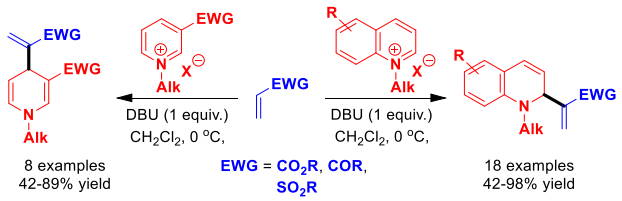
Regioselective Morita-Baylis-Hillman Reaction with N-Alkylpyridinium Salts as Electrophiles

Abhishek Pareek and Marcin Kalek*

Centre of New Technologies, University of Warsaw, Banacha 2C, 02-097 Warsaw, Poland

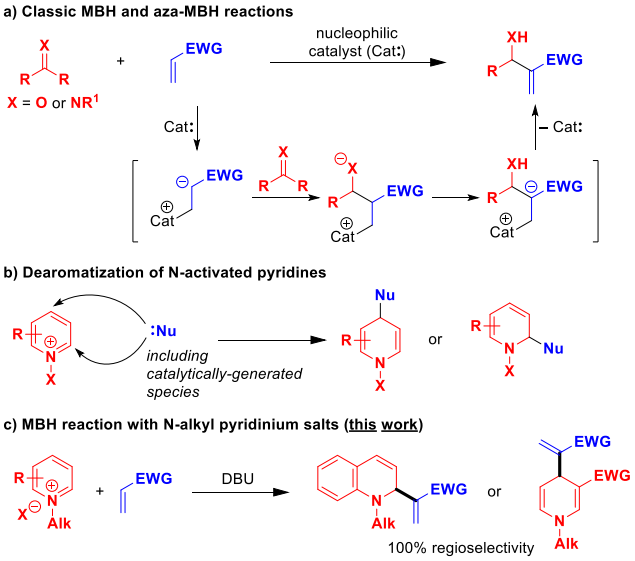
Corresponding author e-mail: m.kalek@cent.uw.edu.pl



ABSTRACT: Morita-Baylis-Hillman reaction employing N-alkylpyridinium salts as electrophiles has been developed. The reaction is promoted by DBU, which acts both as a catalyst activating the electron-poor olefin as well as a base. The transformation delivers a broad range of α-(hydropyridine)vinyl esters, ketones, and sulfones. The dearomatization of N-alkylquinolinium salts occurs regioselctively at the C-2 position, whereas N-alkylpyridinium salts undergo addition at the C-4 position.

INTRODUCTION

Morita-Baylis-Hillman (MBH) reaction is one of the most prominent carbon-carbon bond-forming processes in synthetic organic chemistry with enormous synthetic utility, promise, and potential.[1] The reaction constitutes a very handy means for converting simple starting materials into densely functionalized products under mild, metal-free reaction conditions. The functional group-rich MBH adducts can serve as useful synthons for various transformations further increasing the molecular complexity.[2]



Scheme 1. Morita-Baylis-Hillman reaction and concept to expand its scope by using N-activated pyridines as electrophiles.

In the classic MBH reaction, electron-poor alkenes are activated by a nucleophilic catalyst and coupled with aldehydes or, in the case of aza-MBH version, imines (Scheme 1a). The scope of the olefinic partner in MBH reaction have been thoroughly investigated, covering a wide range of electron withdrawing groups, as well as other related substrate classes, e.g., alkynes and allenes.[3] Conversely, in the majority of the reported MBH variants the electrophilic partners are confined to the standard carbonyl or imine derivatives, with only a handful of exceptions, such as Michael acceptors (Rauhut-Currier reaction[1g,4]), allyl and alkyl halides, or epoxides.[5]

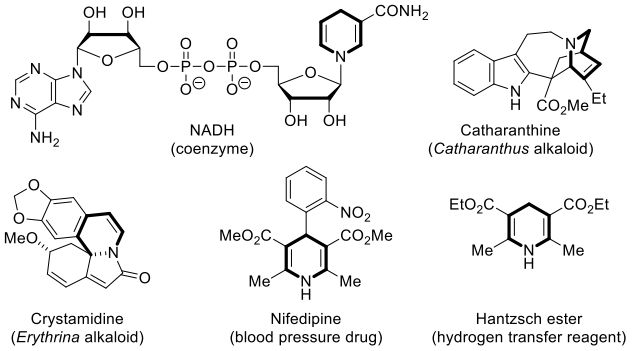


Figure 1. Examples of biologically and synthetically important compounds containing hydropyridine moiety.

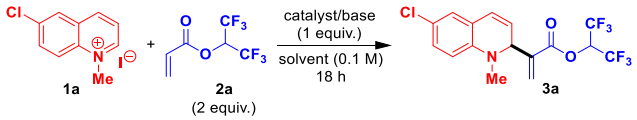
In this context, we envisioned a possibility to extend the range of electrophiles, which can be used in MBH reaction to N-activated pyridines. These species undergo a facile addition of nucleophiles at either C-2 or C-4 position of the ring (Scheme 1b),[6] leading to dearomatized nitrogen-containing heterocycles, and synthetic precursors thereof, that are common molecular motifs in natural products and pharmaceuticals, as well as hydrogen-transfer reagents (Figure 1).[7] The dearomatization of pyridinium derivatives has been shown to be a very robust transformation, proceeding with a multitude of nucleophiles. In many instances, catalytically generated intermediates have been used in this role, employing both transition metal[8] and organocatalysis. In the latter instance, approaches relaying on the catalysis by amines (through enamine activation),[9] N-heterocyclic carbenes,[10] thioureas,[11] phosphoric acids,[12] and anion-binders[13] have been applied. On the other hand, the incipient nucleophilic intermediate of the MBH reaction has up-to-date not been used in the dearomatization of the N-activated pyridines.

In addition to the challenge of breaking the aromaticity, an important issue related to the nucleophilic addition to N-activated pyridines is controlling the regioselectivity of the reaction, which may take place at either C-2 or C-4 position of the ring.[14] Herein, we describe our work on the MBH reaction using N-alkylpyridinium salts as electrophiles, which proceeds with high efficiency and excellent regioselectivity, depending on the structure of the electrophile (Scheme 1c).

RESULTS AND DISSCUSSION

Due to lower resonance stabilization energy of bicyclic heteroaromatic systems resulting in their higher reactivity, we began our investigations using N-alkylquinolinium salts as the electrophiles for the devised MBH process. Thus, the reaction conditions were explored with 6-chloro-N-methylquinolinium iodide (**1a**) and 1,1,1,3,3,3-hexafluoropropan-2-yl acrylate (**2a**) as model substrates (Table 1). A stoichiometric quantity of nucleophilic promoter was used, so that is can serve in a dual role of the catalyst as well as the base sequestering the HI side-product forming during the reaction. Among the series of tested catalysts (entries 1-7), only TMG (entry 4) and DBU (entry 6) provided the desired product **3a** in appreciable amounts, 25% and 12%, respectively. Importantly, a fully regioselective addition at the C-2 position of the pyridinium ring was observed. The reaction does not proceed in the absence of a catalyst/base (entry 8). Using the above two best performing catalysts, we studied the impact of the temperature on the outcome of the reaction. Gratifyingly, lowering the temperature to –10 °C lead to improved yields, in particular in the case of DBU (entry 10). Further fine-tuning of the reaction temperature allowed to obtain **3a** in 79% yield at 0 °C, using CH_2Cl_2 as the solvent (entry 11). We evaluated also other solvents (entries 13-17), as well as the effect of the excess of the promoter (entries 18-19), but no further improvement in the reaction efficiency could be achieved.

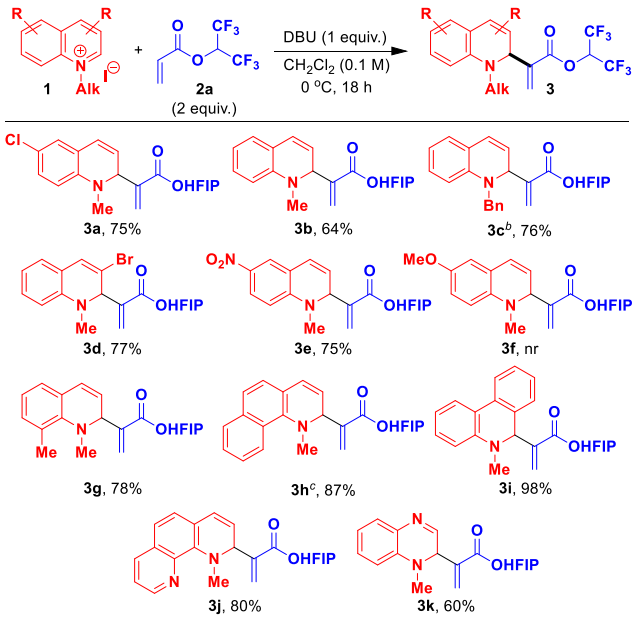
Table 1. Optimization of the reaction conditions.



Entry	Catalyst/Base	Solvent	Temperature (°C)	Yield (%)[a]
1	DABCO	CH_2Cl_2	rt	2
2	PPh_3	CH_2Cl_2	rt	nr
3	DMAP	CH_2Cl_2	rt	nr
4	TMG	CH_2Cl_2	rt	25
5	2,6-lutidine	CH_2Cl_2	rt	nr
6	DBU	CH_2Cl_2	rt	12
7	Et_3N	CH_2Cl_2	rt	nr
8	none	CH_2Cl_2	rt	nr
9	TMG	CH_2Cl_2	–10	54
10	DBU	CH_2Cl_2	–10	75
11	**DBU**	**CH_2Cl_2**	**0**	**79**
12	DBU	CH_2Cl_2	–20	75
13	DBU	CH_3CN	0	27
14	DBU	THF	0	2
15	DBU	toluene	0	nr
16	DBU	Et_2O	0	nr
17	DBU	EtOH	0	nr
18	DBU (1.2 equiv.)	CH_2Cl_2	0	56
19	DBU (1.5 equiv.)	CH_2Cl_2	0	55

[a] Determined by ^{1}H NMR spectroscopy; DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-Diazabicyclo[2.2.2]octane, DMAP = 4-(Dimethylamino)pyridine, TMG = N,N,N′,N′-tetramethylguanidine, nr = no reaction.

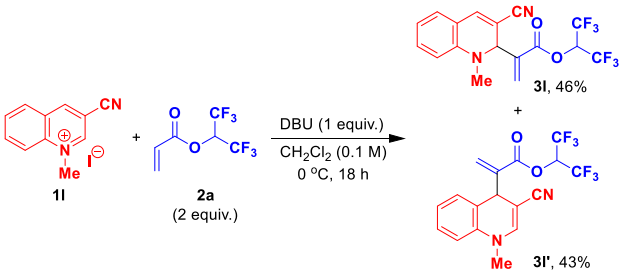
With the optimized conditions in hand, we investigated the scope of the reaction with regard to N-alkylquinolinium salt **1** (Scheme 2). For unsubstituted quinoline, N-methyl and N-benzyl substrates provide the respective products **3b** and **3c** in 64% and 76% yield. The method is compatible with halogen substituents present in either of the rings (**3a**, **3d**). The reaction with a starting material containing a strongly electron-withdrawing group in the carbocyclic ring is uneventful (**3e**), while the introduction of such substituent into the heterocyclic ring leads to the deterioration of regioselectivity (see Scheme 3 and discussion, below). On the other hand, quinolinium salt containing a methoxy group does not react under the developed conditions (**3f**). However, a mildly electron-donating methyl group in position 8 is well-tolerated (**3g**). Noteworthy, products with extended ring systems: 7,8-benzoquinoline (**3h**), phenanthridine (**3i**), as well as 1,10-phenanthroline (**3j**) are afforded in good to excellent yields. Finally, N-methylquinoxalinium iodide provides compound **3k** in 60% yield.



Scheme 2. Scope with regard to the quinolinium salt.[a]

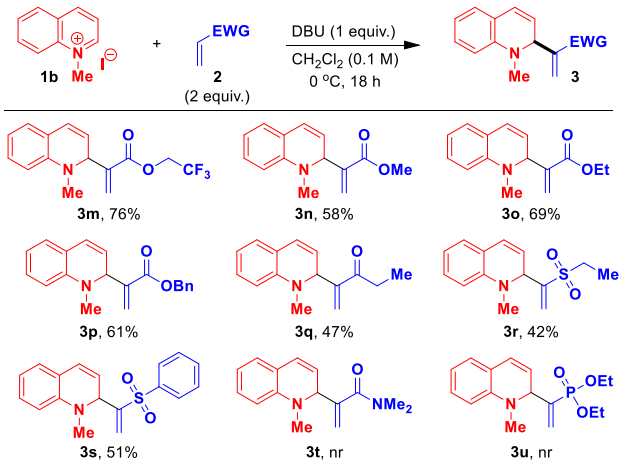
[a] Isolated yields; [b] Br salt was used; [c] PF_6 salt was used; HFIP = 1,1,1,3,3,3-hexafluoroisopropyl, nr = no reaction.

All the products depicted in Scheme 2 were obtained as sole regioisomers, demonstrating that the bicyclic N-alkylquinolinium system displays a preference to react at the C-2 position in the coupling with the MBH nucleophile. However, the reaction with 3-cyano-N-methylquinolinium iodide **1l** affords a nearly equimolar mixture of both 2- and 4-substituted regioisomers (**3l** and **3l'**, respectively), in an excellent combined yield (Scheme 3). We presume that in this case, the strongly electron-withdrawing CN substituent, while facilitating the overall coupling, renders the 4-postion of the pyridinium ring considerably more reactive, partially overriding the intrinsic inclination of the quinolinium moiety to favor the 2-addition.



Scheme 3. Lack of regioselectivity for 3-cyano-N-methylquinolinium substrate.

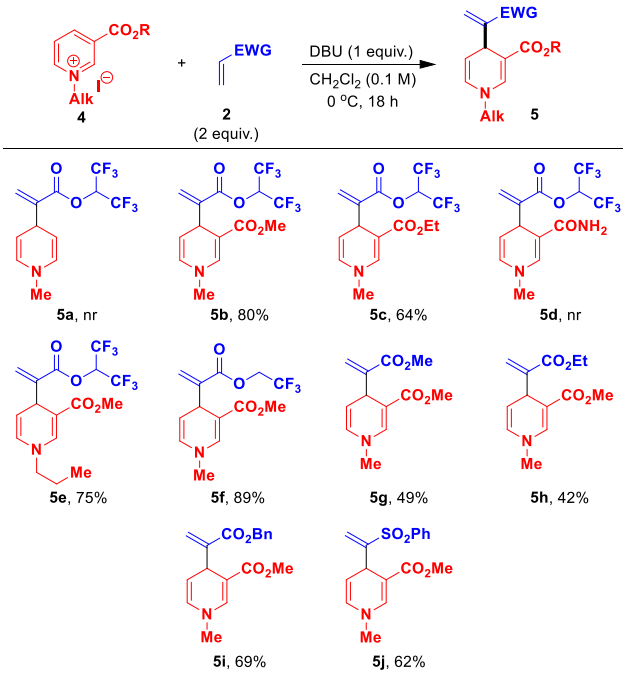
Next, various activated alkenes having an array of electron-withdrawing groups were tested in the developed the MBH reaction (Scheme 4). All examined carboxylic esters successfully participated in the coupling (**3m**-**3p**), affording the corresponding products in yields ranging from 58% for the methyl ester (**3n**) to 76% for the 2,2,2-trifluoroethyl ester (**3m**). For alkyl vinyl ketone the reaction proceeds in moderate 47% yield (**3q**). Similar performance was observed in the case of both alkyl (**3r**) and aryl (**3s**) vinyl sulfones, which provided MBH adducts in 42% and 51%, respectively. Finally, acrylic amide (**3t**) and vinylphosphonate (**3u**) were found to be incompetent substrates for the developed reaction.



Scheme 4. Scope with regard to the alkene.[a]

[a] Isolated yields; nr = no reaction.

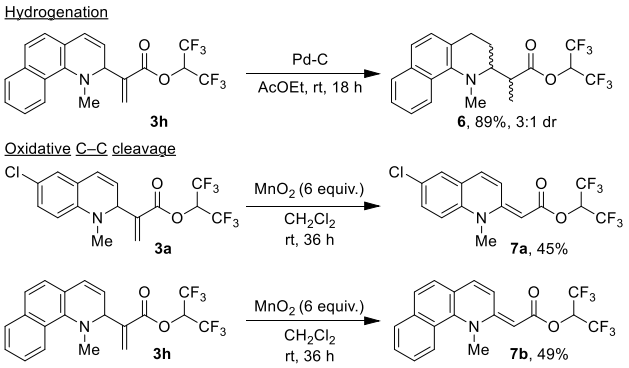
As the final part of our studies, we attempted to apply more difficult to dearomatize monocylic N-alkylpyridinium salts **4** as electrophiles in the MBH reaction (Scheme 5). A simple unsubstituted N-methylpyridinium iodide was found to be completely unreactive (**5a**). However, upon the introduction of an electron-withdrawing methyl ester group into the ring, the formation of the desired product **5b** in 80% yield is attained. Importantly, for this starting material, the addition takes places exclusively at the C-4 position. We argue that such regioselectivity originates from the directing effect of the EWG substituent similar to that observed for substrate **1l** (Scheme 3), combined with the lack of influence from the second aromatic ring. Encouraged by the above result, we further explored the scope of activated N-alkylpyridinium salts that can serve as effective electrophiles in the MBH process. Thus, the corresponding ethyl ester (**5c**) was established to be somewhat less efficient than its methyl counterpart, whereas amide substituent (**5d**) is detrimental for the reaction. On the other hand, the nature of the N-alkyl group does not seem to significantly affect the reactivity (**5e** vs. **5b**). Using 3-(ethoxycarbonyl)-N-methylpyridinium substrate, we examined also other electron-poor alkenes as possible coupling partners. Thus, 2,2,2-trifluoroethyl acrylate affords product **5f** in an excellent 89% yield. Other acrylic esters: methyl, ethyl, and benzyl are less reactive, providing the corresponding products **5g**, **5h**, and **5i** in 49%, 42% and 69%, respectively. Finally, phenyl vinyl sulfone gives product **5j** in 62% yield.



Scheme 5. Scope with regard to the activated pyridinium salt.[a]

[a] Isolated yields; nr = no reaction.

The products of our MBH reaction with N-alkylpyridinium electrophiles can be transformed into other interesting compounds (Scheme 6). For instance, hydrogenation on palladium on carbon reduces both olefins, resulting in propionate ester with 1,2,3,4-tetrahydropyridine substituent in the α position. Furthermore, upon treatment with MnO_2, the MBH products undergo oxidative cleavage of the methylene moiety, leading to peculiar (1*H*-pyridin-2-ylidene)acetate esters.



Scheme 6. Synthetic transformations of the products.

CONCLUSIONS

In conclusion, we have for the first time accomplished Morita-Baylis-Hillman reaction employing N-activated pyridinium species as the electrophilic coupling partners. In the developed conditions, DBU acts in a dual role of the catalyst activating the olefin and as the base. The reaction allows for an effective dearomatization of N-alkylquinolinium salts, proceeding almost uniformly with perfect regioselectivie addition at the C-2 position. N-alkylpyridinium starting materials can also be utilized in the reaction, provided that they contain an activating electron-withdrawing substituent. In this case, an exclusive functionalization at the C-4 position of the ring is observed. The method enables the creation of vinylhydropyridine scaffolds, providing access to a wide range of functional group-rich N-heterocyclic building blocks for synthetic organic chemistry.

Supporting Information

The Supporting Information file contains: experimental procedures, compound characterization data, and copies of NMR spectra for products

ORCIDs

Abhishek Pareek – 0000-0002-1728-2310
Marcin Kalek –0000-0002-1595-9818

Notes

The authors declare no competing financial interest.

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