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ARTICLE TYPE

## Cu(OAc)<sub>2</sub>/Et<sub>3</sub>N mediated oxidative coupling of $\alpha$ -azido ketones with pyridinium ylides: Utilizing *in situ* generated imines for regioselective synthesis of imidazo[1,2-*a*]pyridines

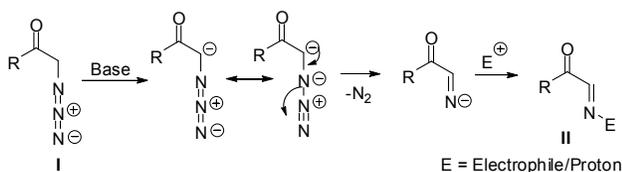
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Phenacyl azides were reacted with pyridinium ylides in the presence of Cu(OAc)<sub>2</sub> (2 mol%) and Et<sub>3</sub>N utilizing molecular oxygen as a green oxidant to yield imidazo[1,2-*a*]pyridines in exclusive regioselectivity. Following the optimized protocol, 28 different fused heterocycles were synthesized in high yields (71-92%). In order to get mechanistic insight of the reaction, a few control experiments were carried out and the role of copper salt was discussed.

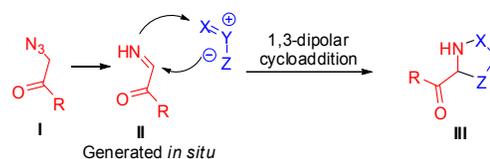
$\alpha$ -Azido ketones **I** are very important building blocks in organic chemistry.<sup>1</sup> In contrast to simple alkyl or aryl azides, these organic synthons exhibit many peculiar chemical behaviours which originate mainly from the increased acidity of the  $\alpha$ -hydrogen due to the presence of oxo functionality. The synthetic potential of these reactive species has been utilized in various inter and intra-molecular fashions to build numerous fine chemicals, pharmaceuticals and natural products.<sup>2</sup> These base sensitive compounds have long been known to decompose readily after deprotonation yielding highly reactive imines **II** (Scheme 1).<sup>3</sup> Depending on the reaction conditions and structure of the  $\alpha$ -azido ketones, the initially formed azomethine anions are hydrolyzed, polymerized, or trapped with various electrophiles. Despite long history, the potential of these reactive imines and therefore of  $\alpha$ -azido ketones for organic transformations has not been explored much.



**Scheme 1.** Base mediated decomposition of  $\alpha$ -azido ketones **I** into imines **II**

Formation of the imine **II** from  $\alpha$ -azido ketones under basic medium was proposed first time by Boyer and Canter.<sup>3a</sup> Characterization of such imines under photochemical and acid catalyzed decomposition of  $\alpha$ -azido ketones has also been reported.<sup>3b</sup> Although generation of such imines from phenyl glyoxal and ammonium salts are reported,<sup>4</sup> their synthetic utility is largely hampered by aqueous reaction medium where water

sensitive reagents may not be used and the inconvenient access of aryl glyoxals. A careful survey of the literature revealed that the application of these reactive imines in organic synthesis is largely unexplored. Only a few scattered examples mentioning their dimerization, inter and intramolecular cyclization in several ways leading to the formation of pyrroles, imidazoles, and pyridines are reported.<sup>5</sup> Exploring the reactivity of these imines towards 1,3-dipoles, which to the best of our knowledge is not investigated so far, might open a new window for diverse valuable heterocycles. We envisioned that the *in situ* generated imines **II** (from readily available phenacyl azides) might be trapped by 1,3-dipoles to yield numerous heterocycles **III** (Scheme 2).

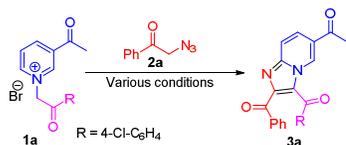


**Scheme 2.** Proposed synthesis of heterocyclic molecules **III** through 1,3-dipolar cycloaddition reaction of the imines **II** (generated *in situ*) with 1,3-dipoles

For the proof of the concept, pyridinium ylides were taken as typical 1,3-dipoles. Herein, we disclose the results of Cu(OAc)<sub>2</sub>/base mediated coupling of pyridinium ylides, generated from pyridine and phenacyl bromides, with phenacyl azides. Imines **II** were generated *in situ* and reacted with pyridinium ylides to form cycloadducts which underwent facile air oxidation yielding pharmaceutically valuable imidazo[1,2-*a*]pyridines.<sup>6</sup> Due to their significant medicinal importance, numerous synthetic protocols for imidazo[1,2-*a*]pyridines have been developed.<sup>7</sup> Most of these methods rely on the annulations of 2-aminopyridines with various reagents, therefore both nitrogen atoms of the imidazo[1,2-*a*]pyridine come from 2-aminopyridines. It is notable that the synthetic route described herein utilizes coupling of pyridines and phenacyl azides to yield imidazo[1,2-*a*]pyridines, hence the nitrogen atoms of the product come from two different coupling partners. The current study not only provides a convenient access to the imidazo[1,2-*a*]pyridines but also opens up the possibilities of reacting phenacyl azides with many other 1,3-dipoles for the synthesis of valuable intermediates and heterocyclic motifs.

At the onset, an ylide of 3-acetylpyridine was taken as the model 1,3-dipole to test the feasibility of the concept. The pyridinium salt **1a** was prepared by refluxing equimolar mixture of 3-acetylpyridine **4a** and 2-bromo-4'-chloroacetophenone **5a** in EtOAc. Next the crude salt **1a** was reacted with phenacyl azide **2a** under various conditions to optimize the formation of imidazo[1,2-*a*]pyridine **3a** (Table 1).

**Table 1.** Optimization of the formation of imidazo[1,2-*a*]pyridine **3a** via the reaction phenacyl azide **2a** with pyridinium salt **1a**<sup>a</sup>



Entry	Base (loading)	Additive (loading)	Solvent	Time (h)	Yield of <b>3a</b> (%) <sup>b</sup>
1	--	--	EtOAc	24	0
2 <sup>c</sup>	--	--	EtOAc	24	0
3	NaOH (2 eq.)	--	EtOAc	24	0
4	K <sub>2</sub> CO <sub>3</sub> (2 eq.)	--	EtOAc	24	0
5	DIPEA (2 eq.)	--	EtOAc	24	0
6	Et <sub>3</sub> N (2 eq.)	--	EtOAc	24	0
7	Et <sub>3</sub> N (2 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	EtOAc	6	(61)
8	Et <sub>3</sub> N (3 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	EtOAc	6	(72)
9	Et <sub>3</sub> N (3 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	THF	2	(55)
10	Et <sub>3</sub> N (3 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	(83)
11	Et <sub>3</sub> N (3 eq.)	Cu(OAc) <sub>2</sub> (2 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	(83)
12 <sup>d</sup>	Et <sub>3</sub> N (3 eq.)	Cu(OAc) <sub>2</sub> (2 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	(82)
13 <sup>e</sup>	Et <sub>3</sub> N (3 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	10
14	Et <sub>3</sub> N (2 eq.)	AgOAc (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	6	0
15	Et <sub>3</sub> N (2 eq.)	AuCl <sub>3</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	6	0
16	Et <sub>3</sub> N (3 eq.)	In(OTf) <sub>3</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	0
17	Et <sub>3</sub> N (3 eq.)	Cu(OTf) <sub>2</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	30
18	Et <sub>3</sub> N (3 eq.)	CuSO <sub>4</sub> ·5H <sub>2</sub> O (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	8
19	K <sub>2</sub> CO <sub>3</sub> (3 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	34
20	NaOH (3 eq.)	Cu(OAc) <sub>2</sub> (5 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	2	64

<sup>a</sup> Reaction conditions: Pyridinium salt **1a** (1 mmol), azide **2a** (1.1 mmol), solvent 15 mL, base, additive, rt, stir, open atmosphere. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR analysis of the crude reaction product using anisole as internal standard; Values in parentheses represent isolated yields. <sup>c</sup> Reaction was done under reflux condition. <sup>d</sup> The reaction was done under oxygen atmosphere. <sup>e</sup> The reaction was done under nitrogen atmosphere.

No reaction between the pyridinium salt **1a** and azide **2a** was observed in absence of a base either at ambient temperature or reflux conditions (Table 1, entry 1, 2). Inorganic bases (NaOH

and K<sub>2</sub>CO<sub>3</sub>) decomposed the azide **2a** but the desired product **3a** was not obtained. The azido ketone remained largely un-reacted in the presence of organic bases (DIPEA and Et<sub>3</sub>N) even after 24 h at ambient temperature. However, we were pleased to achieve good yields of **3a** using 5 mol% Cu(OAc)<sub>2</sub> as an additive and 2 eq. of Et<sub>3</sub>N as base (Table 1, entry 7). Better yield of **3a** was obtained by using 3 eq. of Et<sub>3</sub>N as a base (Table 1, entry 8). Furthermore, the loading of Cu(OAc)<sub>2</sub> could be reduced to 2 mol% without affecting the product yield and reaction time significantly (Table 1, entry 11). Among several solvents screened, CH<sub>2</sub>Cl<sub>2</sub> was found the best in terms of product yield and purity. The yield of **3a** was not much improved when the reaction was carried out under oxygen atmosphere (Table 1, entry 12). However, the yield of **3a** was drastically decreased when the reaction was performed under nitrogen atmosphere (Table 1, entry 13). Under nitrogen atmosphere, formation of **3a** in very low yields can be explained by considering oxidation by Cu(OAc)<sub>2</sub> or residual oxygen. AgOAc, AuCl<sub>3</sub> and In(OTf)<sub>3</sub> were also attempted for the reaction but the desired product **3a** was not formed in these cases (Table 1, entry 14-16). Cu(OTf)<sub>2</sub> and CuSO<sub>4</sub>·5H<sub>2</sub>O were also screened for the reaction but the desired product **3a** was formed in poor yields (Table 1, entry 17-18). The combination of inorganic bases and Cu(OAc)<sub>2</sub> were also attempted but the yields of **3a** were not satisfactory (Table 1, entry 19-20). These results indicated that presence of the copper salt is crucial for the formation of the fused heterocyclic compound **3a**. Furthermore, formation of the only regioisomer **3a** confirmed the exclusive regioselective nature of the reaction.

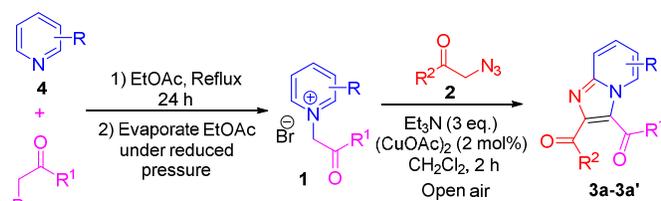
Et<sub>3</sub>N/Cu(OAc)<sub>2</sub> mediated annulations of **1a** with phenacyl azide **2a** were better in CH<sub>2</sub>Cl<sub>2</sub> than the same in EtOAc (Table 1). The pyridinium salt **1a** prepared from pyridine and phenacyl bromide in EtOAc was sufficiently pure for next step reaction. Therefore, after the formation of **1a** was complete the solvent (EtOAc) was removed under reduced pressure and the same reaction vessel was charged with CH<sub>2</sub>Cl<sub>2</sub>, Cu(OAc)<sub>2</sub> and phenacyl azide **2a** for further transformations. Thus, a pseudo three-component, one-pot strategy for the formation of imidazo[1,2-*a*]pyridine **3a** could be achieved. The same strategy was further utilised for the synthesis of a series of imidazo[1,2-*a*]pyridines (Table 2). The protocol worked well with a series of phenacyl azides bearing halogen and electron withdrawing as well as electron donating groups in their aryl part leading to the formation of imidazo[1,2-*a*]pyridines in high yields (75-85%). The reaction was not successful with ethyl azidoacetate. It can be attributed to the difference in the acidity of  $\alpha$ -hydrogen atoms of ketones and esters, which might influence the mode of the decomposition of corresponding azides. The difference in the reactivity patterns of  $\alpha$ -azido ketones and  $\alpha$ -azido esters has already been reported by many researchers.<sup>1a</sup> The reaction also worked well with aliphatic  $\alpha$ -azido ketone giving a good yield (71%) of the corresponding imidazo[1,2-*a*]pyridine **3a'** (Table 2, entry 27).

A number of pyridinium ylides prepared from 3-acetyl pyridine, 3-ethoxycarbonyl pyridine, 4-acetyl pyridine and phenacyl bromides bearing halogen and electron withdrawing as well as electron releasing groups in their aryl part gave high yields of desired imidazo[1,2-*a*]pyridines (Table 2, entry 1-24 & 27). Furthermore, pyridinium ylides derived from 3-acetyl

pyridine and aliphatic  $\alpha$ -bromo ketones such as 1-adamantyl bromomethyl ketone and 1-bromopinacolone were also successfully utilised for the formation of corresponding imidazo[1,2-*a*]pyridines (Table 2, entry 25-26).

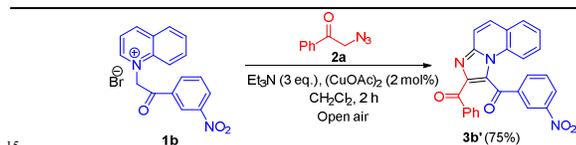
The reaction was not successful with pyridine, 3-bromopyridine or electron donating pyridines (4-dimethylaminopyridine) and yielded a complex mixture. However, the corresponding reaction with quinolinium ylide **1b** gave a clean product **3b'** in 75% yield (Scheme 3).

**Table 2.** Scope of the one-pot synthesis of imidazo[1,2-*a*]pyridines via the reaction of pyridines,  $\alpha$ -bromo ketones and  $\alpha$ -azido ketones<sup>a</sup>



Entry	R	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%) <sup>b</sup>
1	3-COCH <sub>3</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3a</b>	83
2	3-COCH <sub>3</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3b</b>	80
3	3-COCH <sub>3</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	<b>3c</b>	84
4	3-COCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3d</b>	77
5	3-COCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3e</b>	79
6	3-COCH <sub>3</sub>	4-Ph-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3f</b>	85
7	3-COCH <sub>3</sub>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3g</b>	82
8	3-COCH <sub>3</sub>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3h</b>	75
9	3-COCH <sub>3</sub>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3i</b>	77
10	3-COCH <sub>3</sub>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3j</b>	83
11	3-COCH <sub>3</sub>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	3-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	<b>3k</b>	76
12	3-COCH <sub>3</sub>	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3l</b>	82
13	3-COCH <sub>3</sub>	4-F-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3m</b>	85
14	3-COCH <sub>3</sub>	2-Naphthyl	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3n</b>	83
15	3-COCH <sub>3</sub>	4-CN-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3o</b>	83
16	3-COCH <sub>3</sub>	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3p</b>	80
17	3-COOEt	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3q</b>	77
18	3-COOEt	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3r</b>	79
19	3-COOEt	4-Ph-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>3s</b>	81
20	4-COCH <sub>3</sub>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3t</b>	85
21	4-COCH <sub>3</sub>	4-CN-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3u</b>	79
22	4-COCH <sub>3</sub>	4-Ph-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>3v</b>	82
23	3-COCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	4-CN-C <sub>6</sub> H <sub>4</sub>	<b>3w</b>	75
24	3-COCH <sub>3</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	4-CN-C <sub>6</sub> H <sub>4</sub>	<b>3x</b>	79
25	3-COCH <sub>3</sub>	1-adamantyl	4-Ph-C <sub>6</sub> H <sub>4</sub>	<b>3y</b>	77
26	3-COCH <sub>3</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	<b>3z</b>	80
27	3-COCH <sub>3</sub>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	<b>3a'</b>	71

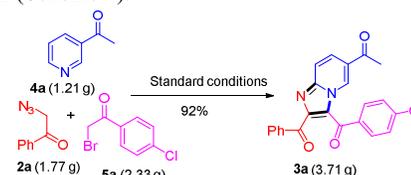
<sup>a</sup> Reaction conditions: i) Pyridine **4** (1 mmol),  $\alpha$ -bromo ketones **5** (1 mmol), EtOAc (20 mL), reflux, 24 h, then evaporate the solvent under reduced pressure, next- ii) azide **2** (1.1 mmol), CH<sub>2</sub>Cl<sub>2</sub> 15 mL, Et<sub>3</sub>N (3 mmol), Cu(OAc)<sub>2</sub> (2 mol%), stir, open atmosphere. <sup>b</sup> Isolated yields.



**Scheme 3.** Reaction of phenacyl azides **2a** with quinolinium ylide **1b**

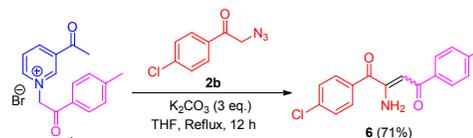
The structure of the products **3a-3b'** was confirmed by MS/HRMS, IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra. Further confirmation of the regioselectivity was done by 2D NOESY of compound **3a** and single crystal X-ray analysis of compound **3d** (For details of 2D NMR and X-ray analysis, see supporting information).

In order to expand the synthetic competence of our strategy, a gram-scale synthesis of **3a** was performed under the standard conditions. The desired imidazo[1,2-*a*]pyridine **3a** was isolated in 92% yield which indicates there is a potential industrial application (Scheme 4).



**Scheme 4.** Synthetic application: Gram scale reaction

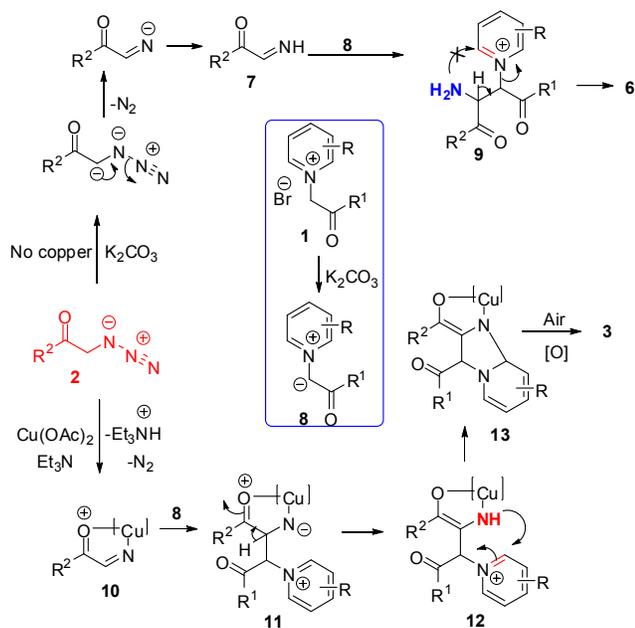
In order to get a better understanding of the annulations process, we planned to study the role of copper salt by taking the reaction of pyridinium salt **1c** with phenacyl azide **2b** as a model reaction (Scheme 5). We were particularly interested in characterizing the product of copper-free reaction. After screening several conditions, a good yield of enaminone **6** was obtained by refluxing the reaction mixture in THF using 3 eq. of K<sub>2</sub>CO<sub>3</sub>.



**Scheme 5.** Control experiment: Formation of enaminone **6** under copper-free conditions

Formation of the enaminone **6** in copper-free reaction and imidazo[1,2-*a*]pyridine **3** in copper mediated reaction might be explained by a plausible mechanism depicted in Scheme 6. In copper-free reaction, imine **7** is generated from the decomposition of phenacyl azide **2** by potassium carbonate. Next it is attacked by pyridinium ylide **8** leading to the formation of an intermediate **9**. In the intermediate **9**, intramolecular attack of the amine (hard base) to the pyridinium imine (soft acid) is disfavored.<sup>8</sup> Such reactions are generally reversible and to the best of our knowledge, they are not known to proceed under basic conditions. Therefore under basic and reflux conditions, the pyridyl group is eliminated yielding a thermodynamically stable enaminone **6**.

In the presence of Et<sub>3</sub>N and Cu(OAc)<sub>2</sub>, the phenacyl azide **2** decomposes to yield a chelated imine **10**. The chelated imine is attacked by pyridinium ylide **8** yielding an intermediate **11** which rapidly isomerizes to another intermediate **12**. Due to the chelation, amine group (NH) of the intermediate **12** behaves as a soft base and attacks the pyridinium imine (soft acid) to yield another intermediate **13**. Although Scheme 6 shows the formation of **13** by step-wise process, a concerted [3+2] dipolar cycloaddition process for the same cannot be discounted. In the presence of atmospheric oxygen, the intermediate **13** rapidly aromatizes to imidazo[1,2-*a*]pyridine **3**.



**Scheme 6.** Proposed mechanism for the formation of imidazo[1,2-*a*]pyridines **3** via copper mediated reaction and enaminone **6** in copper-free condition

## Conclusions

In conclusion, the reactivity of a class of  $\alpha$ -azido ketones towards pyridinium ylides for the formation of pharmaceutically important fused heterocycles has been explored for the first time. Et<sub>3</sub>N/Cu(OAc)<sub>2</sub> mediated one-pot strategy for the synthesis of valuable imidazo[1,2-*a*]pyridines was developed and 28 different chemical entities were synthesized in high yields (71-92%). The experimental results revealed that copper salt plays an important role for controlling the reactivity of *in situ* generated imines towards pyridinium ylides. The reaction and the one-pot protocol we developed has the potential for scale-up production of imidazo[1,2-*a*]pyridines. This novel reactivity pattern of  $\alpha$ -azido ketones towards 1,3-dipoles opens up the possibilities of synthesizing numerous valuable heterocycles as well as fine chemicals in a manner that is atom economical, convenient and scalable. Coupling of the phenacyl azides with other 1,3-dipoles is currently under investigation and the results will be communicated in near future.

## Acknowledgment

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [general experimental procedures, NMR data, and single crystal X-ray data]. See DOI: 10.1039/b000000x/

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