Phosphine-catalyzed annulation of ethyl (arylimino)acetates: synthesis of highly functionalized oxoimidazolidines†

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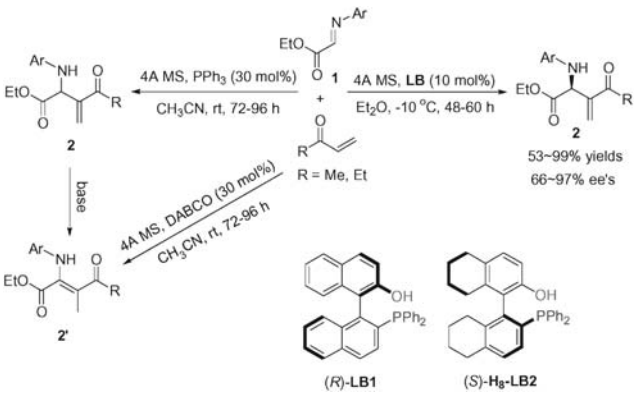
Received (in College Park, MD, USA) 1st July 2008, Accepted 5th August 2008
First published as an Advance Article on the web 18th September 2008
DOI: 10.1039/b811167g

This paper describes an unexpected and novel nucleophilic phosphine-catalyzed annulation of ethyl (arylimino)acetates to give polysubstituted oxoimidazolidine derivatives in moderate to good yields from simple and easily available starting materials under mild conditions. In this reaction, the addition of methyl vinyl ketone (MVK) is essential to induce the formation of oxoimidazolidines.

A number of naturally occurring substances have been found to contain the imidazole nucleus and some of these compounds or their derivatives have important therapeutic value. Thus far, although the synthesis of the imidazole nucleus has been the subject of a large body of literature, the construction of highly functionalized oxoimidazolidine frameworks from easily available starting materials remains a great challenge.[1] Herein, we wish to report a novel and concise synthetic protocol for the construction of multi-substituted oxoimidazolidine frameworks from ethyl (arylimino)acetates.

Recently, phosphine Lewis bases have emerged as efficient organocatalysts for carbon–carbon or carbon–nitrogen bond forming reactions, particularly in the catalysis of Morita–Baylis–Hillman (MBH) reactions.[2] For example, it has been reported that triphenylphosphine-catalyzed aza-Morita–Baylis–Hillman (aza-MBH) reactions of ethyl (arylimino)-acetates **1** with methyl vinyl ketone (MVK) or ethyl vinyl ketone (EVK) produce the corresponding adducts **2** in good yields in acetonitrile (MeCN) along with the asymmetric versions (up to 97% ee) in the presence of bifunctional chiral phosphine Lewis bases (*R*)-**LB1** and (*S*)-**H$_8$-LB2** (Scheme 1).[3,4] Moreover, we also disclosed that using 1,4-diazabicyclo[2.2.2]octane (DABCO) instead of PPh_3 as the catalyst afforded the corresponding products **2′** in moderate to good yields (Scheme 1).[3]

It has been known that different phosphine Lewis bases can give different reaction products in the MBH reaction under identical conditions. For example, using phosphine Lewis bases more nucleophilic than PPh_3, such as PBu_3, $PPhMe_2$ or PPh_2Me, can provide abnormal MBH reaction products in good yields.[5] During our ongoing investigation into the search for a more efficient phosphine Lewis base for the aza-MBH reaction of ethyl (*p*-bromophenylimino)acetate **1a** with MVK, we found that using methyldiphenylphosphine (PPh_2Me) as the catalyst instead of PPh_3 under identical conditions (30 mol% of PPh_2Me, 1.5 equiv. of MVK, in the presence of 4 Å MS (200 mg mmol^{-1} of **1**), CH_3CN, 20 °C) afforded a new product **3a**, which was determined by ^{1}H NMR and ^{13}C NMR spectroscopic data and X-ray diffraction of a single crystal (see ESI†),[6] along with a trace of the aza-MBH adduct **2a**. We envisaged that compound **3a** is derived from the PPh_2Me-catalyzed annulation of three molecules of **1a**. Therefore, our next investigation was aimed at the development of optimal conditions for this unexpected transformation. The results of these experiments are summarized in Table 1.



Scheme 1 Phosphine-catalyzed aza-Marita–Baylis–Hillman reaction.

Initially, we confirmed that in the absence of phosphine Lewis base and MVK, as well as in the presence of PPh_3 (30 mol%) but without MVK, products **3a** and **4a** were not formed at all (Table 1, entries 1 and 2). Then, we employed 30 mol% of PPh_2Me as the catalyst to examine the effect of MVK in this reaction. Surprisingly, in the absence of MVK, a trace of **3a** was formed and a noncyclic compound **4a** was obtained in 63% yield as a major product under otherwise identical conditions, indicating that the more nucleophilic phosphine caused such an unusual reaction outcome (Table 1, entry 3). The structure of **4a** was confirmed based on the ^{1}H NMR, ^{13}C NMR, HRMS and DEPT spectroscopic data. Using **1a** and MVK in a ratio of 1 : 1.5 led to the formation of oxoimidazolidine **3a** in 65% yield along with MVK dimer (Table 1, entry 6). Decreasing the employed amounts of

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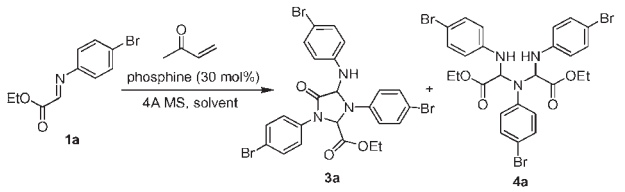
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectroscopic and analytical data of **3a–i** and **4**, X-ray crystal structure of **3a**, and detailed description of the experimental procedure. CCDC reference number 612928. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b811167g

Table 1 Phosphine-catalyzed annulation of ethyl (*p*-bromophenylimino)acetate **1a** under a variety of conditions at 20 °C[a]



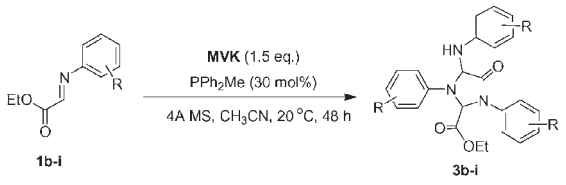
Entry	Ratio of **1a** : MVK	Phosphine	Solvent	*t*/h	Yield (%)[b] **3a**[c]	**4a**
1	1 : 0	—	CH_3CN	48	—	—
2	1 : 0	PPh_3	CH_3CN	48	—	—
3	*1 : 0*	*PPh_2Me*	*CH_3CN*	*48*	*Tr.*	*63*
4	1 : 0.5	PPh_2Me	CH_3CN	36	35	44
5	1 : 1.0	PPh_2Me	CH_3CN	36	47	37
6	*1 : 1.5*	*PPh_2Me*	*CH_3CN*	*36*	*65*	*Tr.*
7	1 : 10	PPh_2Me	CH_3CN	36	48	—[d]
8	1 : 1.5	$PPhMe_2$	CH_3CN	36	63	Tr.
9	1 : 1.5	PMe_3	CH_3CN	24	47	Tr.
10	1 : 1.5	PBu_3	CH_3CN	24	56	Tr.
11	1 : 1.5	PPh_2Me	THF	48	—	35
12	1 : 1.5	PPh_2Me	CH_2Cl_2	48	30	—
13	1 : 1.5	PPh_2Me	Toluene	48	19	—
14	1 : 1.5	PPh_2Me	DCE	48	38	—
15	1 : 1.5	PPh_2Me	Et_2O	48	—	40
16	1 : 1.5	PPh_2Me	DMSO	96	Complex	
17	1 : 1.5	PPh_2Me	DMF	96	Complex	
18[e]	1 : 1.5	PPh_2Me	CH_3CN	48	Complex	

[a] See ESI† for a detailed experimental procedure. [b] Isolated yields (Tr. = trace). [c] The structure was confirmed by the X-ray analysis of a single crystal. [d] The aza-Morita–Baylis–Hillman product was isolated. [e] Reaction performed at 80 °C.

MVK produced the corresponding product mixtures of **3a** and **4a** in lower yields, suggesting that the presence of MVK is critical in this reaction (Table 1, entries 4 and 5). However, using 10 equiv. of MVK afforded **3a** in 48% yield and some of the aza-MBH product **2a**, without the formation of **4a** (Table 1, entry 7). Encouraged by these results, we also examined other more nucleophilic phosphine Lewis bases, such as dimethylphenylphosphine ($PPhMe_2$), trimethylphosphine (PMe_3), tributylphosphine (PBu_3), in this reaction under the standard conditions. The results obtained indicated that they are not as effective as PPh_2Me in this transformation (Table 1, entries 8–10). An examination of the solvent effect revealed that when using CH_2Cl_2, 1,2-dichloroethane (DCE), or toluene as the solvent, the reaction could proceed smoothly to afford **3a** in 19–38% yield as the major products (Table 1, entries 12–14). But in tetrahydrofuran (THF) or ether, only noncyclic product **4a** was produced in moderate yield (Table 1, entries 11 and 15). In dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF), complex product mixtures were formed (Table 1, entries 16 and 17). Increasing the reaction temperature did not give a positive result (Table 1, entry 18).

With these optimal reaction conditions in hand, the scope and limitations of this interesting annulation were explored using a variety of ethyl (arylimino)acetates **1b–i** and the results are outlined in Table 2. For imines **1b–g** bearing electron-withdrawing groups on the benzene rings, the reaction proceeded smoothly to afford the corresponding oxoimidazolidine

Table 2 Phosphine-catalyzed annulation of ethyl (arylimino)acetates **1b–i** under the optimized conditions[a]

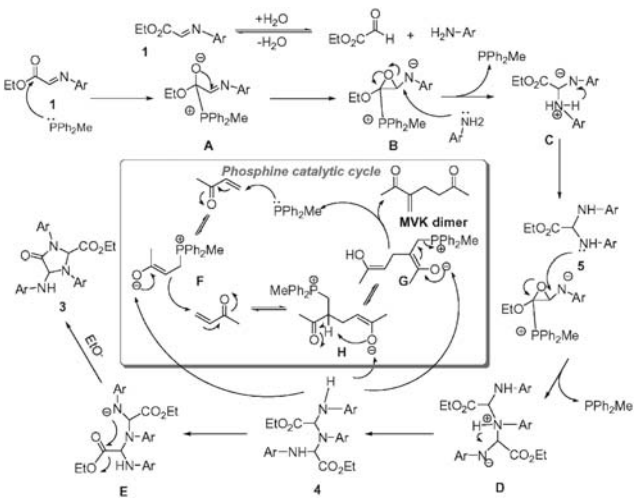


Entry	R	Product	Yield (%)[b] **3b–i**
1	*p*-Cl, **1b**	**3b**	40
2	*p*-F, **1c**	**3c**	64[c]
3	*m*-F, **1d**	**3d**	81[c]
4	*m*-CF_3, **1e**	**3e**	74
5	*m*-Br, **1f**	**3f**	55
6	*p*-CF_3, **1g**	**3g**	57
7	H, **1h**	**3h**	60
8	*m*-CH_3, **1i**	**3i**	29[d]

[a] *Conditions*: ethyl (arylimino)acetate (0.6 mmol), MVK (0.9 mmol), methyldiphenylphosphine (0.18 mmol), and 120 mg of 4Å MS in 1.5 mL of CH_3CN. [b] Isolated yields based on the average of two runs. [c] Trace of MVK dimer was included in the product. [d] The corresponding normal aza-MBH adduct was formed in 25% yield along with some other unidentified products.

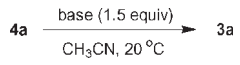
derivatives **3b–g** in moderate to good yields along with MVK dimer (Table 2, entries 1–6). Ethyl (phenylimino)acetate **1h** gave **3h** in 60% yield under identical conditions (Table 2, entry 7). As for ethyl (*meta*-methylphenylimino)acetate **1i**, the desired product **3i** was obtained in 29% yield along with the corresponding aza-MBH product in 25% yield and some other unidentified products (Table 2, entry 8).

The mechanism of this unprecedented cyclization reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 2. Since the starting materials (imines) are highly hygroscopic and are liable to decompose in spite of all the solvents being pretreated with the typical procedure and the addition of 4 Å MS to the reaction system to get rid of ambient moisture, traces of ambient water can still decompose these imines.



Scheme 2 Mechanistic proposal for the formation of **3** and **4** in the presence of PPh_2Me and MVK.

Table 3 Transformation of compound **4a** to **3a** under various conditions[a]



Entry	Base	t/h	Yield (%)[b] **3a**
1	PPh_2Me–MVK	5	>99
2	K_2CO_3	24	20
3	DABCO	2	No reaction
4	DBU	2	Dec.
5	NaH[c]	2	Dec.

[a] See ESI† for a detailed experimental procedure. [b] Isolated yields. [c] THF was used as a solvent.

Therefore, in the reaction system, there is an equilibrium between imine, ethyl glyoxalate, and aniline. This phenomenon can also be identified in the previous literature, where those imines bearing electron-withdrawing groups on the benzene rings are difficult to purify and products are usually obtained as mixtures of these three components.[6] At first, the more nucleophilic phosphine Lewis base PPh_2Me undergoes a nucleophilic attack at the carbonyl group in the α-imino ester to produce intermediate A.[7] Then epoxy intermediate B is formed by the nucleophilic attack of the C═N double bond with the oxonium anion. Free aniline acts as a nucleophile to attack the epoxide in intermediate B, affording intermediate C and regenerating phosphine PPh_2Me. Intermediate C undergoes subsequent intramolecular proton transfer to give intermediate **5**, which acts as a nucleophile to attack intermediate B again, providing intermediate D, which furnishes compound **4** *via* similar intramolecular proton transfer. In this reaction system, there is a phosphine catalytic cycle to generate MVK dimer. The first step of this cycle involves the Michael-type nucleophilic addition of the tertiary phosphine to the activated alkene (MVK) to produce zwitterionic intermediate F, which adds to another molecule of MVK to afford zwitterionic intermediate G. Subsequent proton migration gives zwitterionic intermediate H. Release of the catalyst provides the MVK dimer (Scheme 2). In the phosphine catalytic cycle, the zwitterionic intermediates F, G, and H can act as a base to snatch a proton from **4**, providing anionic intermediate E. Subsequent intramolecular nucleophilic attack onto the ester carbonyl group produces the desired product **3**. Using the more nucleophilic phosphine PPh_2Me can afford zwitterionic intermediates F, G and H in higher concentration, which quickly abstract a proton from compound **4** to produce the final product. In the presence of PPh_3, intermediate F is produced in lower concentration, which only acts as an enolate to react with imine **1**, affording the normal MBH adduct **2**. This proposed mechanism could clearly explain why **3** cannot be produced either in the absence of MVK or using PPh_3 as a catalyst.

To prove that the noncyclic product **4** is an important intermediate for the construction of cyclic product **3**, several control experiments were carried out on the transformation of **4a** to **3a** and the results are shown in Table 3. Using PPh_2Me–MVK as a base, this reaction proceeded smoothly to afford **3a** in quantitative yield after 5 h (Table 3, entry 1). Other bases were also evaluated. K_2CO_3 gave **3a** in 20% yield after 24 h (Table 3, entry 2). Using DABCO as a base, no reaction occurred. However, using DBU and NaH (in THF) as the bases, **4a** decomposed entirely within 2 h (Table 3, entries 4 and 5).

In conclusion, our efforts to extend the scope and limitations of phosphine-catalyzed Morita–Baylis–Hillman reactions have led us to the unexpected discovery of a novel route for the synthesis of polysubstituted oxoimidazolidine derivatives. This method is a potentially powerful synthetic protocol for construction of the oxoimidazolidine ring from simple and easily available starting materials. Our future efforts will focus on applying them to the construction of other biologically significant natural products.

We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), and the National Natural Science Foundation of China (20672127 and 20732008) for financial support.

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