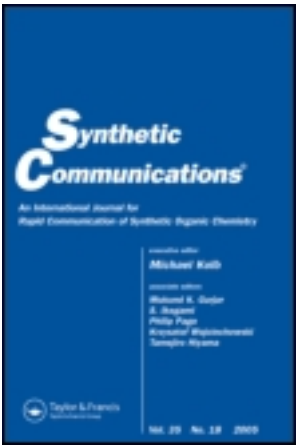



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# An Efficient Method for the N-Debenzylation of Aromatic Heterocycles

T. Srinivasa Rao [a] & Pramod S. Pandey [a]
[a] Department of Chemistry, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi, 110016, India
Published online: 12 Jan 2011.

To cite this article: T. Srinivasa Rao & Pramod S. Pandey (2004) An Efficient Method for the N-Debenzylation of Aromatic Heterocycles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:17, 3121-3127, DOI: 10.1081/SCC-200028570

To link to this article: http://dx.doi.org/10.1081/SCC-200028570

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 17, pp. 3121–3127, 2004



# An Efficient Method for the N-Debenzylation of Aromatic Heterocycles

**T. Srinivasa Rao and Pramod S. Pandey***

Department of Chemistry, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi, India

## ABSTRACT

The N-debenzylation of aromatic heterocycles such as substituted pyrroles and indoles, having functional groups like ester, amide, halo, and nitrile, by using sodium in liquid ammonia in the presence of t-BuOH at −78°C cleanly affords N-debenzylated aromatic heterocycles in good yields.

*Key Words:* N-debenzylation; Aromatic heterocycles; Sodium in liquid ammonia; Substituted pyrroles.

The protection of heterocycles such as pyrroles, imidazoles, and indoles is an important topic due to the importance of nitrogen heterocycles in biological systems.[1] Benzyl group is an important protective group for the nitrogen-

*Correspondence: Pramod S. Pandey, Department of Chemistry, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi, 110016, India; Fax: 91-11-2658-2037; E-mail: pramod@netearth.iitd.ac.in.



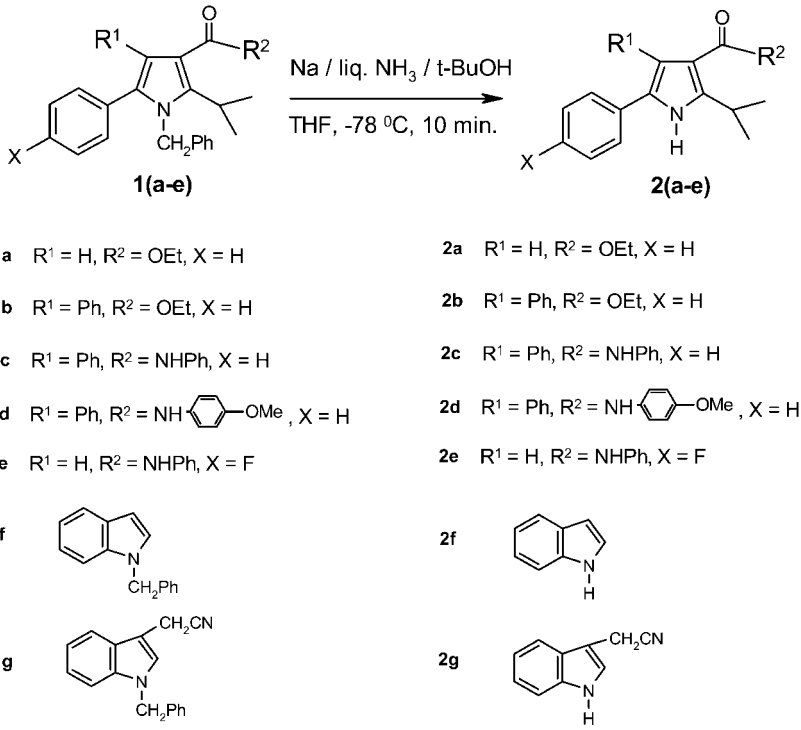
DOI: 10.1081/SCC-200028570 0039-7911 (Print); 1532-2432 (Online)

containing compounds. The N-alkyl-N-benzyl compounds are easily N-debenzylated by the use of hydrogenolysis ($H_2$/Pd-C)[2] or by catalytic transfer hydrogenation (CTH)[3] using a variety of hydrogen donors such as cyclohexene, 1,4-cyclohexadiene, formic acid, ammonium formate, hydrazine hydrate, and sodium hypophosphite. However, these methods are not found suitable for N-debenzylation of N-acyl-N-benzyl compounds and N-benzyl aromatic heterocycles. One of the methods used for the N-debenzylation of aromatic heterocycles includes the utilization of strong Lewis acid $AlCl_3$,[4] which fails to find its general applicability as in some cases;[5] it was found that the ester group present in the molecule gets hydrolyzed in this condition. Also, it is reported that this method is not successful in the N-debenzylation of some of the aromatic heterocycles.[6] The other method is the utilization of strong base potassium t-butoxide/dimethyl sulfoxide (DMSO) and oxygen, which is again found to be problematic if sensitive functional groups are present in the molecule such as ester and nitro groups.[6]

Although dissolving metals in liquid ammonia has been widely used in the case of N-acyl-N-benzyl systems,[7] there is only one report on its application in the N-debenzylation of aromatic heterocycle,[8] in which NaH was also used, which afforded poor yield of N-debenzylated product. Hence, application of dissolving metals in liquid ammonia as a selective and efficient method for N-debenzylation of aromatic heterocycles has limitations and needs to be reexamined in terms of its reaction conditions to find its general applicability.

During our synthesis of atorvastatin, we have found that of all the above methods, only the method of dissolving metal in liquid ammonia at low temperature, for example, sodium in liquid ammonia in the presence of t-BuOH at $-78^{\circ}C$, was successful for the N-debenzylation of N-benzyl pyrrole **1e**.[9] This prompted us to study the general applicability and sensitivity of this method for the N-debenzylation of various substituted pyrroles and indoles having ester, amide, halo, and nitrile functional groups **1(a-g)** (Sch. 1). N-Benzyl pyrrole molecules **1(a-d)** were synthesized by the reactions of 2-[benzyl(isobutyryl)amino]-2-phenylacetic acid with ethyl propiolate, ethyl phenylpropiolate, N1,3-diphenyl-2-propynamide, and N1-(4-methoxyphenyl)-3-phenyl-2-propynamide, respectively, following the procedure of Roth et al.[10] The **1e** was synthesized by the reaction of 2-[benzyl(4-fluorobenzoyl)amino]-3-methylbutanoic acid with N1,3-diphenyl-2-propynamide in the presence of dicyclohexylcarbodiimide (DCC) in toluene.[9] The **1f** and **1g** were synthesized by the reaction of their respective N-H indoles with benzyl bromide in the presence of sodium hydride in tetrahydrofuran (THF).[6]

We have found that the substituted N-benzyl pyrrole **1a** gave N-debenzylated pyrrole **2a** in 92% yield, using sodium in liquid ammonia in the presence

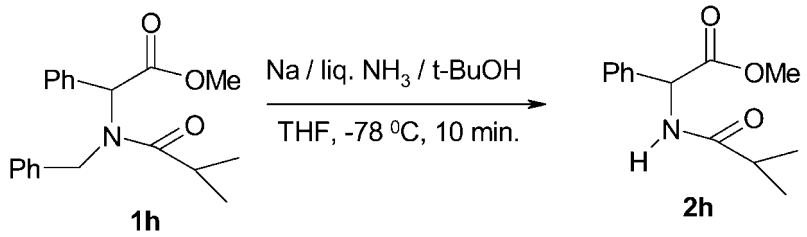



*Scheme 1.*

of t-BuOH as proton donor at $-78^{\circ}C$, without affecting the ester functional group. N-Debenzylation of other substituted pyrrole and indole molecules **1(b–g)** having ester, amide, halo, and nitrile functional groups using the same condition afforded N-debenzylated aromatic heterocyclic compounds **2(b–g)** in excellent yields in 10 min, without affecting the other functional groups.

We have also successfully N-debenzylated the methyl 2-[benzyl(isobutyryl)amino]-2-phenylacetate **1h**[10] in 75% yield to afford methyl 2-(isobutyrylamino)-2-phenylacetate **2h**, where the ester and other groups are unaffected (Sch. 2). This suggests that in this condition, the functional groups, which are not attached to aromatic heterocyclic ring, are also unaffected.

In conclusion, we have developed a mild and efficient methodology for the deprotection of benzyl group of N-benzyl aromatic heterocycles using sodium in liquid $NH_3$ and t-BuOH as a proton donor at $-78^{\circ}C$, which may find its general applications in the synthesis of nitrogen-containing heterocycles.




*Scheme 2.*

## EXPERIMENTAL

Melting points were determined using a SONAR melting point apparatus and are uncorrected. Infrared (IR) absorption spectra were recorded on a Nicolet 5DX FTIR instrument (Thermo Electron Corporation, USA) and values are reported in $cm^{-1}$. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a DPX-300 Brucker spectrometer (Switzerland). Data are reported as follows: integration, chemical shift in parts per million (ppm) from tetramethylsilane (TMS) on the $\delta$ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, and m = multiplet), coupling constant in hertz (Hz), and assignment. The fast atom bombardment (FAB) mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas; m-nitrobenzyl alcohol (NBA) was used as the matrix. Microanalyses were obtained using a Perking-Elmer elemental analyzer PE 2400 Series II instrument. Monitoring of the reactions was performed using silica gel TLC plates (silica gel G with binder). Column chromatography was performed using silica gel (60–120 mesh). Organic solvents were purified by standard procedures.

### Typical Procedure for N-Debenzylation of Aromatic Heterocycles

To a 50-mL two-necked flask cooled to $-78^{\circ}C$ was added freshly cut sodium metal (52 mg, 1.6 mmole) and liquid ammonia (20 mL). When the solution became blue in color (5 min), t-BuOH (84 mg, 0.8 mmole) in THF (2 mL) was added followed by **1a** (200 mg, 0.4 mmole) in THF (8 mL). The reaction mixture was stirred at $-78^{\circ}C$ for 10 min; by then all blue color had disappeared. Ammonia was evaporated by replacing the cooling bath with a water bath ($30^{\circ}C$–$40^{\circ}C$). The reaction mixture was then quenched with 1 mL of aqueous $NH_4Cl$ and extracted with EtOAc (25 mL). The organic layer was dried over $Na_2SO_4$, concentrated, and purified by column chromatography (silica gel) to afford 156 mg of **2a** as a white solid in 92% yield.

Physical and Spectroscopic Data for Ethyl 2-isopropyl-5-phenyl-1H-3-pyrrolecarboxylate **2a**

Yield 92%; m.p.: 100°C; IR (KBr) 3295, 3039–2727, 1668, 1608, 1591, 1525, 1466, 1391, 1232, 1089, 785, 761, 693 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.38 (bs, 1H), 7.71–7.13 (m, 5H), 6.84 (s, 1H), 4.29 (q, $J = 7$ Hz, 2H), 3.86 (septet, $J = 6.9$ Hz, 1H), 1.36 (t, $J = 7$ Hz, 3H), 1.33 (d, $J = 6.9$, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 165.56, 145.96, 131.91, 129.66, 128.89, 126.56, 123.76, 107.58, 59.43, 29.67, 26.07, 21.93, 14.46; FAB MS (m/z) 258 (M+1, 70), 257 ($M^+$, 100%), 242 (20), 228 (6), 212 (20); Anal. Calcd. for $C_{16}H_{19}NO_2$: C 74.68, H 7.44, N 5.44%; Found: C 74.60, H 7.48, N 5.50%.

Ethyl 2-isopropyl-4,5-diphenyl-1H-3-pyrrolecarboxylate **2b**

Yield 84%; m.p.:105°C–107°C; IR (KBr) 3297, 3039–2853, 1672, 1454, 1260, 1189, 1088, 800, 697; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.2 (bs, 1H), 7.19–7.03 (m, 10H), 3.99 (q, $J = 7.0$ Hz, 2H), 3.79 (septet, $J = 6.9$ Hz, 1H), 1.30 (d, $J = 6.9$ Hz, 6H), 0.93 (t, $J = 7.0$, 3H); Anal. Calcd. for $C_{22}H_{23}NO_2$: C 79.25, H 6.95, N 4.20%; Found: C 79.28, H 7.29, N 4.19%.

N3,4,5-Triphenyl-2-isopropyl-1H-3-pyrrolecarboxamide **2c**

Yield 85%; m.p.: 210°C–211°C; IR (KBr) 3404, 3292, 3058–2853, 1642, 1595, 1523, 1436, 1312, 1251, 1191, 757, 694 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.34 (bs, 1H), 7.44–6.98 (m, 16H), 4.09 (septet, $J = 6.9$ Hz, 1H), 1.38 (d, $J = 6.9$, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 163.56, 144.64, 138.42, 135.18, 131.27, 129.16, 128.86, 128.61, 127.81, 126.69, 126.12, 124.96, 124.53, 123.19, 119.44, 119.14, 25.94, 22.23; FAB MS (m/z) 381 (M + 1, 80%), 380 ($M^+$, 60), 307 (20), 288 (100), 279 (10); Anal. Calcd. for $C_{26}H_{24}N_2O$: C 82.08, H 6.36, N 7.36%; Found: C 82.07, H 6.29, N 7.07%.

N3-(4-Methoxyphenyl)-2-isopropyl-4,5-diphenyl-1H-3-pyrrolecarboxamide **2d**

Yield 81%; m.p.: 198°C–200°C; IR (KBr) 3395, 3274, 3026–2865, 1635, 1598, 1528, 1509, 1460, 1348, 1230, 1190, 1095, 824, 702 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.33 (bs, 1H), 7.42–6.71 (m, 15H), 4.07 (septet, $J = 6.9$ Hz, 1H), 3.73 (s, 3H), 1.40 (d, $J = 6.9$, 6H); Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C 79.00, H 6.38, N 6.82%; Found: C 79.19, H 6.27, N 6.66%.

N3,4-Diphenyl-5-(4-fluorophenyl)-2-isopropyl-1H-3-pyrrolecarboxamide **2e**

Yield 83%; m.p.: 208°C–210°C; IR (KBr) 3404, 3291, 3059-2870, 1642, 1528, 1438, 1313, 1253, 1192, 752, 692 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.34 (bs, 1H), 7.43–6.96 (m, 15H), 4.11 (septet, $J = 6.9$ Hz, 1H), 1.41 (d, $J = 6.9$, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 168.67, 165.73, 163.52, 145.3, 144.6, 137.9, 132.19, 131.29, 129.20, 128.64, 127.87, 126.70, 124.65, 123.20, 121.29, 119.13, 118.52, 116.50, 25.95, 22.27; FAB MS (m/z) 397 ($M\text{-}H^+$, 5%), 382 (30), 381 (100), 380 (70), 288 (90), 289 (10), 262 (5), 220 (5); Anal. Calcd. for $C_{26}H_{23}FN_2O$: C 78.37, H 5.82, N 7.03%; Found: C 78.67, H 6.11, N 7.12%.

Methyl 2-(isobutyrylamino)-2-phenylacetate **2h**

Yield 75%; m.p.: 115°C; IR (KBr) 3275, 3036–2873, 1752, 1640, 1533, 1509, 1456, 1347, 1264, 1210, 1163, 1095, 979, 780, 753, 696 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.42–7.26 (m, 5H), 6.43 (bs, 1H), 5.57 (d, $J = 7.1$ Hz, 1H), 3.73 (s, 3H), 2.44 (septet, $J = 6.9$ Hz, 1H), 1.16 (dd, $J = 6.9$, 6H); Anal. Calcd. for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95%; Found: C 66.97, H 7.39, N 5.90%.

## ACKNOWLEDGMENT

T.S.R. thanks the Council of Scientific and Industrial Research, New Delhi, for the award of Senior Research Fellowship.

## REFERENCES

1. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd Ed.; Wiley-Interscience: New York, 1999; Chap. 7, 615.
2. (a) Zhou, Z.; Keana, J.F.W. A practical synthesis of 4-(substituted-benzyl)piperidines and (±)-3-(substituted-benzyl)pyrrolidines via a Wittig reaction. J. Org. Chem. **1999**, *64* (10), 3763–3766; (b) Jorgensen, E.C.; Windridge, G.C.; Lee, T.C. Angiotensin II analogs. 3. Synthesis and biological evaluation of some des-aspartyl-angiotensins. J. Med. Chem. **1970**, *13* (3), 352–356.
3. (a) Bernotas, R.C.; Cube, R.V. The use of Pearlman's catalyst for selective *N*-debenzylation in the presence of benzyl ethers. Synth. Commun. **1990**, *20* (8), 1209–1212; (b) Khan, S.A.; Sivanandaiah, K.M. Catalytic transfer hydrogenation in solid-phase peptide synthesis: synthesis of

bradykinin. Synthesis **1978** (10), 750–751; (c) Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. Rapid removal of protecting groups from peptides by catalytic transfer hydrogenation with 1,4-cyclohexadiene. J. Org. Chem. **1978**, *43* (21), 4194–4196; (d) Adger, B.M.; O'Farrell, C.; Lewis, N.J.; Mitchell, M.B. Catalytic transfer hydrogenolysis of *N*-benzyl protecting groups. Synthesis **1987** (1), 53–55; (e) Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. Heterogeneous catalytic transfer hydrogenation and its relation to other methods for reduction of organic compounds. Chem. Rev. **1985**, *85* (2), 129–170.

4. Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. A novel method for the debenzylation of protected indole nitrogen. Synthesis **1984** (9), 738–740.
5. Forbes, I.T.; Johnson, C.N.; Thompson, M. Syntheses of functionalised pyrido[2,3-b]indoles. J. Chem. Soc., Perkin Trans. 1 **1992** (2), 275–281.
6. Haddach, A.A.; Kelleman, A.; Rewolinski, M.V.D. An efficient method for the *N*-debenzylation of aromatic heterocycles. Tetrahedron Lett. **2002**, *43* (3), 399–402.
7. (a) Webster, F.X.; Millar, J.G.; Silverstein, R.M. Cleavage of hindered $\alpha$-methylbenzylamides, intermediates in the resolution of carboxylic acids. Tetrahedron Lett. **1986**, *27* (41), 4941–4944; (b) Ramesh, N.G.; Klunder, A.J.H.; Zwanenburg, B. Enantioselective synthesis of 4-aminocyclopent-2-ene-1-one from tricyclo[5.2.1.$0^{2,6}$]decenyl enaminones. Tetrahedron Lett. **1998**, *39* (11), 1429–1432; (c) Franceschini, N.; Nascimento, S.D.; Sonnet, P.; Guillaume, D. Efficient enantioselective synthesis of 2-substituted thiomorpholin-3-ones. Tetrahedron: Asymmetry **2003**, *14* (21), 3401–3405.
8. Pardo, D.G.; Desmaele, D.; Angelo, J.D. New approaches to *Corynanthe* alkaloids involving the conjugate addition of dialkyl malonates to unsaturated thiolactams: synthesis of (±)-3-*epi*-dihydrocorynantheol. Tetrahedron Lett. **1992**, *33* (44), 6633–6636.
9. Pandey, P.S.; Rao, T.S. An efficient synthesis of N3,4-diphenyl-5-(4-fluorophenyl)-2-isopropyl-1H-3-pyrrolecarboxamide, a key intermediate for atorvastatin synthesis. Bioorg. Med. Chem. Lett. **2004**, *14* (1), 129–131.
10. Roth, B.D.; Blankley, C.J.; Chucholowski, A.W.; Ferguson, E.; Hoefle, M.L.; Ortwine, D.F.; Newton, R.S.; Sekerke, C.S.; Sliskovic, D.R.; Stratton, C.D.; Wilson, M. Inhibitors of cholesterol biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1H-pyrrol-1-yl)ethyl]-2H-pyran 2-one inhibitors of HMG-CoA reductase. 2. Effects of introducing substituents at positions three and four of the pyrrole nucleus. J. Med. Chem. **1991**, *34* (1), 357–366.

Received in India May 17, 2004