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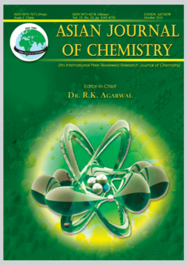

Synthesis and Characterization of 1,3-Diaminoadamantane

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A polycyclic diamine, 1,3-diaminoadamantane has been synthesized from adamantane using trifluoroacetic acid and urea with diphenyl ether as solvent.

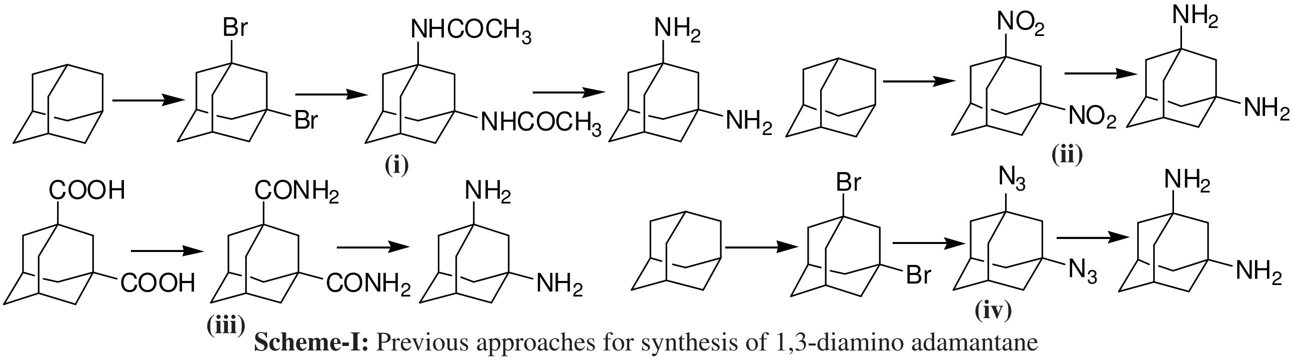
Key Words: 1,3-Diaminoadamantane, 1,3-Dibromoadamantane, Urea, Synthesis.

INTRODUCTION

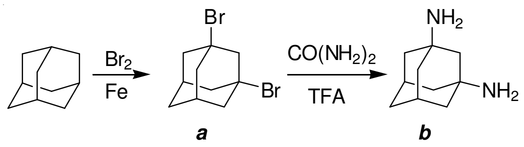
It is well known that amino derivatives of adamantane are widely used in drug industry, polymer synthesis and fine chemicals for their rigid cage hydrocarbon structure[1]. With their psychopharmacological properties, these kinds of compounds are usually used as antidepressants or antiparkinsonic drugs in clinical practice[1-5]. In polymer manufacture, amino derivatives of adamantane can improve the glass transition temperatures and thermal stability of polymer[6-9]. It can be used to synthesize surfactants[10]. But, many amino derivatives of adamantane have not produced in industrial production except amantadine,which had produced by 1-bromoadamantane and urea[11]. By the similar method, synthesis of 1,3-diaminoadamantane from 1,3-dibromoadamantane and urea have not been reported yet. This synthesis was not success because inductive effect of bromine caused C-Br bonds be cleaved hardly and difficult to generate carbonium ion. This phenomena also appears in the synthesis of 1,3-dihydroxy adamantane form 1,3-dibromoadamantane (1-bromoadamantane can be hydrolyze in aqueous sodium oxalate solution[12], but 1,3-dibromoadamantane cann't[13]).

In the case of synthesis 1,3-diaminoadamantane, there were four methods[9,14-16], which was shown in **Scheme-I**. The previous approaches have certain drawbacks (hazardous, expensive, fierce conditions and low yield). Therefore, a convenient method using hazardless and cheap materials with high yield was sought to synthesize 1,3-diaminoadamantane.

Fortunately, acid catalysts and silver salts can make C-Br bonds to cleave easily and acid catalysts make the carbonium ion stably, silver salts were expensive, $AlCl_3$, a Lewis acid, caused the reaction mixture to separate hardly. Shokova *et al.*[17] reported that *N*-adamantylation reaction of carboxylic acid amides was easily reacted in the presence of trifluoroacetic acid (TFA). In this paper, a convenient method for synthesis of 1,3-diaminoadamantane from adamantane was reported. At first, 1,3-dibromoadamantane was synthesized from adamantine and bromine, then, 1,3-diaminoadamantane was synthesized successful in the presence of trifluoroacetic acid from 1,3-dibromoadamantane and urea. The synthetic procedure sketch is shown in **Scheme-II**.



Scheme-I: Previous approaches for synthesis of 1,3-diamino adamantane



Scheme-II Synthesis of 1,3-diaminoadamantane

EXPERIMENTAL

Melting points were collected on a WRS-1B melting-point apparatus and are not corrected. Infrared spectra (KBr disks) were recorded on a Thermo Nicolet 380 using a Ge-KBr beam splitter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus-300 NMR spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz) and chemical shifts are reported in ppm units with referenced to solvent or tetramethylsilane as internal standard. The influence of reaction conditions on the yield of 1,3-diaminoadamantane were investigated.

1,3-Dibromoadamantane (a): 1,3-Dibromoadamantane was prepared according to literature procedures[18] with slight modifications. Liquid bromine was added to the stirred mixture of adamantane, CH_2Cl_2 and iron powder at normal temperature and held at this temperature for 1 day. Then the reaction mixture was treated with aqueous sodium sulfite. The organic layer was concentrated to obtain yellow solid, which was recrystallized form methanol yielding of white solid 1,3-dibromoadamantane(a) (72 %)(m.p. = 112-113 ºC). IR (KBr, ν_{max}, cm^{-1}): 695 (C-Br), 2855, 2930 (CH_2, CH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (m, 2H), 2.26 (m, 2H), 2.30 (m,8H), 2.87 (s, 2H). (2H, s, H-2). C NMR (75 MHz, $CDCl_3$) δ 33.9 (C-6); 35.3 (C-5,7); 47.4 (C-4, 8, 9, 10); 59.3 (C-2); 62.5 (C-1,3). Anal. calcd. for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80. Found: C, 40.89; H, 4.97.

1,3-Diaminoadamantane(b): The target compound 1,3-diaminoadamantane(**b**) was synthesized by amination of 1,3-dibromoadamantane(**a**) with the hazardless and cheap urea using diphenyl ether as the high boiling solvent in the presence of trifluoroacetic acid, which was followed by procedures of acidification, neutralization and extraction to obtain the purified product. The detailed procedure was described as below.

Quantitative dose of 1,3-dibromoadamantane (**a**), trifluoroacetic acid and urea together with diphenyl ether were added into a round flask which was pre-heated to 140 ºC by an oil bath. The mixture was stirred and heated to the desired reaction temperature for setting time. The mixture was cooled and extracted by $CHCl_3$, the organic layer was concentrated by vacuum distillation to obtain white oily solid. Then the white solid was dissolved by 2M HCl and the upper clear solution was separated and basified by NaOH to pH = 11. After that, the solution was extracted by $CHCl_3$, dried over $MgSO_4$ and concentrated by vacuum distillation again to gain the white target compound (**b**). ^{1}H NMR (300 MHz, benzene-d$_6$) δ 1.23 (s, 2H), 1.32 (m, 10H), 1.44 (NH_2, 4H), 1.95 (m, 2H); ^{13}C NMR (75 MHz, benzene-d$_6$) δ 31 (C-5, C-7), 35.38 (C-6),45.3 (C-4, C-8, C-9, C-10), 49.22 (C-1, C-3), 54.7 (C-2). Because 1,3-diaminoadamantane is highly unstable and sensitive to moisture, the elemental analysis results did not agree with the proposed structure[8].

RESULTS AND DISCUSSION

The influences of mole ratio of the reactants, reaction temperatures and reaction times of the reaction on the yield of **b** were investigated, the results were shown in Table-1. It was shown that trifluoroacetic acid was necessary in this procedure. Without trifluoroacetic acid, the target compound was synthesized unsuccessfully. That may be trifluoroacetic acid that facilitated broken the C-Br bonds of 1,3-dibromoadamantane and form tertiary carbocation, the SN1 reaction between amides or amines and the tertiary carbocation took place easily. The reaction for the synthesis of 1,3-diaminoadamantane from 1,3-dibromoadamantane and urea had a high yields of 68.9-71.2 % at 180 ºC for 1.5 h. The optimization of reaction conditions will be further studied later.

TABLE-1
INFLUENCE OF REACTION CONDITION ON YIELD OF 1, 3-DIAMINOADAMANTANE

No.	Urea (mmol)	TFA (mmol)	Temprature (ºC)	Time (h)	Yield **(%)**
1	30	0	160	2.0	0.0
2	30	10	160	1.0	12.5
3	30	20	160	1.0	50.5
4	30	20	180	1.0	68.9
5	30	30	180	1.5	69.6
6	50	30	180	1.5	71.2

1,3-Dibromoadamantane 10 mmol, diphenyl ether 2 g

The result of compared to the previous methods were shown in Table-2. The present method have obvious advantages, at first, it had a high totally yield which was one of the two highest; second, the materials were cheaper; at last, in the present method, only two steps were needed and the reaction condition was mild and convenient, it may be used to produce 1,3-diaminoadamantane in industrial production.

Conclusion

A mild and convenient method for produce 1,3-diaminoadamantane was introduced, in this method, 1,3-

TABLE-2
COMPARED TO THE PREVIOUS METHODS

Method	Main materials	Reaction condition and yields	Total yield[a] (%)
1[9,18]	ADH, Br_2, H_2SO_4, CH_3CN,	1, 15-25 ºC, 24 h, 72 %; 2, refluxed, 24 h, 61 %; 3, 100 ºC, 60 h, 96 %	42.16
2[8,14]	ADH, HNO_3, H_2, Raney Ni	1, 140 ºC and 170 ºC, 10 min, 500 psi, 18 %; 2, 50-60 ºC, 5 h, 50 psi, 65 %	11.7
3[15]	ADH, H_2SO_4, HCOOH, HNO_3, $SOCl_2$, NH_3, Br_2	[b]17-25 ºC, 1.5-2.5 h; 0 ºC, 6h, 52 %; 1, 80 ºC, 3h, 0 ºC, 10 immediately, 89 %; 2, 0 ºC, 1h; 80 ºC, 1 h, 82 %	37.95
4[16]	Br_2, $N_3Si(Me)_3$, H_2, Pd/C	1, rt, 3 h, 75 %; 2, refluxed, 12.5 h, 74 %; 3, rt, 22 h, 93 %	51.62
Present	ADH, Br_2, $CO(NH_2)_2$	1, 15-25 ºC, 24 h, 72 %; 2, 180 ºC, 1.5 h, 71.2 %	51.26

a: yield from adamantane, b: preparation of 1,3-adamantane dicarboxylic acid diaminoadamantane was synthesized from 1,3-dibromoadamantane, trifluoroacetic acid and urea with diphenyl ether as solvent. The influence of reaction conditions on the yield of 1,3-diaminoadamantane were investigated, the yield of the product reached 71.2 % under the optimum condition, the total yield from adamantane was 51.26 %.

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