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Microwave-assisted preparation of cyclic ureas from diamines in the presence of ZnO

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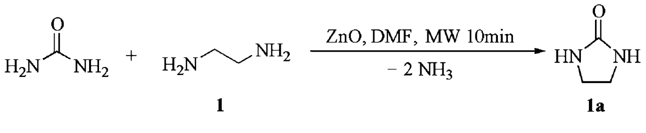
Abstract—A microwave-assisted facile method for the preparation of various ureas, cyclic ureas, and urethanes has been developed that affords nearly quantitative yield of products at 120 °C (150 W), 71 kPa within 10 min using ZnO as a catalyst. The enhanced selectivity in this reaction is attributed to the deployment of ZnO whose absence results in poor yield and the generation of byproducts.

Cyclic ureas have recently attracted much attention due to their manifold applications as intermediates for biologically active molecules, such as the HIV protease inhibitors, DMP 323 and DMP 450,[1] fine chemicals, pharmaceuticals, cosmetics, and pesticides.[2] The conventional methods for preparing cyclic ureas such as imidazolidine-2-one involve the cyclization reaction of 1,2-diamines with phosgene[3] or oxidative carbonylation of diamines.[4] However, the toxicity of phosgene, the formation of polymerized materials and hydrogen chloride as a byproduct, and possible explosion risks arising from the mixture of carbon monoxide and oxygen in the oxidative carbonylation method render these processes cumbersome with respect to both industrial and environmental viewpoints. Consequently, there have been efforts to prepare cyclic ureas via ecofriendly protocols.[5] In yet another approach, the synthesis was accomplished by the introduction of urea as a carbonyl source under dynamic evacuation.[6] However, this reaction suffers from low selectivity and severe reaction conditions such as high temperatures (150 °C) and relatively longer reaction time (3 h) due to the absence of a catalyst.

Recently, there has been considerable interest in the microwave (MW) irradiation protocol for rapid synthesis of a variety of organic compounds due to the selective absorption of microwave energy by polar molecules.[7] Accordingly, with the proper choice of a catalyst such as ZnO, the cyclization reaction could be accomplished in high yield and selectivity using MW energy in the presence of polar solvent such as DMF (Scheme 1).

Herein, we report the facile synthesis of various cyclic ureas from diamines and industrial commodity chemical, urea, using MW approach that proceeds rapidly in the presence of ZnO.

Microwave-assisted coupling reactions of urea with ethylenediamine **1** were carried out in the presence of various metal salts and oxides to identify the best catalyst. The reactions were performed at 120 °C, 100–150 W of MW power, and at a reduced pressure of 71 kPa in DMF for 10 min and the results are summarized in Table 1.[8] In the absence of a catalyst, the yield of imidazolidine-2-one **1a** was only 44% and a considerable amount of 2-oxo-1-imidazolidinecarboxamide **1b** was formed (39%) as a byproduct (entry 1). The conventional heating (120 °C, 71 kPa, 1 h) afforded only 28% yield of **1a** and 12% yield of **1b**, respectively, in the



Scheme 1. Synthesis of imidazolidine-2-one **1a**.

Keywords: Microwave-assisted synthesis; Diamine; Cyclic urea; Urethane; ZnO.

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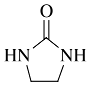
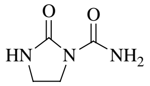
Table 1. Screening of catalysts for the formation of imidazolidine-2-one under MW irradiation[a]

Entry	Catalyst	Product yield (%)[b]	
		 **1a**	 **1b**
1	—	44	39
2[c]	ZnO	28	12
3	ZnO	100 (95)[d]	Trace
4	$ZnBr_2$	88	7
5	CuCl	37	4
6	Cu_2O	82	17
7	TiO_2	88 (82)[d]	12
8	$(n\mathrm{Bu})_2SnO$	66	22
9	NaY[e]	45	5

[a] Conditions: urea 0.6g (10mmol), ethylenediamine 0.6g (10mmol), DMF 1g, catalyst 7.3mol%, $T = 120\,°C$, $P = 71\,kPa$, $t = 10\,min$, MW power = 100–150W.

[b] Yields obtained from GC–MS.

[c] Conventional heating condition ($T = 120\,°C$, $P = 71\,kPa$, $t = 1\,h$).

[d] Isolated yield.

[e] NaY = Sodium Y zeolite.

presence of ZnO (entry 2). However, to our surprise, reaction conducted under MW irradiation conditions with ZnO as a catalyst delivered **1a** in nearly quantitative yield for the coupling reaction within 10min with negligible amount of **1b**. This is in contrast to catalysts that gave lower yield of **1a**. Among the Lewis acid catalysts, $ZnBr_2$ exhibited relatively high activity (88% yield), whereas metal oxides containing some basic site showed moderate yield of **1a** but led to the formation of considerable amount of **1b**.

Figure 1 shows the effects of temperature and amount of ZnO catalyst loading on the yield of cyclization reaction of ethylenediamine and urea under MW irradiation in the range 100–120°C and 1.2–11.1mol%, respectively. The microwave power was varied in the range 100–150W depending on the temperature. The yields of **1a** increased with increasing temperature and catalyst loading, and the yields obtained at 120°C are significantly higher than that of 100°C. The optimized reaction conditions appear to be $T = 120\,°C$ (MW power = 150W), 71kPa, 7.3mol% of catalyst, 10min for the reaction time.

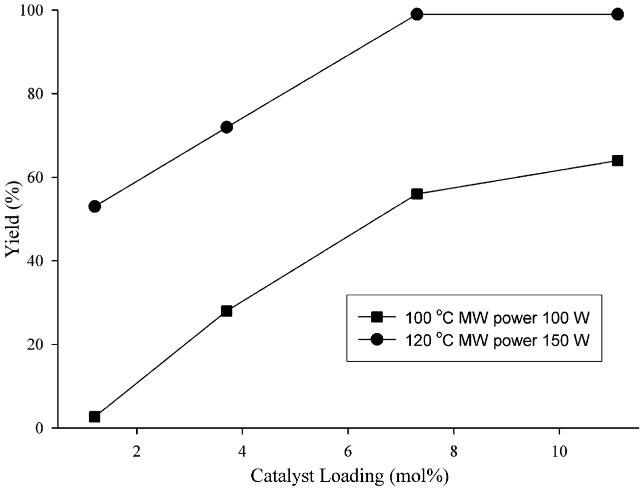
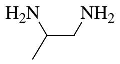
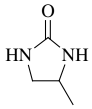
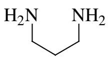
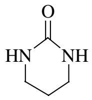
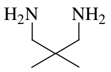
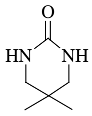
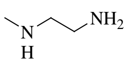
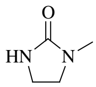
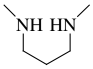
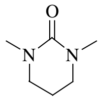


Figure 1. Effect of temperature and catalyst loading on the cyclization reaction.

The results of MW-assisted cyclization reaction of various aliphatic diamines are shown in Table 2. Both the 1,2-propanediamine **2** and 1,3-propanediamine **3** reacted with urea to give corresponding cyclic urea such as 4-methylimidazolidine-2-one **2a** and tetrahydro-2-pyrimidinone **3a** in high yields, respectively (Table 2, entries 1 and 2). As mentioned earlier, in the absence of ZnO, poor yield (46%) of **2a** was obtained, suggesting an important role of ZnO in preventing the formation of carboxamide byproduct. 2,2-Dimethyl-1,3-propanediamine **4** afforded relatively lower yield than that from **2** and **3** probably due to the steric effect of dimethyl group (entry 3). It is worth noting that asymmetric cyclic urea like *N*-methylimidazolidine-2-one **5a** was obtained in high yields (99%) from *N*-methylethylenediamine **5** (entry 4). In contrast, the formation of **6a** did not materialize at all in the case of related secondary amine, *N*,*N*′-dimethyl-1,3-propanediamine (entry 5).

Based on the generally accepted reaction mechanism for coupling reaction as advanced by Butler and Hussain,[9] liberated ammonia originates from the urea component and the intermediacy of an isocyanate is involved. Thus, the reaction mechanism for the formation of **5a** from **5** can be depicted as shown in Scheme 2. The formation of isocyanate intermediate **5″** from **5′** is the key step for the production of *N*-methylimidazolidine-2-one **5a** by the liberation of another ammonia (NH_3) molecule

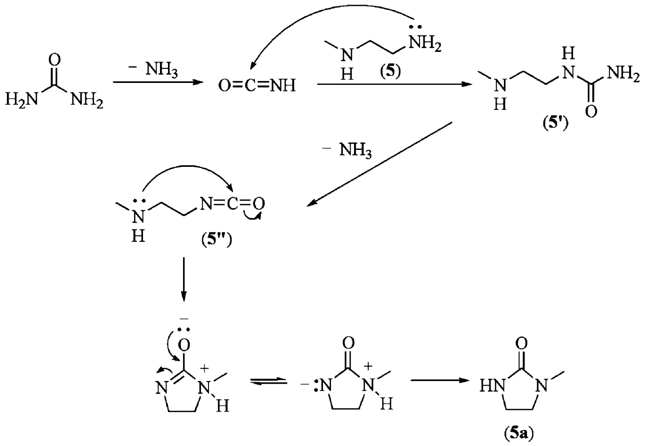
Table 2. Cyclization reactions with various aliphatic diamines[a]

Entry	Diamines	Product yield (%)[b]	
1	 **2**	 **2a**	95 (46)[c]
2	 **3**	 **3a**	99
3	 **4**	 **4a**	68
4	 **5**	 **5a**	99
5	 **6**	 **6a**	0

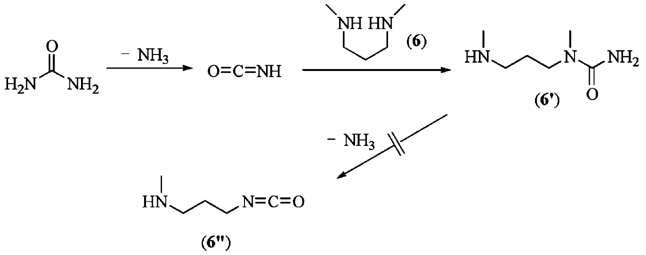
[a] Conditions: urea 0.6g (10mmol), diamine 10mmol, DMF 1g, ZnO 7.3mol%, $T = 120\,°C$, $P = 71\,kPa$, $t = 10\,min$, MW power = 150W.

[b] Yields obtained from GC–MS.

[c] Without catalyst.



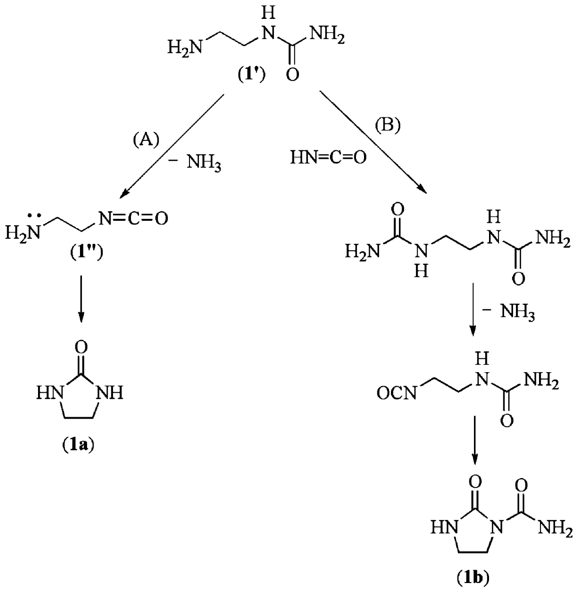
Scheme 2. Reaction mechanism for the formation of **5a**.



Scheme 3. Alternative pathway preventing the formation of **6a**.

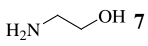
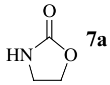
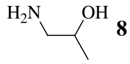
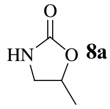
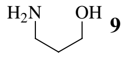
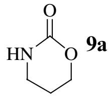
from urea **5′**. However, the alkylated nitrogen in the $-N(CH_3)(C{=}O)NH_2$ of **6′** prevents the expulsion of ammonia moiety and subsequent generation of the isocyanate intermediate **6″** from **6′** as shown in Scheme 3, thus explaining the failure of the formation of **6a** in the coupling reaction (Table 2, entry 5).[10]

The role of ZnO for improving the selectivities to cyclic ureas for the coupling reactions is not clear at this point. However, based on the proposed mechanism,[6] ZnO might play a role in facilitating the liberation of ammonia efficiently from **1′** (path A) rather than allowing the reaction of **1′** with isocyanate ($HN{=}C{=}O$) to give **1b** (path B) as shown in Scheme 4. This may be explained by the fact that the acidic proton in the $-NH(C{=}O)NH_2$ of **1′** is abstracted more readily by moderately basic ZnO than other catalysts or catalyst-free system, thus avoiding the generation of byproduct.



Scheme 4. Reaction pathways for the formation of **1a** and **1b**.

Table 3. The coupling reactions of aliphatic amino alcohols and urea for the formation of cyclic urethanes[a]

Entry	Amino alcohols	Product yield (%)[b]	
1			100
2			98
3			90

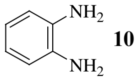
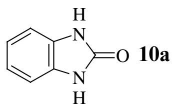
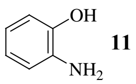
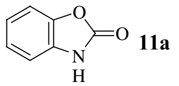
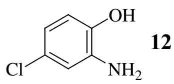
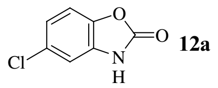
[a] Conditions: urea 0.6g (10mmol), amino alcohols 10mmol, DMF 1g, ZnO 7.3mol%, $T = 120\,°C$, $P = 71\,kPa$, $t = 10\,min$, MW power = 150W.

[b] Yields obtained from GC–MS.

The MW-assisted coupling reaction was extended to aliphatic amino alcohols under same conditions and catalyst (Table 3). The reaction of 2-aminoethanol **7** and 1-aminopropan-2-ol **8** with urea afforded nearly quantitative yield of corresponding cyclic urethanes such as oxazolidin-2-one **7a** and 5-methyloxazolidin-2-one **8a**, respectively.

To broaden the scope of the cyclization reaction, various aromatic compounds bearing diamine and/or amino alcohol functionalities were examined for the formation of corresponding urea and urethanes (Table 4). *o*-Phenylenediamine **10**, being more reactive, afforded 1,3-dihydrobenzoimidazole-2-one **10a** in almost quantitative yield within 10min, whereas 2-aminophenol **11**

Table 4. The coupling reactions of aromatic diamines and urea for the formation of aromatic ureas[a]

Entry	Aromatic diamines	Product yield (%)[b]	
1			98
2			70
3			75

[a] Conditions: urea 0.6g (10mmol), diamine 10mmol, DMF 1g, ZnO 7.3mol%, $T = 120\,°C$, $P = 71\,kPa$, $t = 10\,min$, MW power = 150W.

[b] Yields obtained from GC–MS.

and 2-amino-4-chlorophenol **12** gave the corresponding 2-benzoxazolone derivatives in good yields.

In summary, a MW-assisted protocol for the direct synthesis of cyclic urea has been developed that proceeds expeditiously in the presence of ZnO. The reaction is not only accelerated upon exposure to MW irradiation thus shortening its reaction time but also eliminates the formation of byproducts when compared to the traditional methods involving conventional heating.

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8. The representative experimental procedure is as follows: A mixture of urea (0.6 g, 10 mmol), ethylenediamine (0.6 g, 10 mmol), ZnO (0.06 g, 0.73 mmol), and DMF (1 g) was charged in a round-bottom glass flask containing a magnetic stirring bar and fitted with a reflux condenser, which was attached to a water aspirator for generating reduced pressure to remove ammonia. The flask was placed in a CEM Discover Focused Microwave Synthesis System, which is designed to house a round-bottom flask (50 mL) containing a magnetic stirring bar. The flask was subjected to MW irradiation at 120 °C (power 150–250 W) for 10 min. After the reaction is completed, the flask was removed from the MW cavity and cooled to room temperature. The crude reaction mixture was identified by GC–MS qualitative analysis. Quantification of the products was obtained from the peak area ratios of the reactants based on urea and corresponding products. These yields were verified by comparing with the isolated yields obtained in some cases by the following procedure: The reaction mixture was filtered to remove solid ZnO. Adding acetone to the filtrate resulted in the precipitation of imidazolidine-2-one **1a**, followed by filtration and washing with copious acetone afforded pure **1a**. The dried product **1a** was weighed for quantitative analysis and further identified by ^{1}H and ^{13}C NMR in DMSO-d_6.
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10. The isolation of **6′** was unsuccessful due to the formation of oligomerized product during the reaction.