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NOTE

An Improved One-Pot Synthesis of Hexamethyleneimine from ε-Hexanolactam

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A mild and efficient method for the preparation of hexamethyleneimine was achieved *via* a single one-pot chemoselective reduction of amide group in ε-hexanolactam by freshly prepared $Al(BH_4)_3$ in THF. This approach provides a facile shortcut for the synthesis of this type of compounds with excellent yields, short reaction time, mild reaction conditions, environmentally friendly method, simple work-up procedure, low-cost and easy operation.

Keywords: ε-Hexanolactam, ε-Caprolactam, Hexamethyleneimine, Reduction, Synthesis.

It's well known that hexamethyleneimine is an important intermediate in a very wide of chemistry, including pharmacologicals, dyes, textiles and agrochemicals, such as fungicides, herbicides and insecticides. However, the industrial process of synthesize hexamethyleneimine still use the catalytic hydrogenation of ε-hexanolactam, producing a high amount of contaminated catalyst waste[1-3]. Considering the ecological and economical problems associated with waste management in most civilized countries, an alternative environmentally friendly, simple work-up procedure and low-cost synthesis would be attractive research area in both industrial and academia.

Reports are available in the literature related to the various synthetic access to hexamethyleneimine using $LiAlH_4$ and $NaBH_4$ as reducing agent[4,5], but some limitations (long reaction time, stringent regulatory requirement) of this approach are unfavourable for commercial application. In the course of our synthetic studies toward (+)-biotin, we have recently described a chemoselective reduction reaction protocol to obtain the intermediacy of Roche's lactone with the freshly prepared[6,7] $Ca(BH_4)_2$, which is *in situ* prepared from $NaBH_4$ and $CaCl_2$. The significant advantages of this methodology are excellent yields, short reaction time, mild reaction conditions, environmentally friendly method, simple work-up procedure, low-cost and easy operation. As a continuation of our efforts on the efficient synthesis and potential bioactivities of heterocyclic compounds, the promising work of our group came into our specific attention due to the parallels with our ongoing research concerning the chemoselective synthesis of hexamethyleneimine from ε-hexanolactam.

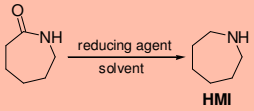
^1H NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz) in $CDCl_3$ using tetramethylsilane (TMS) as internal standards. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. Unless otherwise notes all reactions were conducted in oven dried glassware under inert atmosphere of dried N_2. THF was distilled from sodium/benzophenone, toluene, CH_2Cl_2 from calcium hydride. Chemical reagents were obtained from commercial sources and used as received.

General procedure for the chemoselective reduction of amide group in ε-hexanolactam: Into an ice cold suspension of granulated anhydrous Lewis acid (250 mmol) in anhydrous organic solvent (150 mL) was added $NaBH_4$ (10 g, 260 mmol) under nitrogen atmosphere. After 1 h stirring at 0 °C, the suspension was allowed to warm up to room temperature, ε-hexanolactam (11.3 g, 100 mmol) was then added in one portion into the resulting mixture and the mixture was stirred at refluxing. When analysis (GC-MS) indicated complete consumption of the ε-hexanolactam, cooled the reaction mixture to room temperature and added H_2O (200 mL) into the mixture. The residue was treated with 20 % NaOH to adjust to pH = 12 and the solution was extracted with CH_2Cl_2 (3 × 80 mL). After phase separation, the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was further purified by atmospheric distillation (b.p. 137-140 °C,

lit.[8] 136-137 °C) or vacuum distillation (54-58 °C/40 mmHg) to afford hexamethyleneimine. IR (film): 3310 ν(NH); 2926 ν_{as}(CH); 2857 ν_{s}(CH); 1462 δ(CH); 1075 ν(CN) cm^{-1}; ^{1}H NMR ($CHCl_3$): 1.61 (bs, 8H); 1.83 (s, 1H); 2.82-2.85 (t, J = 5.3 Hz, 4H).

With the above mentioned considerations in mind, we attempted the chemoselective reduction of amide group in ε-hexanolactam with $NaBH_4$ in the presence of anhydrous $CaCl_2$ to evaluate the freshly prepared $Ca(BH_4)_2$ reducing antioxidant power. The reaction proceeded smoothly under stirring at refluxing in Et_2O and the desired product hexamethyleneimine was isolated in 52 % yield (Table-1, entry 1). Thus, the optimization of other reaction conditions (reducing agent, solvent) for this chemoselective synthesis of hexamethyleneimine was also undertaken and the results are illustrated in Table-1. We first investigated the influence of solvent on the isolated yield (Table-1, entries 1-5). It was found that amongst five different solvents examined the aprotic, hydrogen-bond-accepting solvent THF was the most suitable solvent, in which 74 % isolated yield of hexamethyleneimine was obtained (Table-1, entry 2). Having identified the optimized reaction solvent, the effect of the various reducing agent was then studied. As seen from entries 2, 6, 7 in Table-1, a significant increase in the isolated yield and reaction rates occurred upon using the *in situ* prepared $Al(BH_4)_3$ as the reducing agent (Table-1, entry 7).

TABLE-1
OPTIMIZATION OF THE REACTION CONDITIONS
OF THE PREPARATION OF HEXAMETHYLENEIMINE



HMI

Entry	Reducing agent	Solvent	Reaction time[a] (h)	Yield[b] (%)
1	$NaBH_4/CaCl_2$	Et_2O	10	52
2	$NaBH_4/CaCl_2$	THF	9	74
3	$NaBH_4/CaCl_2$	CH_2Cl_2	11	50
4	$NaBH_4/CaCl_2$	MTBE	10	61
5	$NaBH_4/CaCl_2$	Toluene	10	67
6	$NaBH_4/ZnCl_2$	THF	8	81
7	$NaBH_4/AlCl_3$	THF	8	92

[a] Determined by GC-MS analysis of the reaction mixture; [b]Yield of isolated product

In conclusion, we have successfully uncovered an improved synthetic process for the preparation of hexamethyleneimine, which was achieved *via* a single one-pot chemoselective reduction of amide group in ε-hexanolactam by freshly prepared $Al(BH_4)_3$ in THF. This method should be of great value in terms of excellent yields, short reaction time, mild reaction conditions, environmentally friendly method, simple work-up procedure, low-cost and easy operation, which appears to be more compatible with industrial scale and has some advantages over the existing synthesis. Investigation of the others chemical structurally diverse set of amides to extend this methodology is currently under way and the results will be reported in due course.

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REFERENCES

1. Z. Xu and G.P. Jiang, *Chem. Abstr.*, **151**, 248951 (2009).
2. J. Chen, *J. Chem. Ind. Eng.*, **28**, 35 (2007).
3. M. Stein and B. Breit, *Angew. Chem. Int. Ed.*, **52**, 2231 (2013).
4. L. Ruzicka, M. Kobelt, O. Haagier and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).
5. S.R. Wann, P.T. Thorsen and M.M. Kreevoy, *J. Org. Chem.*, **46**, 2579 (1981).
6. J. Huang, F. Xiong and F.E. Chen, *Tetrahedron Asymm.*, **19**, 1436 (2008).
7. F. Xiong, X.X. Chen and F.E. Chen, *Tetrahedron Asymm.*, **21**, 665 (2010).
8. F.F. Blicke and N.J. Doorenbos, *J. Am. Chem. Soc.*, **76**, 2317 (1954).