Organic & Biomolecular Chemistry

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Copper–Mediated Synthesis of Pyrazolo[1, 5–a]pyridines Through Oxidative Linkage of C–C/N–N Bonds

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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Copper–mediated synthesis of pyrazolo[1, 5–a]pyridine-3-carboxylates through oxidative linkage of C–C and N–N bonds under mild reaction conditions is described. This protocol is applicable for variety of pyridyl esters as well as various benzonitriles including nicotinonitrile, isonicotinonitrile and thiophene-2-carbonitrile. Better yields were observed with electron withdrawing substituted benzonitriles.

Over the past decade, substantial progress has been achieved in the transition-metal-catalyzed synthesis of nitrogen containing heterocycles.[1] In particular, pyrazolo[1,5–a]pyridines have been synthesized via the *N*-aminopyridine derivatives with electron withdrawing alkenes/alkynes,[2,3] and direct alkynylation followed by cyclization of *N*–iminopyridinium ylides.[4] Also reports exist on the direct oxidative annulation of *N*-iminopyridinium ylides with terminal alkynes,[5] nitrene insertion reactions[6] and through cyclization of pyrazole derivatives.[7] Development of such molecules received much attention and is the area of current research since their documentation toward biological activity (Fig 1).[8]

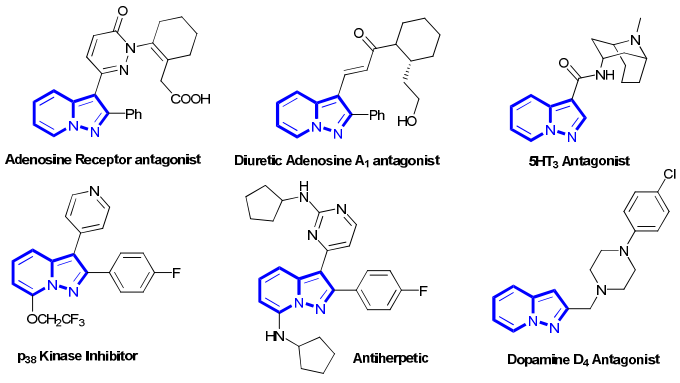
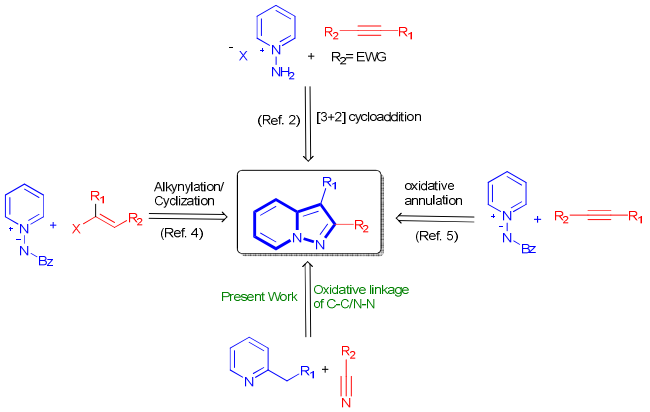


Figure 1. Biologically active pyrazolo [1, 5-a] pyridines.

Although these transformations are high yielding but require several synthetic steps for the synthesis of starting substrates like *N*-aminopyridine derivatives which are commercially not available, hence it hampers the efficiency of the process. Most recently we reported copper-catalyzed aerobic oxidative amination for the synthesis of imidazo heterocycles from pyridine derivatives.[9] Obviously, we became interested to develop new methods for the synthesis of pyrazolo[1, 5–a]pyridines which can be accessed by the annulation of pyridine derivatives. Herein we describe the direct synthesis of substituted pyrazolo[1,5–a]pyridines from commercially accessible pyridine derivatives and nitriles (Scheme 1). This new method toward pyrazolo[1,5–a]pyridines features a much broader scope, in that *N*-aminopyridine derivatives are no longer required.



Scheme 1. Strategies for the synthesis of pyrazolo [1, 5–a] pyridines.

In continuation of our studies on the synthesis of nitrogen-containing heterocycles,[10] we investigated the reaction of ethyl-2-(pyridin-2-yl) acetates with benzonitriles as a potential route to pyrazolo[1, 5–a]pyridines. Our initial experimental efforts focused on the development of conditions for annulation reaction of pyridyl esters and nitriles as these starting substrates are commercially available. An extensive survey on screening of bases and solvents[11] was performed using our previously reported copper catalysts[10] and

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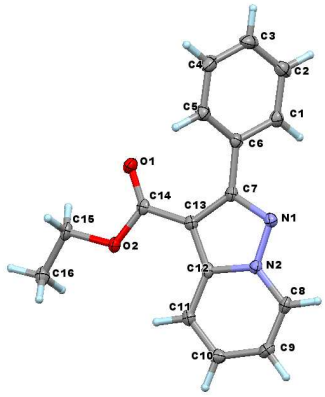
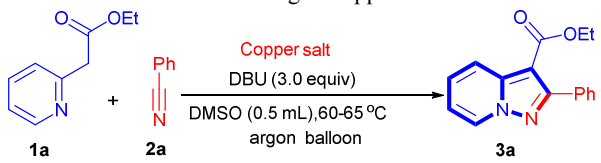


Figure 2. The crystal structure of **3a.**

literature reports.[12] We found that treatment of **1a** with 5.0 equiv of benzonitrile **2a**, 1.0 equiv. of $Cu(OAc)_2$, and 3.0 equiv of DBU in DMSO at 60 °C for 6 h gave the desired product **3a** in 20% yield (Table 1, entry 1). The product was further confirmed by XRD analysis (Fig 2). Increase of $Cu(OAc)_2$ to 1.5 equiv., the yield raised to 39% (Table 1, entry 2). Further increase of $Cu(OAc)_2$ to 3.0 equiv., yield of **3a** was decreased (Table 1, entry 3). This may be due to the hydrolysis of **1a** with increased Lewis acidity of the system. A

Table 1. Screening of copper source[a]

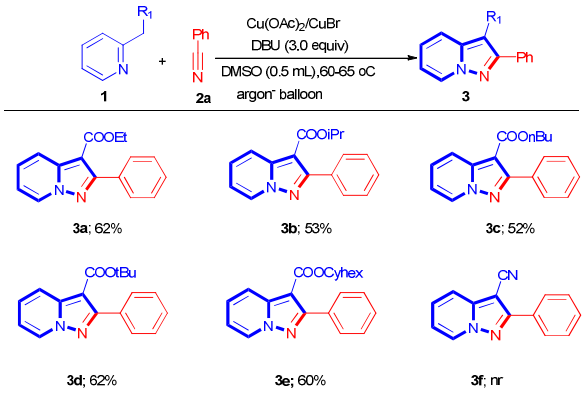


1a **2a** **3a**

Entry	metal salt (equiv)	Yield(%)[b]
1	$Cu(OAc)_2$ (1.0)	20
2	$Cu(OAc)_2$ (1.5)	39
3	$Cu(OAc)_2$ (3.0)	22
4	$CuBr_2$ (1.5)	trace
5	$CuCl_2$ (1.5)	nr
6	$Cu(OTf)_2$ (1.5)	nr
7	CuF_2 (1.5)	nr
8	CuI (1.5)	23
9	CuBr (1.5)	28
10	CuCl (1.5)	25
11[c]	$Cu(OAc)_2$ (1.5)	46
12[c]	**$Cu(OAc)_2$ (1.0)/ CuBr(1.0)**	**62**
13[c]	$Cu(OAc)_2$ (1.0)/ CuCl(1.0)	48
14[c]	$Cu(OAc)_2$ (1.0)/ CuI(1.0)	41
15[d]	$Cu(OAc)_2$ (1.0)/ CuBr(1.0)	53
16[e]	$Cu(OAc)_2$ (1.0)/ CuBr(1.0)	47
17[f]	$Cu(OAc)_2$ (1.0)/ CuBr(1.0)	51
18[d]	$Cu(OAc)_2$ (0.5)/ CuBr(0.5)	49
19[c,g]	$Cu(OAc)_2$ (1.0)/ CuBr(1.0)	trace

[a]Conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), catalyst, solvent (0.5 mL), in an oil bath 6 h. [b]Isolated yield. [c]4.5 mmol of **2a**. [d]5.0 mmol of **2a**. [e]6 mmol of **2a**. [f] Reaction at 80 °C. [g] Open air (nr = no reaction).

Table 2. Scope of pyridyl esters[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2a** (4.5 mmol), $Cu(OAc)_2$ (0.3 mmol), CuBr (0.3 mmol) in an oil bath, 6 h, isolated yield. [nr = no reaction].

trace of the product was observed with $CuBr_2$ (Table 1, entry 4). Other copper (II) sources $CuCl_2$, $Cu(OTf)_2$ and CuF_2 however under the identical conditions, failed to yield the product in detectable amount (Table 1 entries 5−7). Next, we checked the effect of copper (I) sources; the yield was not obviously increased (Table 1 entries 8−10). When 15.0 equiv. of **2a** (w.r.t. **1a**) was used, the yield was marginally improved (Table 1 entry 11). Gratifyingly, a yield of 62% was obtained with 1.0 equiv. of each $Cu(OAc)_2$ and CuBr (Table 1 entry 12). Apparently, these results indicate the combination of Cu(II) and Cu(I) salts plays a crucial role in the present transformation. Attempts to employ other Cu(I) sources (entries 13 and 14), increasing of **2a** (entries 15 and 16) and temperature (entry 17) did not improve the yield. While decreasing the amount of both Cu(II) and Cu(I) source to 0.5 equivalents, the yield was also decreased to 49% (Table 1, entry 18). When the reaction was performed under open atmosphere, the decomposition of pyridyl ester **1a** was observed (Table 1, entry 19). As the co-operation of $Cu(OAc)_2$−CuBr showed the best reactivity, hence these combination was chosen as copper sources for further studies (Table 1, entry 12).

To demonstrate the efficiency and to explore the scope of the $Cu(OAc)_2$−CuBr−DBU mediated oxidative annulation for the synthesis of pyrazolo[1,5-a]pyridines, a number of pyridyl esters were investigated with the optimized procedure (Table 2). Apart from ethyl-2-(pyridin-2-yl)acetate (**1a**), other pyridyl esters, for example, -COO^iPr, -COO^nBu, -COO^tBu, and -COOCyclohexyl, reacted well with benzonitrile to produce the corresponding pyrazolo[1,5–a]pyridine esters **3b-e** in moderate to good yields. However, nitriles containing product **3f** could not be obtained by this procedure as the starting substrate **1** was decomposed. Although this route to the formation of C–C and N–N bond was only realized on one particular class of substrates (pyridyl ester-based), it represents a major development in the search for an annulation strategy to obtain of pyrazolo[1,5–a]pyridines, which does not require *N*-aminopyridine derivatives.

Then, the generality of this reaction with more functionalized benzonitriles **2** was studied with various pyridyl esters **1** (Table 3). The reaction was found to be very facile with both electron rich and electron-deficient benzonitriles. Initially, the reaction of ethyl 2-(pyridin-2-yl)acetate (**1a**), with simple electron rich benzonitrile, for example 4-methylbenzotrile gave the desired product **4a**, in 32% yield under the optimized conditions. However, 4-phenyl benzonitrile provided the product **4b** in moderate yield of 52%.

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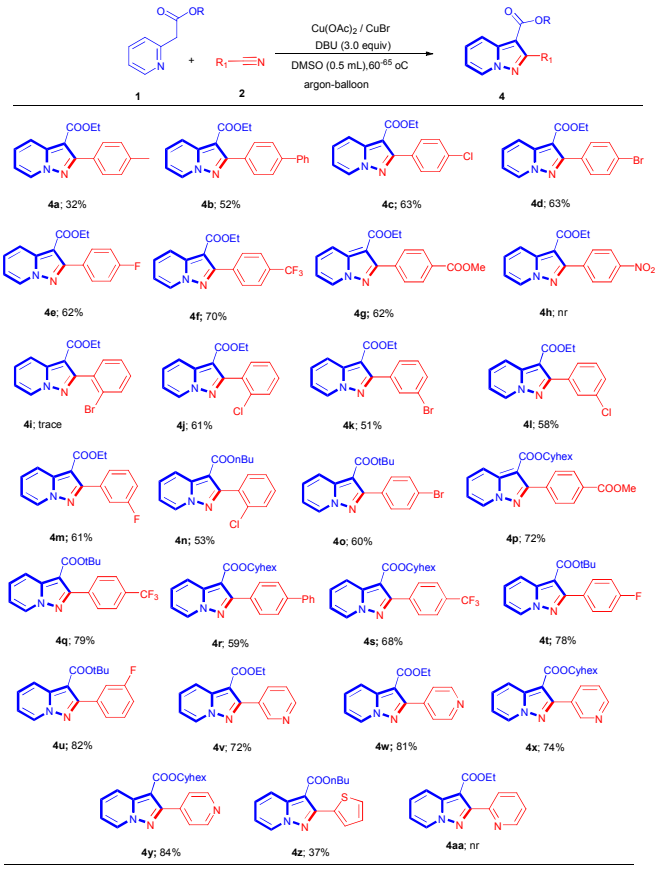
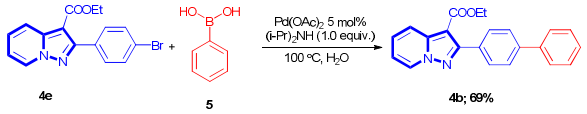
Electron donating substituents on the benzonitrile lowered the reactivity presumably due to increased electron density on the arene

Table 3. Substrate scope of various nitriles[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (4.5 mmol), $Cu(OAc)_2$ (0.3 mmol), CuBr(0.3 mmol) in an oil bath, 6 h, isolated yield. [nr = no reaction].

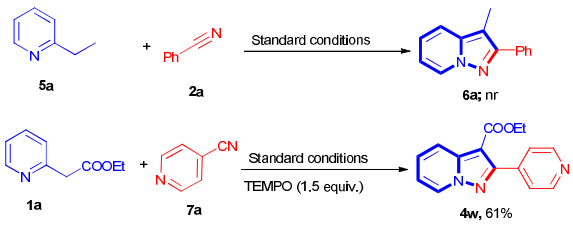
ring. The use of electron-withdrawing substituents at *para*-position of **2**, led to the corresponding products (i.e., **4c**–**g**) in yields ranging from 62 to 70%. We have also attempted with substrates having strong electron withdrawing nitro group **4h**, but without success. 2-Bromobenzonitrile gave traces of desired product **4i** due to steric factor, the corresponding chloro derivative gave the desired product **4j** in 61% yield. Halogens (Br, Cl and F) at *meta*-position benzonitriles accomplished products **4k-m** in 51-61% yields. It may be noted that, halide (Cl, Br and F) substituted pyrazolo[1,5–a]pyridine derivatives were well tolerated, and which could be further applied in traditional cross-coupling reactions (Scheme-2).[13]



Scheme 2. Functionalization of bromo pyrazolo[1,5-a]pyridine through Suzuki reaction

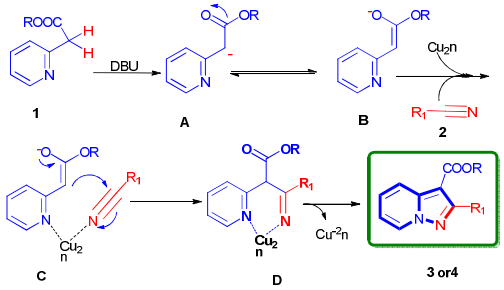
Next, we evaluated the substrate scope of substituted pyridyl esters with various benzonitriles. Pyridyl esters, like isopropyl, *n*-butyl, *tert*-butyl, and cyclohexyl reacted well with benzonitrile derivatives and afforded the desired products **4n-t** in moderate to good yields. Pleasingly we found that, the present system is also applicable to azahetero and thio hetero nitriles under typical conditions, to afford the desired products **4u**–**z** in moderate to good yields. However, no desired product (**4aa**) formation was observed with 2-cyanopyridine and both starting substrates were decomposed. In case of aliphatic nitriles (acetonitrile and pivaloyl nitrile) no reactions were observed, but recovered the starting materials (which were not included in Table 3).

Then, to determine the reaction mechanism, some control experiments were performed (Scheme 3). When the reaction of 2-ethylpyridine **5a** was reacted with benzonitrile **2a** under optimized conditions, no product formation was observed. To confirm the reaction whether ionic or radical pathway, **1a** and **7a** were subjected to the optimized conditions using TEMPO as radical scavenger, no radical adduct formation was observed, it rule out the radical pathway.



Scheme 3. Control experiments

Based on the above control experiments and literature reports[14] we proposed a plausible reaction mechanism as described in Scheme 4. Initially, pyridyl ester **1** in the presence of DBU generates the carbine ion intermediate **A** which will be in equilibrium form as enolate ion intermediate **B**. Simultaneously the reaction of **B** with benzonitrile **2** in presence of copper forms copper complex **C** and its subsequent C-C bond formation generates another intermediate **D**.[14] Finally, its reductive elimination gives the desired product **3** or **4**.



Scheme 4. Plausible mechanism

In conclusion, we have developed a new method for the synthesis of pyrazolo[1,5–a]pyridines, mediated by copper catalysis under mild conditions. The major advantages of the method are: it does not require use of *N*-aminopyridines, use of commercially available pyridyl esters and benzonitriles, broad substrate scope, and mild reaction temperature (65 °C). Although the exact role of copper (I)/copper(II) are not clear at this stage, investigations are underway in our laboratory.

ACKNOWLEDGMENT

CSIR-CSMCRI Communication No. 201/2014. D.C.M, C. R & S. N. R. are thankful to AcSIR for their Ph.D. enrollment and the "Analytical Discipline and Centralized Instrumental Facilities" for providing instrumentation facilities. D.C.M. and S. N. R. are also thankful to UGC & CSIR, New Delhi for their

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DOI: 10.1039/C5OB00018A Journal Name

fellowships. We thank DST, Government of India (SR/S1/OC-13/2011), for financial support. We also thank CSIR-CSMCRI (OLP-0076) for partial assistance.

Notes and references

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^{1}H and ^{13}C NMR spectra for all compounds and HRMS spectra for new compounds. Crystallographic data for compound **3a** (CCDC-1035332) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x.

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