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A practical two-step synthesis of imidazo[1,2-*a*]pyridines from *N*-(prop-2-yn-1-yl)pyridin-2-amines†

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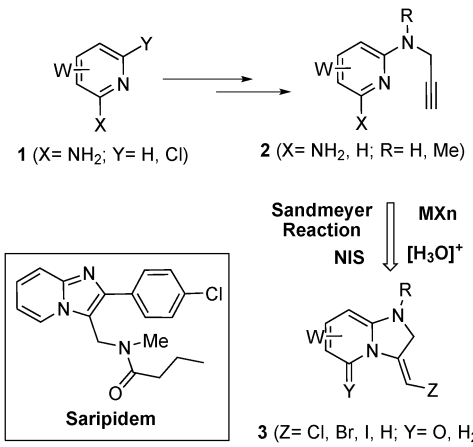
The Sandmeyer reaction of differently C-2 substituted *N*-(prop-2-yn-1-ylamino)pyridines is an efficient, mild, new and practical method for the stereospecific synthesis of (*E*)-*exo*-halomethylene bicyclic pyridones bearing the imidazo[1,2-*a*]pyridine heterocyclic ring system.

Two recent communications by Chernyak and Thiel reporting the transition metal-catalyzed synthesis of imidazoheterocycles,[1] and triazolopyridines,[2] respectively, prompt us to report here a practical two-step synthesis of imidazo[1,2-*a*]pyridines (**3**) from *N*-(prop-2-yn-1-yl)pyridin-2-amines (**2**), prepared from appropriate precursors **1**, by a Sandmeyer reaction (SR),[3] transition metal [$CuCl_2$, CuCl, $Pd(OAc)_2$, $NaAuCl_4$ or $PtCl_2$], *N*-iodosuccinimide (NIS), or acid promoted heterocyclization (Scheme 1).

In the context of our current work on the synthesis of 2-chloro(4*H*-pyrano)pyridines from the corresponding 2-amino substituted heterocycles,[4] when 2-amino-6-(methyl(prop-2-yn-1-yl)-amino)pyridine-3,5-dicarbonitrile (**2a**), prepared from 2-amino-6-chloropyridine-3,5-dicarbonitrile (**1a**),[6a] was submitted to SR[5] (ESI†), instead of the expected product, a new compound was isolated in 62% yield. This product was fully characterized by its analytical, spectroscopic data, and X-ray diffraction analysis (ESI†)[7] as the diastereomerically pure, chlorinated bicylic pyridone **3a**, bearing an imidazo[1,2-*a*]pyridine heterocyclic ring system (Scheme 2, eqn (1)).

Bicyclic pyridones,[8] and imidazo[1,2-*a*]pyridines,[9] such as saripidem (Scheme 1), alpidem or zolpidem, are well known pharmacologically active molecules.[10]

Consequently, and in view of the interest of these compounds, the increased number of communications describing



Scheme 1 Synthesis of imidazo[1,2-*a*]pyridines (**3**) *via* 6-(prop-2-yn-1-yl-amino)pyridines (**2**) from 2-amino-6-chloropyridines (**1**).

the transition metal promoted heterocyclic ring synthesis,[1,2,11] and the synthetic potential of our result, the scope and the generality of this process were investigated. Based on our current interest on highly substituted pyridine derivatives for biological purposes,[12] intermediates **2b,c** (Table 1) have been synthesized from easily available precursors,[6] and submitted to SR experimental conditions.

As shown in Table 1, SR of intermediate **2a**, in the presence of $CuBr_2$ or CuI, afforded similar compounds **3b** and **3c** in 63% and 41% yields (entries a and b), respectively, as the only reaction products, in clean and highly diastereoselective reactions. SR of intermediates **2b** and **2c** gave the reaction products **3d** and **3e** (entries c and d), respectively, in good yields. The configuration at the double bond in compounds **3b–e**, as well as in the other related derivatives prepared here by the same or analogous methods, has been unequivocally assigned by comparison of their NMR data with those of compound **3a**. Compound **2d**,[6c] bearing an ethoxy group at C2, gave the expected bicyclopyridone **3d** in 76% yield (Scheme 2, eqn (2)), identical to the product obtained from compound **2b** (Table 1, entry c). With these results in mind, next we investigated the heterocyclization reaction, using intermediate **2a**, *without any added nitrite*, and $CuCl_2$ or CuCl as catalysts. The reaction was still possible, but very surprisingly afforded the *exo*-methylene product **3f** in moderate to good yields (Table 1, entries e and f). Similarly, other transition metal salts, such as $Pd(OAc)_2$, $NaAuCl_4$ or $PtCl_2$, promoted the reaction giving compound **3f** in

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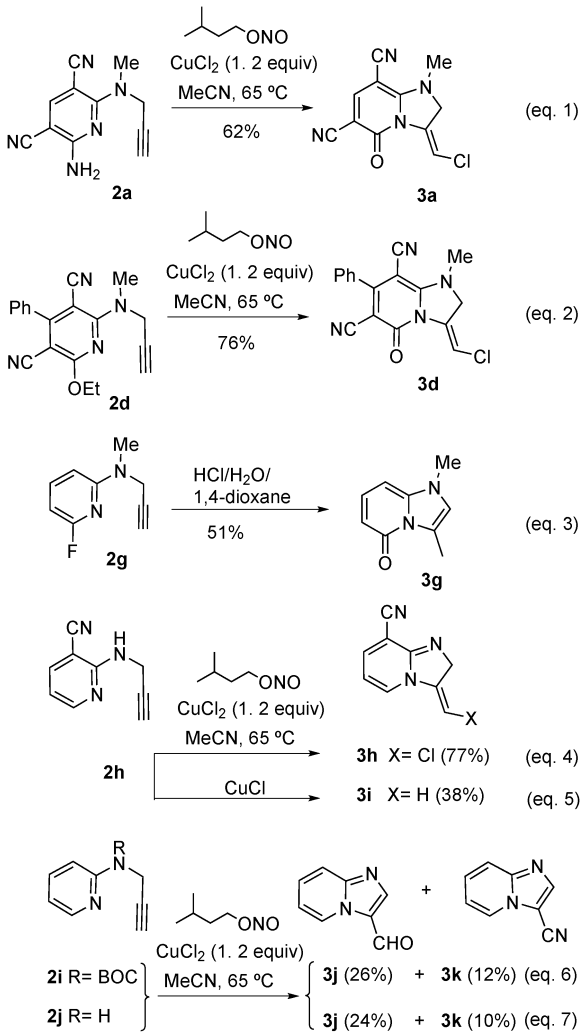
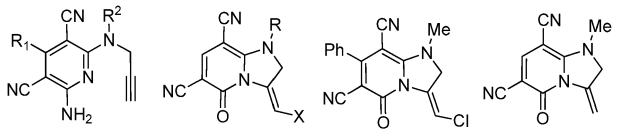


Scheme 2 Heterocyclization of diversely functionalized prop-2-yn-1-ylamino substituted pyridines (**2**).

Table 1 Heterocyclization reaction of 2-amino-6-(prop-2-yn-1-ylamino)-pyridines (**2**)



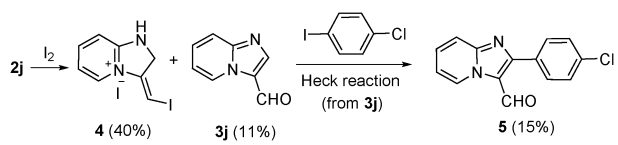
Entry	2	CuX_n	3	Yield (%)
a	**2a**	$CuBr_2$[a]	**3b** (X = Br)	63
b	**2a**	CuI[a]	**3c** (X = I)	41
c	**2b**	$CuCl_2$[a]	**3d**	67
d	**2c**	$CuCl_2$[a]	**3e** (X = Cl)	55
e	**2a**	$CuCl_2$ (0.5 equiv.)	**3f**	46
f	**2a**	CuCl (0.25 equiv.)	**3f**	80
g	**2a**	$Pd(OAc)_2$ (0.1 equiv.)	**3f**	72
h	**2a**	$NaAuCl_4$ (0.1 equiv.)	**3f**	76
i	**2a**	$PtCl_2$ (0.2 equiv.)	**3f**	68

[a] Under Sandmeyer reaction conditions.

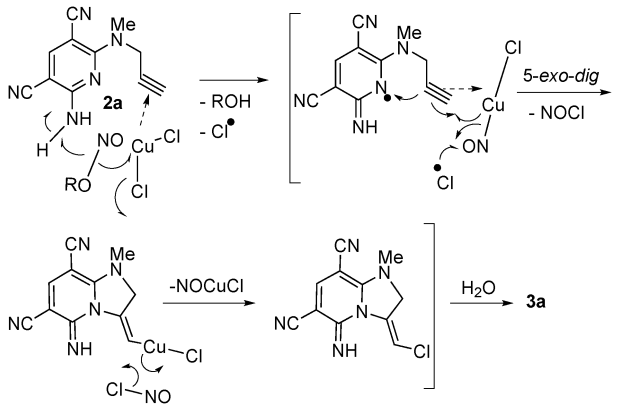
good yields (Table 1, entries g–i). However, compound **2c** did not react under these experimental conditions with none of these catalysts. Based on these results, we tested, but without success, the "one-pot" palladium-catalyzed [$Pd_2(dba)_3$, (+)-BINAP, NaO*t*Bu, toluene, reflux] Buchwald[13a] or the [(IPr)Ni(allyl)Cl][13b] promoted *N*-propargylation of 2-amino-6-halopyridines, followed by *in situ* heterocyclization. Conversely, we have also found that NIS,[14] unlike NBS or NCS, promotes the heterocyclization reaction of intermediate **2a** to give compound **3c** (Table 1), identical to the product obtained in the SR protocol, in higher (68% *vs.* 41%) yield, but similar diastereoselectivity.

Next the scope of the reaction was further investigated by modifying the structure of the intermediates. Unfortunately, SR of N^2-(prop-2-yn-1-yl)pyridine-2,6-diamine (**2e**) or 6-fluoro-*N*-(prop-2-ynyl)pyridin-2-amine (**2f**) (ESI†) gave complex reaction mixtures, and 6-fluoro-*N*-methyl-*N*-(prop-2-yn-1-yl)-pyridin-2-amine (**2g**) did not react. However, when we submitted compound **2g** to reaction with aqueous hydrochloric acid in 1,4-dioxane,[8b] 1,3-dimethylimidazo[1,2-*a*]pyridin-5(1*H*)-one (**3g**) was obtained in 51% yield (Scheme 2, eqn (3)). Very interestingly, under the usual SR conditions, 2-(prop-2-ynylamino)nicotino-nitrile (**2h**) provided stereospecifically imidazo[1,2-*a*]pyridine **3h** in 77% yield (Scheme 2, eqn (4)); similarly, when only CuCl was used as catalyst, compound **3i** was the sole product isolated in moderate yield (Scheme 2, eqn (5)). Finally, SR of *tert*-butyl prop-2-yn-1-yl(pyridin-2-yl)carbamate (**2i**), and *N*-(prop-2-yn-1-yl)-pyridin-2-amine (**2j**),[11c] prepared from 2-aminopyridine,[15] afforded the same reaction products **3j** and **3k** (Scheme 2, eqn (6) and (7)) in moderate chemical yields, but still competitive regarding the methods previously described in the literature for the synthesis of aldehyde **3j**[16a] and nitrile **3k**.[16b] The use of $CuCl_2$ or NIS to promote the heterocyclization reaction did not improve these results, but only aldehyde **3j** was isolated in 8% and 10% yields, respectively. The unexpected formation of compounds **3j** and **3k** shows that SR results on *N*-(prop-2-yn-1-ylamino)-pyridines are very substrate-dependent, but has precedent in the I_2-mediated heterocyclization of ethyl 2-(pyridin-2-yl)pent-4-ynoates leading to ethyl 3-formylindolizine-1-carboxylates.[17] In fact, under these reaction conditions, *N*-(prop-2-yn-1-yl)pyridin-2-amine (**2j**) gave (*E*)-3-(iodomethylene)-2,3-dihydro-1*H*-imidazo-[1,2-*a*]pyridin-4-ium iodide **4** (40%), and aldehyde **3j** (11%) which after a Heck reaction [DIPEA (4 equiv.), Ag_2CO_3 (0.7 equiv.), PPh_3 (0.11 equiv.), $Pd(OAc)_2$ (0.05 equiv.), acetonitrile, reflux, 48 h],[11d] with 1-chloro-4-iodobenzene, afforded compound **5** in 15 % yield (not optimized) (Scheme 3), a known intermediate in the synthesis of saripidem (Scheme 1).[18]

The transition metal promoted (or the NIS-mediated) heterocyclization of 2-amino-6-(prop-2-yn-1-ylamino)pyridines seems to proceed through an alkyne–metal complexation followed by a pyridinic nitrogen NH_2–(C2) assisted ring closure, ending by protonolysis/demetallation, with recovery of the catalyst,[1] affording compound **3f** (Table 1).



Scheme 3 Formal total synthesis of saripidem from imidazo-[1,2-*a*]pyridine-3-carbaldehyde (**3j**).



Scheme 4 A tentative free radical based mechanism for the formation of bicyclo pyridone **3a** from 2-amino-4-phenyl-6-(prop-2-yn-1-ylamino)-pyridine-3,5-dicarbonitrile (**2a**).

In Scheme 4 we show a tentative reaction mechanism for SR heterocyclization of 2-amino-6-(prop-2-yn-1-ylamino)pyridines, exemplified for intermediate **2a**, but extensive to other related intermediates. As proposed for the SR mechanism,[5,19] the formation of nitrosyl complexes of anhydrous copper halides, strongly coordinated to the alkyne moiety, should be the first step.

Then, the weak RO–NO bond of the nitrite should be broken, leading to an alkoxy radical that would trap a hydrogen, breaking the weak H–NH(C2) bond, starting then the free radical chain reaction by a 5-*exo*-*dig* free radical heterocyclization of the nitrogen centered radical at N(1) into the activated alkyne. Next, and possibly due to the steric hindrance, the resulting vinyl radical stereospecifically would afford the chlorinated *E*-*exo*-chloromethylene intermediate. Final hydrolysis of the HN=(C2)N moiety would afford the bicyclic pyridone **3a**.[20] The formation of imidazo[1,2-*a*]-pyridines **3j** and **3k** could be explained assuming that the presumed (*E*)-*exo*-halomethylene intermediate is too unstable, and decomposes *in situ* in the presence of traces of an external water source to the corresponding aldehyde, that evolves to aldehyde **3j** by oxidation, and to nitrile **3k**, by reaction with hydroxylamine, or nitrous acid, followed by dehydration.

In conclusion, we have discovered that SR, in the presence of organic nitrites and copper halides, of *N*-(prop-2-yn-1-yl-amino)pyridines synthesized by reacting easily available or commercial 2-halopyridines and *N*-propargylamines is a mild, new and practical method for the stereospecific synthesis of highly substituted (*E*)-*exo*-halomethylene bicyclic pyridones bearing the imidazo[1,2-*a*]pyridine heterocyclic ring system of potential biological interest. These are suitable intermediates for further synthetic transformations and modulation. In the course of this prospective study we have also found that 2-amino-6-(prop-2-yn-1-ylamino)pyridines afford *exo*/*endo*-methylene bicyclopyridones in transition metal-catalyzed [$CuCl_2$, $Pd(OAc)_2$, $PtCl_2$], NIS, or HCl/H_2O-mediated heterocylization reactions in convenient chemical yields.

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