

Nano cerium oxide as a recyclable catalyst for the synthesis of *N*-monosubstituted ureas with the aid of acetaldoxime as an effective water surrogate

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Abstract: A new method for the synthesis of *N*-monosubstituted ureas has been developed by the reaction of cyanamides with acetaldoxime in the presence of nano cerium oxide as an efficient and recyclable catalyst.

Keywords: Cyanamide, acetaldoxime, *N*-monosubstituted urea, nano cerium oxide, reusable catalyst

Introduction

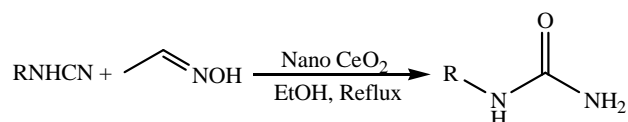
N-Monosubstituted ureas have potential medical and agricultural applications.^{1,2} Several methods for their preparation have been reported, but synthetic approaches for these compounds are needed. Classical methods for the synthesis of *N*-monosubstituted ureas have involved reaction of primary or secondary amines with isocyanates,³ toxic phosgene or its derivatives,⁴ insertion of CO or CO₂ into amino compounds in the presence of different catalysts in organic solvents at high temperature and pressure,^{5,6} reaction of amines with sodium or potassium cyanate in aqueous solution in the presence of one equivalent of HCl,⁷ acid or base-catalyzed hydration of cyanamides,^{8,9} and reaction of *S,S*-dimethyl dithiocarbonate with ammonia in water-dioxane.¹⁰

There is considerable interest in the applications of cyanamides as an efficient reagent for the organic synthesis.¹¹⁻¹⁹ Among currently available synthetic routes to *N*-monosubstituted

ureas, the most widely used one is based upon hydration of cyanamides,^{8,9} which involves the treatment of cyanamides with corrosive acids or bases. Thus, the development of an efficient and versatile method for the hydration of cyanamides to *N*-monosubstituted ureas is an active ongoing research area.

In recent years there has been a tremendous interest in various chemical transformations performed under the heterogeneous catalysis.²⁰⁻²⁵ Among heterogeneous catalysts, metal nanoparticles have been used widely as efficient catalysts in organic reactions due to their high catalytic activity, ease of handling, reusability, and benign character.²⁶ The application of metal oxides, especially ceria, as effective catalysts for CO₂ fixation and transalkylation and organic synthesis has received considerable attention in the recent years due to their high catalytic activity.^{27,28} Nagarkar and co-workers recently published Ullmann type coupling between 4-nitrochlorobenzene and variety of phenols, amines and thiophenols in the presence of nano CeO₂ an efficient, inexpensive, and environmentally benign heterogeneous catalyst.²⁹

In continuation of our recent studies on the application of heterogeneous catalysts,³⁰ we hereby report a new protocol for the preparation of *N*-monosubstituted ureas via hydration of cyanamides with acetaldoxime in the presence of nano cerium oxide²⁹ as a heterogeneous catalyst (Scheme 1).



Scheme 1. Hydration of cyanamides using acetaldoxime and nano cerium oxide as a reusable heterogeneous catalyst.

Results and Discussion

The CeO₂ nano particles were prepared according to literature.²⁹ Nagarkar and co-workers studied the characterization of the catalyst using powder XRD, TEM, SEM and EDAX.²⁹

Control experiments show that there is no reaction in the absence of catalyst (Table 1, entry 1 and 2). Our experiments showed that the catalyst was necessary for the hydration reaction (Table 1, entry 11). In order to examine the feasibility of our rationale and find optimum conditions, we carried out the reaction of 3-bromophenylcyanamide with

acetaldoxime in the presence of various solvents and catalysts under various temperature conditions. Several organic solvents such as toluene, ethanol, ethyl acetate and acetonitrile were examined. According to data given in Table 1, ethanol was the most efficient solvent for this reaction (Table 1, entry 7). After choosing ethanol as the solvent, we examined several different catalysts. Among the selected catalysts, CeO₂ nano acted as the most effective one (Table 1, entry 7). The ratio of acetaldoxime to cyanamide was chosen 2.0:1.0. When we reduced the amounts of acetaldoxime to 1.0 equiv., the yield was significantly reduced (Table 1, entry 12). Conversely, when we increased the amounts of acetaldoxime to 2.0 equiv., the reaction time was reduced and the yield was slightly increased (Table 1, entry 7). We then used the optimal reaction conditions (cyanamide (1.0 mmol), acetaldoxime (2.0 mmol), CeO₂ nano (5.0 mol%) and ethanol as solvent) for hydration of different cyanamides under thermal conditions and the results are shown in Table 2.

Table 1 Optimization of reaction conditions in hydration of 3-bromocyanamide with acetaldoxime in the presence of various catalysts

Entry	Catalyst (mol%)	Acetaldoxime (mmol)	Solvent	Temperature (°C)	Time (h)	Yield ^a (%)
1	0	2	EtOH	Reflux	8	22
2	0	4	EtOH	Reflux	8	32
3	MnO ₂ (20)	2	EtOH	Reflux	6	34
4	TiO ₂ (20)	2	EtOH	Reflux	6	38
5	SiO ₂ (20)	2	EtOH	Reflux	6	41
6	CeO ₂ (20)	2	EtOH	Reflux	2	80
7	CeO ₂ (nano) (5)	2	EtOH	Reflux	2	91
8	CeO ₂ (nano) (5)	2	EtOAc	Reflux	2	45
9	CeO ₂ (nano) (5)	2	CH ₃ CN	Reflux	2	73
10	CeO ₂ (nano) (5)	2	Toluene	Reflux	2	77
11	CeO ₂ (nano) (5)	2	EtOH	r.t.	2	72
12	CeO ₂ (nano) (5)	1	EtOH	Reflux	2	60
13	CeO ₂ (nano) (5)	3	EtOH	Reflux	2	92
14	CeO ₂ (nano) (10)	2	EtOH	Reflux	2	91
15	CeO ₂ (nano) (3)	2	EtOH	Reflux	2	85

^aYields are after work-up.

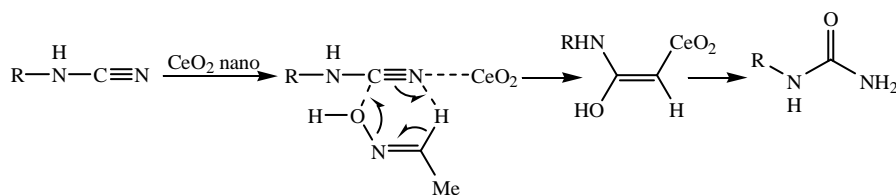
Table 2 Hydration reaction of various cyanamides using acetaldoxime in the presence of CeO₂ nano under reflux conditions^a

Entry	Substrate	Product	Yield ^b (%)	M.p. (°C)	Reference
1	C ₆ H ₅ NHCN	C ₆ H ₅ NHCONH ₂	85	143-145	31
2	<i>p</i> -OMeC ₆ H ₄ NHCN	<i>p</i> -OMeC ₆ H ₄ NHCONH ₂	87, 86 ^c	167-169	31
3	<i>p</i> -MeC ₆ H ₄ NHCN	<i>p</i> -MeC ₆ H ₄ NHCONH ₂	89	181-182	33
4	<i>o</i> -MeC ₆ H ₄ NHCN	<i>o</i> -MeC ₆ H ₄ NHCONH ₂	87	195-197	32
5	<i>m</i> -BrC ₆ H ₄ NHCN	<i>m</i> -BrC ₆ H ₄ NHCONH ₂	91	166-168	This work
6	<i>p</i> -ClC ₆ H ₄ NHCN	<i>p</i> -ClC ₆ H ₄ NHCONH ₂	87	205-208	31
7	<i>p</i> -NO ₂ C ₆ H ₄ NHCN	<i>p</i> -NO ₂ C ₆ H ₄ NHCONH ₂	84	237-239	34
8	1-C ₁₀ H ₇ NHCN	1-C ₁₀ H ₇ NHCONH ₂	86	220-222	This work
9	C ₆ H ₅ CH ₂ NHCN	C ₆ H ₅ CH ₂ NHCONH ₂	84	149-151	33
10	<i>p</i> -OMeC ₆ H ₅ CH ₂ NHCN	<i>p</i> -OMeC ₆ H ₅ CH ₂ NHCONH ₂	85	111-112	31
11	<i>p</i> -MeC ₆ H ₅ CH ₂ NHCN	<i>p</i> -MeC ₆ H ₅ CH ₂ NHCONH ₂	83	198-199	33

^a Reaction conditions: Catalyst (5.0 mol%), cyanamide (1.0 mmol), acetaldoxime (1.0 mmol), EtOH (5.0 mL) at reflux, 2h. ^b Yields are after work-up. ^c Yield after the third cycle.

To study the effects of the nature of the substituents on the benzene ring of the cyanamides, various *N*-monosubstituted ureas were synthesized from different arylcyanamides containing both electron-releasing and electron-withdrawing groups with acetaldoxime and CeO₂ nano in ethanol in excellent yields under reflux conditions. We showed that the nature of the substituent had no effects on the reaction time. In the case of aliphatic cyanamides the hydration process was similar to aromatic cyanamides. The hydration of aliphatic cyanamides gave the corresponding *N*-monosubstituted ureas in high yields.

As shown in Scheme 2, the CeO₂ nano probably has an important role in promotion of the synthesis of *N*-monosubstituted ureas as a heterogeneous catalyst. It involves activation of the nitrile group over surface of the catalyst and subsequent treatment of the acetaldoxime as an effective water surrogate.



Scheme 2. Proposed mechanism for the hydration of cyanamides.

In a typical experiment, after the reaction was completed, The CeO₂ nano particles as a catalyst were isolated from the reaction mixture by centrifugation in the work-up stage. We found that CeO₂ nano can be reused several times without the loss of activity, by simply filtering the catalyst, washing with dichloromethane, drying and immediately reusing (Table 2, entry 2).

The simplicity, together with the use of inexpensive, non-toxic and environmentally benign catalyst under thermal conditions is remarkable features of the procedure. The products were characterized by IR, ¹H NMR and ¹³C NMR spectroscopy and from melting points. The structure of the *N*-monosubstituted ureas was in agreement with their IR and ¹H NMR spectra. *N*-Monosubstituted ureas contain a NH₂ bond, a NH bond and a CO bond. The comparison of the IR spectra of arylcyanamides with *N*-monosubstituted ureas clearly confirmed the product. In the IR spectra of products, CN peak was disappearance.

In conclusion, we have developed an efficient procedure for the hydration of cyanamides using acetaldoxime as an effective water surrogate and nano cerium oxide as a reusable heterogeneous catalyst under thermal conditions. This method has the advantages of high yields, elimination of toxic reagents and corrosive acids, simple methodology and easy work-up.

Experimental

General

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterized by comparison of their physical and spectral data with authentic samples. The NMR spectra were recorded in DMSO. ¹H NMR

spectra were recorded on a Bruker Avance DRX 250 MHz instruments. The chemical shifts (δ) are reported in ppm relative to the TMS as an internal standard and J values are given in Hz. ^{13}C NMR spectra were recorded at 62.5 Hz. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. The elemental analysis was performed using Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel polygram SIL G/UV 254 plates. The catalyst was prepared according to the literature.²⁹

Preparation of cyanamides

The cyanamides were prepared according to the literature.¹⁷

General procedure for the hydration of cyanamides using acetaldoxime and nano cerium oxide as a reusable heterogeneous catalyst

To a 25 mL round-bottom flask equipped with magnetic stirrer were added cyanamide (1.0 mmol), acetaldoxime (2.0 mmol), nano cerium oxide²⁹ (5.0 mol %) and EtOH (5 mL). The mixture was heated to reflux under nitrogen atmosphere for 2 h. After cooling to room temperature, the solid was filtered, washed with EtOH and the filtrate evaporated. The filtered catalyst can be recycled after washing with CH_2Cl_2 and drying for 2 h. The crude product was purified by column chromatography. All the isolated compounds were characterized by mp, IR, ^1H NMR, ^{13}C NMR and elemental analysis. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature.³¹⁻³⁴

Spectral data of some compounds

N-(3-Bromophenyl)urea (Table 2, entry 5):

M.p. 166-168 °C; FT-IR (KBr, cm^{-1}) 3375, 3333, 3189, 1679, 1578, 1476, 1410, 1091, 861, 777, 674, 599; ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ_{H} = 8.74 (s, 1H), 7.83 (s, 1H), 7.23-7.15 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (62.5 MHz, $\text{DMSO}-d_6$) δ_{C} = 156.2, 142.7, 131.0, 123.0, 120.4, 120.2, 116.8; Anal. Calcd for $\text{C}_7\text{H}_7\text{N}_2\text{OBr}$: C, 39.10; H, 3.28; N, 37.16. Found: C, 39.20; H, 3.34; N, 37.26.

N-(1-Naphthyl)urea (Table 2, entry 8):

M.p. 220-222 °C; FT-IR (KBr, cm^{-1}) 3444, 33055, 3206, 3052, 2922, 1651, 1608, 1555, 1530, 1505, 1360, 1335, 1278, 1101, 785, 772, 608, 530; ^1H NMR (250 MHz, $\text{DMSO-}d_6$) δ_{H} = 8.70 (s, 1H), 8.17 (s, 1H), 8.00 (d, J = 7.3 Hz, 1H), 7.85 (s, 1H), 7.73-7.37 (m, 4H), 6.22 (s, 2H); ^{13}C NMR (62.5 MHz, $\text{DMSO-}d_6$) δ_{C} = 157.1, 135.9, 134.5, 128.9, 126.6, 126.4, 126.0, 122.7, 122.3, 117.5; Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.82; H, 5.34; N, 14.91.

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