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Research Article

A SIMPLE AND CONVENIENT PROTOCOL FOR THE SELECTIVE MONO DEBENZYLATION OF DIBENZYLAMINES USING 10% Pd/C AND $HCOONH_4$

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ABSTRACT

Simple and practical method for partial debenzylation of a dibenzylamine to corresponding monobenzylamine have been achieved by catalytic transfer hydrogenation employing 10% palladium on carbon as catalyst and ammonium formate as hydrogen source.

Keywords: Debenzylation, Catalytic Transfer Hydrogenation, Ammonium formate

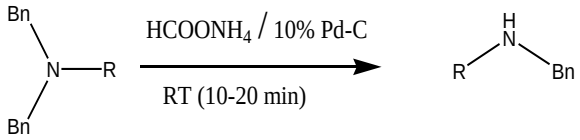
INTRODUCTION

The benzyl group is commonly employed for the protection of amino and hydroxyl groups[1]. The simple and practical method for partial debenzylation of a dibenzylamine to corresponding monobenzylamine resulting *N*-benzyl amines are key component in peptides synthesis and general organic synthesis[2]. This *N*-benzyl group has found wide application in synthesis because of its remarkable stability towards acidic and basic conditions. Many other functional groups can be easily deprotected keeping the benzyl group intact. Monobenzyl amine has got wide scope in the synthesis of asymmetric *N*-substituted amines, peptide mimetic and homochiral β-amino acid derivatives over the dibenzyl amines which have valuable therapeutic applications[3-4].

Generally dibenzyl amines were prepared by alkylation of amine with excess of benzyl halide[5]. Monobenzylated amines are obtained by either one of the methods; direct alkylation of amine with benzyl halide[6], most commonly benzyl bromide or benzyl chloride and the other method involves the formation of a Schiff base followed by reduction with a hydride or catalytic hydrogenation. These Schiff bases may also be reduced using Zn reagents[7]. Both the methods suffer from drawbacks such as, direct alkylation yields mixture of mono, dibenzylated and esterified products[8]. On the other hand, condensation and reduction requires additional workup and involve expensive reagents or a special apparatus.

Application of catalytic transfer hydrogenation has increased in recent years[9]. Large number of functional groups are reduced using variety of hydrogen donors such as Cyclohexene[10], Ammonium formate[11-12], Formic acid[13], 1,4-Cyclohexadiene[14], and Hydrazine[15]. Debenzylation of *N*-benzyl amine derivatives by catalytic transfer hydrogenation to corresponding amines under drastic condition also are reported in literature[16]. Partial debenzylation of tertiary and dibenzyl amines can also be achieved by oxidising agent such as ceric ammonium nitrate[17].

Here we wish to report simple and practical method for partial debenzylation of a dibenzylamine to corresponding monobenzylamine by catalytic transfer hydrogenation using 10% Pd/C as catalyst and ammonium formate as hydrogen donor (**Scheme-1**).



Scheme 1: Mono debenzylation of dibenzylamines

where R = various substituents as shown in Table-1

MATERIALS AND METHODS

The IR spectra were recorded on Shimadzu FTIR-9300 spectrometer. The melting points were determined by using Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded at 400 MHz in DMSO-d_6 and the chemical shifts were reported in ppm (**Table 2**) using DMSO singlet at 2.5 ppm as the reference. Thin layer chromatography was carried out on silica gel plates obtained by Merck (India). Dibenzyl derivatives were prepared by using established method by Goff and co-worker. All the melting points were matched with reported value (**Table 1**). All other chemicals were purchased from Sigma-Aldrich chemical company (St. Louis, USA) and Spectrochem, India. All chemicals were used as received without any further purification and the reaction was monitored by TLC, visualized in UV chamber and ethanolic ninhydrin.

General procedure for selective mono debenzylation of dibenbenzylamines

The substrate dibenzyl compounds (1 mmol), ammonium formate (3 mmol), 10% Pd/C (100 mg) and methanol (20 mL) were charged in to a 50 ml reactor. Reaction was stirred for 15-20 min at room temperature under nitrogen. After completion of the reaction (monitored by TLC) catalyst was removed by filtration, catalyst was washed with 5ml of methanol. The combined filtrate was concentrated to dryness. Then the residue was stirred with methyl *tert*- butyl ether and filtered to yield desired product.

RESULTS AND DISCUSSION

The reaction conditions are quite mild (RT) and the reactions are fairly fast (less than 20 min), the yields are also quite good. The products have been isolated in all cases except the entry **1** and **10** by simple filtration of the catalyst followed by concentration. The residue was stirred in methyl *tert*- butyl ether and again filtered. In the case of entry **1** and **10**, the products were purified and isolated by column chromatography. All isolated products were characterized by IR and ^{1}H-NMR spectroscopic techniques. The appearance of a strong absorption band between 3400 and 3200 cm^{-1} for the –NH group clearly confirms its presence.

A control experiment was carried out using dibenzylamine with ammonium formate, but without palladium carbon catalyst which did not yield the desired product. This clearly indicates the requirement of palladium carbon catalyst to catalyze the reaction. Further, mono debenzyaltion of dibenzylamine was also attempted with palladium carbon and methanol but without ammonium formate. Even after long duration we could not obtain any debenzylated product. This confirms that methanol serves only as solvent and not as hydrogen source.

Table 1: Data for Dibenzyl amines

Sl. No.	Dibenzyl amine	M.P in °C	
		Obs.	Lit.
1.	*N,N*-Dibenzyl -GABA-OEt	87-88	88-90[18]
2.	*N,N*-Dibenzyl -Gly-OH	187-188	190-192[19]
3.	*N,N*-Dibenzyl -Ile-OH	75-77	89-91[20]
4.	*N,N*-Dibenzyl-Leu-OH	80-83	84-88[21]
5.	*N,N*-Dibenzyl-Ala-OH	85-88	90-92[22]
6.	*N,N*-Dibenzyl-Val-OH	269-272	273-275[23]
7.	*N,N*-Dibenzyl-Phe-OH	249-251	253-254[21]
8.	*N,N*-Dibenzyl-Glu-OH	211-213	214-215[21]
9.	*N,N*-Dibenzyl-aminoethanol	39-40	42-43[24]
10.	*N,N*-Dibenzyl- benzylamine	91-92	91-94[25]

Table 2: Data for mono benzyl amines

Sl. No	Monobenzyl amine	M.P/ B.P in °C		^{1}H NMR
		Obs.	Lit.	
1.	*N*-benzyl-GABA-OEt	B.P 114 -124 at 0.2 torr	B.P 114 -124[26] at 0.2 torr	1.16(t, *J* = 7.0Hz, 3H), 1.92(m, 2H), 2.48(t, *J* = 7.1Hz, 2H), 2.88(t, *J* = 7.3Hz, 2H), 3.36(s, 2H), 4.08(m, 2H), 7.38-7.57(m, 5H), 9.54(brs, 1H).
2.	*N*-benzyl-Gly-OH	195-196	196 - 198[19]	3.16(s, 2H), 3.74(s, 2H), 7.23-7.36(m, 5H), 10.14(brs, 1H).
3.	*N*-benzyl-Ile-OH	249-251	258 - 259[27]	0.89(t, *J* = 7.1Hz, 3H), 1.09(d, *J* = 7.1Hz, 3H), 1.48(m,2H), 1.78(m, 1H), 3.44(d, *J* = 7.2Hz, 1H), 3.74(s, 2H), 5.97(brs, 1H), 7.26-7.34(m, 5H).
4.	*N*-benzyl-Leu-OH	251-253	253-255[7]	0.95(d, *J* = 4.4Hz, 6H), 1.70(m, 1H), 1.83(t, *J* = 5.5Hz, 2H), 3.39(t, *J* = 6.5Hz, 1H), 3.65(s, 2H), 5.89(brs, 1H), 7.41-7.49(m, 5H).
5.	*N*-benzyl-Ala-OH	244-246	251-255[7]	1.48(d, *J* = 7.3Hz, 3H), 3.44(q, *J* = 7.3Hz, 1H), 3.69(s, 2H), 6.41(brs, 1H), 7.41-7.43(m, 5H).
6.	*N*-benzyl-Val-OH	266-269	273-275[7]	0.82(d, *J* = 6.8Hz, 6H), 1.85(m, 1H), 3.45(d, *J* = 4.9Hz, 1H), 3.67(s, 2H), 6.17(brs, 1H), 7.33-7.22(m, 5H).
7.	*N*-benzyl-Phe-OH	245-249	251-255[7]	3.11(d, *J* = 13.2Hz, 2H), 3.42(t, *J* = 13.2Hz, 1H), 3.71(s, 2H), 7.20-7.45(m, 10H).
8.	*N*-benzyl-Glu-OH	145-148	156-157[28]	1.90(m, 2H), 2.28(t, *J* = 7.4Hz, 2H), 3.42(t, *J* = 7.6Hz, 1H), 3.71(s, 2H), 7.28-7.36(m, 5H), 9.61(brs, 1H).
9.	*N*-benzyl-aminoethanol	113-117 at 0.2 torr	114-116[29] at 0.2 torr	2.51(brs, 1H), 2.61(t, *J* = 6.7Hz, 2H), 3.51(t, *J* = 6.7Hz, 2H), 3.65(s, 2H), 7.24-7.36(m, 5H).
10.	*N*-benzyl-benzylamine	B.P 298-300	B.P 298-300[30]	2.49(brs, 1H), 3.67(s, 4H), 7.19-7.39(m, 10H).

CONCLUSION

In summary, we have developed a method to selective mono debenzyaltion of dibenzylation amines using ammonium formate as hydrogen source and palladium carbon as catalyst, under normal laboratory condition. The major advantages of this method are clean work up, catalyst recovery and high yield.

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REFERENCES

1. Green T and Wuts PGM. *Protective Groups in Organic Chemistry,* 4th edition. John Wiley & Sons. New York. 2006, 814-822.
2. David PF, Michael LW, Allan KW. Towards Protein Surface Mimetics. *Curr. Med. Chem.* 1998, 5: 29-62.
3. Cecile B, Arnaud LeTiran, James P, Robert DV, Harold K. *N*-Substituted Amino Acid N- benzylamides: Synthesis, Anticonvulsant, and Metabolic Activities. *Bioorg. Med. Chem.* 2004, 12: 3079-3096.
4. Souza AE, Pissinate K, Nascimento MG, Grynberg NF, Aurea E. Synthesis, Cytotoxicity and DNA-topoisomerase Inhibitory Activity of New Asymmetric Ureas and Thioureas. *Bioorg. Med. Chem.* 2006, 14: 492-499.
5. Goff, Nicolas Le Carrer-Le, Audin, Patrick, Bernard. New Organometallic Approach to Derivatives of α-substituted Statines from *N,N*-dibenzylamino aldehydes. *Tett. Lett.* 2002, 43: 6325-6328.
6. Green T, Wuts PGM. *Protective Groups in Organic Chemistry*. 4th edition. John Wiley & Sons, New York. 2006, 814-815.
7. Quitt P, Hellerbach J, Vogler K. The Synthesis of Optically Active *N*-Monomethyl Amino Acids. *Helv. Chim. Acta*. 1963, 46: 327-333.
8. Beaulieu, Dominik W. Preparation of Aminoalkyl Chlorohydrin Hydrochlorides: Key Building Blocks for Hydroxyethylamine-Based HIV Protease Inhibitors. *J. Org. Chem*. 1996, 61: 3635-3645.
9. Johnstone RA, Willy AM, Entwistle ID. Heterogeneous Catalytic Transfer Hydrogenation and its Relation to Other Methods for Reduction of Organic Compounds. *Chem. Rev.* 1985, 85: 129-170.
10. Anantharamaiah GM, Sivanandaiah M. Transfer Hydrogenation: A Convenient Method for Removal of Some Commonly used Protecting Groups in Peptide Synthesis. *J. Chem. Soc., Perkin trans. 1.* 1977, 5: 490-496.
11. Ram S, Ehrekaufer RE. Ammonium Formate in Organic Synthesis: A Versatile Agent in Catalytic Hydrogen Transfer Reductions. *Synthesis.* 1988, 91-96.
12. Gowda DC, Abiraj K. Heterogeneous Catalytic Transfer Hydrogenation in Peptide Synthesis. *Lett. Pep. Sci.* 2002, 9: 153-65.
13. Babiker E, Anantharamaiah GM, Garfield PR, Gary EM. Removal of Benzyl-type Protecting Groups from Peptides by Catalytic Transfer Hydrogenation with Formic Acid. *J. Org. Chem*. 1979, 44: 3442-3444.
14. Arthur MF, Edgar PH, Theodore JL, Chryssa T, Johannes M. Rapid Removal of Protecting Groups from Peptides by Catalytic Transfer Hydrogenation with 1,4-Cyclohexadiene. *J. Org. Chem*. 1978, 43: 4194-4196.
15. Anwer MK, Khan SA, Sivanandaiah KM. Catalytic Transfer Hydrogenolysis of Protected Peptides using Hydrazine. *Synthesis.* 1978, 751-754.

16. Ram S, Spicer LD. Debenzylation of *N*-Benzylamino Derivatives by Catalytic Transfer Hydrtyation with Ammonium Formate. *Synth. Comm*. 1987, 17: 415-417.
17. Steven DB, Stephen GD, Andrew WM, Shyam P, Andrew DS, Garry F. Chemoselective Oxidative Debenzylation of Tertiary *N*-benzyl Amines. *J. Chem. Soc. Chem. Comm*. 2000, 5: 337-338.
18. Morosawa, Yokoo. Synthesis and Pyrolysis of *N*-Substituted γ-Aminobutyrates and N-Substituted Bis(β-ethoxycarbonylethyl)amines. *Bull. Chem. Soc. Japan.* 1963, 36: 179-183.
19. Rowley. Specificity of Creatine Kinase. New Glycocyamines and Glycocyamine Analogs Related to Creatine. *J. Am. Chem. Soc.* 1971, 93: 5542-5551.
20. Tomasz. Modro. Acidic Cleavage of the Cyclic Phosphorochloridites with
21. Alkanolamines. *Phosph. and Sulphur*. 1979, 7: 333-334.
22. Robert, Hoffman, Junhua Tao. An Improved Enantiospecific Synthesis of Statine and Statine Analogs via 4-(*N*,*N*-Dibenzylamino)-3-keto Esters. *J. Org. Chem.* 1997, 62: 2292-2297.
23. Camps Pelayo. (*R*) and (*S*)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone as Chiral Auxiliaries in the Enantioselective Preparation of α-Amino Acids. *Tetrahedron: Asymmetry.* 1999, 10: 493-509.
24. Velluz. The Chemistry of Cortisone in its New Developments. *Bulletin de la Societe Chimique de Franc.,* 1955, 201-203.
25. Enders, Dietera, Schiffers R. Enantioselective Synthesis of Differently Protected 1,2-Diamines via *α*-Alkylation of Dibenzylaminoacetaldehyde SAMP-Hydrazone. *Synthesis* 1996, 53-58.
26. Trapani, Giuseppe R, Antonia, Latrofa, Andrea. Trimethylamine-Borane as Useful Reagent in the *N*-Acylation or *N*-Alkylation of Amines by Carboxylic Acids. *Synthesis.*1983, 1013-1014.
27. Casy, Birnbaum. Synthesis and Reactions of Some Azacycloheptan-4-ols. *J. Chem. Soc*. 1964, 5130-5134.
28. Shoji. Configuration of N,β-Dimethylleucine, a Constituent Amino Acid of Triostin C. *J. Org. Chem*. 1965, 30: 2772-2776.
29. Ohfune, Yasufumi, Higuchi, Naoki. An Efficient One-step Reduction of *N*-monoalkylation of α Amino Acids. *Chem. Lett.* 1984, 441-444.
30. Janin, Aubertin, Anne M, Angele, Claude. Imidazo[1,5-g][1,4]diazepines, TIBO Analogues Lacking the Phenyl Ring: Synthesis and Evaluation as Anti-HIV Agents. *Tetrahedron.* 1996, 52: 15157-15170.
31. Rani, Sharma N, Manrao JR, Kaul MR, Secondary Amines: Synthesis and Effect of Length of Spacer Linking Two Phenyl Rings on Biological Activity. *J. Ind. Chem. Soc.* 2008, 85: 1041-1044.