Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(12):1320-1324

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Simple and convenient method of synthesis of N-ethyl-2,6-diethyl aniline and derivatives

Sanket Gudekar*[1], Rama Lokhande[1], Rajiv Sutar[2], Sanjay Pednekar[1], Sandip Surve[1] and Surekha Kolhal[1]

[1]School of Basic Sciences, Department of Chemistry, Jaipur National University, Jagatpura, Jaipur, Rajasthan, India
[2]General Manager Production, Sandoz Pvt. Ltd., India

ABSTRACT

N-alkylation of 2,6-diethyl aniline and its derivatives using various aldehydes by Pd/C catalyst in aqueous 2-propanol solvent using ammonium formate as insitu hydrogen donor facilitate the formation of N-ethyl-2,6-diethyl aniline and its derivatives which is the simple method of formation of this compound. The reaction proceeds smoothly and selectively with excellent yield at room temperature .Our method presents a facile, economical and environmentally benign alternative for reductive amination.

Keywords: N-alkylation, reductive alkylation, 2,6-diethyl aniline, Pd/C catalyst, Ammonium formate.

INTRODUCTION

N-Alkylation of aniline derivatives is an important reaction in organic synthesis, which has been widely applied in the preparation of dyes, fluorescence probes, agrochemicals and pharmaceuticals. The challenge of this reaction is to obtain excellent selectivity for mono or dialkylation products and to avoid the formation of corresponding quaternary ammonium salts. Many methods have been reviewed for the synthesis of substituted amines [2,3]. However, there are still suffering some problems, such as the use of toxic reagents [4] and the control of the selectivity of mono- and dialkylation aniline derivatives [5]. In order to overcome these problems, noble metal complexes and salts involving Ru [6], Ir [7,8], Pt [9], Au[10,11], and Pd[12,13] as catalysts and alcohols as alkylating agents have been reported extensively in homogeneous phase. Transition metal-free protocols have also been described, although they normally require harsh reaction conditions, such as high temperatures and pressures, to achieve reasonable yields of products [14]. Compared to homogeneous catalysts, heterogeneously catalyzed methodologies based on Ra-Ni [15] and magnetite [16] has been proposed as alternatives to prepare mono-alkylation products. Recently, microwave irradiation has been proved to be efficient for the syntheses of N-alkyl anilines [17]. However, they are all suffered from high temperatures and long reaction times. Direct reductive amination of aldehydes and ketones is one of the most attractive methods for the synthesis of amine derivatives. This is particularly advantageous because the imine intermediate is avoided. There have been many reagents developed recently to effect reductive amination of carbonyls. These include following the following: LiClO4-zirconiumborohydridepiperzine complexes, $H_3PW_{12}O_{40}$-$NaBH_4$, NaBH $(OAc)_3$,Ph_2SiH_2 ,or Ph_2SiH_3 with catalytic Bu_2SnClH-pyridine N-oxide, $Cu(PPh_3)_2BH_4$ with thiourea with Hantzsch ester, amino borane derivatives with $NaBH_4$. These methods have some drawbacks in one way or another such as prolonged reaction time; inert

conditions higher reaction temperature, excess amount of reagents, and toxic byproducts. Thus, it is necessary to develop an alternative method that employs simple and mild as well as environmentally benign conditions. In addition, there is also growing specific interest in developing controlled synthesis of secondary and tertiary amines due to its vast applications.

Herein we report an efficient, facile mild and environmentally benign one-pot reductive N-alkylation of 2,6-diethyl aniline and its derivatives using various aldehydes by Pd/C catalyst in aqueous alcoholic solvents with ammonium formate as in situ hydrogen donor.

EXPERIMENTAL SECTION

Solvents and common reagents were obtained commercially and used as received .Spectra were determined on a Bruker AC-200 spectrometer (400MHz for ^{1}H- NMR, 100MHz for ^{13}C-NMR) for^{1}H- NMR spectra were recorded with Me_4Si as the internal reference. Column chromatography was conducted on Merck silica gel 60.

1)Preparation of N-ethyl-2,6-diethyl aniline:
A mixture of 2-propanol (90 ml) was added to a flask containing Pd/C (0.5 mmol).ammonium formate (50 mmol) dissolved in l water (10 ml) was transferred to the same flask .The reaction mixture stirred for 5 min to activate the Pd/C.2,6-diethyl aniline(5 mmol) and acetaldehyde (5mmol) were added to the reaction mixture ,and stirred for 30 min at room temperature. Based on the TLC monitoring after completion of the reaction ,Pd/C catalyst was filtered off on celite and the solvent is removed under reduced pressure at 45-50°C. The reaction mixture then diluted with Dichloromethane and washed with brine solution. Organic phase separated and dried on Na_2SO_4 .The organic layer then distilled under reduced pressure . The residue was purified by silica gel column chromatography using Ethyl Acetate/Cyclohexane.

^{1}H-NMR: (400 MHz,$CDCl_3$)**:**2.869 (2H, q, J=6.901), 1.217 (3H, t, J=6.901), 6.827 (1H, dd, J=7.674, J=0.000), 2.412 (2H, q, J=7.424), 6.827 (1H, dd, J=7.674, J=0.000), 2.516 (2H, q, J=7.424), 6.645 (1H, t, J=7.674), 1.15 (3H, t, J=7.424), 1.15 (3H, t, J=7.424)

^{13}C-NMR (100 MHz,CDCl3): δ = 11.463, 13.395, 22.262, 40.866, 44.110, 125.452, 125.941, 128.017, 136.574, 140.618

2)Preparation of N,2,6-triethyl-N-(2-propoxyethyl)benzamine:
A mixture of 2-propanol(90 ml) was added to a flask containing Pd/C(0.5 mmol).ammonium formate (50 mmol) dissolved in l water (10 ml) was transferred to the same flask .The reaction mixture stirred for 5 min to activate the Pd/C. N-ethyl-2,6-diethyl aniline(5 mmol) and 2-propoxyacetaldehyde (5mmol) were added to the reaction mixture ,and stirred for 30 min at room temperature. Based on the TLC monitoring after completion of the reaction ,Pd/C catalyst was filtered off on celite and the solvent is removed under reduced pressure at 45-50°C. The reaction mixture then diluted with Dichloromethane and washed with brine solution. Organic phase separated and dried on Na_2SO_4 .The organic layer then distilled under reduced pressure. The residue was purified by silica gel column chromatography using Ethyl Acetate/Cyclohexane.

^{1}H-NMR: 3.415 (2H, t, J=7.280), 3.317 (2H, t, J=7.090), 3.198 (2H, t, J=7.280), 1.567 (2H, qt, J=7.567, J=7.090), 0.878 (3H, t, J=7.567), 3.074 (2H, q, J=6.960), 1.042 (3H, t, J=6.960), 7.106 (1H, dd, J=7.821, J=0.000), 2.677 (2H, q, J=7.400), 7.083 (1H, dd, J=7.669, J=0.000), 2.677 (2H, q, J=7.400), 7.048 (1H, dd, J=7.821, J=7.669), 1.032 (3H, t, J=7.400), 1.032 (3H, t, J=7.400)

^{13}C-NMR: (100 MHz,CDCl3): δ = 10.625, 12.056, 15.128, 18.673, 23.014, 24.276, 26.938, 29.741, 30.217, 50.016, 54.615, 125.654, 126.188, 126.484, 126.739, 144.325

3)Preparation of 1-chloro-3-((2,6-diphenyl ethyl)amino)propane-2-one
A mixture of 2-propanol (90 ml) was added to a flask containing Pd/C (0.5 mmol).ammonium formate (50 mmol) dissolved in l water (10 ml) was transferred to the same flask .The reaction mixture stirred for 5 min to activate the Pd/C. N-ethyl-2,6-diethyl aniline(5 mmol) and 3-chloro-2-oxo-propanal (5mmol) were added to the reaction mixture ,and stirred for 30 min at room temperature. Based on the TLC monitoring after completion of the reaction, Pd/C catalyst was filtered off on celite and the solvent is removed under reduced pressure at 45-50°C. The reaction

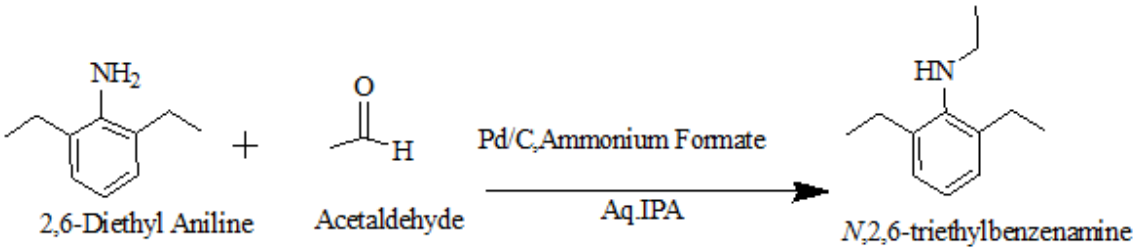
mixture then diluted with Dichloromethane and washed with brine solution. Organic phase separated and dried on Na_2SO_4 .The organic layer then distilled under reduced pressure. The residue was purified by silica gel column chromatography using Ethyl Acetate/Cyclohexane.

^{1}H-NMR: 4.179 (2H),4.165(2H), 3.581 (2H, q, J=7.108), 1.178 (3H, t, J=7.108), 7.200 (1H, dd, J=7.864, J=0.000), 2.440 (2H, q, J=7.451), 7.160 (1H, dd, J=7.865, J=0.000), 2.440(2H, q, J=7.451), 7.111 (1H, dd, J=7.865, J=7.864), 1.087 (3H, t, J=7.451), 1.087 (3H, t, J=7.451)

^{13}C-NMR (100 MHz,CDCl3): δ = 11.46, 13.39, 13.39, 22.65, 22.65, 40.86, 44.11, 125.45, 125.94, 125.95, 128.02, 128.02, 136.57, 140.62

RESULTS AND DISCUSSION

2,6-diethyl aniline is a key raw material or an intermediate for various pharmaceutical and agrochemical products. By thorough literature search, it is observed that there are very few data available for N-alkylation of 2, 6-diethyl aniline. Also, their derivatives which are available commercially are too expensive. It is of our interest to work on the N-alkylation of 2,6-diethyl aniline to provide an easy and simple route of N-alkylation of 2,6-diethyl aniline and its derivatives by utilizing reductive amination process which is simple and easy to reproduce. To begin with our study, we checked for suitable solvent using 2,6-diethyl aniline and acetaldehyde as our test of reaction as shown in Scheme 1. We found that 2-propanol/water (9:1,v/v) would give the best yield and also enhance the rate of reaction.(Table 1.)



Scheme 1

Using the same reaction and chosen solvent system, we checked the optimum amount of catalyst (Pd/C) and ammonium formate necessary to affect reductive amination (Table 2). Equimolar amount of aldehyde and 2,6-diethyl aniline was reacted at room temperature for 30 min using 0.1 equiv. Of Pd/C catalyst with 10 equiv. of ammonium formate in 2-propanol /water (9:1,v/v) system. Excellent yield of mono alkylation product was obtained (Table 2).

Table 1 Solvent Effect in One-Pot Reductive Amination of Acetaldehyde with 2,6-diethyl aniline[a]

			Yield(%)	
Entry	Solvent	Reaction Time(min)	N-ethyl-2,6diethyl aniline	N,N-diethyl-2,6-diethyl aniline
1	MeOH	30	30	25
2	EtOH	30	No reaction[b]	
3	i-PrOH	30	No reaction[b]	
4	MeOH/H_2O[c]	30	55	40
5	EtOH/ H_2O[c]	30	65	30
6	i-PrOH/ H_2O[c]	30	75	20

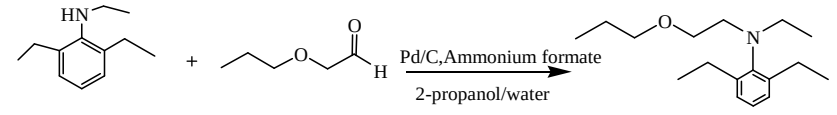
[a]Used 0.1 equiv of Pd/C and 10 equiv of ammonium formate.
[b]Ammonium formate does not dissolved in EtOH and i-PrOH.
[c]9:1, v/v.

Table 2 Optimization of Pd/C and Ammonium Formate Ratio

Entry	Solvent	Pd/C (equiv)	Ammonium Formate (equiv)	Reaction Time (min)	Yield (%)
1	i-PrOH/ H_2O (9:1,v/v)	0.1	1	180	15
2	i-PrOH/ H_2O (9:1,v/v)	0.1	5	60	50
3	i-PrOH/ H_2O (9:1,v/v)	0.1	10	30	75
4	i-PrOH/ H_2O (9:1,v/v)	0.05	10	60	50
5	i-PrOH/ H_2O (9:1,v/v)	0.005	10	180	10

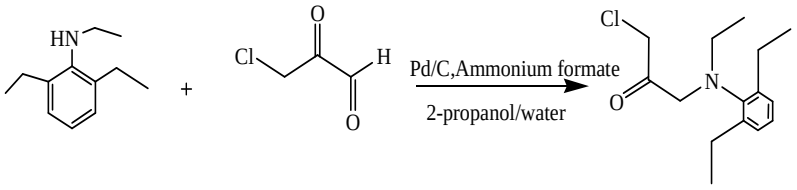
We further validated the reaction conditions by considering the reaction of N-ethyl-2,6-diethyl aniline with various aldehydes .The N,N-dialkylated products are very useful intermediates and key raw materials for various pharmaceutical, agrochemical products as shown in Scheme 2 & 3.

Scheme 2



N-ethyl-2,6-diethyl aniline 2-propoxyacetaldehyde *N*,2,6-triethyl-*N*-(2-propoxyethyl)benzenamine

Scheme 3



N-ethyl-2,6-diethyl aniline 3-chloro-2-oxopropanal 1-chloro-3-((2,6-diethylphenyl) (ethyl)amino)propan-2-one

CONCLUSION

In conclusion, we have demonstrated an efficient and economic process for the synthesis of secondary and tertiary amines by reductive *N*-alkylation of primary or secondary amines with various aldehydes in an aqueous alcoholic medium in the presence of Pd/C and Ammonium Formate. Some of the advantages of this process include mild reaction conditions, higher product yields, scalability, the absence of quaternary ammonium salt formation and operationally convenient conditions. The selective formation of secondary amines and mixed tertiary amines will find useful applications in organic synthesis.

REFERENCES

[1] Eunyoung Byun, Bomi Hong, Kathlia A. De Castro, Minkyung Lim, and Hakjune Rhee," *J. Org. Chem.* **2007**, *72*, 9815-9817
[2] R. N. Salvatore, C. H. Yoon, and K. W. Jung, *Tetrahedron*, vol. 57, no. 37,pp. 7785–7811, **2001**.
[3] M. Johannsen and K. A. Jørgensen, *Chemical Review*, vol. 98, no. 4, pp. 1689–1708,**1998**.
[4] M. Selva, P. Tundoand, and A. Perosa, *Journal of Organic Chemistry*, vol. 66, no. 3, pp. 677–680, **2001**.
[5] C. Chiappe and D. Pieraccini, *Green Chemistry*, vol. 5, no. 2, pp. 193–197, **2003**.
[6] C. Feng, Y. Liu, S. Peng, Q. Shuai, G. Deng, and C.-J. Li, *Organic Letters*, vol. 12, no. 21, pp. 4888–4891, **2010**.
[7] K. I. Fujita, Y. Enoki, and R. Yamaguchi, *Tetrahedron*, vol. 64, no. 8, pp. 1943–1954, **2008**.

[8] S. Michlik and R. Kempe, *Chemistry-An European Journal*, vol. 16, no. 44, pp. 13193–13198, **2010**.
[9] S.-C. Yang, Y.-C.Tsai, and Y.-J. Shue, *Organometallics*, vol. 20, no. 25, pp. 5326–5330, **2001**.
[10] A. Leyva-Pérez, J. R. Cabrero-Antonino, Á. Cantín, and A. Corma, *Journal of Organic Chemistry*, vol. 75, no. 22, pp.7769–7780, **2010**.
[11] L. He, X. B. Lou, J. Ni et al., *Chemistry*,vol. 16, no. 47, pp. 13965–13969, **2010**.
[12] L. L. Hill, J. L. Crowell, S. L. Tutwiler et al., *Journal of Organic Chemistry*,vol. 75, no. 19, pp. 6477–6488, **2010**.
[13] G. Mora, B. Deschamps, S. Van Zutphen, X. F. Le Goff, L. Ricard, and P. Le Floch, *Organometallics*, vol. 26, no. 8, pp.1846–1855, **2007**.
[14] G. Guillena, D. J. Ramón, and M. Yus, *Chemical Reviews*, vol.110, no. 3, pp. 1611–1641, **2010**.
[15] J. L. García Ruano, A. Parra, J. Alemán, F. Yuste, and V. M. Mastranzo, *Chemical Communications*, no. 4, pp. 404–406, **2009**.
[16] R. Martínez, D. J. Ramón, and M. Yus, *Organic and Biomolecular Chemistry*, vol. 7, no. 10,pp. 2176–2181, **2009**.
[17] G. Marzaro, A. Guiotto, and A. Chilin, *Green Chemistry*, vol. 11, no. 6, pp. 774–776, **2009**.
[18] Y. Ju and R. S. Varma, *Green Chemistry*, vol. 6, no. 4, pp. 219–221, **2004**.