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One-pot and one-step novel *N*-methylation of 2,6-diaminopyridine

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Abstract

2,6-Diaminopyridine is extensively used as a pharmaceutical intermediate and a hair dye coupler. It is soluble in protic solvents. Primary and secondary amines are *N*-methylated by various methods such as direct alkylation of amines with Hofmann mechanism, but in many of these methods due to over-alkylations, we earn a mixture of amino products. Consequently, they aren't selective in the case of secondary amines preparation. Also, the synthesis of secondary amines is a problematic field in organic chemistry. In this research, 2,6-diaminopyridine *N*-methylated-selictivity was done from reaction with sodium azide and orthoformic ester in low time with good yields.

Keywords: 2,6-Diaminopyridine; *N*-methylation; one-pot reaction; one-step reaction.

Introduction

2,6-Diaminopyridine (2,6-DAP) is formally prepared from pyridine by substitution of the 2 and 6 positions with an amino group under severe conditions [1]. It is a medium-production-volume chemical used as a pharmaceutical intermediate and a hair dye coupler in oxidation/permanent formulations [2]. It is soluble in water, acetone, ethanol, methanol, isopropanol and ethyl acetate [3]. 2,6-Diaminopyridine is used as coupler in oxidation hair dye formulations [4], epoxy curing agent intermediate in the production of polyamides [5] and intermediate in the manufacturing of the analgesic phenazopyridine hydrochloride [6]. Preparation of amines has received more attention in organic chemistry [7]. Secondary amines, due to their physio-

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logical activities, are important pharmacophores in biologically active compounds [8]. Direct *N*-alkylation is, in principle, the most common and straightforward route for secondary amine formation. Treatment of primary amines with alkyl halides is known as the Hofmann alkylation [9]. However, many methods were reported for conversion of primary amines to secondary amines by various reagents in recent years [10-17]. Gaponic et al. in 1985 reported that primary amines were converted to the corresponding 1-substituted tetrazoles in the presence of sodium azid and orthoformic ester under reflux condition [18]. In the present work, we have reported this method to 2,6-diaminopyridine and showed that the reaction of 2,6-DAP with sodium azide and orthoformic ester is a convenient preparative route for the *N*-methylation of pyridine derivatives.

Experimental

The reaction was carried out under dry argon gas to exclude moisture from the system because sodium azide is highly moisture sensitive reagent and the hydrazoic acid was generated [19]. All the chemicals were purchased from Merck Company. The solvents were distilled and stored over a drying agent. IR spectra were recorded with a Shimadzu FTIR-408 spectrophotometer as KBr disk. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 250 AC spectrometer in DMSO.

N-Methylation of 2,6-diaminopyridine

The reaction was carried out in various conditions (Table 1). In the best condition, while stirring, 120 mL of glacial acetic acid was added to a suspension of 5 g (46 mmol) of 2,6-diaminopyridine and 21.9 g (276 mmol) sodium azide in 57 mL (276 mmol) of ethyl orthoformate, and the mixture was heated on a boiling water for 6 h under dry argon. After this period of time the reaction mixture was cooled and 4 mL of concentrated HCl was added; and filtered. The product was crystallized from water and dried in air (Scheme 1). This brown compound (Figure 1(a)) was impure. Then the crude product was recrystallized from hot isopropanol. The white precipitate (impurity) (Figure 1(b)) was separated by filtration. Then the filtrate was evaporated under rotary, and the light brown product (Figure 1(c)) was dried in the air. The product has no melting point because it has been destroyed. The weight of product (Figure 1(d**)**) was 3.5 g (%71). IR (cm^{-1}): 3383 (stretching N-H), 3210 (stretching C-H of pyridine ring), 2940 (stretching C-H of methyl groups) and 1655 (stretching C=C and C=N). ^{1}H NMR (FT-250 MHz, DMSO): δ;

1.89 (s, $6H_e$), 4.5 (d, N-H), 5.32 (s, $3H_a$), 5.6 (d, $2H_c$), 7 (t, $1H_d$). ^{13}C NMR (FT-250 MHz, DMSO): δ; 21.99 (C_e), 95.66 (C_a), 138.79 (C_c), 159.13 (C_d), 172.83 (C_b).

The proposed mechanism for formation of methylated 2,6-DAP has been shown in Figure 2. In this route, carbene intermediate (A), that we trapped it by reaction with ethylene, is prepared. The B product is characterized with FT IR and ^1H NMR analyses. The stretching C-H bond peak of cyclopropyl is appeared in 3124 cm^{-1}. The B product-^1H NMR (FT-250 MHz, DMSO): δ; 0.73 (m, 8H of NH-cyclopropyl), 1.45 (m, 4H of pyridine-cyclopropyl), 2.23 (s, $2H_d$), 4.81 (s, N-H), 5.76(s, $1H_a$), 5.92 (d, $2H_b$), 7.8 (t, $1H_c$).

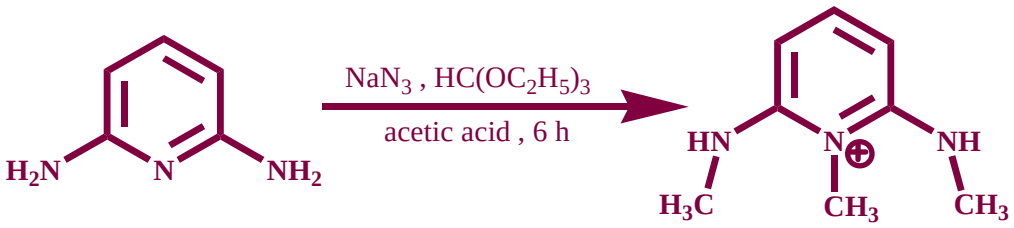
Result and discussion

Preparation of secondary amines due to their applications is very interesting in organic synthesis field. There are various methods for these compounds preparation. However, despite the widespread interest, traditional methods for secondary amines formation and preparation are often problematic because of severe reaction conditions and generally poor yields. Direct *N*-alkylation is the most common route to secondary amine formation. However, although the conversion appears simple, it is well known that the yield of this method is limited due to the overalkylations, giving mixtures of primary, secondary and tertiary amines and quaternary ammonium salts. Consequently, secondary amine yields depend on the nature of the starting amines. In the present work, we introduced a novel method for synthesis of secondary amines with good yields under mild conditions. We prepared this secondary amine by treatment of 2,6-diaminopyridine with sodium azide and orthoformic acid. The product is very stable under pressure, heat and moisture.

Table 1. Product yield in various conditions

2,6-DAP (mmol)	NaN_3 (mmol)	$HC(OC_2H_5)_3$ (mmol)	Time (h)	Yield (%)
46	92	92	6	**15**
46	138	138	6	**23**
46	276	276	2	**25**

46	276	276	4	**47**
46	276	276	6	**71**
46	276	276	24	**70**
46	322	322	6	**72**



Scheme 1. One-step *N*-methylation of 2,6-diaminopyridine

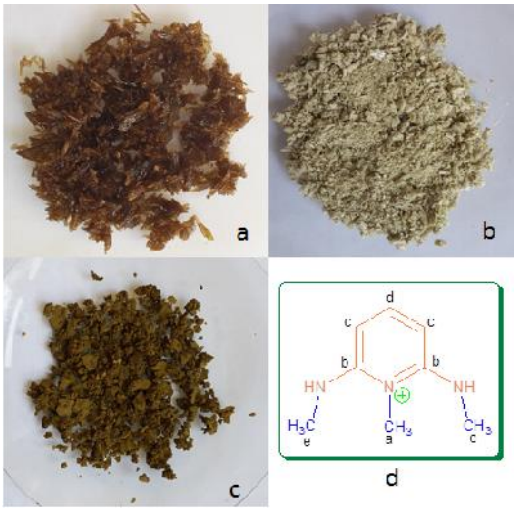


Figure 1. (a) the product before recrystallization; (b) the impure powder from recrystallization; (c) the main product; (d) structure of main product

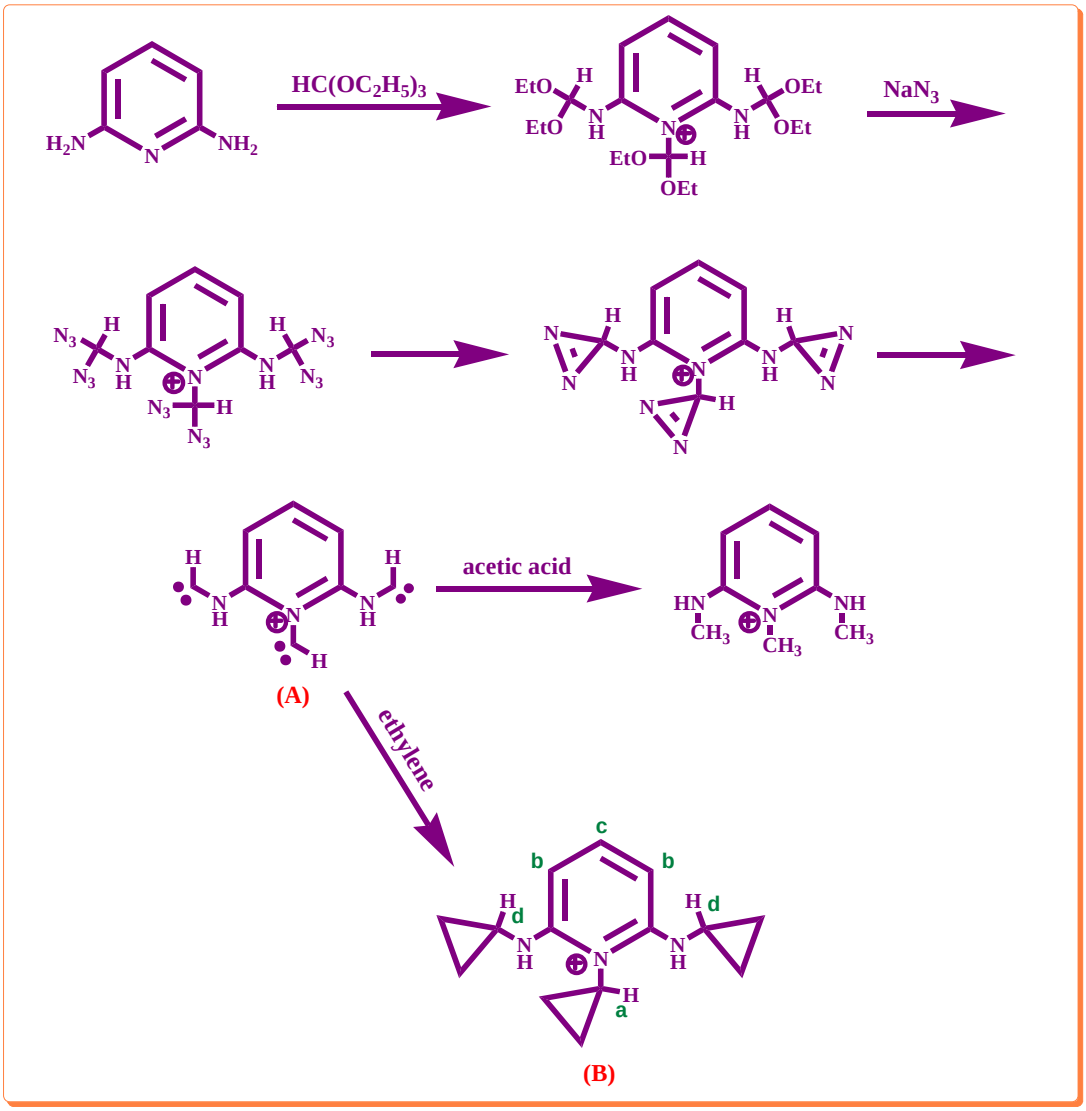


Figure 2. Proposed mechanism for formation of desired product

Conclusion

In this study, we synthesized the secondary *N*-methylated derivative of 2,6-diaminopyridine with its reaction with NaN_3 and $HC(OC_2H_5)_3$. After synthesis of this derivative, we saw that the product is very stable under various conditions. Low reaction time, good yield and product formation without over alkylation are the advantages of this one step procedure.

Acknowledgments

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