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A Base Promoted Cyclization of *N*-Propargylaminopyridines. Synthesis of Imidazo[1,2-*a*]pyridine Derivatives

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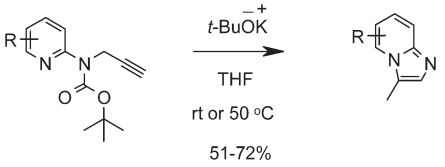
ABSTRACT



A base promoted cyclization of the protected *N*-propargylaminopyridines was shown to be an efficient method for the preparation of imidazo[1,2-*a*]pyridine derivatives. The reactions were carried out with a small excess of base, at room temperature or slightly above producing the heterocyclic products in moderate to good yields. The stereoelectronic properties of substituents on the pyridine ring were shown to influence the cyclization process.

The imidazo[1,2-*a*]pyridine scaffold (Figure 1) is present in a large number of compounds showing an impressive variety of biological properties.[1]

It is also a core structure of several drugs such as zolpidem (hypnotic), alpidem (anxiolytic), and zolimidine (antiulcer).

A number of synthetic methods have been designed for the preparation of this heterocyclic skeleton with majority of them relying on the formation of the imidazole ring.[2] The most common process involves the condensation of 2-aminopyridines with α-halocarbonyl compounds, either in solution[3a−c] or in the solid phase.[3d−h]

Perhaps, a more versatile method, producing the 3-amino derivatives, involves three-component coupling transformations.[4] Condensation reactions of aldehydes, 2-aminopyridine, and isocyanides is usually carried out in the presence of acidic catalysts, either protic or Lewis acids. In

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(1) For selected recent examples of biological activity, see: Antibiotic activity: (a) Lhassani, M.; Chavignon, O.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271. Antiinflammatory activity:(b) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347. Antibacterial activity:(c) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170. Bradykinin B2 receptor antagonists:(d) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K.; Inamura, N.; Asano, M.; Hatori, C.; Katayama, A.; Oku, T.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 564. Antiulcer activity: (f) Katsura, Y.; Nishino, S.; Inoue, Y.; Tomoi, M.; Takasugi, H. *Chem. Pharm. Bull.* **1992**, *40*, 371. Cyclin dependent kinase inhibitors:(g) Hamdouchi, C.; Zhong, B.; Mendoza, J.; Collins, E.; Jaramillo, C.; De Diego, J. E.; Robertson, D.; Spencer, C. D.; Anderson, B. D.; Watkins, S. A.; Zhanga, F.; Brooks, H. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1943. GABA receptor agonists:(h) Goodacre, S. C.; Street, L. J.; Hallett, D. J.; Crawforth, J. M.; Kelly, S.; Owens, A. P.; Blackaby, W. P.; Lewis, R. T.; Stanley, J.; Smith, A. J.; Ferris, P.; Sohal, B.; Cook, S. M.; Pike, A.; Brown, N.; Wafford, K. A.; Marshall, G.; Castro, J. L.; Atack, J. R. *J. Med. Chem.* **2006**, *49*, 35. Benzodiazepine receptor agonists:(i) Trapani, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934.

(2) For selected recent examples, see: (a) Guchhait, S. K.; Madaan, C. *Org. Biomol. Chem.* **2010**, *8*, 3631. (b) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079. (c) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013. (d) Aginagalde, M.; Vara, Y.; Arrieta, A.; Zangi, R.; Cebolla, V. L.; Delgado-Camon, A.; Cossio, F. P. *J. Org. Chem.* **2010**, *75*, 2776. (e) Adib, M.; Mohamadi, A.; Sheikhi, E.; Ansari, S.; Bijanzadeh, H. *Synlett* **2010**, 1606. (f) Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941. (g) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4487. (h) Dai, W.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 6647.

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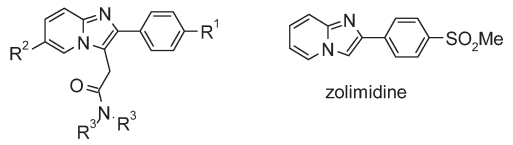
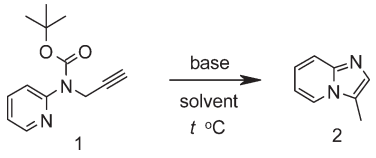


Figure 1. Imidazo[1,2-*a*]pyridine derivatives.

the past decade several transformations based on metal catalysis have been discovered.[5] Particularly interesting is a recently reported condensation process of 2-aminopyridines, aldehydes, and terminal alkynes catalyzed by the binary catalytic system Cu(I)/Cu(II).[5a] This method provides an efficient approach to functionalizing C(2) and C(3) of the imidazopyridine skeleton and was used for the one-pot synthesis of alpidem and zolpidem.

Our continuing interest in the chemistry of allenes and alkynes[6] prompted a study which resulted in the discovery of a new process for the preparation of imidazo[1,2-*a*] pyridine derivatives. Attempts to synthesize allene by the base promoted alkyne isomerization of N-propargylated aminopyridine **1** resulted in the formation of a compound which did not contain the allenic moiety. The reaction was carried out in THF using a slight excess of *t*BuOK as a base (Table 1, entry 1), at room temperature to afford the product in 70% yield after essentially just a few minutes, as judged by TLC. Analysis of $^{1}H/^{13}C$ NMR and mass spectral data fully supported the structure of compound **2**. Very few examples of the related cyclization process of the pyridine derivatives have been reported in the literature, but they employed acid as a solvent or a strong acidic conditions (HCOOH or H_2SO_4) and high temperatures.[7] Since our transformation offers some advantages, we decided to investigate it in more detail.

Table 1. Optimization of the Reaction Conditions



entry[a]	solvent	*t* °C[b]	base	yield (%)[c]
1	THF	rt/5 min	*t*BuOK	70
2	DMSO	rt/16 h	*t*BuOK	37(45)
3	DMSO	60 °C/16 h	*t*BuOK	31(41)
4	benzene	60 °C/16 h	*t*BuOK	47(65)
5	THF/*t*BuOH	60 °C/3 h	*t*BuOK	–
6	THF	60 °C/16 h	NaOH	–
7	THF	60 °C/16 h	NaH	17(40)
8	MeOH	60 °C/3 h	NaOH	–
9	THF	60 °C/16 h	DBU	–

[a] The reactions were performed using the following conditions: **1** (0.3 mmol), base (0.36 mmol) in solvent (3 mL) at indicated temperatures. [b] Reactions were initially carried out at rt and then at indicated temperatures. [c] Isolated yields and, in parentheses, yield based on conversion.

After the initial results we briefly investigated the effects of various reaction parameters in order to optimize the reaction conditions (Table 1). The use of a more polar solvent, such as DMSO (Table 1, entries 2 and 3), either at room temperature or at 60 °C over significantly longer reaction times than in the initial experiment, resulted in incomplete reactions and consequently lower yields. Slightly better results were produced with nonpolar benzene as a solvent (Table 1, entry 4) but with no general improvement. Attempts to use THF/*t*BuOH (v/v, 1:2) resulted in complete inhibition of the reaction (Table 1, entry 5). Several bases were also investigated. While NaOH, in either MeOH or THF (Table 1, entries 6 and 8), resulted in recovery of the starting materials, NaH in THF (Table 1, entry 7) afforded the expected product but in an unsatisfactory yield. On the other hand, a weak base such as DBU (Table 1, entry 9) was shown to be inefficient. In addition to the above experiments, attempts were made to decrease the amount of base under the conditions outlined in Table 1. Unfortunately, the reaction carried out with 20 mol % of *t*BuOK afforded only a proportional amount of the product. This brief study showed the superiority of the initially used reaction conditions, and they were employed for further investigation of the cyclization process.

Having optimized the reaction conditions we further explored the scope of this transformation (Table 2). The required propargylated pyridine substrates were synthesized using the standard two-step procedure (see

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(4) For selected examples, see: (a) Masquelin, T.; Bui, H.; Brickley, B.; Stephenson, G.; Schwerkosked, J.; Hulmea, C. *Tetrahedron Lett.* **2006**, *47*, 2989. (b) Lyon, M. A.; Kercher, T. S. *Org. Lett.* **2004**, *6*, 4989. (c) Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031. (d) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369.

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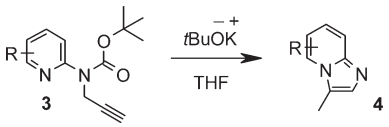
Table 2. Cyclisation Reactions of *N*-Propargyl Aminopyridines



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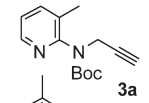
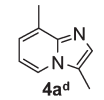
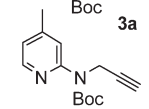
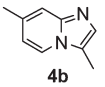
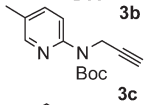
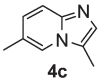
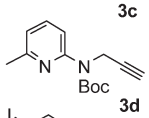
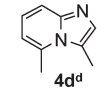
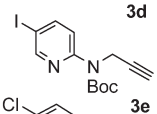
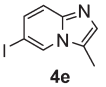
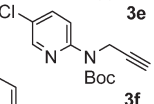
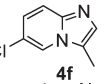
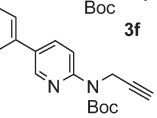
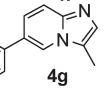
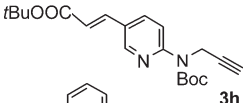
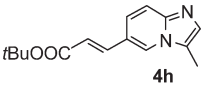
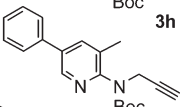
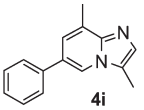
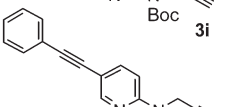
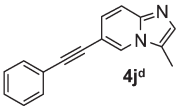
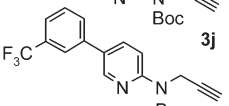
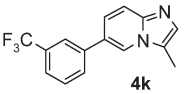
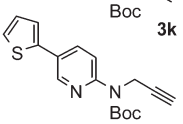
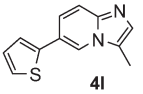
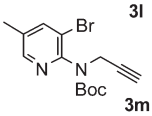
1			53
2			52
3			73
4			58
5			58
6			53
7			59
8			51
9			63
10			72
11			58
12			68
13		-	-

[a] The cyclizations of **3** to form **4** were performed using the following conditions: **3** (0.3 mmol), *t*BuOK (0.36 mmol), THF (3 mL), room temperature, 5 min (entries 2, 3, 5–7, 11, 12) or 50 °C/16 h (entries 1, 4, 8–10, 13). [b] Isolated yields after column chromatography.

Supporting Information), and these results will be discussed elsewhere. The cyclization step was carried out as outlined in Table 1, employing *t*BuOK as a base in THF as a solvent. Methyl derived pyridines, **3a**–**3d** and **3i**, afforded products **4a**–**4d** and **4i** in good yields (Table 2, entries 1–4 and 9), but derivatives possessing a methyl substituent close to the reacting moieties, at C(3) or C(6) (**3a**, **3d**, and **3i**), required higher temperatures and longer reaction times. This is not surprising since, due to steric effects, they are likely to prevent the molecule from adopting the planar (or near planar) conformation necessary for the cyclization step to occur. Variation of substituents at C(5) did not influence the reaction significantly (Table 2, entries 5–8 and 10–12), and all products were isolated in yields ranging from 51 to 72%. Due to their position the C(5) substituents are not expected to influence the reaction sterically. On the other hand, their electronic features may affect the process by altering the pyridine nitrogen nucleophilicity. Therefore the higher reaction temperatures and longer reaction times required for compounds **3h**–**3j** (Table 2, entries 8 and 10) could be attributed to the electronic effects of the C(5) substituents. The base employed in all of these transformations, *t*BuOK, proved to be compatible with potentially reactive functionalities such as the pyridylhalide (Table 2, entries 5 and 6) or an α,β-unsaturated ester (Table 2, entry 8). Contrary to the 3-methyl compound **3a**, the derivative **3m** possessing bromine at the same position (Table 2, entry 13) did not afford the expected product even at a higher temperature and longer reaction time (70 °C, 16 h). This surprising outcome is most likely a result of the stereoelectronic effect of the bromine substituent. In order for the cyclization to occur the propargyl group should be orientated toward the pyridine nitrogen. This positions the Boc moiety close to the C(3) substituent causing repulsive interactions of the Br/O electron densities.

We also carried out several experiments in order to gain further insight into the cyclization process. Attempts to cyclize the unprotected aminopyridine **5** (Figure 2) using either NaH or BuLi as a base did not result in product formation. This result may suggest that the Boc removal step probably does not precede the cyclization step. Additionally, attempts to cyclize compound **6** (Figure 2), possessing a methyl group on the alkyne terminus, failed as well, although it is not clear at present whether this was caused by the steric effects of an additional substituent or by the absence of the terminal alkyne C–H bond. We were also unable to cyclize pyrimidine derivative **7** (Figure 2), which possesses less nucleophilic nitrogens than the pyridine derivatives discussed above. Finally, attempts were

made to monitor the cyclization reaction by ^{1}H NMR, and for this purpose we selected the transformation of **3d** leading to **4d**. Although the majority of the reactions take a few minutes, this one is slower, and when monitored by TLC, the formation of an intermediate product was observed. The reaction was carried out in DMSO-d_6, and the ^{1}H NMR was recorded immediately after mixing the reactants in the solvent. Analysis of the spectrum showed the disappearance of the terminal alkyne C−H and the CH_2 groups completely, partial formation of the product, and additional signals in the region δ 5.7−7.8, with a distinctive doublet at δ 5.72.

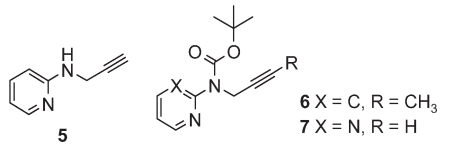


Figure 2. Reactivity of other derivatives.

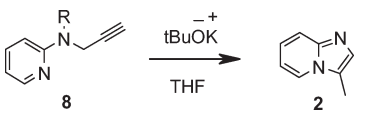
These results suggest intermediate formation of the allene via the alkyne−allene isomerization promoted by *t*BuOK as the first step.[8] The isomerization may be followed by the cyclization involving the allene/pyridine nitrogen moieties[9] and subsequent removal of the Boc group.

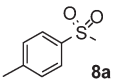
The proposed cascade implies that the *N*-Boc functionality is not essential, and therefore some related N-protecting groups were explored. When the Boc group was replaced by the tosyl substituent (Table 3, entry 1) the reaction resulted in the recovery of the starting material,

(8) For a recent review, see: Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. For recent examples, see:(a) Lohse, A. G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3430. (b) Beccalli, E. M.; Broggini, G.; Clerici, F.; Galli, S.; Kammerer, C. *Org. Lett.* **2009**, *11*, 1563. (c) Gonzales-Gomez, A.; Anorhbe, L.; Poblador, A.; Doninguez, G.; Perez-Castells, J. *Eur. J. Org. Chem.* **2008**, 1370. (d) Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 2214. (e) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.

(9) (a) Boisse, T.; Rigo, B.; Millet, R.; Henichart, J.-P. *Tetrahedron* **2007**, *63*, 10511. (b) Fomum, Z. T.; Mbafor, J. T.; Landor, P. D.; Landor, S. R. *Tetrahedron Lett.* **1981**, *22*, 4127. (c) Landor, S. R.; Landor, P. D.; Johnson, A.; Fomum, Z. T.; Mbafor, J. T.; Nkengfack, A. E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 975.

Table 3. Variations of the N-Protecting Group



entry	R	conditions[a]	yield(%)[b]
1	 **8a**	rt 16 h than 60 °C 3 h	-
2	 **8b**	rt 5 min	68
3	 **8c**	rt 16 h than 60 °C 3 h	traces

[a] The reactions were performed using the following conditions: **8** (0.3 mmol), *t*BuOK (0.36 mmol), THF (3 mL) at indicated temperatures. [b] Isolated yields after column chromatography.

while the *N*-benzoyl derivative (Table 3, entry 3) produced only a trace amount of the product. Contrary to these, the *N*-acetyl substituent (Table 3, entry 2) was as efficient as Boc in affording the product after just a few minutes in 68% yield.

In conclusion, a mild and efficient intramolecular cyclization of the protected N-propargylated pyridine derivatives leading to imidazo[1,2-*a*]pyridines has been developed. The transformation affords the products under basic conditions in good yields, in most cases at room temperature. The stereoelectronic properties of the substituents on the pyridine ring were shown to influence the cyclization process.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.