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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5750

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COMMUNICATION

Development of strong Brønsted base catalysis: catalytic direct-type Mannich reactions of non-activated esters *via* a product-base mechanism†‡

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Received 10th March 2012, Accepted 2nd April 2012
DOI: 10.1039/c2ob25522g

A catalytic Mannich reaction of a simple ester with no activating functionality at the α-position *via* a product-base mechanism was reported. The desired Mannich adducts were obtained in high yields using a catalytic amount of KH. This is a rare example of a Brønsted base-catalyzed Mannich reaction of unactivated esters as substrates.

Brønsted base-catalyzed carbon–carbon bond forming reactions are among the most fundamental and atom economical reactions for the construction of organic molecules.[1] In the reactions, one key point for efficient promotion of the reaction is basicity of catalysts, and strong Brønsted bases could enhance the reactions smoothly and also expand the scope of available substrates significantly. On the other hand, protonation of intermediates after bond-forming steps is also another key point for smooth catalyst turnover in base-catalyzed processes. When strong Brønsted base catalysts are employed in reactions, the protonation step often is not efficient due to the low Brønsted acidity of the corresponding conjugate acids of their counter anions, and the catalyst turnover could be stopped. Furthermore, when the protonation step is not efficient, retro reactions from the formed intermediates could occur. Therefore, base species with high Brønsted basicity have yet to be used as effective catalysts. However, if an intermediate, which could be preferred to be a "product-base," had strong Brønsted basicity, smooth deprotonation of the next substrate by this reaction intermediate could smoothly complete the catalytic cycle and so catalyst turnover would successfully occur even when a strong base species is used as the catalyst.[2]

Direct-type Mannich reactions of enolizable carbonyl compounds with imines provide an efficient method for the preparation of β-aminocarbonyl compounds in a single step.[3] Recently, catalytic activation of carbonyl compounds by basic catalyst systems to form carbanions or their equivalents has been widely developed in several carbon–carbon bond forming reactions.[4] However, methodology for catalytic activation of carbanion precursors bearing less acidic hydrogens, such as esters with no activating functionality at the α-position, has not been well established.[5] Deprotonation of esters to form the corresponding enolate species is generally conducted using a stoichiometric amount of a strong Brønsted base system, for example, metallated carbon or nitrogen molecules such as alkyl lithiums, lithium diisopropylamide (LDA), *etc.* However, their conjugate acids, for example diisopropylamine in the case of LDA, are less acidic to protonate the intermediates efficiently. On the other hand, in the case of Mannich reactions, it has been known that anionic nitrogen species form after the addition of carbanions to the imino carbons, which could then subsequently deprotonate the next ester substrate and so promote the reaction catalytically. In this report, we describe a very rare example of strong base-promoted catalytic Mannich reactions using simple esters as substrates.

Based on our concept, we focused on use of *N*-aryl imines containing a methoxy group as a substrate. It was anticipated that this formed a more basic nitrogen anion as a Mannich intermediate after addition of a carbanion, and that the aryl group in the subsequently formed products could be removed by oxidative cleavage using cerium ammonium nitrate (CAN),[6] *etc.* Firstly we attempted the Mannich reaction of *N*-*o*-methoxyphenyl (OMP) benzaldehyde imine (**1a**) with 2 equivalents of *tert*-butyl isobutyrate (**2a**) in THF (0.4 M) at 0 °C for 24 h in the presence of 5 mol% of potassium bistrimethylsilylamide (KHMDS). The OMP group was expected to prevent undesired intramolecular cyclization to the corresponding β-lactam by increasing steric hindrance around the nitrogen atom. As expected, the desired Mannich adduct was obtained in 88% yield. To simplify the reaction system, we then employed a strong Brønsted base, potassium hydride (KH, 5 mol%), whose conjugate acid is H_2, not an acidic species. To our delight, the desired product was obtained in high yield (Table 1, entry 1). This result clearly indicated that the Mannich reaction proceeded *via* the product base mechanism.[7] Optimization of the reaction conditions showed that the reaction proceeds smoothly in *tert*-butyl methyl ether (TBME) using a slight excess of the imine to afford the desired product in high yield (entry 2). Next we investigated the effect of imine substrates; other OMP imines derived from aromatic aldehydes were also found to be reactive under the same optimized reaction conditions. Imines bearing electron-donating groups reacted with **2a** smoothly, with the corresponding

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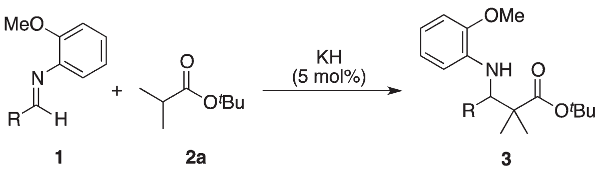
† This article is part of the *Organic & Biomolecular Chemistry* 10th Anniversary issue.

‡ Electronic supplementary information (ESI) available: General procedure of the Mannich reaction, ^{1}H and ^{13}C NMR data of the products obtained. See DOI: 10.1039/c2ob25522g

Table 1 Catalytic Mannich reactions of ester **2** in the presence of KH as a catalyst[a]

Entry	R	Product	Conditions	Yield (%)[b]
1[c]	Ph (**1a**)	**3aa**	THF, 18 h	98
2	Ph (**1a**)	**3aa**	TBME, 12 h	94
3	*p*-MeOC_6H_4 (**1b**)	**3ba**	TBME, 12 h	80
4	*p*-MeC_6H_4 (**1c**)	**3ca**	TBME, 12 h	76
5	*p*-ClC_6H_4 (**1d**)	**3da**	TBME, 12 h	94
6	*p*-$CF_3C_6H_4$ (**1e**)	**3ea**	TBME, 12 h	93
7	2-Naphthyl (**1f**)	**3fa**	TBME, 12 h	99
8	1-Naphthyl (**1g**)	**3ga**	TBME, 12 h	37
9	1-Furyl (**1h**)	**3ha**	TBME, 12 h	86
10	PhCH═CH (**1i**)	**3ia**	THF, 12 h	Trace
11[cd]	Ph (**1a**)	**3ab**	TBME, 18 h	84 (*syn*/*anti* = 63 : 37)
12[e]	Ph (**1a**)	**3ac**	TBME, 18 h	Trace

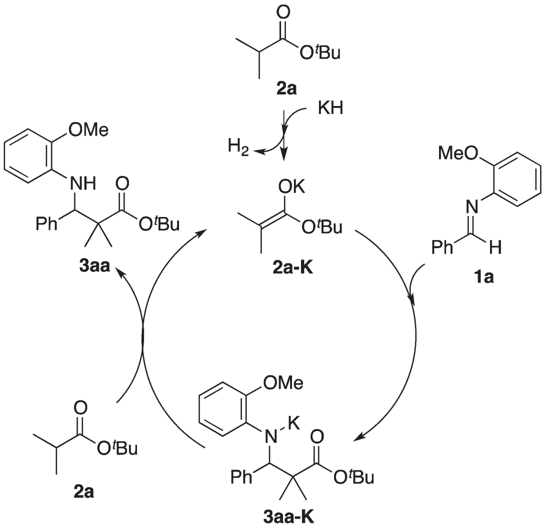
[a] The reaction of **1** (2.40 mmol) with **2a** (2.00 mmol) was conducted at 20 °C in 1.0 M in the presence of 5 mol% of KH (0.10 mmol, 5 mol%) under argon atmosphere. [b] Isolated yield (%). [c] **1a** (2.00 mmol) and **2a** (4.00 mmol) were used. [d] *tert*-Butyl propionate (**2b**) was used instead of **2a**. [e] *tert*-Butyl acetate (**2c**) was used instead of **2a**.



Scheme 1 Catalytic Mannich reaction of ester **2a**.

products being obtained in good yields (entries 3 and 4). On the other hand, the effect of electron-withdrawing groups was also positive, with high yields also being obtained (entries 5 and 6). To examine steric effects, 1-naphthyl and 2-naphthyl imines were investigated; while a high yield was obtained for the reaction when the imine containing 2-naphthyl group (entry 7), the imine with the 1-naphthyl group showed lower reactivity, probably due to large steric hindrance (entry 8). While the imine with a heteroaromatic, 1-furyl group, reacted with **2a** (entry 9), the reaction with α,β-unsaturated aldehyde-derived imine did not proceed (entry 10). Other esters were also examined; *tert*-butyl propionate (**2b**) was found to be a good substrate, with the desired Mannich products being obtained in good yield, although the diastereoselectivity was still moderate. When *tert*-butyl acetate (**2c**) was employed, only a trace amount of the desired product was obtained (Scheme 1).

The proposed catalytic cycle is shown in Scheme 2. Firstly, the α-hydrogen of ester **2a** was extracted by a strong base, KH, to form molecular hydrogen and the corresponding potassium enolate **2a-K**, which reacts with imine **1a** to form the product base **3aa-K**. The product base **3aa-K** deprotonates the next ester **2a** to afford the desired product **3aa**, with the potassium enolate **2a-K** being regenerated to complete the catalytic cycle. The key of the base catalysis should be an effective deprotonation of the ester by the strong product-base **3aa-K**. On the basis of this reaction mechanism, Mannich reactions of other carbanion precursors with less acidic active hydrogens should be possible.



Scheme 2 Proposed catalytic cycle.

In conclusion, we have revealed that a truly catalytic Mannich reaction of a simple ester with no activating functionality at the α-position proceeds smoothly *via* a product-base mechanism. The desired Mannich adducts of *tert*-butyl isobutyrate **2a** and several aromatic imines were obtained in high yields using a catalytic amount of KH as a strong base species. This is a very rare example of a Brønsted base-catalyzed Mannich reaction of unactivated esters as substrates. This concept, the product-base mechanism, could be applicable to other base catalyzed reactions using carbanion precursors bearing less acidic hydrogens, and positive planning with regards to reactions based on this concept could expand the utility of base catalysis. Further investigations to improve the Mannich reaction as well as to investigate stereoselective catalysis by means of functionalizing the metal are ongoing.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS) and Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), the University of Tokyo, MEXT, Japan.

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