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The Influence of Ketones on the Formation of Symmetrical Secondary Amine: A New Method for Preparation of N, N-Bis-(dimethoxyphenylethyl)amine

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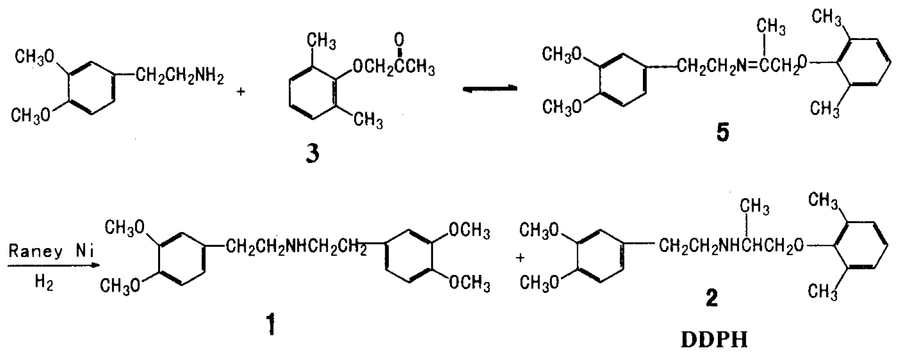
Abstract: The influence of some ketones on the formation of symmetrical secondary amine N, N-bis-(3, 4-dimethoxyphenylethyl)amine **1** were discussed and a new method for preparing **1** was described.

Keywords: Symmetrical secondary amine, N, N-bis-(3, 4-dimethoxyphenylethyl)amine, ketone.

In the course of hydrogenation of imine to prepare DDPH, which is an adrenoreceptor antagonist and undergoes clinic study in China now[1], one foreign material N, N-Bis-(dimethoxyphenylethyl)amine **1** was formed (**Scheme 1**)[2]. **1** is an important intermediate for the preparation of arrhythmic agent YS 035[3, 4]. Here we would like to explain its formation and the influence of ketone on its yield.

In **scheme 1**, when we used Raney Ni W_2 as catalyst under 40 atm. H_2 pressure, 40% **2** and 5% **1** were obtained. For improving the yield of **2**, we are attempting to replace Raney Ni W_2 by basic Raney nickel to prepare **2** under 1 atm H_2 pressure. Unexpectedly, the primary product was **1**, its yield was up to 68%, but the amount of **2** was small.

Scheme. 1



According to literatures[5,6], primary amines can be converted into symmetricalsecondary amine by Raney nickel under high temperature or other conditions. Indeed, we also found that 3, 4-dimethoxyphenylethylamine can be converted into 1 by Raney nickel at 1 atm H2, but the yield was considerably low. According to the above facts, we deduced that ketone 3 may influence the yield of 1 dramatically. To verify this hypothesis, we selected cyclohexanone, butanone, acetone to replace 3 (Scheme 2), the result was listed in Table 1.

According to literatures[2,7], **1** can be prepared from amide via reduction by KBH4/ZnC12 system, however, those methods are not convenient and the yield is low. Comparing with those methods, our method is more convenient and the yield is higher when suitable ketones were used.

In conclusion, The formation of **1** and the influence of ketone on the yield of **1** were discussed, meanwhile, a new approach to prepare **1** was reported. The influence of ketones on the formation other symmetrical amine is being studied by our group.

Scheme. 2

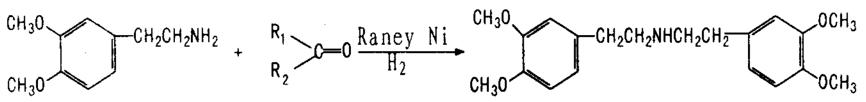


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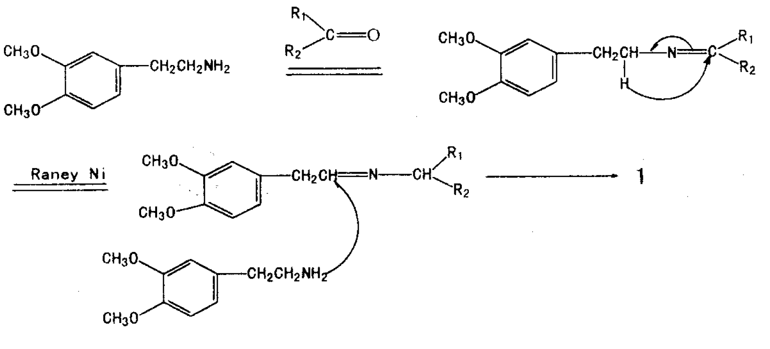
Table 1. The influence of ketones on the yield of **1**

ketone	reaction time (hour)	temperature (°C)	yield (%)**
3	15	50	68.0^{a}
cyclohexanone	36	50	49.0^{b}
acetone	36	50	22.0^{c}
butanone	36	50	11.0^{b}
*	36	50	5.0

** the yield after isolation * no ketone is added ; a if the reaction time is 6 h, the yield of 1 is 52% ; b the mole ratio between amine and ketone is 1:1.2 ; c the mole ratio between acetone and amine is 5:1.

Scheme 3



Experimental

Melt point was uncorrected. IR spectra was recorded on Shimadzu IR-900. H-NMR spectra was measured with JEOL-90Q spectrometer using DMSO as solvent. Mass spectra was recorded on Nicolet FTMS-200 spectrometer

Preparation of Raney Nickel

1. 6 g 50% aluminium-nickel alloy powder and 20 ml distilled water were added into 150 ml beaker to give a suspension. To the stirring suspension, 3. 6 g KOH was added portion-wise in 10 min. at room temperature. Until no gas emitted, the mixture with stirring was heated to 70°C over water-bath for 0. 5 h, then it was cooled to room temperature and the upper layer was decanted to give precipitate, the precipitate was washed with 20×3 ml distilled water and 20×3 ml anhydrous ethanol to give Raney nickel (PH=8). The catalyst was covered with small amount of anhydrous alcohol.

Typical procedure

1. 8 g (10 mmol) homoveratrylamine and 20 ml anhydrous methanol were added into 100 ml three neck-flask, the solution was heated to reflux under N_2 atmosphere. To the solution, 20 ml methanol solution containing 2. 1 g (12 mmol) 1-(2, 6-dimethylphenoxy)acetone was added drop-wise in 1 h, the refluxing solution was stirring for further two hours. After the mixture was cooled, fresh Raney nickel was added to give a suspension. The suspension was stirring under 1 atm. H_2 at 55°C for 15 h, cooled to room temperature and the catalyst was filtered off, residue oil was obtained after evaporating off methanol in vacuum. The residue was dissolved in 15 ml anhydrous alcohol, then ethanol-hydrochloride solution was added to give white precipitate. The solid was recrystallized from alcohol. or purified by silica chromatograph (m. p. :202-204℃[2, 7]). Its structure is identified by comparing its TLC and IR, H-NMR and MS with authentic sample.

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