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Synthesis and Characterization of N-Substitutional Ethylenediamine Derivatives

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N-Substituted and N,N-disubstituted ethylenediamine derivatives were prepared rapidly in aqueous conditions from 30 to 76 % yields, respectively, on a multi-gram scale starting from inexpensive and commercially available starting materials. The steps involved Michael addition, hydrazinolysis and Curtius rearrangements. The highlight of this method lies on its convenience and economy in accessing these intermediates.

Key Words: Substituted ethylenediamine derivatives, Michael addition, Hydrazinolysis, Curtius rearrangements.

INTRODUCTION

N-Substituted ethylenediamine derivatives are important organic intermediates and medicine fragment. For example, 2-(1-imidazol)ethanamine is a fragment of carbamate-appended N-alkylsulfonamides as γ-secretase inhibition[1]. And 2-(1-piperidino)ethylamine is a fragment of chroman derivatives as treatment of central nerve system (CNS) disorders[2]. For this reason some methods for synthesis of these derivatives have been reported, which can be classified into four categories. (1) It was synthesized from amine by reaction of nucleophilic substitution with N-(2-bromoethyl)phthalimide to give N-(2-amine)phthalimide, which was subjected to hydrazinolysis with an overall yield *ca.* 55 %[3-5] and the yield is not satisfactory. (2) It was synthesized from amine and 2-chloroethylamine hydrochloride with an overall yield *ca.* 60 %[6-8]. (3) It was prepared from amine and 2-ethyl-2-oxazoline by ring cleavage and hydrolysis with hydrochloric acid with an overall yield *ca.* 52 %[9,10] and the yield is lower. (4) It was prepared from amine and 2-oxazolidone with an overall yield *ca.* 78 %[11,12], but the 2-oxazolidone is expensive. Also, the costs of 2-chloroethylamine hydrochloride in (2) and 2-ethyl-2-oxazoline in (3) are expensive. Therefore, the development of a cheaper, simpler and more universal method for synthesis of these derivatives is highly desirable. In this work toward an efficient, economical route to N-substituted ethylenediamine derivatives, we became intrigued by the idea of using amines and α,β-unsaturated compounds as initial materials which were subjected to Michael addition, then hydrazinolysis and Curtius rearrangement.

EXPERIMENTAL

Representative experimental procedures are shown for synthesis of compounds **4h**.

3-Piperidinopropionic acid ethyl ester (2h): A mixture of piperidine (5.45 mL, 55 mmol) and ethyl acrylate (5.32 mL, 50 mmol) in water (50 mL) in the presence of $FeCl_3 \cdot 6H_2O$ (1.35 g, 5 mmol) was stirred at room temperature for 12 h[13]. After this time, the crude reaction mixture was extracted with ethyl acetate (3 × 200 mL) and the combined organic layers were washed with diluted hydrochloric acid and dried with Na_2SO_4. The solvent was removed under reduced pressure and yielded residue (8.89 g, 96 %). ^{1}H NMR ($CDCl_3$) δ: 4.13 (q, 2H), 2.66 (t, 2H), 2.50 (t, 2H), 2.40 (t, 4H), 1.57 (m, 4H), 1.42 (m, 2H), 1.26 (t, 3H).

3-(Piperidin-1-yl)propanehydrazide (3h): Hydrazine hydrate (5.83 mL, 120 mmol) was added to a solution of 3-piperidinopropionic acid ethyl ester (7.41 g, 40 mmol) in ethanol (15 mL) at 20 ºC. After stirring for 0.5 h at 20 ºC and refluxing for 5 h. The solvent and excess of hydrazine were removed under vacuum and recycled then reuse. After cooling, it afford **3h** as a lightyellow oil (6.51 g, 95 %). ^{1}H NMR ($CDCl_3$) δ: 8.97 (s, H), 4.15 (s, 2H), 2.86 (t, 2H), 2.44 (m, 6H), 1.57 (m, 4H), 1.42 (m, 2H).

N-(2-Aminoethyl)piperidine (4h): To a water (30 mL) solution of 3-(piperidin-1-yl)propanehydrazide (5.14 g, 30 mmol) and hydrochloric acid (7.47 mL, 90 mmol) was added sodium nitrate (2.69 g, 39 mmol) under 0-5 ºC. The reaction mixture was stirred at 0-5 ºC for 1 h and stirred at 80 ºC for 6 h. The pH was raised to 9 with sodium hydroxide. Then the

mixture was purified by basic alumina (200-300 mesh) and afforded **4h** as a light yellow oil (3.12 g, 81 %). ^{1}H NMR ($CDCl_3$) δ: 2.78 (t, 2H), 2.37 (m, 6H), 1.89 (s, 2H), 1.57 (m, 2H), 1.44 (m, 2H).

RESULTS AND DISCUSSION

As shown in Table-1, we investigated the yields of N-substituted ethylenediamine derivatives *via* various amines and methyl acrylate. It indicated that first step had a significant effect on the yield of product. In general, aliphatic and heterocyclic amines as initial amine gave better results which is 71-77 %. When primary aromatic amines such as aniline and α-naphthylamine were used, even matched with more highly active catalyst $RuCl_3$[14] instead of $FeCl_3$ in first step, but the corresponding product formed only in moderate yield which is 65-70 %. Under the same condition,the reaction of a secondary aromatic amine, diphenylamine, did not work well which is only 30 %. This can be explained by diphenylamine and ethyl acrylate working worst in the first step with yield 42 %. On the other hand, in order to embody green chemistry, we recycled and reused methanol and hydrazine in the second step.

As a next trial,we also attempted to study the yield of N,N-disubstituted ethylenediamine derivatives *via* kinds of primary amines and ethyl acrylate. The results are summarized in Table-2. Primary aliphatic amines as initial amine gave better results. Although, using more highly active catalyst $RuCl_3$[14] instead of $FeCl_3$ in first step, the reaction of a primary aromatic amine did not work well.

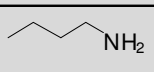
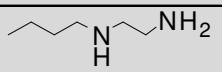
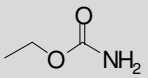
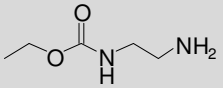
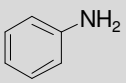
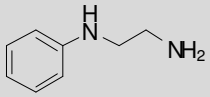
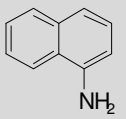
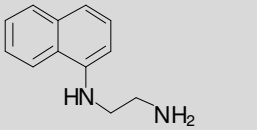
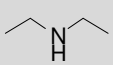
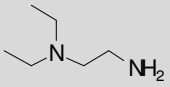
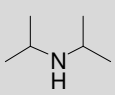
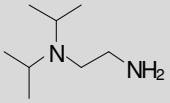
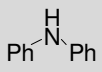
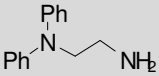
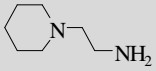
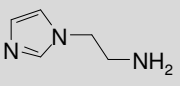
As a final trial, seen from Table-3, we also investigated a variety of α,β-unsaturated compounds undergoing with imidazole in high yield. These β-carbon with electron-withdrawing group, ethyl *cis*-(β-cyano)acrylate and ethyl cinnamate, gave little higher yield. This β-carbon with electron-donating group, ethyl crotonate, gave lower yield. This can be explained by imidazole and E-2-butenoic acid ethyl ester working worse in the first step with yield 89 %.

Conclusion

We have developed an economical and universal three-step sequence, which is first use of amines and α,β-unsaturated compounds as initial materials, for synthesis of N-substituted or N,N-disubstituted ethylenediamine derivatives. Even

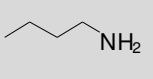
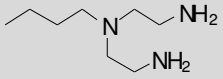
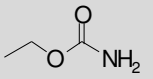
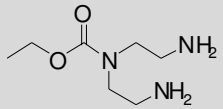
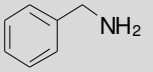
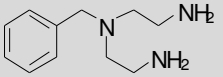
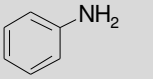
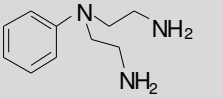
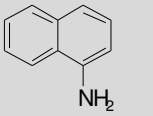
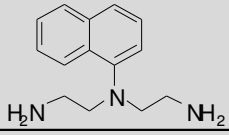
TABLE-1
THREE-STEP SEQUENCE FOR SYNTHESIS OF N-SUBSTITUTED ETHYLENEDIAMINE DERIVATIVES OF SEVERAL REPRESENTATIVE AMINES*

1a-i 2a-i 3a-i 4a-i

Entry	Amine	Product	Step 1 yield (%)	Step 2 yield (%)	Step 3 yield (%)	Total yield (%)
a			95[e]	95	83	75
b			90[e]	95	83	71
c			91[e,f]	94	82	70
d			90[e,f]	93	78	65
e			95	95	83	75
f			95	94	82	73
g			42[e]	92	78	30
h			96	95	81	76
i			95	95	83	75

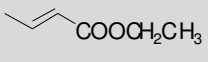
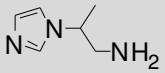
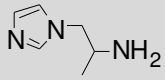
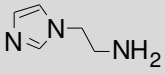
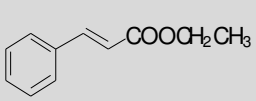
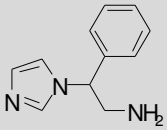
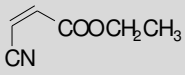
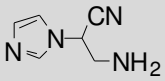
[a]All isolated products were characterized by ^{1}H NMR and HPLC. [b]Reagents and conditions: Amine (1.1 equiv), $FeCl_3 \cdot 6H_2O$ (10 mol %), water, room temperature, 15 h[13]. [c]Reagents and conditions: Hydrazine hydrate (3 equiv), ethanol, reflux, 12 h. [d]Reagents and conditions: Hydrochloric acid (3 equiv), sodium nitrate (1.5 equiv), water, 0-5 ºC, 1 h; 80 ºC, 6 h. [e]Reagents and conditions: Amine (1.5 equiv). [f]PEG 2,000 as solvent, $RuCl_3$ as catalyst[14]. [g]MeOH as solvent.

TABLE-2
THREE-STEP SEQUENCE OF N,N-DISUBSTITUTED ETHYLENEDIAMINE DERIVATIVES OF SEVERAL REPRESENTATIVE AMINES

Entry	Amine	Product	Step 1 yield[a] (%)	Step 2 yield[a] (%)	Step 3 yield[a] (%)	Total yield (%)
1			92	92	72	62
2			85	92	72	57
3			92	92	72	62
4			72[b]	90	72	47
5			72[b,c]	90	70	45

[a]Isolated yield. [b]PEG 2,000 as solvent, $RuCl_3$ as catalyst. [c]MeOH as solvent.

TABLE-3
THREE-STEP SEQUENCE FOR SYNTHESIS OF N-SUBSTITUTED ETHYLENEDIAMINE DERIVATIVES OF SEVERAL REPRESENTATIVE α,β-UNSATURATED COMPOUND

Entry	Amine	Product	Step 1 yield* (%)	Step 2 yield* (%)	Step 3 yield* (%)	Total yield (%)
1			89	95	82	69
2			93	93	82	70
3			95	95	83	75
4			96	95	83	76
5			96	95	83	76

*Isolated yield.

aromatic amines could be used as nucleophiles for step 1. The advantages of this methodology are simple, stable, environmentally benign and less expensive processes, which will contribute to the progress of green chemistry.

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