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OPPI BRIEFS

YTTERBIUM PERFLUOROOCTANESULFONATE-CATALYZED KNOEVENAGEL CONDENSATION IN A FLUOROUS BIPHASIC SYSTEM

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(07/07/06)

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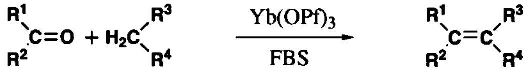
Recently, transition metal-catalyzed reactions in a fluorous biphasic system (FBS) have become one of the most important methods for facile catalyst separation from the reaction mixture and recycling of the catalyst.[1] In this catalytic system, the metal catalyst coordinated by perfluoroalkylated ligands can dissolve into the fluorous phase containing the product after the reaction.[1] Furthermore, FBS has the advantage of possible use for water-sensitive reactions unlike aqueous biphase systems.[2, 3] In continuation of our interest in the utility of lanthanide perfluorooctanesulfonates catalyzed reactions in fluorous media,[4-6] we report herein our newest results on a successful approach to FBS, *i. e.* perfluorodecalin/toluene system for the Knoevenagel condensation, a classical synthetic transformation to prepare electrophilic alkenes,[7] catalyzed by ytterbium perfluorooctanesulfonate [$Yb(OPf)_3$] complex. Rare earth (III) perfluorooctanesulfonates ($RE(OPf)_3$, RE = Sc,Y, La~Lu), a novel type of Lewis acids, has been of special interest in that they have characteristic features such as low hygroscopicity, ease of handling, robustness for recycling and high solubility in fluorous solvent.[8-10] A catalytic amount of $RE(OPf)_3$ successfully promotes several synthetically useful reactions such as Friedel-Crafts acylation [11] and alkylation,[4] aldol condensation,[6] nitration,[12] Mannich reaction [13] and Diels-Alder reactions.[8] The catalyst immobilized in the fluorous phase was recovered by simple phase separation and reused directly for the next reaction without significant loss of catalytic activity.



The Knoevenagel condensation of aldehydes and ketones was carried out with active methylene compounds employing fluorous phase technology. The condensation of benzaldehyde with ethyl cyanoacetate in a FBS was examined with various Lewis acid catalysts (*Scheme 1*).

We found that $Yb(OPf)_3$ and $Sc(OPf)_3$ complexes had similar activity for the reaction with a quantitive conversion to condensation product in the presence of 0.5 mol% catalyst at 80°C over 8 h, while other lanthanide perflates, such as $Eu(OPf)_3$, $Tm(OPf)_3$ or $La(OPf)_3$, yielded desired products in 61%, 43% or 39% respectively. This could be ascribed to the higher Lewis acidity of $Yb(OPf)_3$ and $Sc(OPf)_3$ relative to other lanthanide perflates.[8] Heptadecafluorooctanesulfonic acid ($C_8F_{17}SO_3H$, PfOH) itself can promote the reaction, but it was found to be less effective than $RE(OPf)_3$. When the reaction was complete, the reaction mixture was cooled to room temperature. The fluorous phase with $RE(OPf)_3$ catalysts separated from the organic layer as the bottom layer. In addition, based on ^{19}F NMR and UV-Vis and GC-MS data, no loss of catalyst or fluorous solvent to the organic phase was detected, and no organic compounds were found in the fluorous phase. There were no significant differences between the UV-Vis spectra of the initial and recovered fluorous phase which may indicate that the fluorous lanthanide catalyst is recovered unaltered after the condensation process has taken place. $RE(OPf)_3$ was completely (>99%) recovered as determined by atomic emission spectrometry (ICP) and was then reused.

We decided to use the relatively inexpensive and similarly active catalyst $Yb(OPf)_3$ for other condensations (*Scheme 1*). The products were isolated and identified as alkenes, and no side-reactions were observed. Based on ^1H NMR and GC-MS data, the reaction was found to give the *E*-stereoisomer as the sole product. Aromatic aldehydes containing electron-donating and electron-withdrawing groups readily condensed with ethyl cyanoacetate or malononitrile. The condensation of heterocyclic aldehydes such as 2-furfuryl- and 3-pyridylaldehyde also gave quantitive conversion to products. Greater reaction times were required for aliphatic aldehydes and ketones than for aromatic aldehydes in order to obtain moderate yields in the reaction of malononitrile or ethyl cyanoacetate, while aromatic ketones (e. g., acetophenone, entry 16) were practically unchanged. Notably, aromatic aldehydes reacted with other activated methylene compounds such as diethyl malonate, ethyl acetoacetate and acetylacetone in FBS to give condensation products in high yields. However, apart from the major product, i.e. the Knoevenagel product, some other products were also detected on GC in the case of diethyl malonate. The Knoevenagel product, benzylidene malonate, which is an excellent Michael acceptor, underwent subsequent Michael addition with diethyl malonate to give the Michael adduct (*Scheme 2*).[17] The catalytic activity of $Yb(OPf)_3$ was further clearly established by the condensations of aromatic aldehydes with malonic acid and β-ketoacid derivatives, allowing readily access to cinnamic acid derivatives and cinnamyl ketones. Such results benefit greatly from both the efficient Lewis acidity of $Yb(OPf)_3$ and unique solution properties of FBS. Moreover, it is worth pointing out that $Yb(OPf)_3$ is applicable to a wider range of substrates than other reported Lewis acid catalysts in the Knoevenagel reaction.[15, 22]

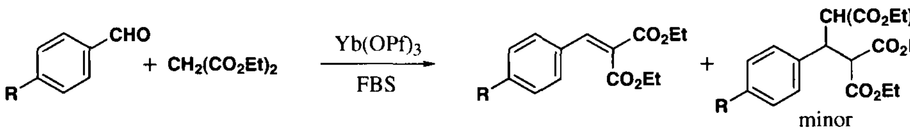


Table 1. $Yb(OPf)_3$ catalyzed Knoevenagel condensation in FBS[a]

Entry	R^1	R^2	R^3	R^4	Time (h)	Yield (%)	mp or bp (mm Hg) /°C
1	4-ClPh	H	CN	COOEt	8	99	92-93 [*lit.*[14] 90-91]
2	4-MePh	H	CN	COOEt	8	83	91-92 [*lit.*[15] 90-92]
3	4-NO_2Ph	H	CN	COOEt	6	99	170-172 [*lit.*[15] 170-171]
4	4-HOPh	H	CN	COOEt	8	72	169-171 [*lit.*[15] 169-171]
5	4-$(Me)_2$NPh	H	CN	COOEt	10	77	126 [*lit.*[15] 126-127]
6	4-MeOPh	H	CN	COOEt	8	76	80-81 [*lit.*[15] 79-80]
7	Cinnamyl	H	CN	COOEt	6	98	113-114 [*lit.*[15] 115-116]
8	2-Furfuryl	H	CN	COOEt	3	99	86-89 [*lit.*[15] 89-91]
9	3-Pyridyl	H	CN	COOEt	3	99	75-76 [*lit.*[15] 75-77]
10	*i*-C_3H_7	H	CN	COOEt	8	60	88-91 (5.0) [*lit.*[16] 86-87 (4.9)]
11	*n*-C_5H_{11}	H	CN	COOEt	8	62	84-85 (1.0) [*lit.*[16] 83-85 (1.0)]
12	$(CH_2)_5$		CN	COOEt	12	52	113-115 (1.5) [*lit.*[14] 112-114 (1.5)]
13	Ph	H	CN	CN	2	99	81-83 [*lit.*[14] 82]
14	$(CH_2)_5$		CN	CN	12	72	147 (15) [*lit.*[14] 138 (10)]
15	Me	Me	CN	CN	16	50	111 (25) [*lit.*[14] 108 (23)]
16	Ph	Me	CN	CN	18	----	----
17	Ph	H	COOEt	COOEt	12	58	33 [*lit.*[17] 33]
18	4-MePh	H	COOEt	COOEt	12	56	45-46 [*lit.*[17] 46-47]
19	Ph	H	MeCO	COOEt	7	78	44-45 [*lit.*[18] 46]
20	Ph	H	MeCO	MeCO	8	80	185-188 (15) [*lit.*[19] 185-188 (15)]
21	Ph	H	COOH	COOH	8	91	131-132 [*lit.*[20] 133]
22	4-ClPh	H	COOH	COOH	8	99	162-163 [*lit.*[21] 162-163]
25	Ph	H	MeCO	COOH	12	90	40-41 [*lit.*[22] 42]

a) All condensations were carried out at 80°C in the presence of 0.5 mol% catalyst.

In summary, the efficiency of $Yb(OPf)_3$ as Lewis acid catalyst in FBS as an eco-friendly reaction system was demonstrated for the Knoevenagel reaction. We believe that the following results endow the catalytic approach with great potential for synthetic applications: (1) The catalytic system can be applied in a great range of substrates for the Knoevenagel reaction; (2) the catalyst, completely immobilized in the fluorous phase, can be recovered and reused; (3) high yields and purities of Knoevenagel condensation products can be obtained under fluorous biphasic catalytic condition.

EXPERIMENTAL SECTION

MPs were obtained with a Shimadzu DSC-50 thermal analyzer. IR spectra were recorded on a Bomem MB154S infrared analyzer. UV-Vis spectra were obtained with a UV-1601 apparatus. ^1H NMR and ^{19}F NMR spectra were recorded on Bruker Advance RX300. Mass spectra were recorded on a Saturn 2000GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN recorder. The perfluorodecalin (octadecafluorodecahydronaphthalene) and rare earth (III) salts were purchased from Aldrich Co. Heptadecafluorooctanesulfonic acid was commercially obtained from ARCOS Co. Commercially available reagents were used without further purification.

Typical Procedure for Ytterbium Perfluorooctanesulfonates.[4]- **Method A**: A mixture of a solution of heptadeca- fluorooctanesulfonic acid (PfOH, 0.77 g, 1.5 mmol) in water (5 mL) and solution of $YbCl_3•6H_2O$ (0.2 g, 0.5 mmol) in water (0.8 mL) was stirred at room temperature for 18 h. **Method B**: A mixture of a solution of PfOH (0.77 g, 1.5 mmol) in water (5 mL) and Yb_2O_3 (0.12 g, 0.25 mmol) powder was refluxed with stirring for 3 h. In both methods, the resulting gelatin-like solid was collected, washed and dried at 150°C in vacuo to give a white solid (0.82 g, 98%), which does not melt up to 500°C, but shrinks around 380°C and 450°C. IR (KBr): 1237 (CF_3), 1152 (CF_2), 1081 (SO_2), 1059 (SO_2), 747 (S-O) and 652 (C-S) cm^{-1}. ICP: Calcd for $C_{24}O_9F_{51}S_3Yb•H_2O$: Yb, 10.24. Found: Yb, 9.99.

Anal. Calcd for $C_{24}O_9F_{51}S_3Yb•H_2O$: C, 17.21; H, 0.10. Found: C, 17.03 ; H, 0.18.

Typical Procedure for Knoevenagel Condensation in FBS.- The aldehyde (10 mmol) or ketone (10 mmol) was slowly added into a mixture of $Yb(OPf)_3$ (50 mg, 0.03 mmol), toluene (2 mL) and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture, 2 mL) containing the active methylene compound (10 mmol). The mixture was stirred at 80°C for the time indicated in *Table 2*. The bottom fluorous layer was then separated (to be reused). The upper organic phase was washed with water (10 mL), 10% $NaHCO_3$ solution (10 mL) and water (10 mL x 2), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography (40% EtOAc in petroleum ether) or by recrystallization from ethanol to give the Knoevenagel product.

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