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A Selective Approach to Pyridine Appended 1,2,3-Triazolium Salts

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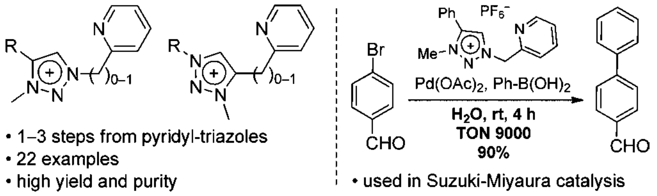
ABSTRACT



A selective and highly efficient strategy to obtain a library of pyridine appended 1,4-disubstituted-3-methyl-1,2,3-triazolium salts is described. It features pyridine nitrogen protection at click-derived pyridyl-triazoles through *N*-oxidation with subsequent N3 alkylation of the triazole ring and deprotection. Triazolium salts are obtained in high yield and purity in either a stepwise or one-pot protocol. Preliminary data indicate their remarkable efficiency in palladium-catalyzed Suzuki–Miyaura catalysis in the environmentally benign solvent water.

Since the discovery of copper catalyzed cycloaddition of organic azides and alkynes into 1,4-disubstituted-1,2,3-triazoles **1**,[1] also referred to as click triazoles,[2] 1,3,4-trisubstituted-1,2,3-triazolium salts **2** have emerged as a powerful subclass of nitrogen heterocycles (Scheme 1).[3,4] These compounds are readily prepared by N3 alkylation of click triazole **1**.[5] The properties of triazolium salts **2** to serve as ionic liquids,[6] organocatalysts,[7,8] and receptors for anion recognition[7,9,10] and other noncovalent interactions[11] are being widely explored. Prominent is their application in coordination chemistry, serving as easily accessible precursors for abnormal *N*-heterocyclic carbene (*tz*NHC) ligands of a mesoionic nature that possess unique complexation ability to transition metals.[12] Commenced from the first report on transition-metal complexes by Albrecht et al.,[13] and the subsequent isolation and characterization of a free *tz*NHC ligand by Bertrand et al.,[14] these compounds have become intensively investigated

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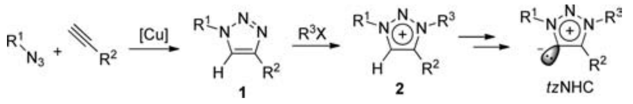
Scheme 1. Generalized Approach to *tz*NHC through Consecutive Click Chemistry, N3 Alkylation, and H5 Deprotonation



especially in the field of homogeneous metal-based catalysis.[15]

Potentially bi- and multidentate 1,3,4-trisubstituted-1,2,3-triazol-5-ylidene ligands having a phosphine,[16] sulfide,[17,18] selenide,[17] alkylamine,[19] pyrrole,[10] imidazolium,[20] and pyridine[21] coordinative side arm at R^1 and/or R^2 offering an additional dent for coordination have been developed (Scheme 1).[3] Their preparation through the alkylation of the 1,2,3-triazole ring, however, often represents some selectivity challenges because these nucleophilic groups are also readily alkylated, resulting in a mixture of mono- and polyalkylated undesired derivatives. Although protective group chemistry has been employed in some instances[3,19] to achieve mono-alkylation, to our knowledge no such strategy is reported for the synthesis of pyridine-functionalized analogues. In some cases, to obtain the pyridyl-triazolium salt a preparative TLC separation after alkylation was used due to the unselective reaction that occurred at both triazole and pyridine nitrogen atoms.[22] The lack of a selective approach to pyridyl-triazolium salts is surprising, as coordination compounds with pyridyl-triazolylidene bidentate ligands show remarkable catalytic, spectroscopic, and electrochemical properties.[21−24]

Induced by our research interest in the synthesis and coordination chemistry of click triazole derivatives[25,26] we have developed an approach to isomeric and homologous pyridine appended 1,2,3-triazolium salts **2A**−**D** depicted in Figure 1. Considering the click derived pyridyl-triazoles **1** as starting compounds (Figure 2), we surmised that the most electron rich pyridine nitrogen atom[25] should allow for its selective protection by *N*-oxidation into **3** (Scheme 2). Subsequent N3 methylation of the triazole should easily afford pyridine *N*-oxide triazolium salt **4′**. Although concomitant *N*-oxide methylation of **3** into *N*-methoxypyridinium salt **4** is expected at this stage, this should not be an issue, as convenient methods for the reductive cleavage of the N−O bond in both pyridine *N*-oxides and *N*-alkyloxypyridinium salts are available.

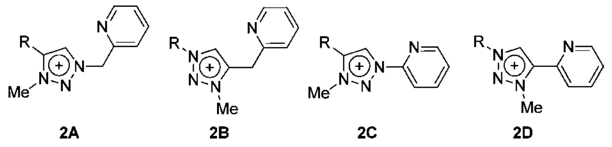
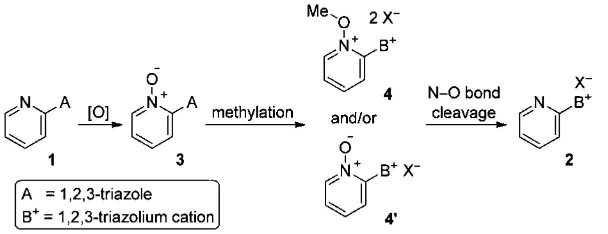


Figure 1. Four types of triazolium ions from this investigation.

Scheme 2. Strategy to Pyridyl-triazolium salts **2**



Pyridyl-triazoles **1A**−**D** (Figure 2) used for this investigation were easily prepared by copper-catalyzed cycloaddition between the appropriate click partners.[27]

Before pursuing the strategy from Scheme 2 we decided to probe the selectivity of commonly used methylating reagents toward the pyridine unprotected triazoles **1A**−**D**. This was urged by the report on some pyridyl-triazoles being selectively methylated with the pyridine group remaining unaffected.[21]

Briefly, methylation of **1Aa** was probed with Me_3OBF_4 (1 equiv, CH_2Cl_2, rt, 24 h) and MeOTf (1 equiv, CH_2Cl_2, 0 °C, 30 min), both giving mixtures of mono- and bis-methylated products (Scheme S1, Supporting Information). Less reactive dimethyl sulfate, Me_2SO_4, which had to be used in excess amounts (4 equiv), under heating at reflux (14 h), performed similarly. Dimethyl carbonate (DMC), a substitute for methyl halides and dimethyl sulfate in the methylation of a variety of nucleophiles,[28,29] resulted in

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(15) For a list of publications on 1,3,4-trisubstituted-1,2,3-triazolium salts used in the preparation of transition-metal−*tz*NHC complexes and their catalytic properties, please see the Supporting Information.

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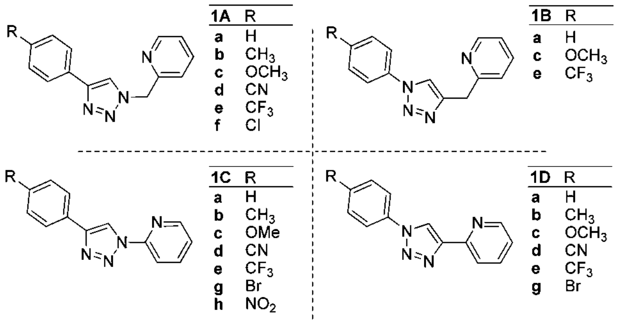
selective $-CH_2-$ bridge methylation at **1Aa** into 2-(1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethyl)pyridine (Scheme S1, Supporting Information). Based on these results, the reactivity of the best performing MeOTf was tested on **1Ba**, **1Ca**, and **1Da**. Whereas **1Ba** was dimethylated at both the pyridine and triazole N3 nitrogens, **1Da** gave a mixture of the monomethylated products (Scheme S2, Supporting Information).



1A	R
a	H
b	CH_3
c	OCH_3
d	CN
e	CF_3
f	Cl

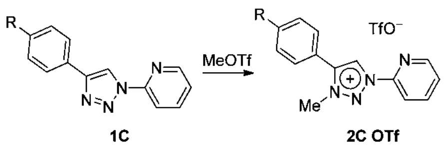
1B	R
a	H
c	OCH_3
e	CF_3

1C	R
a	H
b	CH_3
c	OMe
d	CN
e	CF_3
g	Br
h	NO_2

1D	R
a	H
b	CH_3
c	OCH_3
d	CN
e	CF_3
g	Br

Figure 2. Starting pyridyl-triazoles **1A**–**D**.

Scheme 3. Selective Monoalkylation of **1C**



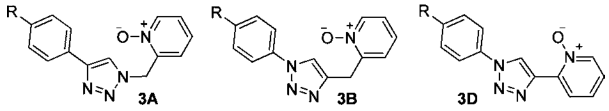
R	2C OTf	yield[a]
H	a	80
CH_3	b	81
OCH_3	c	75
CN	d	81
CF_3	e	74
Br	g	86
NO_2	h	83

[a] Isolated pure product.

In sharp contrast to **1Ba** and **1Da**, clean triazole N3 monoalkylation of **1Ca** with MeOTf produced the desired triazolium triflate **2Ca OTf** (Scheme 3). This selectivity turned out to be general for all 1-(2-pyridyl)-1,2,3-triazoles **1C**, and the corresponding triazolium salts **2C** were prepared in 74–86% yield. This selectivity could be explained by the decreased nucleophilicity of the pyridine lone pair that is caused by electronegative triazole nitrogen atom N1 attached in the **1C** series directly to the pyridine ring.

Electrophilic attack at the pyridine nitrogen atom such as protonation and salt formation, alkylation, acylation, and oxidation are well documented.[30−32] For the protection of the pyridine ring in pyridyl-triazoles **1** we selected *N*-oxidation based on the following two reasons: (*i*) it is easily introduced by a variety of reagents, and (*ii*) several methods exist for deoxygenation of both pyridine *N*-oxide in **4′** and the *N*-methoxypyridinium ion in **4** that can potentially be formed by methylation of triazole **3**.

The standard method for the oxidation of pyridines into *N*-oxides makes use of peroxy acids or hydrogen peroxide in carboxylic acid solutions.[30,33,34] For *N*-oxidation of **1A**, **1B**, and **1D** we selected *m*-chloroperoxybenzoic acid (*m*-CPBA). Heating these compounds with 2 equiv of *m*-CPBA in chloroform at reflux temperature for 30 min furnished pyridine *N*-oxides **3A**, **3B**, and **3D**, respectively, in nearly quantitative isolated yields (Figure 3).



R	3A	yield[a]	3B	yield[a]	3D	yield[a]
H	a	95	a	100	a	90
CH_3	b	99			b	98
OCH_3	c	88	c	95	c	94
CN	d	98			d	86
CF_3	e	92	e	96	e	90
Cl	f	80				
Br					g	96

[a] Isolated pure product.

Figure 3. *N*-Oxides **3** derived from pyridyl-triazoles **1**.

With triazolyl-pyridine *N*-oxides **3A**, **3B**, and **3D** in hand the reagent suitable for their alkylation was selected on the basis of test experiments with **3Aa** (Scheme S3, Supporting Information). Briefly, exposure of **3Aa** to MeOTf or Me_3OBF_4 afforded dimethylated product **4Aa**. As described above for **1Aa**, the reaction of **3Aa** with Me_2SO_4 required excess amounts of the reagent and heating. The reaction of **3Aa** with DMC gave a complex mixture of products whereas methyl iodide reacted sluggishly (Scheme S3, Supporting Information). Thus, MeOTf and Me_3OBF_4 were selected to be suitable for the alkylation of **3A**, **3B**, and **3D**, and the results are shown in Schemes 4–6.

Methods for deoxygenation of heteroaromatic *N*-oxides are reviewed.[34−37] Molybdenum hexacarbonyl ($Mo(CO)_6$) is a mild and selective reagent, successfully employed for the reductive cleavage of the N–O bond in pyridine *N*-oxides and alkoxyamines.[38] This prompted us to use it

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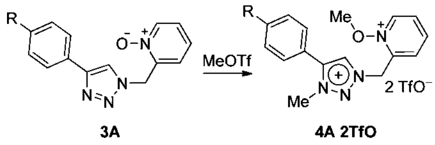
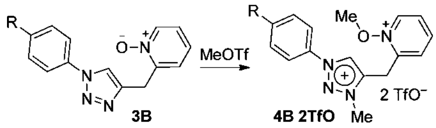
Scheme 4. Alkylation of **3A** (up) and **3B** (bottom) with MeOTf



R	**4A OTf**	conv[a]
H	**a**	96
CH_3	**b**	96
OCH_3	**c**	94
CN	**d**	93
CF_3	**e**	92
Cl	**f**	94

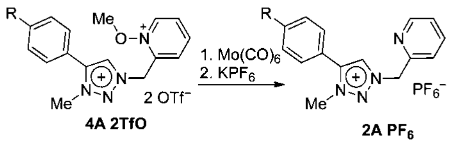
[a] Conversion.



R	**4B OTf**	yield[a]
H	**a**	83
OCH_3	**c**	61
CF_3	**e**	78

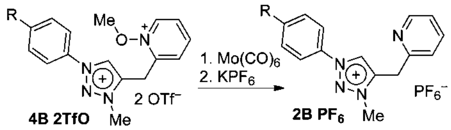
[a] Isolated pure product.

Scheme 5. Reductive N–O Bond Cleavage in **4A 2OTf** (up) and **4B 2OTf** (bottom)



R	**2A PF$_6$**	yield[a]
H	**a**	98
CH_3	**b**	93
OCH_3	**c**	97
CN	**d**	99
CF_3	**e**	94
Cl	**f**	92

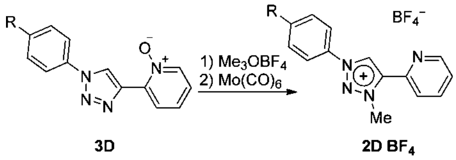
[a] Isolated pure product.



R	**2B PF$_6$**	yield[a]
H	**a**	98
OCH_3	**c**	90
CF_3	**e**	97

[a] Isolated pure product.

Scheme 6. One-pot alkylation and N–O bond cleavage at **3D**

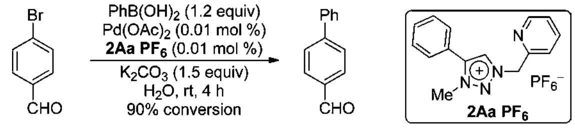


R	**2D BF$_4$**	yield[a]
H	**a**	85
CH_3	**b**	98
OCH_3	**c**	65
CN	**d**	60
CF_3	**e**	94
Br	**g**	85

[a] Isolated pure product.

for the reduction of **4A** and **4B** into the triazolium salts **2A** and **2B**, respectively (Scheme 5). Bis(pinacolato)diboron, recently reported as a nonmetal reagent for the reduction of amine *N*-oxides,[39] failed to react with **4Aa 2OTf**.

Scheme 7. Performance of **2Aa PF$_6$** in Suzuki–Miyaura Catalysis



Finally, having established the stepwise reaction protocol for the preparation of pyridyl-triazolium salts **2** from Scheme 2, to save the experimental time, triazolyl-pyridine *N*-oxides **3D** were transformed into the corresponding triazolium salts **2D** by a one-pot telescoped alkylation–reduction protocol (Scheme 6). The desired products were obtained in good to excellent yields.

With the pyridyl-triazolium salts in hand, we were eager to test their performance in the catalysis of the Suzuki–Miyaura type.[40] The preliminary catalysis results for 4-benzaldehyde and phenyl boronic acid in the environmentally benign solvent water are shown in Scheme 7. At room temperature, with catalyst ($Pd(OAc)_2$) and ligand (**2Aa PF$_6$**) loadings of 0.01 mol %, a 90% conversion into 4-phenylbenzaldehyde was observed in 4 h (Scheme 7).

Facile entry to pyridine appended triazolium salts is described that features pyridine nitrogen protection. In coordination chemistry, these analogous yet structurally diverse compounds **2A–D** will be examined as mono- and multidentate *tz*NHC ligands in systematic investigations of their coordination properties. They should offer both structurally flexible **2A–B** and rigid **2C–D** bidentate coordination to the metal, with or without resonance stabilization between the two heterocyclic rings.

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Supporting Information Available. Literature survey, Schemes S1–S3, experimental details and characterization data for all compounds, copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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