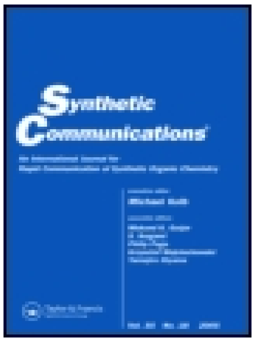

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Catalyst-Free Synthesis of Amines from Cyclic Ketones and Formamides in Superheated Water

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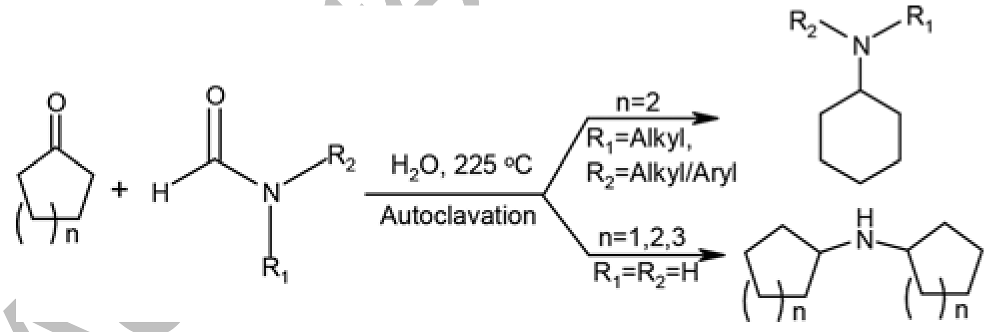
Abstract

A novel and environmentally benign protocol for the synthesis of amines from cyclic ketones and formamides is demonstrated. The reaction proceeds under catalyst-free and superheated water conditions and yields range from low to excellent.

Graphical Abstract:



KEYWORDS: Amine; catalyst-free; formamides; superheated water

INTRODUCTION

The research of alternative, environmentally more acceptable processes for the manufacture of chemicals is of fundamental importance.[1] In recent years, the impact of chemicals on the environment and human health become a concern. Consequently, there is a considerable current research activities in the development of sustainable chemical processes and products by using the principles of green chemistry.[2] However, the application of green chemistry in industry is perhaps the main challenge for researchers, who are often limited to academic developments.

Water exhibits special properties as compared to commonly employed organic solvents. Reactions using this solvent have attracted great attention from a synthetic point of view because water is environmentally friendly and safe, and the problems of pollution that arise with organic solvents can be avoided.[3] This purpose renewed a long time interest for water as a reaction medium for organic synthesis.

Over the past decade the use of superheated water has emerged as an efficient, clean and economic media for organic synthesis because of its unique properties.[4-6] Depending on the conditions of temperature and pressure, SHW supports either free radical or polar and ionic reactions. This means that SHW is an adjustable solvent, reactant and catalyst for various organic transformation such as hydrolysis,[7,8] condensations,[9] rearrangements,[10] alkylations,[11] reductions[12,13] and Heck coupling reactions.[14] Materials such as zeolites,[15] metal organic frameworks[16] and mesoporous oxides[17] are often synthesized under SHW conditions.

The C-N bond formation reaction is an important transformation in modern synthetic chemistry.[18] Amines are ubiquitous functionalities in current drugs, pharmaceutical intermediates and agrochemicals.[19] The reductive amination of carbonyl compounds with ammonia is one of the most efficient and direct route for the preparation of amines.[20] Catalytic hydrogenation and metal hydride reduction are the two most commonly used direct reductive amination methods. The first method is catalytic hydrogenation with platinum, palladium, or nickel catalysts.[21] Catalytic hydrogenation has limited use with compounds containing carbon-carbon multiple bonds and in the presence of reducible functional groups such as nitro, cyano and furfuryl groups. The catalysts are expensive and may be inhibited by compounds containing divalent sulfur. The second method utilizes hydride reducing agents, particularly sodium cyanoborohydride ($NaBH_3CN$) for reduction.[22] $NaBH_3CN$ is highly toxic and produces toxic by-products, such as HCN and NaCN upon workup.

Owing to the limitations of the above-mentioned approaches and the widespread interest in amine compounds, still there is a need for the development of a simple, efficient and green protocol for the synthesis of amines. From the green chemistry point of view, a non-catalytic process is very significant and alternative for synthetic organic chemistry.

Herein, we describe a novel and environmentally benign approach for the synthesis of higher amines by reductive amination of ketones using *in situ* generated amines by thermal decomposition of formamides in superheated water without any catalyst (Scheme 1).

RESULTS AND DISCUSSION

Initially, we investigated the suitable reaction conditions for the reductive amination of cyclohexanone (**1a**) with formamide (**2a**) to the corresponding dicyclohexylamine (**3a**). As shown in Table 1, a variety of parameters such as effect of amount of water (solvent), molar ratio of reactants, reaction temperature and time were investigated to achieve optimal conditions. The results revealed that a 1:1.5 mole ratio of cyclohexanone and formamide in 300 mL of water at 225 ^{o}C in 3 h was found to be optimum to achieve highest yield of dicyclohexylamine (**3a**) (Table 1, entry 7).

After optimizing the reaction conditions, we explored the scope of this superheated water system with a variety of *N*-substituted formamides and ketones and the results are summarized in Table 2. The *N*-substituted formamides including *N*,*N*-dimethylformamide, *N*-methyl-*N*- phenylformamide, *N*-formylpiperidine and 4-formylmorpholine reacted with cyclohexanone smoothly to give the corresponding tertiary amines **3b, 3c, 3d** and **3e** in 45%, 49%, 71% and 81% yields, respectively (Table 2, entries 1-5). The reductive amination was widely used for the synthesis of secondary amines in which various types of homogeneous and heterogeneous catalysts have been employed. However, only few reports are available for the synthesis of tertiary amines through reductive amination.[23]

Next, we investigated the efficiency of this method by reacting a variety of ketones with formamide under similar reaction conditions (Table 2, entries 6-10). Cyclic ketones such as cyclopentanone and cycloheptanone provided the corresponding secondary amines **3f** and **3g** in 59% and 34% yields, respectively (Table 2, entries 6-7). In the case of aromatic ketones, acetophenone furnished the corresponding olefin in 38% yield, along with alcohol (24% yield) (Table 2, entry 8), while tetralone afforded the respective olefin in 30% yield (Table 2, entry 9). This is possibly due to the reduction of ketones to alcohols followed by dehydration (to give olefins) instead of reductive amination. However, the reaction of aliphatic ketone i.e., 2-nonanone with formamide was not quite successful and only starting material was recovered (Table 2, entry 10).

A plausible reaction mechanism for the formation of amines is depicted in Scheme 2. It is assumed that, hydrolysis of formamide in presence of water to provide the formic acid and ammonia. Formic acid plays multiple roles in this reaction (as a reducing agent and acid catalyst). The *in situ* generated ammonia reacts with ketone in presence of formic acid to give the imine, which subsequently reduced by formic acid to afford the corresponding amine. The resulting amine reacts with another ketone in presence of formic acid to give the corresponding imine and then it undergoes reduction by formic acid to form the corresponding secondary amine (Path A). In the case of *N*-substituted formamides, amides hydrolyzed to form formic acid and corresponding amine. Then, amine reacts with ketone in presence of formic acid to provide corresponding iminium ion. Finally, formic acid promotes the reduction of iminium ion to the corresponding amine product (Path B).

CONCLUSIONS

An efficient and green method has been developed for the synthesis of amines from cyclic ketones and formamides without any catalyst under superheated water conditions. Notable advantages offered by this strategy are catalyst-free and superheated water conditions, high atom economy (only H_2O, CO_2 and H_2 are by-products), environmentally benign and simple work-up procedure, which make it an attractive and useful alternative to the existing methods.

EXPERIMENTAL

All chemicals used were reagent grade and used as received without further purification. ^{1}H NMR spectra were recorded at 300, 400 and 500 MHz and ^{13}C NMR spectra 75 MHz in $CDCl_3$ or DMSO-D_6. The chemical shifts (δ) are reported in ppm units relative to TMS as an internal standard for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR spectra. Coupling constants (*J*) are reported in hertz (Hz) and multiplicities are indicated as follows: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet). Column chromatography was carried out using silica gel (100-200 mesh).

General Procedure For The Synthesis Of Amines From Cyclic Ketones

The reactions were carried out in Parr autoclave (600 ml capacity, 20 cm height and 6.3 cm inner diameter) at 225 ^{o}C temperature and 30 bar autogenous pressure under constant stirring (50–60 revolutions per minute). The reactants cyclic ketone (0.1 mole), formamide (0.15 mole) and water (300 ml) were loaded in an autoclave at room temperature. Then, the autoclave was sealed and the temperature was increased to 225 °C under stirring. Agitation was maintained for required time (3-6 h). After completion of the reaction, the autoclave was cooled to room temperature slowly. When the atmospheric pressure was reached, the autoclave was opened and the reaction mixture was extracted with DCM. Finally, the combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude was further purified by column chromatography using silica gel (100-200 mesh) afforded the pure products. All the products were identified on the basis of NMR data and quantified by GC using EB-5 column.

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SUPPLEMENTARY MATERIAL

Experimental details and ^{1}H and ^{13}C NMR spectral data for this article can be accessed on the publisher’s website.

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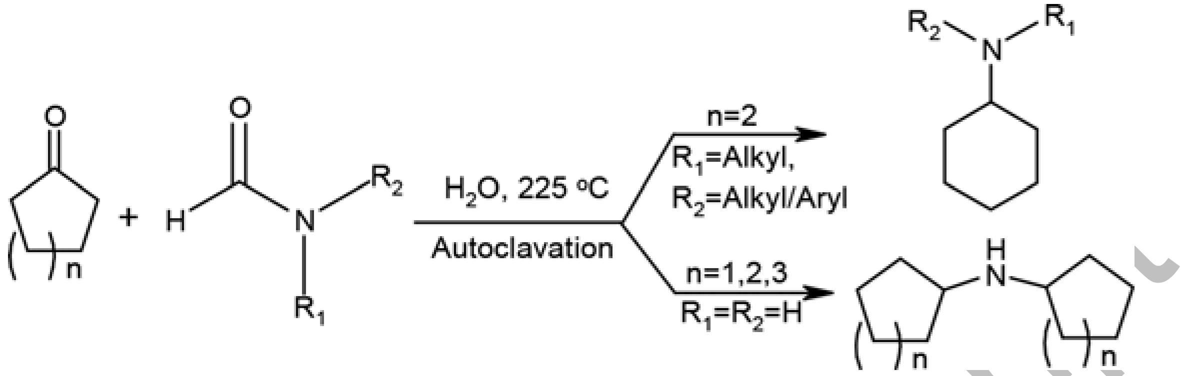
Scheme 1. Synthesis of amines from cyclic ketones and formamides.



Scheme 2. Plausible reaction mechanism.

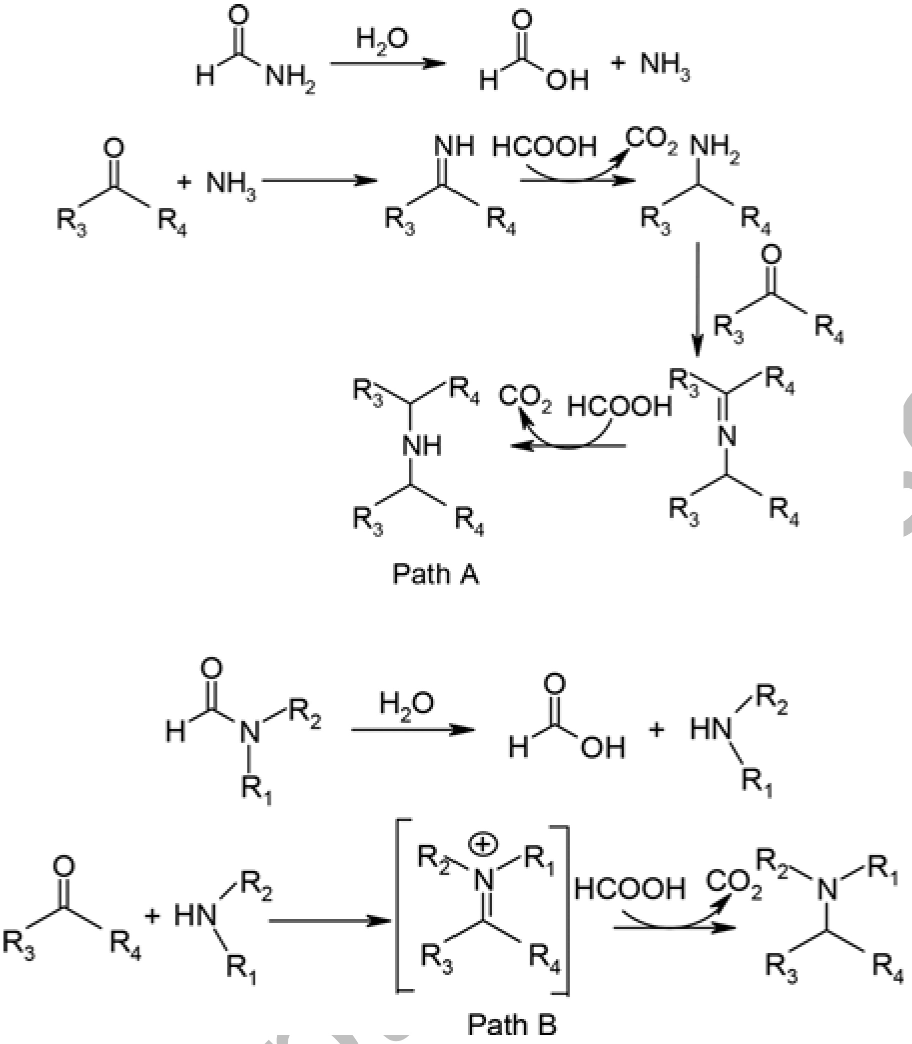
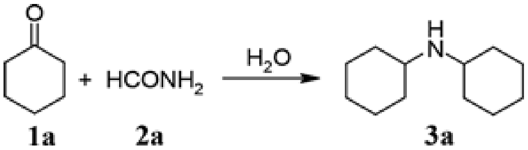


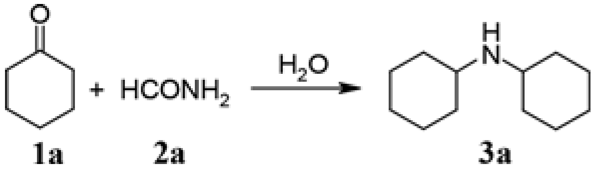
Table 1. Optimization of reaction conditions

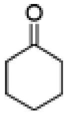
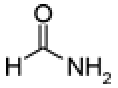
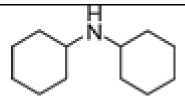
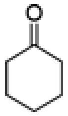
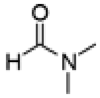
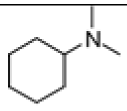
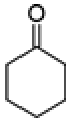
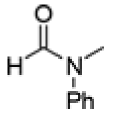
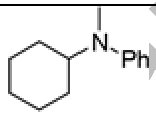
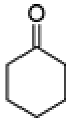
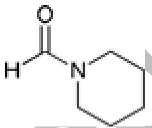
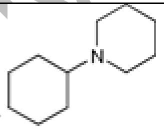
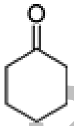
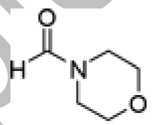
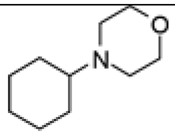
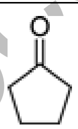
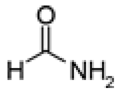
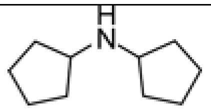
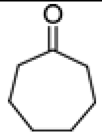
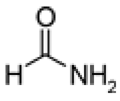
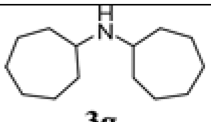


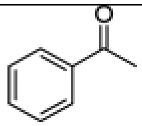
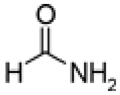
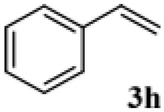
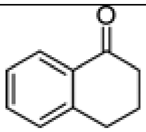
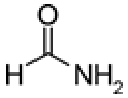
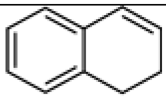
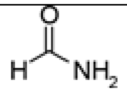
Entry	H_2O (ml)	Molar ratio (**1a**:**2a**)	Time (h)	Temperature (^{o}C)	Yield (%)^{a}
1	220	1:1	3	225	62
2	250	1:1	3	225	64
3	300	1:1	3	225	70
4	350	1:1	3	225	54
5	300	1:0.25	3	225	05
6	300	1:0.5	3	225	20
7	**300**	**1:1.5**	**3**	**225**	**88**
8	300	1:2	3	225	85
9	300	1:1.5	3	150	-
10	300	1:1.5	3	175	-
11	300	1:1.5	3	200	20
12	300	1:1.5	3	250	70
13	300	1:1.5	1	225	57
14	300	1:1.5	2	225	71
15	300	1:1.5	4	225	80
16	300	1:1.5	5	225	76
17	300	1:1.5	6	225	72

[a] The products were characterized by NMR and quantified by GC.

Table 2. Synthesis of amines from various ketones and formamides[a]



Entry	Ketone	Formamide	Product	Yield (%)[b]
1			 **3a**	88
2			 **3b**	45
3			 **3c**	49
4			 **3d**	71
5			 **3e**	81
6			 **3f**	59[c]
7			 **3g**	34[c]

8			 **3h**	38 (24)[d]
9			 **3i**	30
10			-	-

[a] Ketone (0.1 mole), Formamide (0.15 mole), H_2O (300 mL), 225 °C, 30 bar (autogenous pressure), 3 h.

[b] The products were characterized by NMR and quantified by GC.

[c] Reaction time 6 h.

[d] 1-Phenylethanol.