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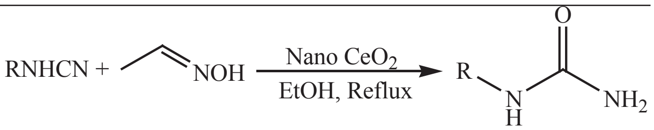
A new method for the synthesis of *N*-monosubstituted ureas has been developed by the reaction of cyanamides with acetaldoxime in the presence of nano cerium oxide as an efficient and recyclable catalyst.

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

N-Monosubstituted ureas have potential medical and agricultural applications.[1,2] Several methods for their preparation have been reported, but new synthetic approaches to 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 CO_2 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-catalysed 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 efficient reactants in the organic synthesis.[11–19] Among currently available synthetic routes to *N*-monosubstituted ureas, the most widely used is based on the hydration of cyanamides.[8,9] This involves the treatment of cyanamides with corrosive acids or bases. Consequently, the development of an efficient and versatile method for the hydration of cyanamides to *N*-monosubstituted ureas is an active on-going research area.

Recently there has been interest in various chemical transformations using heterogeneous catalysis,[20–25] involving metal nanoparticles 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 CO_2 fixation and transalkylation and in organic synthesis has recently been examined because of 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 CeO_2 an efficient, inexpensive, and environmentally benign heterogeneous catalyst.[29]



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

In continuation of our studies on the application of heterogeneous catalysts,[30] we report a new method for the preparation of *N*-monosubstituted ureas *via* hydration of cyanamides with acetaldoxime in the presence of nano cerium oxide[29] as a heterogeneous catalyst (Scheme 1).

Results and discussion

The CeO_2 nano particles were prepared according to literature.[29] Nagarkar and co-workers studied the characterisation 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 proposal and to find the optimum conditions, we carried out the reaction of 3-bromophenylcyanamide with acetaldoxime in the presence of various solvents and catalysts

Table 1 Optimisation 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_3CN	Reflux	2	73
10	CeO_2 (nano) (5)	2	Toluene	Reflux	2	77
11	CeO_2 (nano) (5)	2	EtOH	RT	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

[a]Yields are after work-up.

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Table 2 Hydration reaction of various cyanamides using acetaldoxime in the presence of CeO_2 nano under reflux conditions[a]

Entry	Substrate	Product	Yield/%[b]	M.p./°C	Ref.
1	C_6H_5NHCN	$C_6H_5NHCONH_2$	85	143–145	31
2	*p*-$OMeC_6H_4NHCN$	*p*-$OMeC_6H_4NHCONH_2$	87, 86[c]	167–169	31
3	*p*-MeC_6H_4NHCN	*p*-$MeC_6H_4NHCONH_2$	89	181–182	33
4	*o*-MeC_6H_4NHCN	*o*-$MeC_6H_4NHCONH_2$	87	195–197	32
5	*m*-BrC_6H_4NHCN	*m*-$BrC_6H_4NHCONH_2$	91	166–168	This work
6	*p*-ClC_6H_4NHCN	*p*-$ClC_6H_4NHCONH_2$	87	205–208	31
7	*p*-$NO_2C_6H_4NHCN$	*p*-$NO_2C_6H_4NHCONH_2$	84	237–239	34
8	1-$C_{10}H_7NHCN$	1-$C_{10}H_7NHCONH_2$	86	220–222	This work
9	$C_6H_5CH_2NHCN$	$C_6H_5CH_2NHCONH_2$	84	149–151	33
10	*p*-$OMeC_6H_5CH_2NHCN$	*p*-$OMeC_6H_5CH_2NHCONH_2$	85	111–112	31
11	*p*-$MeC_6H_5CH_2NHCN$	*p*-$MeC_6H_5CH_2NHCONH_2$	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, 2 h.
[b] Yields are after work-up.
[c] Yield after the third cycle.

under various temperature conditions. Several organic solvents such as toluene, ethanol, ethyl acetate and acetonitrile were examined. According to the data shown 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, nano CeO_2 acted as the most effective (Table 1, entry 7). The ratio of acetaldoxime to cyanamide was chosen to be 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), nano CeO_2 (5.0 mol%) and ethanol as solvent) for hydration of different cyanamides under thermal conditions and the results are shown in Table 2.

To study the effects of the nature of the substituents on the benzene ring of the cyanamides, various *N*-monosubstituted ureas were synthesised from different arylcyanamides containing both electron-releasing and electron-withdrawing groups using acetaldoxime and nano CeO_2 in ethanol. The reactions proceeded with 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 nano CeO_2 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.

In a typical experiment, after the reaction was completed, the nano CeO_2 catalyst was isolated from the reaction mixture by centrifugation in the work-up stage. We found that nano CeO_2 can be reused several times without loss of activity, by simply filtering the catalyst, washing it with dichloromethane, drying and immediately reusing (Table 2, entry 2).

The simplicity, together with the use of an inexpensive, non-toxic and environmentally benign catalyst under thermal conditions is remarkable feature of this procedure. The products were characterised by IR, ^1H NMR and ^{13}C NMR spectroscopy and from their melting points. The structure of the *N*-monosubstituted ureas was in agreement with their IR and ^1H NMR spectra. *N*-Monosubstituted ureas contain a NH_2 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, the CN absorption had disappeared.

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

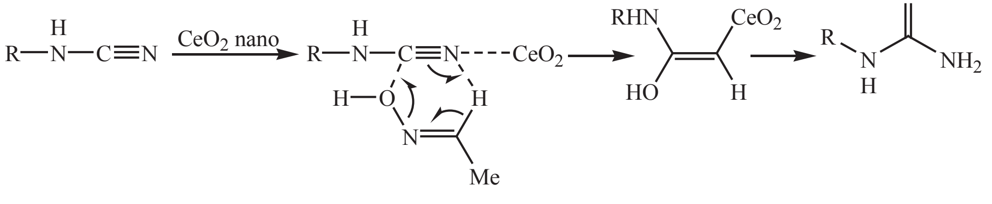
All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterised by comparison of their physical and spectral data with authentic samples. The NMR spectra were recorded in DMSO. ^1H NMR spectra were recorded on a Bruker Avance 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. Elemental analysis was performed using Heraeus CHN-O-Rapid analyser. TLC was performed on silica gel polygram SIL G/UV 254 plates. The catalyst was prepared according to the literature.[29]

Synthesis of cyanamides

The cyanamides were prepared according to the literature.[17]

Hydration of cyanamides using acetaldoxime and nano cerium oxide as a reusable heterogeneous catalyst; general procedure

Cyanamide (1.0 mmol), acetaldoxime (2.0 mmol), nano cerium oxide[29] (5.0 mol%) and EtOH (5 mL) were added to a 25 mL round-bottom flask equipped with magnetic stirrer. The mixture was heated



Scheme 2 Proposed mechanism for the hydration of cyanamides.

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to reflux under a 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 characterised by m.p., IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The physical data (m.p., IR, NMR) of known compounds were found to be identical with those reported in the literature.[31–34]

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; ^{1}H NMR (250 MHz, DMSO-d_6) $\delta_H = 8.74$ (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, DMSO-d_6) $\delta_C = 156.2$, 142.7, 131.0, 123.0, 120.4, 120.2, 116.8; Anal. Calcd for $C_7H_7N_2OBr$: 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; ^{1}H NMR (250 MHz, DMSO-d_6) $\delta_H = 8.70$ (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, DMSO-d_6) $\delta_C = 157.1$, 135.9, 134.5, 128.9, 126.6, 126.4, 126.0, 122.7, 122.3, 117.5; Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.82; H, 5.34; N, 14.91%.

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