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Highly efficient KF/Al_2O_3-catalyzed versatile hetero-Michael addition of nitrogen, oxygen, and sulfur nucleophiles to α,β-ethylenic compounds

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Abstract—The first example of KF/Al_2O_3-catalyzed versatile hetero-Michael addition reaction of nitrogen, oxygen, and sulfur nucleophiles was developed for facile preparation of organic compounds of widely different structures. In contrast with the existing methods using many acidic catalysts, this method is very general, simple, high-yielding, environmentally friendly, and oxygen and moisture tolerant.
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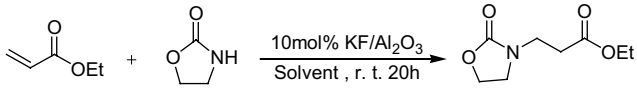
The Michael reaction is one of the most important reactions in organic chemistry. In general, conjugate addition reaction of nucleophiles to unsaturated carbonyl compounds requires basic conditions or acidic catalysts.[1] This classical procedure often suffers from the drawback of many side reactions such as polymerization of starting olefins. Recently, the development of novel synthetic methods of atomic economical hetero-Michael addition reactions has attracted much attention due to the importance of this structure motif in organic synthesis.[2] The heteroatom conjugate addition of nucleophiles to α,β-unsaturated compounds is noteworthy as a widely used method for carbon–heteroatom bond formation. Several nucleophiles such as aliphatic and aromatic amines have been used in this reaction and a variety of Lewis acidic reagents or catalysts such as $Bi(OTf)_3$, $FeCl_3$, $InCl_3$, $CeCl_3{\cdot}7H_2O$–NaI, $Bi(NO_3)_3$, palladium, and other Lewis acids have been used successfully in hetero-Michael additions.[3]

The conjugate addition of carbamates to α,β-unsaturated carboxylic acid derivatives can directly provide the N-protected β-amino carbonyl compounds. Compared to other Michael reaction, aza-Michael reaction of carbamates have only been recently the subject of investigations. Spencer and co-workers[4] demonstrated that $PdCl_2(MeCN)_2$, Brønsted acids, polymer-supported acids, and $Cu(OTf)_2$ could be used in the aza-Michael reactions of enones with carbamates. Kobayashi et al.[5] surveyed catalytic activity of various transition metal salts in the aza-Michael reaction of enones with benzyl carbamate and demonstrated that noble transition metal salts, such as platinum salts, iridium salts, gold salts are effective for this aza-Michael reaction. Very recently, bismuth nitrate[6] and TMAF[7] were also found to be effective catalysts in this aza-Michael reaction of enones with carbamates. We are also interested in aza-Michael reactions of enones with carbamates and other nitrogen-containing reagent, and have first reported several novel catalyst systems that could be used in the aza-Michael reaction of chalcone with carbamates.[8] Although recent advances have made this route more attractive, some of these methods are limited by long reaction times, expensive catalysts. Especially, there are few report in the literature for the intermolecular Michael addition of carbamates to



Scheme 1.

Keywords: Michael reaction; Oxygen; Nitrogen; Heteroatom; Lewis base.
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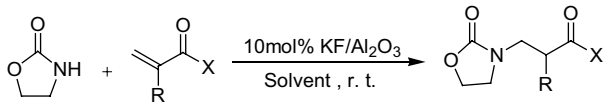
α,β-unsaturated esters, acrylates, or acylonitrile.[7] Therefore, the development of a cheaper, simpler, milder, and more efficient method for this transformation is highly desirable.

In our search toward an economical, environmentally friendly route to β-amino carbonyl compounds, we became intrigued by the idea of using catalytic amounts of cheap, readily available, and nontoxic bases. Although large amount of strong base mediated, mostly intramolecular aza- and oxa-Michael reactions have been described, and no universal method for base-catalyzed hetero-Michael reactions has been reported. Herein, we reported a novel catalyst, KF/Al_2O_3,[9] which is quite effective for the aza-Michael reactions of α,β-unsaturated compounds with oxazolidinone. In the initial studies of the screening of catalysts, we found the application of KF/Al_2O_3 as catalyst in this aza-Michael reaction of ethyl acrylate with oxazolidinone resulted in excellent yield (Scheme 1). Rapid conversion was observed when the reaction was carried out in CH_3CN (97% yield) or DMF (96% yield). Low conversion (21%) was obtained in CH_2Cl_2 when 10 mol% KF/Al_2O_3 as catalyst. And moderate yield (65%) was achieved in THF.



Scheme 2.

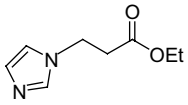
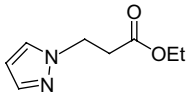
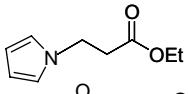
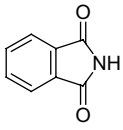
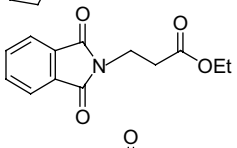
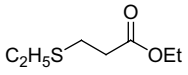
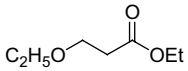
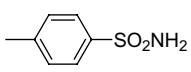
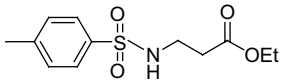
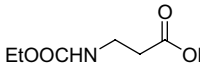
Table 1. KF/Al_2O_3 catalyzed aza-Michael addition of oxazolidinone to α,β-unsaturated compounds[10]

Entry[a]	α,β-Unsaturated compound	Time (h)	Yield [b] (%)
1	CH_2=CHCN	20	96
2	CH_2=CH–COOMe	20	97
3	CH_2=CH–COOEt	20	96
4	CH_2=CH–COOBu	20	95
5	CH_2=CH–$CONH_2$	24	93
6	CH_2=CH–COC_2H_5	24	94
7	CH_2=C(CH_3)–COOMe	24	92

[a] Reaction conditions: α,β-unsaturated compound (1 mmol), oxazolidinone (1.2 mmol), KF/Al_2O_3 (10 mol %), in CH_3CN, rt.
[b] Isolated yield.

With the effective catalyst system in hand, the conjugate addition of oxazolidinone to other α,β-unsaturated compounds were also investigated (Scheme 2). As shown in Table 1, the catalytic system is suitable for a variety of α,β-unsaturated compounds including enones, α,β-unsaturated esters, α,β-unsaturated amide, and α,β-unsaturated nitriles. This pathway offers a possible route to the corresponding aza-Michael adducts in high yields. These N-protected β-amino derivatives can be easily converted into corresponding β-amino acids and other derivatives that are very useful intermediates in the synthesis of various biologically active compounds.[11] And it

Table 2. KF/Al_2O_3 catalyzed hetero-Michael addition of ethyl acrylate with other weakly nucleophiles

Entry[a]	Nucleophile	Solvent	Time (h)	Product	Yield[b] (%)
1		CH_3CN	18		96
2		CH_3CN	18		98
3		DMF	24		42
4		DMF	24		36
5	C_2H_5SH	CH_3CN	12		99
6	C_2H_5OH	CH_3CN	18		90
7		DMF	24		48
8	NH_2COOEt	DMF	24		16

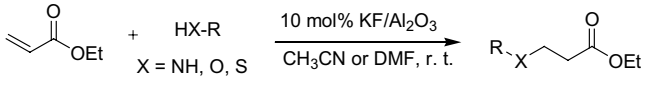
[a] All reactions were carried out using 10 mol%KF/Al_2O_3 as catalyst, ethyl acrylate (1 mmol), nucleophile (1.2–1.5 mmol) in CH_3CN or DMF at rt.
[b] Isolated yield.

is noteworthy to mention that it is the first example of the catalytic aza-Michael reaction of oxazolidinone (carbamate) with α,β-unsaturated compounds other than enones.

In contrast to previous transition metal catalysts, KF/Al_2O_3 also efficiently mediates oxa-Michael reactions of alcohol and other hetero-Michael reaction of sulfur nucleophiles, heterocyclics. As shown in Table 2, although both imidazole and pyrromonazole are weak nucleophiles,[12] they both are suitable nucleophiles and good yields were obtained with the preparation of 1-alkylimidazoles and 1-alkylpyrazoles. Alcohols are considerably less reactive than carbamate,[13] hence poor yields were obtained with many transition metal-based catalyst. However, with this KF/Al_2O_3 catalyst, good yield was obtained interestingly in CH_3CN. Extension of this method with aliphatic thiols also gives Michael products in good yield. Other nucleophiles such as pyrrole, phthalimide, *p*-toluene sulfonamide, was used in the hetero-Michael reaction, moderate yields were obtained in the presence of 10 mol%KF/Al_2O_3 in DMF (Scheme 3). However, NH_2-based carbamates such as ethyl carbamate, was not suitable nucleophile and low yield (16%) was obtained with ethyl carbamate and ethyl acrylate in DMF at room temperature. And only little aza-Michael adducts were obtained when using chalcone, cyclic enones as Michael acceptors. Compared to conventional methods, enhanced reaction rates, improved yields, and versatile utility are the features observed in KF/Al_2O_3-catalyzed hetero-Michael reactions. These examples demonstrate that Lewis base catalysis can be superior to metal ion and Lewis acid catalysis when weakly basic nucleophiles and versatile α,β-unsaturated compounds are used in the hetero-Michael reaction. In addition, this inorganic Lewis base is not only advantageous in terms of reactivity, but also regarding waste disposal and cost.

To check the catalytic efficiency of recycling KF/Al_2O_3, acrylonitrile was subjected to the conjugate addition of oxazolidinone. KF/Al_2O_3 could be reused in several times, after four runs, the yield of corresponding compound was decreased to moderate (96%, 76%, 70%, 55%).

In conclusion, we have demonstrated the first use of KF/Al_2O_3 as green catalyst for the conjugate addition of oxazolidinone to a series of α,β-unsaturated compounds. And it is the first example of catalytic aza-Michael reaction of α,β-ethylenic compounds with oxazolidinone. The present catalytic system was also exhibited efficient catalytic activity in the hetero-Michael reaction of α,β-unsaturated compounds with other nitrogen, oxygen, and sulfur nucleophiles. Apart from the experimental simplicity, the advantage of methodology is the use of a cheaper, milder, and efficient catalyst for the hetero-Michael addition reaction.



Scheme 3.

Acknowledgements

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was stirring for given time, the catalyst was removed by simple filtration. The solvent was evaporated to give the crude and then purified by silica column chromatography to afford pure product.

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