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Synthesis of Imidazopyridines from the Morita–Baylis–Hillman Acetates of Nitroalkenes and Convenient Access to Alpidem and Zolpidem

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ABSTRACT

A variety of functionalized imidazo[1,2-a]pyridines have been synthesized through a one-pot, room temperature, and reagent-free reaction between MBH acetates of nitroalkenes and 2-aminopyridines. The reaction involves a cascade inter-intramolecular double aza-Michael addition of 2-aminopyridines to MBH acetates. Our methodology is marked by excellent yield, regioselectivity and, above all, adaptability to synthesize imidazopyridine-based drug molecules such as Alpidem and Zolpidem.

Imidazopyridines are prominent among polynitrogen containing heterocycles that exhibit a plethora of biological properties, especially as inhibitors of benzodiazepine receptors.[1] Imidazo[1,2-a]pyridine, in particular, constitutes the core structure of currently marketed anxiolytic drug Alpidem, hypnotic drug Zolpidem and antiulcer drug Zolimidine.[2,3] Imidazo[1,2-a]pyridine derivatives are also known for their anticancer, antiviral, antiparasitic and anti-HIV properties.[4] Their effect on neuroactive steroids, their role as NO synthase and $GABA_A$ inhibitors and as L-Dopa and Dopamine prodrugs have been documented recently.[5]

The wide range of pharmacological properties shown by imidazopyridines inspired synthetic organic and medicinal

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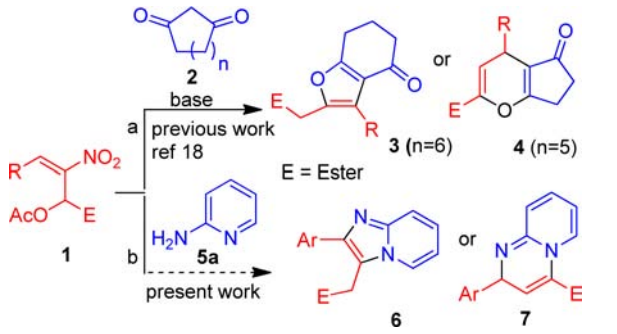
chemists to pursue the synthesis of numerous imidazopyridine derivatives[6] and study their properties.[7] Synthetic approaches include reaction of aminopyridines with α-functionalized and α,β-unsaturated carbonyl compounds, 1,3-dicarbonyl compounds, vicinal diols as well as with simple aldehydes and ketones, often in a multicomponent reaction.[8−10] Reactions involving Sandmeyer conditions, rearrangement, cycloaddition, Michael addition and other miscellaneous ones were also employed for the synthesis of imidazopyridines.[11−13]

From another perspective, the Morita−Baylis−Hillman (MBH) reaction has emerged in recent decades as one of the most sought after reactions for the synthesis of various multifunctional scaffolds.[14] The MBH acetates of electron-deficient alkenes have been subjected to substitution, often S_N2', by numerous nucleophiles including amines under uncatalyzed, organocatalyzed and metal-catalyzed conditions.[14−16] However, to our knowledge, synthesis of imidazopyridines from the MBH adducts of electron-deficient alkenes, including nitroalkenes, remains unreported.[17]

Recently, Chen et al. and we have independently reported the synthesis of fused and functionalized furans and pyrans through the reaction of MBH acetates of nitroalkenes **1** with β-dicarbonyl compounds **2** thus demonstrating for the first time the potential of **1** to undergo multiple nucleophilic additions in a cascade fashion (Scheme 1, path a).[18] We realized that imidazopyridines **6** and/or pyrimidopyridines **7** with a strategically positioned ester group would be accessible if 2-aminopyridine **5a** and similar nucleophiles react with MBH acetates **1** in a cascade inter-intramolecular double Michael reaction (Scheme 1, path b).

Scheme 1. MBH Adducts of Nitroalkenes **1** as Novel Synthetic Scaffolds



We began by treating MBH acetate **1a** with aminopyridine **5a** under different conditions (Table 1) and were pleased to note the formation of imidazopyridine **6a** as the

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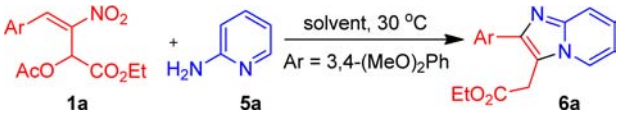
sole product in 44% yield when THF was used as solvent at room temperature (entry 1). Since the reaction was incomplete even after 60 min, other aprotic solvents such as CH_3CN, toluene and CH_2Cl_2 were screened (entries 2–4). While the first two were found not suitable for our reaction (entries 2–3), the reaction in CH_2Cl_2 afforded the product in 72% yield (entry 4). But, since the reaction was still incomplete, we turned to protic solvents (entries 5–7). However, the reaction in MeOH/H_2O (1:1) at room temperature and elevated temperature (60 °C) provided the product in low yield, again due to incomplete conversion (entries 5–6).[19] Surprisingly, the reaction was complete in just 5 min in MeOH alone as solvent to afford the product in nearly quantitative yield (94%, entry 7).

Table 1. Optimization Studies[a]



entry	solvent	time (min)	% yield[b]
1	THF	60	44[d]
2	CH_3CN	60	15[d]
3	Toluene	60	<5[d]
4	CH_2Cl_2	60	72[d]
5	MeOH/H_2O (1:1)	60	27[d]
6	MeOH/H_2O (1:1)[c]	60	30[d]
7	**MeOH**	**5**	**94**

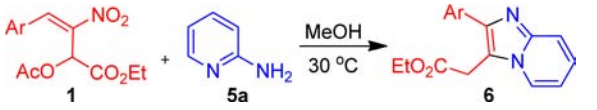
[a] Reaction was carried out with 0.3 mmol each of **1a** and **5a** in 3 mL MeOH. [b] Isolated yield after silica gel column chromatography. [c] Heated to 60 °C. [d] Reaction incomplete (20–80% of **1a** and **5a** were recovered).

Having established a simple, reagent-free and room temperature method for the synthesis of imidazopyridines, we proceeded to investigate the scope of the reaction first by reacting 2-aminopyridine **5a** with different MBH acetates **1b**–**k** (Table 2). Quite remarkably, all of the reactions were complete in ≤60 min to afford the desired imidazopyridines **6b**–**k** in good to excellent yield (entries 2–11). The yields were particularly excellent (90–94%) with MBH acetates possessing electron-donating aromatic substituents **1a**–**c** and heteroaromatic substituents **1h**–**i** (entries 1–3 and 8–9). The yields were also high (82–87%) when unsubstituted and weakly deactivating aromatic rings were present in MBH acetates (**1d**–**f**, entries 4–6). However, lower yields were encountered in the case of an MBH acetate with strongly electron withdrawing aromatic substituent **1g** and nitrodiene derived MBH acetates **1j**–**k** (entries 7 and 10–11).

Subsequently, the scope of aminopyridines **5** was explored by reacting a representative MBH acetate **1b** with various substituted aminopyridines **5b**–**f** under the optimized conditions, that is, in MeOH at room temperature

(19) For synthesis of pyrimidone via addition of aminopyridine to acrylate and acrylonitrile derived MBH acetate in MeOH/H_2O: Shahrisa, A.; Ghasemi, Z. *Chem. Heterocycl. Compd.* **2010**, *46*, 30.

Table 2. Scope of MBH Acetates **1**[a]

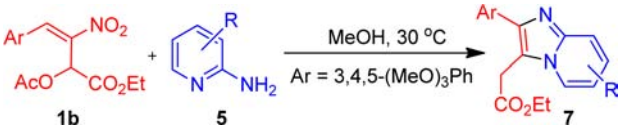


entry	**1**	Ar	time (min)	% yield[b]
1	**1a**	3,4-$(OMe)_2$Ph	5	94
2	**1b**	3,4,5-$(OMe)_3$Ph	5	96
3	**1c**	4-MePh	20	90
4	**1d**	Ph	5	86
5	**1e**	4-ClPh	20	87
6	**1f**	3-BrPh	20	82
7	**1g**	2-NO_2Ph	60	71
8	**1h**	2-Furyl	5	93
9	**1i**	2-Thienyl	5	92
10	**1j**	PhCH=CH	10	64
11	**1k**	*o*-MeOPhCH=CH	10	63

[a] Reaction was carried out with 0.3 mmol each of **1** and **5a** in 3 mL MeOH. [b] Isolated yield after silica gel column chromatography.

(Table 3). We were pleased to note the formation of imidazopyridines **7a**–**e** with diverse substituents at 3, 4, and 5 positions in the pyridine ring (entries 1–5). While the yields of imidazopyridines **7b**–**d** are excellent when aminopyridines **5c**–**e** with substitution at positions 4 or 5 are employed (entries 2–4), good and moderate yields of imidazopyridines **7a** and **7e**, respectively, are obtained with aminopyridines **5b** and **5f** (entries 1 and 5).

Table 3. Scope of 2-Aminopyridines **5**[a]



entry	**5**	R	time (min)	**7**	% yield[b]
1	**5b**	3-Me	10	**7a**	76
2	**5c**	4-Me	15	**7b**	91
3	**5d**	5-Cl	25	**7c**	88
4	**5e**	5-Br	20	**7d**	85
5[b]	**5f**	3-OR^1	20	**7e**	62

[a] Reaction was carried out with 0.3 mmol each of **1b** and **5** in 3 mL MeOH. [b] Isolated yield after silica gel column chromatography. R^1 = TBDMS in **5f** and H in **7e**.

The above conditions were, however, not suitable for reacting MBH acetates with aminoheterocycles **5g**–**i** (Figure 1). Thus, there was no reaction even after 3 h when aminopyrimidine **5g** and aminopyrazine **5h** were treated with MBH acetate **1b**. On the other hand, a complex mixture was isolated from the reaction between MBH acetate **1b** and aminothiazole **5i**.

The structure and regiochemistry of imidazopyridines **6** and **7** were confirmed by single crystal analysis of a

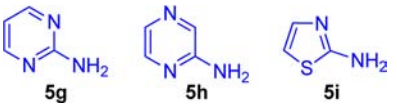
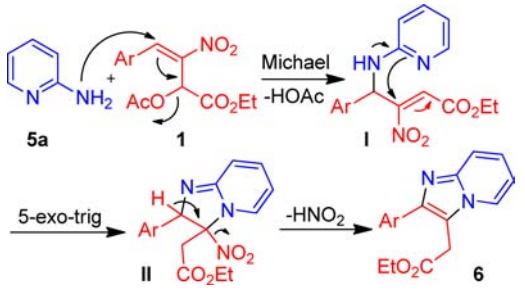


Figure 1. Aminoheterocycles **5g**–**i**.

representative compound **6d** (see the Supporting Information). The proposed mechanism taking 2-aminopyridine **5a** as the representative nucleophile is outlined in Scheme 2. It begins with Michael addition of **5a** involving the primary amino group as the nucleophilic center to MBH acetate **1** followed by elimination of acetate in an overall S_N2' reaction to generate intermediate **I**. Further intramolecular Michael addition involving the pyridine nitrogen in a regioselective 5-exo trig fashion leads to cyclic intermediate **II**, which undergoes elimination of HNO_2 to afford imidazopyridine **6** (or **7**).[20] The regioselectivity observed in the intramolecular Michael addition is attributable to geometric factors as well as formation of aromatized products **6** as opposed to **7** (see Scheme 1).

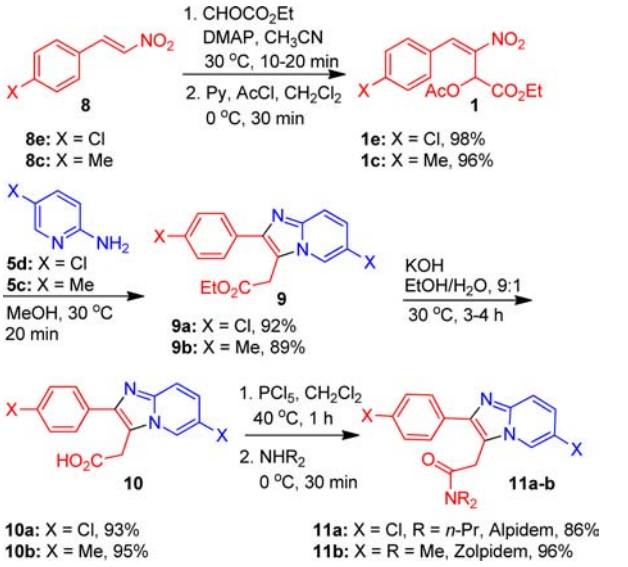
Scheme 2. Proposed Mechanism for the Formation of Imidazopyridines **6**



Our methodology appeared suitable for the synthesis of imidazopyridine drugs Alpidem and Zolpidem.[2] Besides the recent one-pot 3-component synthesis of Alpidem and Zolpidem in high yields (83 and 72%, respectively) from appropriate aminopyridine, aldehyde and acetylenic amide,[21] synthetic approaches to these drug molecules were often complicated by low overall yields and requirement of lachrymatory α-haloketones as well as multistep reaction sequences.[22]

The MBH acetates **1e** and **1c**, required for the synthesis of Alpidem and Zolpidem, respectively, were prepared in nearly quantitative yield by hydroxyalkylation of nitroalkenes **8e** and **8c** followed by acetylation (Scheme 3).[17,18] The acetates **1e** and **1c** were then treated with aminopyridines **5d** and **5c**, respectively, under our optimized conditions, that is, in MeOH at room temperature, to afford imidazopyridines **9a** and **9b**, respectively, in 92 and 89% yield. After room temperature hydrolysis of the ester group in **9a** and **9b** in nearly quantitative yield (93 and 95%, respectively), the resulting acids **10a** and **10b** were transformed to amides **11a** (Alpidem) and **11b** (Zolpidem) by treating the corresponding acid chlorides with appropriate amines, again in very high yield (86 and 96%, respectively). This 6-step synthesis of Alpidem **11a** and Zolpidem **11b** from nitroalkenes **8** involves simple reagents and conditions and proceeds in excellent overall yields (72 and 78%, respectively).

Scheme 3. Synthesis of Alpidem **11a** and Zolpidem **11b**



In conclusion, a one-pot methodology for the regioselective synthesis of imidazo[1,2-a]pyridines taking advantage of the binucleophilic character of 2-aminopyridines and the bielectrophilic character of the MBH acetates of nitroalkenes has been developed. This room temperature, reagent-free methodology has been successfully applied for the efficient synthesis of anxiolytic drug Alpidem and hypnotic drug Zolpidem.

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Supporting Information Available. Complete characterization data and copies of NMR spectra for all the new compounds as well as CIF and checkcif for compound **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) Although HOAc and HNO_2 are liberated in these reactions, these are very weakly ionized in MeOH and therefore there is no salt formation.

(21) Reference 10c and the references cited therein.

(22) Alpidem: (a) Reference 2a. Zolpidem: (b) References 2b, 2c. (c) Reference 8c and the references cited therein. (d) Reference 8e and the references cited therein.