope of this C–H activation methodology, another methyl azaarene that is 4-amino quinaldine was also tested. The reaction of 4-amino quinaldine, pyridine, aromatic aldehydes, and meldrum acid in acetonitrile with iodine and triethylamine went smoothly (Scheme 3). These 1-(1-(4-aminoquinolin-2-yl)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-arylethyl) pyridiniums were obtained in low yields (Table 2, entries 20–21). It should be mentioned that the yields of the 4-amino quinaldine derived AAP zwitterion salts (**7a**, **7b**) are lesser than those of the zwitterionic salts synthesized from quinaldine (**5a**–**5q**). The structures of the prepared 1-(1-(4-aminoquinolin-2-yl)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2 arylethyl)pyridinium were fully characterized by spectroscopic methods and elemental analysis. These results clearly demonstrated that this multicomponent reaction has great generality and can be developed for other inactivated methylene compounds.

Scheme 3. Synthesis of AAP Zwitterions from 4-Amino Quinaldine, Pyridine, Aromatic Aldehydes, and Meldrum Acid



Our working hypothesis is shown in Figure 1. Activation of methyl azaarenes by coordination to a Lewis acid iodine would increase the acidity of the benzylic C–H bonds. Cleavage of the C–H bond by either counterions of the Lewis acid would generate a 1-iodo-2-methylene-1,2-dihydroquinoline species (**2**). Pyridine as a nucleophile attacks **2** to form 1-(quinolin-2-ylmethyl)pyridinium iodide (**3**). This iodide salt attacks an arylidene dione (an aromatic aldehyde meldrum acid adduct obtained via Knoevenagel condensation) to form AAP zwitterions.

In conclusion, we described here an interesting transition-metal-free sp^3 C–H bond activation of an alkyl azaarene to form AAP zwitterions in a new multicomponent reaction. A series of unusual charge separated AAP zwitterionic salts were prepared in moderate to good yields in a very convenient manner. Prominent among the advantages of this new methodology are operational simplicity, novelty, and good yields. Further extension of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

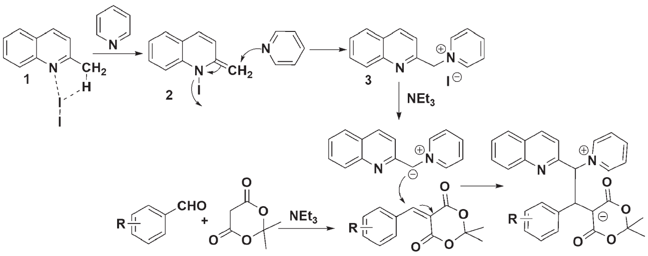


Figure 1. Plausible mechanism for the formation of AAP zwitterions.

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Supporting Information Available. Detailed experimental and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.