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## KF/Al<sub>2</sub>O<sub>3</sub>-Mediated Michael Addition of Thiols to Electron-Deficient Olefins

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# **KF**/Al<sub>2</sub>O<sub>3</sub>-Mediated Michael Addition of Thiols to Electron-Deficient Olefins

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**Abstract:** Potassium fluoride supported on alumina efficiently catalyzes Michael addition of aromatic and aliphatic thiols to a variety of conjugated alkenes such as  $\alpha,\beta$ -unsaturated carbonyl compounds, carboxylic esters, amides, nitriles and chalcones. The Michael adducts are produced in good to excellent yields and relatively in short times. The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.

Keywords: Electron-deficient olefins, KF/Al<sub>2</sub>O<sub>3</sub>, Michael addition, thiols

#### INTRODUCTION

The 1,4-addition of thiols to electron-deficient olefins to form a carbon–sulfur bond constitutes a key reaction in biosynthesis as well as in synthetic organic chemistry. Usually this conjugate addition is based either on the activation of thiols by base or activation of the acceptor olefins with Lewis acids.<sup>[1,2]</sup>

Recently various ionic liquid–catalyzed conjugate additions of thiols have also been reported in the literature.<sup>[3–6]</sup> Expensive reagents, harsh reaction conditions, uncommon reagents, long reaction times, side reactions, and difficult workup are major disadvantages of the reported methods.

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Scheme 1.

We report here an efficient conjugate addition of thiols to some activated alkenes in the presence of potassium fluoride supported on alumina<sup>[7]</sup> as a base (Scheme 1).

#### **RESULTS AND DISCUSSION**

Our investigations showed that aromatic and aliphatic thiols react smoothly with various conjugated alkenes in the presence of KF/Al<sub>2</sub>O<sub>3</sub>. The corresponding 1,4-adducts were obtained in high to excellent yields. To obtain the optimized reaction condition, different types of solvents as well as solventfree conditions were examined. Acetonitrile, dichloromethane, and diethyl ether were found to be suitable for this reaction. The results are summarized in Table 1. Because of its high yields and shorter reaction times, acetonitrile was found to be the best solvent for this reaction. Solvent-free conditions also gave good results (Entries 4, 8, 13, Table 1). Most of these reactions proceeded at 45–55°C in relatively short time periods, and pure products were obtained by crystallization or PTLC. In the case of acrylonitrile and metaacrylonitrile, the reaction was accomplished at room temperature. The results of optimized conditions are shown in Table 2. Aliphatic thiols such as n-butylmercaptane and benzylmercaptane reacted faster than thiophenol (Entries 1-7, Table 2). It has also been observed that the reaction is greatly influenced by the  $\beta$ -substitution of the conjugated alkene; that is,  $\beta$ -substituted conjugated olefins react slower than the nonsubstituted alkenes on the  $\beta$ -position (Entries 6, 13, Table 2). The aryl substituent in  $\beta$ -position in particular has more pronounced effect on retarding the reaction (Entries 6, 12, 13, Table 2). In contrast, acrylonitrile and metaacrylonitrile reacted in almost the same manner (Entries 1, 15, Table 2). In the case of dibenzylideneacetone, a bis-1,4-adduct of thiols were observed under the optimized reaction conditions (Entries 18, 19, Table 2). The Michael addition of thiophenols to acrylamide and metaacrylamide have also been studied and afforded high yields (Entries 16, 17, Table 2). In conclusion, KF/Al<sub>2</sub>O<sub>3</sub> has shown to be an efficient catalyst for the Michael addition of thiols to electron-deficient olefins in good to excellent yields. The support is prepared conveniently compared to other reported reagents. Also this support is nonvolatile, nonflammable, ecofriendly, inexpensive, safe, clean, and recyclable.

Entry	Electrophile	Nucleophile	Solvent	Time (min)	Yield (%)
1	CN	PhSH	Acetonitrile	15	92
2	CN	PhSH	Dichloromethane	25	86
3	CN	PhSH	Diethylether	30	70
4	CN	PhSH	Solvent-free	30	90
5	O I	PhSH	Acetonitrile	15	91
6	O I	PhSH	Dichloromethane	30	81
7		PhSH	Diethyl ether	30	72
8		PhSH	Solvent-free	30	85
9		PhCH <sub>2</sub> SH	Diethyl ether	20	90
10	COOMe	PhSH	Acetonitrile	20	90
11	COOMe	PhSH	Dichloromethane	35	80
12	COOMe	PhSH	Diethyl ether	45	80
13	COOMe	PhSH	Solvent-free	30	82

Table 1. Effect of solvent on thio-Michael addition

#### **EXPERIMENTAL**

The compounds gave satisfactory spectroscopic data. IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids on a Nicolet spectrometer (Magna 550). A bruker (DRX-500 Avance) NMR was

Entry	Electrophile	Nucleophile	Product <sup>b</sup>	Time (min)	Yield (%) <sup>a</sup>
1	CN	PhSH	CN	15	95
2	CN	n-BuSH	n-BuS	10	98
3		PhSH	PhS	15	91
4		n-BuSH	n-BuS	10	98
5		PhCH <sub>2</sub> SH	PhCH <sub>2</sub> S	10	98
6	COOMe	PhSH	COOMe	20	90
7	COOMe	n-BuSH	n-BuS	10	93
8	COOMe	PhSH	PhS	20	91
9	COOMe	n-BuSH	n-BuS	15	92
10	(Z) COOMe COOMe	PhSH	COOMe PhS COOMe	20	90
11	(Z) COOMe COOMe	n-BuSH	COOMe PhS COOMe	15	95
12	COOEt	PhSH	COOEt Ph SPh	50	80

Table 2. KF/Al<sub>2</sub>O<sub>3</sub> mediated conjugate addition of thiols to electron-deficient olefins

(continued)

Entry	Electrophile	Nucleophile	Product <sup>b</sup>	Time (min)	Yield $(\%)^a$
13	(E) COOEt	PhSH	COOEt SPh	40	85
14	COOEt	PhSH	SPh	60	80
15	CN	PhSH	PhS	20	95
16	CONH <sub>2</sub>	PhSH	CONH <sub>2</sub>	30	85
17	CONH <sub>2</sub>	PhSH	PhS CONH <sub>2</sub>	30	85
18	Ph (E) Ph	PhSH	PhS O SPh Ph Ph	100	60
19	Ph (E) Ph	n-BuSH	n-BuS O SBu-n Ph Ph	70	85

<i>ubie 2.</i> Continued	Table	2.	Continued
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<sup>*a*</sup>All yields refer to isolated products.

<sup>*b*</sup>All products were characterized by m p, IR, and <sup>1</sup>HNMR, and their physical data were similar to those reported in the literature.<sup>[3-5,9-14]</sup>

used to record the <sup>1</sup>H NMR spectra. All NMR spectra were determined in CDCl<sub>3</sub> at ambient temperature. Melting points were determined on a Buchi B540 apparatus.

#### Procedure for the Preparation of KF/Al<sub>2</sub>O<sub>3</sub> Support

The KF/Al<sub>2</sub>O<sub>3</sub> support was prepared according to the previously reported procedure<sup>[8]</sup> with some modifications. A mixture of potassium fluoride (45 g) and basic alumina (55 g, type T, Merck) in water (100 mL) was stirred at room temperature for 10 min. The resulting suspension was concentrated in vacuo and dried in a vacuum oven at 120°C for 15 h. The use of basic alumina in the solid support gave better results compared to the neutral one.

#### General Procedure for Michael Additions: Representative One (Entry 7, Table 2)

To a suspension of KF/basic Al<sub>2</sub>O<sub>3</sub> (600 mg) in acetonitrile (10 ml) n-buthylmercaptane (91.1 mg, 1.01 mmol) was added and stirred at room temperature for 5 min. Then, methylacrylate (86.1 mg, 1 mmol) was added to the mixture and stirred at 45-55°C for 10 min as indicated by TLC (ethyl acetate/ petroleum ether 1:4) for a complete reaction. After filtration of the catalyst, the filtrate was washed with aqueous NaOH (8%), and the organic phase was evaporated under reduced pressure to furnish methyl 3-thiobutylpropionate as colorless oil. The crude product was sufficiently pure (TLC and <sup>1</sup>H NMR) and more pure product (93%) was obtained by PTLC. IR 2956, 1741 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.7 (s,3H), 2.78 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 1.62–1.52 (m, 2H), 1.47–1.37 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); <sup>13</sup>C NMR  $\delta$  172.8, 52.1, 35.1, 32.2, 31.9, 27.3, 22.3, 14.0. The residual KF/Al<sub>2</sub>O<sub>3</sub> support was dried under vacuum at 120°C for 10 h and reused for subsequent reactions. No loss of efficiency with regard to reaction time and yield was observed after three uses.

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