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Nano-silica PAMAM Dendrimer as a Novel Catalyst for Knoevenagel Reactions

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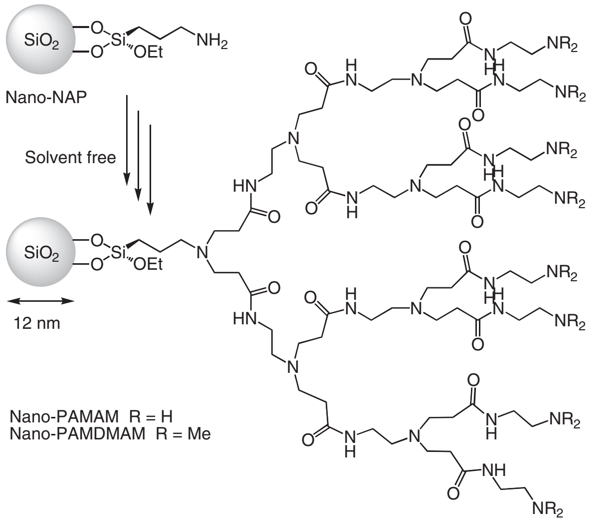
A nano-silica dendrimer, poly(amidoamine)-grafted nano-silica (nano-PAMAM), catalyzed the Knoevenagel reaction of aryl and aliphatic aldehydes with various active methylene compounds at room temperature in good yields. The reaction conditions were mild enough that base-sensitive AcO or acid-sensitive THPO groups remained intact in the products. The catalyst was recycled up to 4 times in 78% average yield.

The Knoevenagel reaction is one of the most powerful procedures for the production of α,β-unsaturated carbonyl compounds, which are important substrates as acceptors in Michael reactions or as dienophiles in Diels–Alder reactions and as useful building blocks with many applications in the synthesis of fine chemicals.[1] The Knoevenagel reaction can be catalyzed by a broad range of catalysts ranging from homogeneous amine to heterogeneous dendrimers,[2] however, environmentally benign and sustainable catalysts are increasingly desired due to the requirements of green chemistry.[3]

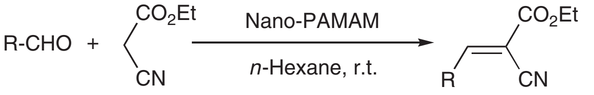
Based on this concept, we have successfully utilized amorphous aminopropylated-silica of micrometer particle size as sustainable catalysts for 1,4-conjugate additions[4] and self-aldol condensations[5] of naked aldehydes, transesterifications,[6] Michael reactions,[7] hydropyran synthesis by three component condensations,[8] Knoevenagel reactions,[9] and subsequent Mislow–Evans rearrangements[10] in environmentally benign reaction media such as water or ionic liquids.

We have recently developed an efficient solvent-free protocol for grafting aminopropyl residues on nano-silica particles having an average size of 12 nm to provide aminopropylated nano-silica (nano-NAP), in which a solution of (3-aminopropyl)-triethoxy silane in ethanol is sprayed directly onto the silica nanoparticles,[11] which is environmentally benign and favorable for large-scale preparation. Subsequently, syntheses of hyperbranched polyamidoamine (PAMAM)-grafted nano-silica third generation dendrimer (nano-PAMAM) and polyamidodimethylamine (PAMDMAM)-grafted nano-silica third generation dendrimer (nano-PAMDMAM) were achieved by spraying methyl acrylate and then ethylenediamine alternately starting from nano-silica NAP (Scheme 1).

As a part of our ongoing efforts directed towards the development of supported-organocatalysts on silica,[12] we investigated the catalytic activity of the nano-silica dendrimers nano-PAMAM and nano-PAMDMAM as novel supported-organocatalysts for the Knoevenagel reaction[13] (Scheme 2). The catalytic use of PAMAM in Knoevenagel reactions was quite limited until a recent report by Kapoor et al., in which second generation PAMAM was supported inside of mesoporous FSM silica in a study to remove volatile organic compounds.[14] Subsequently, during the course of our study, Krishnan and Sreekumar published their work on Knoevenagel reactions that were catalyzed by polystyrene bead-supported third generation PAMAM.[2b]



Scheme 1. Nano-silica dendrimer, nano-PAMAM, nano-PAMDMAM, and nano-silica NAP.

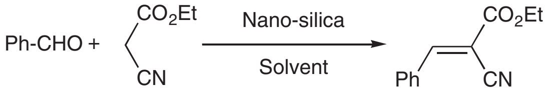


Scheme 2. Knoevenagel reaction catalyzed by nano-PAMAM.

Nano-silica dendrimers, nano-PAMAM, nano-PAMDMAM, and nano-silica NAP, all disperse homogeneously into various solvents—even into *n*-hexane—without forming a gel, unlike the original nano-silica particles. The optimum reaction conditions for the Knoevenagel reaction were investigated using the reaction of benzaldehyde and ethyl cyanoacetate, and the results are shown in Table 1. Our investigation into the optimum reaction medium was first carried out employing nano-PAMAM (amine residue: $2.4\,\mathrm{mmol\,g^{-1}}$), and *n*-hexane was found to give the best results (Table 1, Entries 4 and 6). Among the catalysts, nano-PAMAM exhibited the best catalytic performance in *n*-hexane at room temperature (Table 1, Entries 4 and 6). Nano-PAMDMAM was less reactive (Table 1, Entry 7), which suggests that the present reaction proceeds via initial imine formation followed by nucleophilic attack of ethyl cyanoacetate and subsequent elimination of the dendrimeric amine. The high density of amino groups on the surface of nano-PAMAM might be responsible for its catalytic activity.

Employing the optimized reaction conditions (Table 1, Entry 4, TOF = 3), reactions with various aldehydes are shown in Table 2. Aryl aldehydes bearing not only electron-withdrawing (Table 2, Entries 2 and 3) but also electron-donating (Table 2, Entries 4 and 5) substituents reacted in good yields to give unsaturated cyanoesters. The wide applicability of nano-PAMAM

Table 1. Investigation of optimum reaction conditions



Entry[a]	Catalyst (equiv)[b]	Solvent	Time/h	Yield/%
1	PAMAM (0.05)	[bmim]PF_6	4	72
2	PAMAM (0.05)	H_2O	4	71
3	PAMAM (0.05)	—	4	82
4	PAMAM (0.05)	*n*-Hexane	6	90
5	PAMAM (0.05)	*n*-Hexane/H_2O	6	86
6	PAMAM (0.05)	*n*-Hexane	15	91
7	PAMDMAM (0.05)	*n*-Hexane	6	64
8	NAP (0.01)	H_2O	7	0
9	NAP (0.05)	*n*-Hexane	16	0

[a]Product was isolated by medium pressure LC after trituration with ether and subsequent evaporation. [b]Reaction was carried out with 0.1 equiv (40 wt %) of catalyst unless otherwise indicated.

Table 2. Reactions with a variety of aldehydes[a]

Entry	R	Time/h	Yield/%
1	Ph	6	90
2	4-Cl–C_6H_4	5	88
3	4-NO_2–C_6H_4	5	91
4	4-MeO–C_6H_4	9	93
5	4-HO–C_6H_4	5	98
6	4-AcO–C_6H_4	6	88
7	4-THPO–C_6H_4	11	66
8	Citronellal	6	78
9	C_9H_{19}	4	75
10	C_6H_{13}	4	51

[a]Reactions were carried out at room temperature with 0.1 equiv of nano-PAMAM.

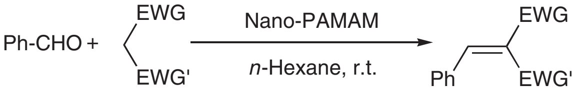
was exemplified by its catalytic activity toward aliphatic aldehydes (Table 2, Entries 8–10). Self-aldol condensation of the aliphatic aldehydes was not observed,[5] probably due to the higher reactivity of ethyl cyanoacetate. The reaction conditions were mild enough to ensure that base or acid-sensitive protecting groups such as an AcO or THPO group remained intact in the products (Table 2, Entries 6 and 7). Only Z isomers were obtained in all cases.

Nano-PAMAM was effective for other active methylene compounds in reactions with benzaldehyde as shown in Table 3. Low conversion in Entry 4 might be due to enamine formation of pentane-2,4-dione.

Next, we focused on recycling nano-PAMAM and found that the catalysts could be recycled after light centrifugation up to three times in 76% average yield. Since the loss of reactivity was due to the loss of the catalyst powder during trituration, water was added to confine the catalyst in the aqueous phase, which improved recycle-use up to four times in 78% average yield. Separation of the product from the catalyst became facile in this two-phase system.

In summary, we have developed a new protocol for the Knoevenagel reaction catalyzed by a nano-silica gel dendrimer—nano-PAMAM—at room temperature in *n*-hexane to afford a variety of electron-deficient olefins. The catalyst was effective not only for aryl aldehydes but also for aliphatic aldehydes and could be recycled several times. The present protocol is more efficient due to easy operation and recycle use in addition to its wide applicability to a variety of substrates than our previous Knoevenagel reaction catalyzed by amorphous aminopropylated silica (NAP) in water,[9] which is comparable to the work by Krishnan and Sreekumar.[2b]

Table 3. Reactions with other active methylene compounds[a]



Entry	EWG	EWG′	Time/h	Yield/%
1	CO_2Et	CN	6	90
2	CN	CN	1	99
3	CO_2Et	COMe	22	60
4	COMe	COMe	24	5
5	CO_2Me	CO_2Me	24	7

[a]Reactions were carried out at room temperature with 0.1 equiv of nano-PAMAM.

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