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Reductive N-alkylation of aromatic amines and nitro compounds with nitriles using polymethylhydrosiloxane☆

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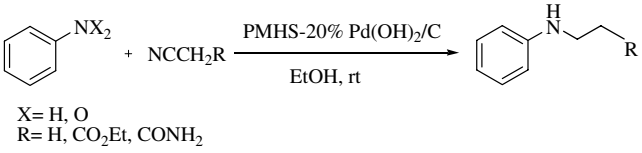
Abstract—The potential utility of polymethylhydrosiloxane (PMHS) as a reducing agent for reductive N-alkylation of aromatic amines and nitro compounds using nitriles as an alkylating agent and $Pd(OH)_2/C$ as a catalyst is described. The application of this method for the synthesis of several heterocyclic compounds is also reported.

The development of new reduction procedures using safe and practically useful reducing agents is of great importance. Existing reducing agents such as H_2 (gas), $NaBH_4$, $LiAlH_4$ and DIBAL-H, although efficient in producing good yields of the desired products, require precautions in handling. The title reagent, namely, polymethylhydrosiloxane (PMHS) is being investigated as a safe, easy-to-handle, cheap and environmentally benign reagent for the reduction of organic functional groups.[1] This reagent is very inert making it safe-to-handle, but in the presence of an activator, it acts as an excellent reducing agent. In continuation of our interest in exploring the potential use of PMHS as a reducing agent,[2] herein we report a new and efficient method for the reductive mono N-alkylation of nitro compounds and amines with nitriles as an alkylating agent using PMHS in the presence of $Pd(OH)_2/C$ as a catalyst (Scheme 1).



Scheme 1.

Traditional methods for this transformation are base mediated N-alkylation using toxic and corrosive alkylating agents,[3] reductive amination,[4] alkylative amination[5] and other alkylation methods,[6] but most of these suffer from disadvantages. There are reports on reductive alkylation of amines using nitriles as the alkylating agent with hydrogen (gas) as a reductant in the presence of different types of catalysts, but only a few examples of selective mono N-alkylation have been reported.[7] Some of these procedures are limited to only a few substrates, require large quantities of amine and elevated hydrogen pressure and/or higher temperature or longer reaction times. Recently, Hudson et al. have used ammonium formate as a reducing agent for this reductive alkylation.[8]

Initially, aniline **1a** and acetonitrile were reacted in the presence of polymethylhydrosiloxane and 10% Pd/C in ethanol as solvent at room temperature and the formation of *N*-ethylaniline **2a** was observed in 82% yield (entry 1). A similar reaction in the presence of 20% $Pd(OH)_2/C$ (20 mg/mmol)[9] gave the mono N-alkylated product in 86% yield (entry 2). To rationalize this finding, various anilines were alkylated with acetonitrile in the presence of PMHS and 20% $Pd(OH)_2/C$ in ethanol to give the corresponding *N*-ethyl products in reasonably good yields (entries 3–5). The debrominated product was isolated in the case of entry 5. Alkylation of anilines **1a** and **1d** were also studied using ethyl

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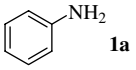
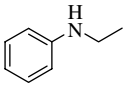
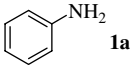
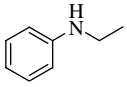
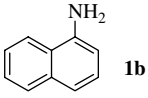
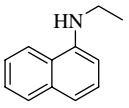
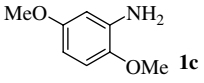
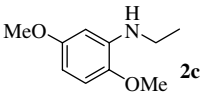
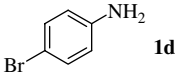
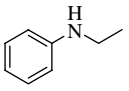
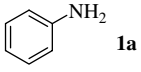
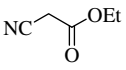
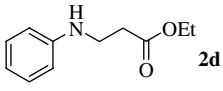
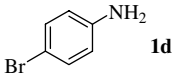
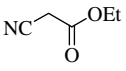
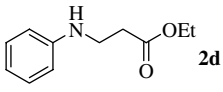
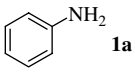
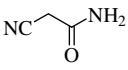
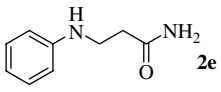
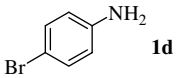
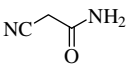
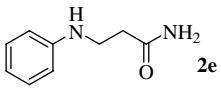
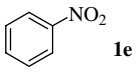
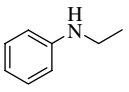
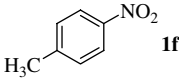
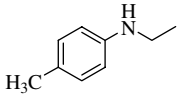
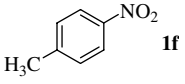
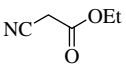
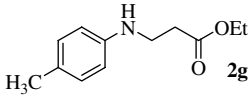
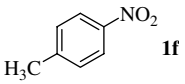
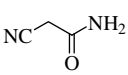
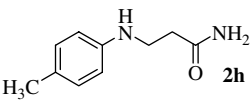
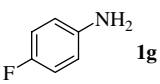
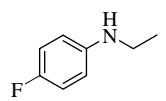
Table 1. Reductive N-alkylation of aromatic amines and nitro compounds

Entry	Substrate	Nitrile	Time (h)	Product[a]	Yield[b] (%)
1	 **1a**	CH_3CN	4	 **2a**	82[c]
2	 **1a**	CH_3CN	2	 **2a**	86
3	 **1b**	CH_3CN	4	 **2b**	64
4	 **1c**	CH_3CN	5	 **2c**	75
5	 **1d**	CH_3CN	0.5	 **2a**	88
6	 **1a**		3	 **2d**	68
7	 **1d**		2	 **2d**	75
8	 **1a**		4	 **2e**	76
9	 **1d**		3	 **2e**	74
10	 **1e**	CH_3CN	0.5	 **2a**	72
11	 **1f**	CH_3CN	1	 **2f**	73
12	 **1f**		1.5	 **2g**	69
13	 **1f**		2	 **2h**	65
14	 **1g**	CH_3CN	0.5	 **2i**	63

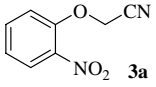
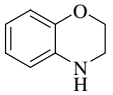
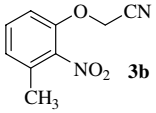
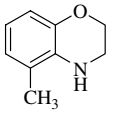
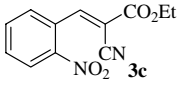
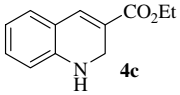
[a] All the products were characterized by ^1H NMR, mass and IR spectroscopy.
[b] Isolated yields.
[c] 10% Pd/C was used as the catalyst.

cyanoacetate and cyanoacetamide to afford the products **2d** and **2e** in good yields without affecting the ester and amide functionalities (entries 6–9). Debromination of **1d** (entries 5, 7 and 9) is, however, noted as a limitation. We next turned our attention to alkylation of nitro compounds. Accordingly, nitrobenzene **1e** was treated with acetonitrile in the presence of polymethylhydrosiloxane and 20% $Pd(OH)_2/C$ in ethanol at room temperature to give *N*-ethylaniline **2a** in 72% yield. Similarly, *p*-nitrotoluene was alkylated with acetonitrile, ethyl cyanoacetate and cyano acetamide under similar conditions to yield **2f**, **2g** and **2h** (Table 1, entries 11–13). Substrate **1g** having an electron-withdrawing substituent also underwent reaction with the present reagent system to provide the corresponding mono alkylated product **2i** in 63% yield (Table 1, entry 14). An attempt was made to reuse the catalyst, but was unsuccessful.

In order to demonstrate the scope of this method, we have prepared several starting materials possessing nitro and cyano groups and studied the intramolecular reductive N-alkylation reaction. Accordingly, compound **3a** was subjected to PMHS in the presence of 20% $Pd(OH)_2/C$ in ethanol at room temperature to give the corresponding 3,4-dihydro-2*H*-1,4-benzoxazine (**4a**) in 73% yield. Similarly, **3b** gave the corresponding benzoxazine **4b** in 67% yield. When compound **3c** was subjected to the present reductive N-alkylation conditions, 3-substituted-1,2-dihydroquinoline **4c** was obtained in 72% yield.

In conclusion, we have demonstrated that PMHS is a versatile reducing agent for reductive mono N-alkylation of aromatic amines and nitro compounds with nitriles as alkylating agents. The applicability of this method for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines and dihydroquinolines is also described and further applications towards expanding the substrate scope are underway. We believe that the reagent system described herein may find wide applicability in organic synthesis due to its efficiency, economy, simplicity and safety.

Table 2. Intramolecular reductive N-alkylation

Entry	Substrate	Time (h)	Product[a]	Yield[b] (%)
1	 **3a**	0.5	 **4a**	73
2	 **3b**	0.5	 **4b**	67
3	 **3c**	1	 **4c**	72

[a] All the products were characterized by ^1H NMR, mass and IR spectroscopy.
[b] Isolated yields.

General experimental procedure: To a stirred solution of substrate (1 mmol) in ethanol (5 mL) was added the nitrile (1 mmol), polymethylhydrosiloxane (180 mg, 3 mmol) and 20% $Pd(OH)_2/C$ (~20 mg) and the reaction mixture was stirred at room temperature for the given time (see Tables 1 and 2). After completion of the reaction, the mixture was filtered through Celite and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give the corresponding N-alkylated products.[10]

Acknowledgement

K.V., P.B.B. and P.P.M. are thankful to the CSIR, New Delhi, for fellowships.

References and notes

1. For an exhaustive review on PMHS, see: (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381–3391; and also see: (b) Senapati, K. K. *Synlett* **2005**, 1960–1961.
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9. Reactions using 20% $Pd(OH)_2/C$ in smaller quantities (10 mg or 15 mg/mmol) did not proceed to completion even after longer reaction times.
10. *Spectral data*: Compound **2g**: ^1H NMR ($CDCl_3$, 300 MHz): δ 6.96–6.87 (m, 2H), 6.53–6.46 (m, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.39 (t, $J = 6.4$ Hz, 2H), 2.55 (t,

$J = 6.0$ Hz, 2H), 2.22 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H); IR (KBr): ν 3415, 1729, 1602, 1518, 1281, 1182 cm^{-1}; ESI-MS: m/z 230 $(M+Na)^+$; HRMS (EI): m/z calcd for $C_{12}H_{17}NO_2Na$ 230.2586 $[M+Na]^+$, found 230.2591. Compound **2h**: ^1H NMR ($CDCl_3$, 200 MHz): δ 6.95–6.84 (m, 2H), 6.54–6.48 (m, 2H), 5.75 (br s, 1H), 5.65 (br s, 1H), 3.41 (t, $J = 5.5$ Hz, 2H), 2.47 (t, $J = 5.9$ Hz, 2H), 2.22 (s, 3H); IR (KBr): ν 3353, 3347, 3195, 1666, 1518, 1409, 1121 cm^{-1}; ESI-MS: m/z 201 $(M+Na)^+$; HRMS (EI): m/z calcd for $C_{10}H_{14}N_2ONa$ 201.2207 $[M+Na]^+$, found 201.2201. Compound **4b**: ^1H NMR ($CDCl_3$, 300 MHz): δ 6.61–6.48 (m, 3H), 4.18 (t, $J = 4.5$ Hz, 2H), 3.44 (t, $J = 4.5$ Hz, 2H), 2.08 (s, 3H); IR (KBr): ν 3410, 2924, 1485, 1281, 765 cm^{-1}; ESI-MS: m/z 150 $(M+H)^+$; HRMS (EI): m/z calcd for $C_9H_{12}NO$ 150.1977 $[M+H]^+$, found 150.1972.