Simple and Fast Cross Aldol Reation by NiO Nanoparticles as an Efficient Catalyst

Elahe Keshavarz
Assistant Professor, Department of Basic Sciences, Farhangian University, Tehran, Iran, Email: iyc.2011@yahoo.com

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Abstract
Objective(s): This paper describes the synthesis of aldol adducts using nickel oxide nanoparticles with two size distributions at room temperature.
Methods: Eleven β-hydroxyl carbonyl compounds were obtained by the aldol reaction of cycloalkanones and various aromatic aldehydes using nickel oxide nanoparticles. Their structures were confirmed by spectral data (IR, ^{1}HNMR and ^{13}CNMR). Diastereoselectivities determined by ^{1}HNMR analysis.
Results: The results indicated that the cross aldol reaction of cycloalkanones with various aldehydes using catalytic amount of NiO NPs proceeded smoothly at room temperature to give the β-hydroxy ketone derivatives in moderate to good yields and good diastereoselectivities. A low annealing temperature would be useful to gain a high specific surface area of NiO NPs, as an efficient catalytic process.
Conclusion: The catalytic method provides access to various aldol products from modest to good yields with good diastereoselectivity for all reported substrates. The investigation continues toward the asymmetric version of cross aldol reaction.

Keywords: Aldol reaction, Catalytic synthesis, NiO NPs, Cycloalkanone.

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INTRODUCTION

Carbon-carbon bond formation is the essence of organic synthesis and its variants have been used extensively in many important syntheses.[1-3] Cross-aldol reaction has been considered one of the most powerful and efficient measures for the formation of carbon-carbon bond.[4-6] The reaction has proven to be a powerful and general method for the stereocontrolled construction of β-hydroxy ketone derivatives[7-10] and has relevant application in the synthesis of carbohydrates, amino sugars, steroids, natural heteroatomic molecules, fine chemicals and pharmaceuticals.[11-13] There are several methods to synthesized aldol products. Also, many efforts have been addressed towards the synthesis of organocatalysts that have produced systems able to afford very good stereoselectivities. Diaz-Jua´rez et al. described the use of proline for the enantioselective synthesis of aldol adducts.[14] Min et al. disclosed the asymmetric cross aldol reaction of cyclic ketone with various benzaldehydes by organocatalyst[15], and Ishihara et al. developed highly stereoselective

multi-fluorous proline catalyst for asymmetric aldol reactions.[16] Genc et al. used organocatalysts for the enantioselective cross aldol reaction of acetone with aromatic aldehydes.[17] Duss et al. demonstrated the cross aldol reaction of cyclohexanone with aldehydes by lipidic mesophases as novel nanoreactor scaffolds for organocatalysts.[18]
presented herein show the catalytic role of NiO NPs at room temperature in the diastereoselective aldol reaction between ketones and aldehydes Over the last years, seminal research have established this venerable reaction as the principal chemical method for the stereoselective construction of complex polyol architecture.[19] Since the control of stereochemistry during aldol additions is a crucial problem, the metal catalyzed direct aldol reaction of aldehydes with unmodified ketones still remains a challenge for synthetic chemist.[20] Zi-Bin Qiu et al. used $MgBr_2.OEt_2$ as an efficient catalyst for the synthesis of aldol derivatives with up to 99% diastereoselectivity at 5 °C.[21] Wu et al. studied the proline functionalized pillar-layered chiral MOF as a catalyst in the reaction of 4-nitrobenzaldehyde and cyclohexanone. They reported the products with diastereoselectivities up to 98% for the aldol reaction at 40 °C, after 5 days.[22] On the other hand, metal oxide nanoparticles (NPs) find excellent applications as catalysts for various organic transformations.[23,24] Choudary et al. reported direct asymmetric aldol reaction catalyzed by MgO NPs.[25] Yang et al. used self-assembled bio-organometallic nanocatalysts for enantioselective direct aldol reactions.[26] Kantam et al. reported direct asymmetric aldol reaction of aldehydes with acetone using CuO NPs to afford optically active β-hydroxy carbonyl compounds.[27] Despite these reports, it is still important to develop new efficient method for the cross aldol reactions in mild reaction conditions.
This paper describes a successful cross coupling reaction between cycloalkanones and various aromatic aldehydes in the presence of nano catalyst. The results presented herein show the efficient catalytic role of NiO NPs at room temperature in the diastereoselective aldol reaction between ketones and aldehydes.

METHODS

General

The synthesis of NiO NPs has been carried out according to literature procedure.[28] Solvents, organic and inorganic compounds were purchased from Merck and used without further purification. The isolation of pure products was carried out via preparative thin layer chromatography (Silica Gel 60 GF_{254}; Merck). IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. ^1H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and ^{13}C NMR were achieved on a Bruker DRX-125 Avance spectrometer. Samples were analyzed in $CDCl_3$, and the chemical shift values are expressed relative to Me_4Si as an internal standard.

Typical Procedure for Nio Nps-Catalyzed Aldol Reaction

In the presence of NiO NPs (3.8 mg), KOH (0.4 mmol) and dioxane (3 mL), a mixture of cycloalkanone (3 mmol) and aldehyde (1 mmol) was stirred for the appropriate time at room temperature. Completion of the reaction was indicated by TLC monitoring. After the indicated reaction time, the reaction mixture was purified by thin layer chromatography (silica gel, petroleum ether/ethyl acetate 12:4) in order to give the corresponding aldol.

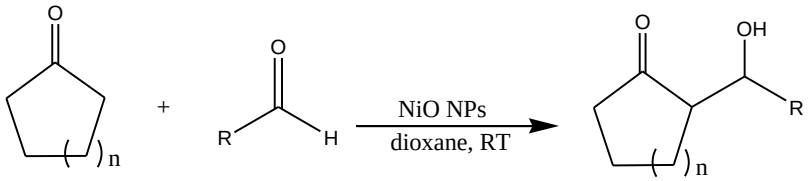
RESULTS AND DISCUSSION

Earlier, the aldolization of cycloalkanones and aldehydes under traditional catalyst was studied.[29] As a part of our ongoing interest to develop efficient synthetic strategies for the preparation of β-

hydroxy ketone moiety units.[30,31] a facile and efficient nano heterogeneous catalytic approach for the direct one-pot synthesis of aldol adducts have been developed. In this study, NiO NPs were successfully synthesized by sol-gol method[28], and then annealed at two temperature (300 and 500 °C). The annealing temperature played an important role in controlling the particle size. NiO NPs with two size distributions were used as the efficient catalyst for synthesis of β-hydroxy units using cycloalkanones and aldehydes. At first, to get the optimum conditions for the reaction, reaction of cyclohexanone and 4-nitrobenzaldehyde for synthesis of aldol product was selected as model reaction and different parameters such as the reaction time, amount of catalyst and temperature were tested.

To find the most effective NiO NPs catalyst for the synthesis of aldol adduct, the NiO NPs with two size distributions were studied. When the aldol reaction was carried out in the presence of 300 °C annealed NiO nanoparticle, yield obtained was higher (72 %) as compared to that carried out in the presence of 500 °C (62 %). This may be due to decrease in surface area of NiO NPs. The surface-to-volume ratio of the catalyst increases tremendously when size decreases, which are responsible for the higher activity and enhanced yield of NiO NP at 300 °C.

The amount of catalyst was optimized for the model reaction using different quantities of NiO NPs. It can be seen that the best yield was achieved by 3.8 mg of catalyst. Moreover, in the absence of NiO NPs, no product was obtained after 7 h. For the optimization of the reaction temperature, reaction was performed in different temperature. The best yield was obtained at RT. Finally, after some preliminary experiments, we found that a mixture of cyclohexanone (3 mmol) and 4-methoxybenzaldehyde (1 mmol) in the presence of NiO NPs (3.8 mg) afforded aldol product at room temperature in moderate to good yields (45-73 %). The generality of the reaction was assessed using cycloalkanones and aromatic aldehydes (Table 1).



n = 1 2a
n = 2 2b

1a-i

A proposed mechanism for the formation of the aldol product would be as follows. The NiO nanoparticle facilitates the formation of enolate through Lewis acid sites (Ni^{2+}) coordinated to the oxygen of carbonyl group.

CONCLUSION

In summary, the cross aldol reaction of various cycloalkanones with aromatic aldehydes using catalytic amount of NiO NPs proceeded smoothly under extremely mild conditions to give the corresponding aldol adducts in moderate to good yields. A low annealing temperature would be useful to gain a high specific surface area of NiO NPs, as an efficient catalytic process. The reaction can efficiently proceed at room temperature with a small excess of ketone. Also, the reactions can be performed over a short period of time without preactivation of the donor substrates. Further investigations focusing on the mechanism and asymmetric synthesis of this reaction are currently underway.

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Table 1. Aldol reaction of cycloalkanones with aldehydes by NiO NPs[a] (annealed at 300 °C).

Entry[e]	R		Product[b]	Yield (%)[c]	Time (h)	Dr (syn:anti)[d]
1	4-ClC_6H_4-	a	3ba	65	5	80:20
2	3-ClC_6H_4-	b	3bb	66	4	81:19
3	2-ClC_6H_4-	c	3bc	60	3	70:30
4	4-BrC_6H_4-	d	3bd	58	3	65:35
5	4-FC_6H_4-	e	3be	62	1	62:38
6	4-$O_2NC_6H_4$	f	3bf	72	2	80:20
7	4-$O_2NC_6H_4$	f	3af	73	2	72:28
8	2-$O_2NC_6H_4$	g	3bg	70	2.5	75:25
9	2-$O_2NC_6H_4$	g	3ag	71	2	67:33
10	4-$CH_3C_6H_4$-	h	3bh	50	5.5	72:28
11	4-$CH_3OC_6H_4$-	i	3bi	45	3.5	71:29

[a]Reaction conditions: aldehyde (1 mmol), cycloalkanone (3 mmol), KOH (0.4 mmol), NiO NPs catalyst, solvent, RT.

[b]All products were characterized by ^{1}HNMR, ^{13}CNMR and IR data. [c]Yields after purification by chromatography.

[d]Determined by ^{1}HNMR analysis. [e]Identified by comparison with authentic samples.[29]