Three Component Mannich Reaction and 1,5-Benzodiazepine Synthesis Catalyzed by a Tetranitrile-Silver Complex

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Abstract: This manuscript describes the first example of silver ion complex of a dendritic tetranitrile ligand catalyzed one-pot three component Mannich reaction and 1,5-benzodiazepine synthesis. The catalyst can be separated from the products by a change in the solvent. The catalyst is reusable.

Keywords: Homogeneous catalysis, tetranitrile, silver complex, Mannich reaction, 2-aminoketones, 1,5 benzodiazepine.

INTRODUCTION

The search for novel catalysts, which show atom efficiency and environmental friendliness, is continuing in academic and industrial laboratories due to the rising concern over environmental issues and the need for more efficient catalysts. Homogeneous catalysis using organometallic complexes is advancing into the modern fine chemical and bulk chemical industry [1]. In this paper we describe a novel homogeneous catalyst derived from silver complex of a tetranitrile ligand. Polydentate ligands have found extensive application in molecular and crystal engineering [2]. Among the polydentate ligands, polynitrile ligands have received particular attention due to their special property to co-ordinate with silver ions. This property was exploited in the synthesis of silver complexes having excellent properties and beautiful topologies [3]. But catalysis using these polynitrile-silver complexes is a less explored area.

The synthetic utility of Mannich reaction is evident from its application in the synthesis of many natural products and biologically important compounds [4]. Recently the focus has been shifted to catalyst assisted three component Mannich reaction because of the simplicity and atom economy of the reaction [5, 6]. Snapper and Hoveyda [7] have exploited catalytic properties of some silver complexes in Mannich reactions of enol ethers and silylketene acetals with various imines, while Asao [8] used AgOTf as the catalyst in Mannich and nitro Mannich reactions of pre-formed alkynylaryl aldimines.

1,5-benzodiazepines are biologically important molecules and are extensively used clinically as analgesic, hypnotic, sedative and antidepressive agents [9]. 1,5-benzodiazepines are generally synthesized by acid catalyzed condensation of o-phenylenediamines with ketones. A large number of catalytic processes are reported for the synthesis of benzodiazepines which include the use of various metal salts, CAN, heteropolyacids, ionic liquids etc. [10]. However many of these processes are associated with problems like long reaction time, high temperature, use of expensive catalysts, low yields and occurrence of side products. Search for novel catalytic methods which eliminate these problems is going on. An interesting example to mention is the use of $AgNO_3$ under solvent free conditions [11].

The present paper reports the primary results of three component Mannich reaction and 1,5-benzodiazepine synthesis catalyzed by silver complex of a tetranitrile ligand. To the best of our knowledge this is the first report of one pot three component Mannich reaction catalyzed by a tetranitrile silver complex. The present catalyst eliminates the requirement of pre-formed imines and enolates for obtaining good results. This provides a more simplified process to obtain Mannich product in high yield. Even though some inorganic silver derivatives are used for 1,5-benzodiazepine synthesis under solventless conditions, this is the first example of benzodiazepine synthesis catalyzed by silver complexes under homogeneous conditions. Thus the Ag complex is able to catalyze two mechanistically distinct reactions of synthetic importance under mild conditions. The pinpointing of such "privileged" catalyst classes showing general superiority for many reaction types is undoubtedly one of the most intriguing aspects and may have a considerable impact on the development of new catalytic systems [12].Moreover the present catalyst can be easily removed and recycled.

RESULTS AND DISCUSSION

The tetranitrile ligand used to prepare the catalyst was propylenediaminetetrapropionitrile (**1**). The ligand was derived from 1,3-diaminopropane and acrylonitrile according to a standard procedure (Scheme **1**) [13].

The complex (**2**) was prepared by stirring the ligand and $AgNO_3$ (1:2 ratio) in methanol. The formation of the complex was indicated by the development of a reddish brown color. On evaporation of the solvent, a brownish mass was formed which in turn changed to black on exposure to light and air. Even if the complex underwent blackening upon exposure to light and air, there was no reduction in the catalytic activity. UV-Vis-NIR spectra of the complex, ligand and silver nitrate in methanol were compared. The spectrum of the complex showed an additional band in the NIR region

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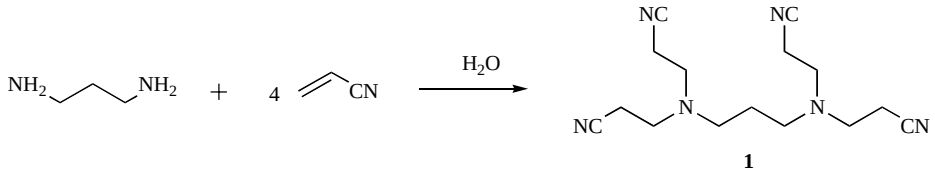

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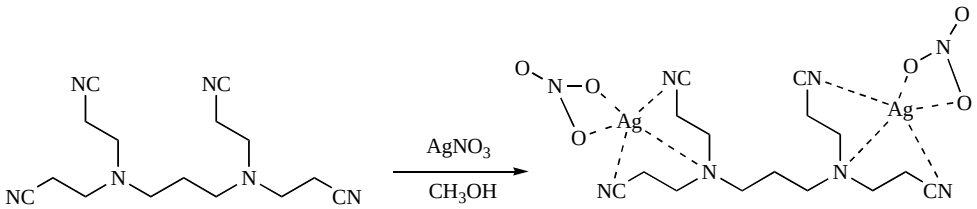
Scheme 1. Synthesis of the ligand.



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Scheme 2. Synthesis of the catalyst.

at 491 cm^{-1}, which was assigned to be due to the formation of Ag-N bond. FTIR spectral analysis revealed that the stretching band due to the nitrile group underwent a shift from their original values after complex formation and occupied a higher value [14]. The efficiency of ligands carrying nitrile groups towards complex formation with silver was previously shown by many researchers [3]. The synthetic scheme and tentative structure of the complex is shown in Scheme **2**. The structure of the complex was predicted according to previous reports [3a, c].

A similar complex was previously reported with another tetranitrile ligand [3a]. But the solubility of that was limited and was soluble in DMSO only. The present complex is soluble in methanol also but is insoluble in most other organic solvents including ethanol. This offers the possibility of using the catalyst more fruitfully and easy separation of the catalyst from the product mixture.

Initially, the three component Mannich reaction between benzaldehyde, aniline and cyclohexanone and the synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine from acetone and o-phenylene diamine were performed in the presence of various amounts of the catalyst as model reactions. The results are presented in Table **1**.

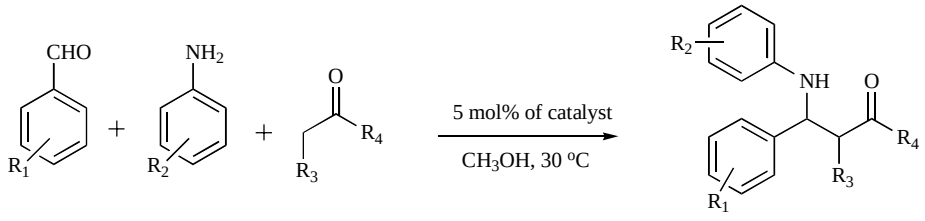
The yield of the Mannich product (**3**) was poor with low catalyst loading and there was a gradual increase in the yield of product with increase in the catalyst loading. Maximum yield was obtained when the catalyst loading was 5 mol% with respect to the aldehyde. Since the catalyst was soluble in methanol, the reaction was performed in methanol and after the reaction, the solvent was evaporated and the product mixture was extracted by ethanol leaving the catalyst behind. The general scheme of the reaction is shown in Scheme **3**.

Table1. Effect of the Concentration of the Catalyst on Reaction

Enrty	Mol % of Catalyst	% Yield [a]	
		Mannich Reaction [b]	Benzodiazepine Synthesis [c]
1	0	20	0
2	1	50	30
3	2	65	62
4	5	93	94

[a]Isolated yield.
[b]Reaction conditions: 5mmol benzaldehyde, 5 mmol cyclohexanone, 5.1 mmol aniline, 5 mol% catalyst, 5 mL methanol.
[c]Reaction conditions: 1 mmol o-phenylene diamine, 2.5 mmol acetone, 5 mol% catalyst, 5 mL methanol.

The feasibility of the catalyzed process was shown by using various substrates. The reaction procedure and characterization data of selected products are given in the experimental section. The results are presented in Table **2**. Generally, all substrates gave good yields. Comparatively low yield was observed with substrates carrying electron withdrawing groups (Table **2**, entry 5). When acetophenone was used instead of cyclohexanone the yield of the product was



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Scheme 3. Three component Mannich reaction catalyzed by the silver complex.

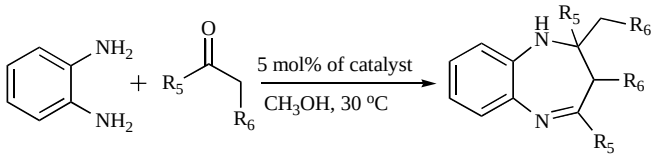
little lower and the reaction required longer time to get completed (Table **2**, entry 6 & 7).

Table 2. Three Component Mannich Reaction Catalyzed by the Silver Complex

Entry	R1	R2	Ketone	Time h	% Yield [a,b]
1	H	H	$C_6H_{10}O$	4	93
2	4-OCH_3	H	$C_6H_{10}O$	4	91
3	4-Cl	H	$C_6H_{10}O$	6	90
4	2-OH	H	$C_6H_{10}O$	6	94
5	H	NO_2	$C_6H_{10}O$	8	85
6	H	H	$C_6H_5COCH_3$	10	90
7	4-Cl	H	$C_6H_5COCH_3$	10	87

[a]Reaction conditions: 5mmol aldehyde, 5 mmol ketone, 5.1 mmol aniline, 5 mol% catalyst, 5 mL methanol.
[b]Isolated yield.

The tetranitrile-Ag complex was used as a homogeneous catalyst in the preparation of benzodiazepine derivatives (**4**) from o-phenylene diamine and various ketones. Generally benzodiazepine synthesis is carried out using solid catalysts under solventless conditions. The present paper deals with the synthesis of benzodiazepine in methanol which eliminates problems associated with solventless synthesis. The catalyst was highly efficient and the reaction was completed within a very short period of time. But the reaction was slow compared to the procedure using $AgNO_3$ alone under solvent free conditions reported by Kumar *et al.* [11]. As observed from Table **1** only five mol percent of catalyst was required for efficient conversion. After the completion of the reaction, the catalyst was removed without any difficulty. For this, the reaction medium i.e. methanol was removed under vacuum and the product was extracted using ethyl acetate. The pure product was isolated by column chromatography on silica. The catalyst remained in the reaction vessel was used for another cycle of reaction. The general scheme of the reaction is shown in Scheme **4** and the results are summarized in Table **3**.



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Scheme 4. Benzodiazepine synthesis catalyzed by the silver complex.

Table 3. Benzodiazepine Synthesis Catalyzed by the Silver Complex

Enrty	Ketone	Time h	% Yield [a,b]
1	CH_3COCH_3	1	94
2	$C_6H_5COCH_3$	1	91
3	$C_6H_5COC_6H_5$	2.5	90
4	$C_6H_{10}O$	2	90

[a]Reaction conditions: 1 mmol o-phenylene diamine, 2.5 mmol ketone, 5 mol% catalyst, 5 mL methanol.
[b]Isolated yield.

The catalyst was recycled after the completion of each set of reactions. The catalyst showed no practical loss of efficiency for three cycles under the given conditions for both the reactions and the results of the recycling experiment is summarized in Table **4**.

Table 4. Effect of Recycling on Catalysis

Enrty	No. of recycling steps	% Yield [a]	
		Mannich Reaction [b]	Benzodiazepine Synthesis [c]
1	1	93	94
2	2	93	93
3	3	92	93
4	4	89	87

[a]Isolated yield.
[b]Reaction conditions: 5mmol benzaldehyde, 5 mmol cyclohexanone, 5.1 mmol aniline, 5 mL methanol.
[c]Reaction conditions: 1 mmol o-phenylene diamine, 2.5 mmol acetone, 5 mol% catalyst 5 mL methanol.

CONCLUSION

In summary, a tetranitrile silver complex was prepared and used as homogeneous catalyst for one pot three component Mannich reaction and benzodiazepine synthesis from o-phenylene diamine and ketones. The reactions proceeded efficiently with good yields. The catalyst can be separated from the product by changing the solvents. The catalyst is reusable.

EXPERIMENTAL

Preparation of Propylenediaminetetrapropionitrile (1)

1,3 diaminopropane (5 mL, 59 mmol) was dissolved in water (30 mL) in a round bottom flask. Acrylonitrile (19.7 mL, 297 mmol) was added to it with constant stirring at room temperature. The exothermic reaction caused the temperature to rise to 40 ^oC. After this exothermic effect, the reaction mixture was transferred to an oil bath kept at 80 ^oC and stirred at that temperature for 1 h to complete the reaction. The excess of acrylonitrile was removed as a water azeotrope by vacuum distillation in the rotavapour (16 mbar, bottom temperature 40 ^oC). The oily material formed was dissolved in 20 mL methanol. The product was obtained in pure form by evaporating the solvent under vacuum. Yield 16.05 g, 95%. FTIR (KBr, ν_{max} (cm^{-1})): 2954, 2924, 2832, 2247, 1465, 1420, 1365, 1136, 759.

Preparation of Propylenediaminetetranitrile-Silver Complex (2)

The nitrile ligand (0.035 g, 0.125 mmol) was dissolved in 5 mL methanol in a two necked round bottom flask. N_2 gas was bubbled through the solution for half an hour. $AgNO_3$ (0.042 g, 0.250 mmol) was added and stirred for 1 h. Initially the reaction mixture was colorless. A light orange color started developing after 10 minutes and it intensified to maximum within one hour. On evaporating the solvent a light brown solid was formed which turned black on expo-

sure to air and light for some time. Anal. Calc. for $C_{15}H_{22}Ag_2N_8O_4$ C, 30.32; H, 3.73; N, 18.86; O, 10.77. Found: C, 30.30; H, 3.69; N, 18.94; O, 10.74 FTIR (KBr, ν_{max} (cm^{-1})): 2954, 2924, 2832, 2257, 1465, 1420, 1365, 1100, 835, 759, 723, 491.

General Procedure for Three-Component One Pot Mannich Reaction

In a two-necked round bottom flask the tetranitrile-silver complex (0.25 mmol) was prepared in methanol (5 mL) as described above. To this solution aldehyde (5 mmol), ketone (5 mmol) and aniline(5.1 mmol) were added and stirred at room temperature. The progress of the reaction was monitored by TLC on silica gel plate with hexane, ethyl acetate (10:1) as eluent. After the completion of the reaction the solvent was removed by evaporation and the reaction mixture was extracted with absolute ethanol. Since the catalyst is insoluble in ethanol it can be removed by simple filtration or careful decantation. The pure 2-aminoketones were obtained by column chromatography on a small column of alumina using hexane: ethyl acetate mixture (25:1) as eluent. All the products were known compounds and were characterized by FTIR and ^{1}HNMR spectroscopic data [5].

[1'-(N-phenylamino)-1'-(4-methoxyphenyl)] methylcyclohexanone (Table 2 Enrty 2)

FTIR (KBr, ν_{max} (cm^{-1})): 3364, 2935, 1706, 1604, 1512 ; ^{1}H NMR (300MHz, $CDCl_3$): δ 1.61-1.88 (m, 6H), 2.31-2.43 (m, 2H), 2.71-2.72 (m,1H), 3.65 (s, 3H), 4.50 (br, 1H), 4.54 (0.68H, d, *J* = 7.3 Hz, *anti*), 4.73(0.32H, d, *J* = 4.2 Hz, *syn*), 6.47-6.52 (m, 2H), 6.62-6.67 (m, 2H), 7.19-7.36 (m, 5H).

1,3-diphenyl-3-phenylamino-1-propanone (Table 2 Entry 6)

FTIR (KBr, ν_{max} (cm^{-1})): 3373, 2924, 1666, 1507, 1489, 1286, 1003; ^{1}HNMR ($CDCl_3$, 300 MHz): δ 2.03-2.62 (m, 2H), 4.15 (br, s, 1H), 4.75-4.90 (m, 1H), 6.34–6.45 (m, 2 H), 7.20–7.25 (m, 2 H), 7.25–7.37 (m, 4 H), 7.39–7.48 (m, 3 H), 7.50–7.58 (m, 2 H), 7.87–7.96 (m, 2 H).

General Procedure for the Synthesis of 1,5-Benzodiazepine

In a two-necked round bottom flask the catalyst (0.1 mmol) was prepared in 5 mL methanol. To this solution o-phenylene diamine (1 mmol) and ketone (2.5 mmol) were added. The reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC on silica gel plate with hexane, ethyl acetate (5:1) as eluent. After the completion of the reaction, methanol was removed by evaporation and the reaction mixture was extracted with ethyl acetate. The pure product was obtained by column chromatography on a small column of silica using hexane, ethyl acetate mixture (1:1) as eluent. All the products were known compounds and were characterized by FTIR and ^{1}HNMR spectroscopic data [10].

2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (Table 3 Entry 1)

FTIR (KBr, ν_{max} (cm^{-1})): 3340, 1650; ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (s, 6H), 2.21 (s, 2H), 2.35 (s, 3H), 3.45 (s, 1H), 6.62-7.31 (m, 4H).

2-Methyl-2, 4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (Table 3 Entry 2)

FTIR (KBr, ν_{max} (cm^{-1})): 3330, 1635; ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.80 (s, 3H), 2.95 (d, 1H, *J*=13.1 Hz), 3.16 (d, 1H, *J*=13.1 Hz), 3.44 (s, 1H), 6.53-7.02 (m, 3H), 7.16-7.34 (m, 7H), 7.55-7.65 (m, 4H).

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